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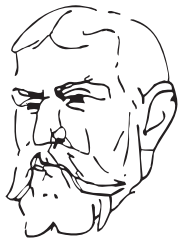

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ORIGINAL ARTICLE

# SELECTED PROBLEMS IN THE REHABILITATION OF PATIENTS IN A NURSING AND CARE INSTITUTION

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## ABSTRACT

**The aim** of the study was to assess selected problems in the rehabilitation of patients staying at a nursing and care institution.

**Materials and methods:** The study included 33 patients aged 55 to 96 years who were staying at the nursing and care institution in Lipsko. Study patients were examined over a period of 3 months using the standardised Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (I-ADL) scores, the Abbreviated Mental Test Score (AMTS) and the Timed Up and Go Test (TUG).

**Results:** Standardised ADL testing showed that a considerable proportion of study patients (60%) aged 66–75 years had moderate disability. Standardised Lawton scale testing showed that the most difficult complex activities were home maintenance (96.97%), shopping (90.91%), cooking (87.88%), cleaning (87.88%) and doing laundry (78.79%). The standardised Timed Up and Go Test showed that a large proportion of study patients (71.43%) aged 66–75 years had considerable functional mobility limitations. The AMTS, which assessed the cognitive function, revealed normal results in 36.36% of study patients.

**Conclusions:**

1. Study patients had significant functional disability.
2. The patients' sex did not influence the ability to perform complex activities of daily living.
3. Sociodemographic determinants did not influence cognitive functioning.
4. Physical therapy and rehabilitation in the elderly should be performed on a regular basis and in the entire society.

**KEY WORDS:** aging process, health problems, rehabilitation

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## INTRODUCTION

The issues related to aging and old age are broad and affect everyone. The aging process is progressive and irreversible. There are three different aspects to aging, namely the biological, psychological and social aspect, which are closely interconnected. Individual organs and systems in the body begin to age in middle-aged people and the process intensifies with time.

The beginning of the biological aging process is associated with typical gait changes and visible muscle atrophy caused by reduced muscle strength. The so-called senile posture, characterised by an increased thoracic kyphosis and a decreased lumbar lordosis, is the most pronounced musculoskeletal symptom. This abnormal posture contributes to a shift in the body's centre of gravity and joint mobility impairment [1-9].

The progressive population aging currently taking place in Poland and worldwide is caused by an increasing proportion of the elderly in the general population, a decreasing birth rate and increasing longevity, which result in a growing number of people aged 60 years and older. In the European Union (EU), the proportion of individuals aged 65 years or over is approximately 20%. According to Statistics Poland (GUS), the proportion of people aged 60 years and older in Poland at the end of 2019 was over 24% [10-14].

The elderly experience multiple diseases, including neurological and psychiatric disorders, which are common in this age group. These include stroke, dementia, parkinsonism, delirium and depression [2,3,11].

The main medical conditions associated with old age include osteoarthritis (affecting 80% of people over the age of 75 years), hypertension (60–70%) and ischaemic heart disease (30%). Diabetes occurs in approximately 20%, chronic obstructive pulmonary disorder in 25% and constipation and urinary incontinence in approximately 20% of the elderly. Depressive disorders affect approximately 30% of the elderly population while dementia can be found in 40% of those over the age of 90 years [2,3,11].

Elderly patients also experience weakening of the masseter, tooth loss, dysphagia and loss of appetite.

With age, the respiratory system is affected by the increasing thoracic kyphosis, whose causes include osteoporosis. This leads to chest stiffness, resulting in limited lung ventilation and mobility.

Moreover, aging causes skeletal changes occurring together with changes in the other parts of the musculoskeletal system. For example, decreased muscle strength reduces mechanical stimulation and has a negative effect on bones.

The aging process is commonly believed to be associated with osteogenesis deficits, which are accompanied by a hormonal imbalance; for instance, oestrogen deficiency additionally increases bone resorption [4-11].

A low level of physical activity or its gradual decrease with age undoubtedly contribute to bone mass loss in the elderly. Osteoporosis intensifies the risk of falls and bone fractures. Osteopenia contributes to an increased mortality rate not associated with falls or fractures [8-10].

The loss of muscle mass and strength, which significantly worsens the functional status in the elderly, is another cause of aging. Regular exercise reduces the loss of muscle mass [15-18].

The endocrine system also undergoes changes, which result in reduced production of different hormones. The metabolism and transport of hormones is reduced as well.

With age, the number of certain nerve cells in the nervous system decreases, which results in brain mass reduction [19-22].

A higher incidence of injuries due to falls is another problem in the elderly. A number of factors play a role in the aetiology of those injuries, and repeated injuries do not always have a single cause.

Falls in the elderly are an important geriatric problem and it is crucial to introduce prophylaxis to prevent falls as part of comprehensive geriatric care. Sequelae of stroke are another health problem often found in people over the age of 60 years. This disorder is the most common cause of long-term disability. Every year, 15 million people suffer from stroke worldwide, including 1 million in Europe and 70,000 in Poland. Stroke is one of the main causes of death in developed countries [2,19].

The main goal of rehabilitation conducted in elderly patients is to maintain or improve their ability to perform basic activities of daily living unassisted as well as to rehabilitate selected organs and systems of the body whose function is impaired. Elderly patients should undergo various forms of rehabilitation, namely kinesiotherapy and physical therapy [23-25].

The rehabilitation performed in elderly patients should avoid static and anaerobic exercise.

## THE AIM

The aim of the study was to assess selected problems in the rehabilitation of patients staying at a nursing and care institution.

## MATERIALS AND METHODS

### RESEARCH PROBLEMS

The main research problem is to monitor and analyse any problems observed during rehabilitation in patients staying at a nursing and care institution.

Detailed research problems:

1. Does age influence the ADL disability level?
2. Does sex influence the ability to perform complex activities of daily living, such as home maintenance, shopping, cooking, cleaning and doing laundry?
3. Does age influence gait and functional mobility?
4. Do sociodemographic determinants influence cognitive functioning?

### STUDY METHODS, TECHNIQUES AND TOOLS

Study patients were assessed using the standardised Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (I-ADL) scores, the Abbreviated Mental Test Score (AMTS) and the Timed Up and Go Test (TUG).

The Katz ADL score is used to assess basic self-care activities, such as dressing, mobility, toileting, continence, personal hygiene and feeding. Patients may score between 0 and 6 points, and the result is used to identify three functional status groups. A score of 6 or 5 points indicates full function, a score of 4 to 3 points indicates moderate disability, and a score of fewer than 3 points indicates inability to perform self-care activities and severe disability, requiring constant care and institutional care.

The Lawton I-ADL score is used to assess complex instrumental activities, such as home maintenance and repairs, ability to use the telephone, shopping, food preparation, taking medication and ability to handle finances. The maximum Lawton score is 27 points.

The Hodkinson AMTS is used to identify the presence of cognitive impairment and to measure the degree and severity of the cognitive impairment. The Polish version of the test consists of 11 questions; each correctly answered question scores one point. The results of the test are interpreted as follows: a score of 10–9 points is normal, a score of 8–7 points suggests mild memory impairment, a score of 6–4 points indicates moderate memory impairment and a score of 3–0 points reflects severe memory impairment.

The TUG test assesses gait and functional mobility. During the test, the subject is sitting in a chair with their back resting against the backrest (the distance between the floor and the seat is 46 cm). On the word "go," the subject stands up from the chair, walks 3 metres at their normal pace, crosses the line marking the end of the 3-metre distance, turns around 180 degrees, walks back to the chair and sits back down. The time required to perform this task is the result of the test, with subjects taking ≥14 seconds to complete the test being at a high risk of falls. The results of the TUG test are interpreted as follows:

<10 seconds = normal result, indicating normal functional mobility;

10–19 seconds = the subject is able to walk unassisted, without walking aids; a more in-depth assessment of the risk of falls is recommended;

20–29 seconds = partly limited functional mobility; a detailed assessment is recommended;

≥30 seconds = significantly limited functional mobility; walking aids are recommended.

The variables and their indicators are presented in Table I.

The study assessed a group of 33 patients aged 55 to 96 years staying at the nursing and care institution in Lipsko. Study patients were examined over a period of 3 months. All patients were informed about the aim and methods of the study and consented to participate. Participation in the study was voluntary and anonymous.

The material collected in the study was verified, selected and statistically analysed. The results were displayed graphically and in tables. The statistical analysis used a

**Table I.** Variables and indicators

| Independent variables | Indicators |
|---|---|
| Sex | - female<br>- male |
| Age | - 55–65 years<br>- 66–75 years<br>- 76–85 years<br>- over 86 years |
| Place of residence | - rural area<br>- urban area |
| Dependent variables | Indicators |
| ADL | - full function<br>- moderate disability<br>- severe disability |
| I-ADL | - unable<br>- needs some assistance<br>- independent |
| TUG | - <10 s = normal result, indicating normal functional mobility<br>- 10–19 s = subject able to walk unassisted, without walking aids<br>- 20–29 s = partly limited functional mobility<br>- ≥30 s = significantly limited functional mobility, walking aids recommended |
| AMTS | - severe memory impairment<br>- moderate memory impairment<br>- mild memory impairment<br>- normal |

**Table II.** Age of study patients

| Age | Men | | Women | | Overall | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| 55–65 years | 3 | 21.43 | 1 | 5.26 | 4 | 12.12 |
| 66–75 years | 3 | 21.43 | 3 | 15.79 | 6 | 18.18 |
| 76–85 years | 5 | 35.71 | 6 | 31.58 | 11 | 33.34 |
| over 86 years | 3 | 21.43 | 9 | 47.37 | 12 | 36.36 |
| Total | 14 | 100 | 19 | 100 | 33 | 100 |

chi-squared test, which assesses agreement for measurable and non-measurable parameters.

Results were deemed statistically significant at a significance level of less than or equal to 0.05.

## RESULTS

Of the 33 (100%) study patients, 59% were female and 41% were male. With respect to the largest age groups, 9 women (43.37%) were over the age of 86 years and 5 men (35.71%) were aged 76–85 years (Table II). The majority of study patients (21 patients, 63.64%) lived in rural areas and the others (12 patients, 36.36%) lived in urban areas.

Overall, sequelae of stroke (18.18%) and atherosclerosis (18.18%) were the most common underlying diseases. When divided by sex, vascular dementia was present in 4 women (21.05%) and sequelae of stroke in 4 men (28.57%).

Alzheimer's disease was present in 1 female patient (5.26%), as was heart failure (5.26%). The male patients had limb amputation (7.14%), multiple bone fractures (7.14%), osteoarthritis (7.14%) and vascular dementia (7.14%) (Table III).

The most common concomitant diseases were hypertension (13 patients, 39.39%), atrial fibrillation (6 patients, 18.18%), heart failure (6 patients, 18.18%) and diabetes (5 patients, 15.15%) (Table IV). Statistical analysis showed the following:

$\chi^2$ calc. = 1.74 < $\chi^2$ = 12.591 $_{p > 0.05}$

No relationship was found between age and level of disability according to the ADL score (significance level $\alpha = 0.05$).

Testing performed with the use of the ADL score, which assesses basic activities of daily living, showed that before the start of rehabilitation, a considerable proportion of study patients (15 patients, 45.46%) had moderate disability; the number of patients with either full function or severe disability was lower (9 patients, 27.27% each). After 3 months of rehabilitation, moderate disability was found in 15 patients (45.46%), full function in 11 patients

**Table III.** Underlying diseases in study patients

| Underlying disease | Men | | Women | | Overall | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Alzheimer's disease | - | - | 1 | 5.26 | 1 | 3.03 |
| Parkinson's disease | 2 | 14.29 | - | - | 2 | 6.06 |
| Vascular dementia | 1 | 7.14 | 4 | 21.05 | 5 | 15.15 |
| Osteoporosis | - | - | 2 | 10.53 | 2 | 6.06 |
| Osteoarthritis | 1 | 7.14 | 3 | 15.79 | 4 | 12.12 |
| Spinal cord injury | 2 | 14.29 | - | - | 2 | 6.06 |
| Multiple/femoral fractures | 1 | 7.14 | 2 | 10.53 | 3 | 9.09 |
| Limb amputation | 1 | 7.14 | - | - | 1 | 3.03 |
| Sequelae of stroke | 4 | 28.57 | 2 | 10.53 | 6 | 18.18 |
| Heart failure | - | - | 1 | 5.26 | 1 | 3.03 |
| Atherosclerosis | 2 | 14.29 | 4 | 21.05 | 6 | 18.18 |
| Total | 14 | 100 | 19 | 100 | 33 | 100 |

**Table IV.** Concomitant diseases in study patients

| Concomitant disease | Men | | Women | | Overall | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Diabetes | 3 | 9.09 | 2 | 6.06 | 5 | 15.15 |
| Hypertension | 3 | 9.09 | 10 | 30.3 | 13 | 39.39 |
| Atrial fibrillation and flutter | 2 | 6.06 | 4 | 12.12 | 6 | 18.18 |
| Cardiac arrhythmia | 1 | 3.03 | 3 | 9.09 | 4 | 12.12 |
| Atherosclerosis | 2 | 6.06 | 2 | 6.06 | 4 | 12.12 |
| Sequelae of stroke | 2 | 6.06 | 1 | 3.03 | 3 | 9.09 |
| Heart failure | 3 | 9.09 | 3 | 9.09 | 6 | 18.18 |
| Abdominal aneurysm | - | - | 1 | 3.03 | 1 | 3.03 |
| Parkinson's disease | - | - | 1 | 3.03 | 1 | 3.03 |
| Osteoarthritis | 1 | 3.03 | - | - | 1 | 3.03 |
| Osteoporosis | - | - | 1 | 3.03 | 1 | 3.03 |
| Mental retardation | 1 | 3.03 | - | - | 1 | 3.03 |
| CNS disorders | 1 | 3.03 | 2 | 6.06 | 3 | 9.09 |

Notes: Response percentages do not add up to 100% because study patients could have more than one concomitant disease.

**Table V.** Study patients divided by sex and three ADL functional groups before and after rehabilitation

| Function | Men | | | | Women | | | | Overall | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | before | | after | | before | | after | | before | | after | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| **full function** | **5** | **35.72** | **6** | **42.86** | **4** | **21.05** | **5** | **26.32** | **9** | **27.27** | **11** | **33.33** |
| moderate disability | 8 | 57.14 | 7 | 50.00 | 7 | 36.84 | 8 | 42.11 | 15 | 45.46 | 15 | 45.46 |
| severe disability | 1 | 7.14 | 1 | 7.14 | 8 | 42.11 | 6 | 31.58 | 9 | 27.27 | 7 | 21.21 |
| Total | 14 | 100 | 14 | 100 | 19 | 100 | 19 | 100 | 33 | 100 | 33 | 100 |

(33.33%) and severe disability in 7 patients (21.21%) (Table V).

Full function was found in 4 patients (33.33%) aged 76–85 years while moderate disability was seen in 5 patients (45.46%) over the age of 86 years and in 5 patients aged 76–85 years. Severe disability was present in 4 patients (36.36%) over the age of 86 years (Table VI).

The empirical I-ADL score material indicated that before the start of rehabilitation, a considerable proportion of study patients (19 patients, 57.58%) were unable to perform

**Table VI.** Functional performance according to ADL score versus age of study patients

| ADL score | Age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 55-65 years | | 66-75 years | | 76-85 years | | over 86 years | | Overall | |
| | n | % | n | % | n | % | n | % | n | % |
| full function | 2 | 40.00 | 1 | 20.00 | 4 | 33.33 | 2 | 18.18 | 9 | 27.27 |
| moderate disability | 2 | 40.00 | 3 | 60.00 | 5 | 41.67 | 5 | 45.46 | 15 | 45.45 |
| severe disability | 1 | 20.0 | 1 | 20.00 | 3 | 25.00 | 4 | 36.36 | 9 | 27.27 |
| Total | 5 | 100 | 5 | 100 | 12 | 100 | 11 | 100 | 33 | 100 |

**Table VII.** Degree of independence for complex activities of daily living according to I-ADL score before and after rehabilitation

| Degree of independence | Men | | | | Women | | | | Overall | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | before | | after | | before | | after | | before | | after | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| independent | 2 | 14.29 | 3 | 21.43 | 1 | 5.26 | 2 | 10.53 | 3 | 9.09 | 5 | 15.15 |
| needs some assistance | 5 | 35.71 | 6 | 42.86 | 6 | 31.58 | 9 | 47.37 | 11 | 33.33 | 15 | 45.45 |
| unable | 7 | 50.00 | 5 | 35.71 | 12 | 63.16 | 8 | 42.11 | 19 | 57.58 | 13 | 39.40 |
| Total | 14 | 100 | 14 | 100 | 19 | 100 | 19 | 100 | 33 | 100 | 33 | 100 |

**Table VIII.** Complex activities of daily living versus sex

| Performing complex activities of daily living | Men | | | | | | Women | | | | | | Overall | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | unable | | needs some assistance | | independent | | unable | | needs some assistance | | independent | | unable | | needs some assistance | | independent | |
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| using the telephone | 3 | 9.09 | 4 | 12.1 | 7 | 21.21 | 13 | 39.39 | 4 | 12.12 | 2 | 6.06 | 16 | 48.48 | 8 | 24.24 | 9 | 27.27 |
| long walks | 2 | 6.06 | 7 | 21.2 | 5 | 15.15 | 5 | 15.15 | 11 | 33.33 | 3 | 9.09 | 7 | 21.21 | 18 | 54.55 | 8 | 24.24 |
| shopping | 12 | 36.36 | 2 | 6.06 | - | - | 18 | 54.55 | 1 | 3.03 | - | - | 30 | 90.91 | 3 | 9.09 | - | - |
| cooking | 12 | 36.36 | 2 | 6.06 | - | - | 17 | 51.52 | 2 | 6.06 | - | - | 29 | 87.88 | 4 | 12.12 | - | - |
| cleaning | 12 | 36.36 | 2 | 6.06 | - | - | 17 | 51.52 | 2 | 6.06 | - | - | 29 | 87.88 | 4 | 12.12 | - | - |
| repairs/ home maintenance | 13 | 39.39 | 1 | 3.03 | - | - | 19 | 57.58 | - | - | - | - | 32 | 96.97 | 1 | 3.03 | - | - |
| laundry | 10 | 30.3 | 3 | 9.09 | 1 | 3.03 | 16 | 48.48 | 2 | 6.06 | 1 | 3.03 | 26 | 78.79 | 5 | 15.15 | 2 | 6.06 |
| preparing and taking medicines | 11 | 33.33 | 3 | 9.09 | - | - | 15 | 45.45 | 4 | 12.12 | - | - | 26 | 78.79 | 7 | 21.21 | - | - |
| handling finances | 10 | 30.3 | 3 | 9.09 | 1 | 3.03 | 14 | 42.42 | 3 | 9.09 | 2 | 6.06 | 24 | 72.73 | 6 | 18.18 | 3 | 9.09 |

complex activities of daily living, 11 study patients (33.33%) needed some assistance and only 3 patients (9.09%) were independent. After 3 months of rehabilitation, 15 patients (45.45%) needed some assistance, 5 patients (15.15%) were independent and 13 patients (39.40%) were unable to perform the activities of daily living (Table VII).

The study revealed that minor repairs constituted the most difficult activity for 13 men (39.39%) and 19 women (57.58%). In turn, 12 men (36.36%) and 18 women (54.55%) found shopping difficult. Cooking and cleaning were also difficult for a considerable proportion of study patients (12 men, 36.36%; 17 women, 51.52%). Doing laundry was difficult for 10 men (30.3%) and 16 women (48.48%) (Table VIII). Statistical analysis showed the following:

$\chi^2$ calc. = 7.57 < $\chi^2$ = 55.758 $_{p > 0.05}$

Consequently, there is no relationship between sex and performing complex activities of daily living (significance level $\alpha = 0.05$).

Before the start of rehabilitation, 32 study patients (96.97%) had difficulty with minor repairs, 30 patients (90.91%) with shopping and 29 patients (87.88%) with cook-

**Table IX.** Performing complex activities of daily living according to I-ADL score before and after rehabilitation

| Performing complex activities of daily living | Before | | | | | | After | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | unable | | needs some assistance | | independent | | unable | | needs some assistance | | independent | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| using the telephone | 16 | 48.48 | 8 | 24.24 | 9 | 27.27 | 13 | 39.39 | 11 | 33.33 | 9 | 27.27 |
| long walks | 7 | 21.21 | 18 | 54.55 | 8 | 24.24 | 5 | 15.15 | 16 | 48.48 | 12 | 36.36 |
| shopping | 30 | 90.91 | 3 | 9.09 | - | - | 26 | 78.79 | 5 | 15.15 | 2 | 6.06 |
| cooking | 29 | 87.88 | 4 | 12.12 | - | - | 23 | 69.70 | 7 | 21.21 | 3 | 9.09 |
| cleaning | 29 | 87.88 | 4 | 12.12 | - | - | 27 | 81.82 | 3 | 9.09 | 2 | 6.06 |
| repairs/ home maintenance | 32 | 96.97 | 1 | 3.03 | - | - | 30 | 90.91 | 2 | 6.06 | 1 | 3.03 |
| laundry | 26 | 78.79 | 5 | 15.15 | 2 | 6.06 | 23 | 69.70 | 6 | 18.18 | 4 | 12.12 |
| preparing and taking medicines | 26 | 78.79 | 7 | 21.21 | - | - | 25 | 75.76 | 7 | 21.21 | 1 | 3.03 |
| handling finances | 24 | 72.73 | 6 | 18.18 | 3 | 9.09 | 22 | 66.67 | 6 | 18.18 | 5 | 15.15 |

**Table X.** Gait and functional mobility assessment in study patients using Timed Up and Go Test before and after rehabilitation

| Timed Up and Go Test | Men | | | | Women | | | | Overall | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | before | | after | | before | | after | | before | | after | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| <10 s = normal result, normal functional mobility | 1 | 7.14 | 1 | 7.14 | 2 | 10.53 | 2 | 10.53 | 3 | 9.09 | 3 | 9.09 |
| 10–19 s = subject able to walk unassisted, without walking aids | 1 | 7.14 | 3 | 21.43 | 1 | 5.26 | 3 | 15.79 | 2 | 6.06 | 6 | 18.18 |
| 20–29 s = partly limited functional mobility | 3 | 21.43 | 4 | 28.57 | 4 | 21.05 | 5 | 26.32 | 7 | 21.21 | 9 | 27.27 |
| ≥30 s = significantly limited functional mobility | 9 | 64.29 | 6 | 42.86 | 12 | 63.16 | 9 | 47.37 | 21 | 63.64 | 15 | 45.45 |
| Total | 14 | 100 | 14 | 100 | 19 | 100 | 19 | 100 | 33 | 100 | 33 | 100 |

ing and cleaning. Doing laundry was selected as the most difficult activity by 26 patients (78.79%). After 3 months of rehabilitation, 2 patients (6.06%) were able to go shopping and clean the house unassisted, 3 patients (9.09%) were able to prepare meals unassisted, and 1 patient (3.03%) could perform home maintenance activities unassisted (Table IX).

Before rehabilitation, the Timed Up and Go Test showed that 21 study patients (63.64%) had significantly limited functional mobility, 7 study patients (21.21%) had partly limited functional mobility, 2 study patients (6.06%) were able to ambulate unassisted and 3 study patients (9.09%) had normal functional mobility. After 3 months of rehabilitation, partly limited functional mobility was found in 9 patients (27.27%) and significantly limited functional mobility was seen in 15 patients (45.46%) (Table X).

The Timed Up and Go Test indicated that 7 study patients (63.64%) over the age of 86 years had significantly limited functional mobility (Table XI). Statistical analysis showed the following:

$\chi^2$ calc. = 1.75 < $\chi^2$ = 16.919 $_{p > 0.05}$

Consequently, there is no relationship between age and gait and functional mobility (significance level $\alpha = 0.05$).

AMTS testing, which helps assess the cognitive ability of a patient, showed moderate memory impairment in 6 women (31.58%) while 8 men (57.14%) had normal cognitive function (Table XII). Statistical analysis showed the following:

$\chi^2$ calc. = 4.99 < $\chi^2$ = 7.814 $_{p > 0.05}$

Consequently, there is no relationship between sex and cognitive function measured with the AMTS (significance level $\alpha = 0.05$).

The study showed severe memory impairment in 4 patients (50%) over the age of 86 years, moderate memory impairment in 3 patients (30%) aged 76–85 years and normal memory in 4 patients (44.44%) aged 66–75 years as well as 5 patients (62.50%) aged 55–65 years (Table XIII). Statistical analysis showed the following:

$\chi^2$ calc. = 7.94 < $\chi^2$ = 16.919 $_{p > 0.05}$

Consequently, there is no relationship between age and cognitive function measured with the AMTS (significance level $\alpha = 0.05$).

A considerable proportion of study patients (6 patients, 28.57%) living in rural areas had severe memory impairment. In turn, 5 patients (41.66%) living in urban areas had

**Table XI.** Gait and functional mobility of study patients according to Timed Up and Go Test versus age

| Timed Up and Go Test | Age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 55-65 years | | 66-75 years | | 76-85 years | | over 86 years | | Overall | |
| | n | % | n | % | n | % | n | % | n | % |
| <10 s = normal result, normal functional mobility | 1 | 20.00 | 1 | 14.29 | 1 | 10.00 | - | - | 3 | 9.09 |
| 10–19 s = subject able to walk unassisted, without walking aids | - | - | - | - | 1 | 10.00 | 1 | 9.09 | 2 | 6.06 |
| 20–29 s = partly limited functional mobility | 1 | 20.00 | 1 | 14.29 | 2 | 20.00 | 3 | 27.27 | 7 | 21.21 |
| ≥30 s = significantly limited functional mobility | 3 | 60.00 | 5 | 71.43 | 6 | 60.00 | 7 | 63.64 | 21 | 63.64 |
| Total | 5 | 100 | 7 | 100 | 10 | 100 | 11 | 100 | 33 | 100 |

**Table XII.** Cognitive function assessment with AMTS versus sex

| AMTS score | Men | | Women | | Overall | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| severe memory impairment | 3 | 21.43 | 5 | 26.32 | 8 | 24.24 |
| moderate memory impairment | 2 | 14.29 | 6 | 31.58 | 8 | 24.24 |
| mild memory impairment | 1 | 7.14 | 4 | 21.05 | 5 | 15.15 |
| normal memory | 8 | 57.14 | 4 | 21.05 | 12 | 36.36 |
| Total | 14 | 100 | 19 | 100 | 33 | 100 |

**Table XIII.** Cognitive function assessment with AMTS versus age

| AMTS | Age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 55-65 years | | 66-75 years | | 76-85 years | | over 86 years | | Overall | |
| | n | % | n | % | n | % | n | % | n | % |
| severe memory impairment | 1 | 12.50 | 1 | 11.12 | 2 | 20.00 | 4 | 50.00 | 8 | 24.24 |
| moderate memory impairment | 1 | 12.50 | 2 | 22.22 | 3 | 30.00 | 2 | 25.00 | 8 | 24.24 |
| mild memory impairment | 1 | 12.50 | 2 | 22.22 | 1 | 10.00 | 1 | 12.50 | 5 | 15.15 |
| normal memory | 5 | 62.50 | 4 | 44.44 | 2 | 20.00 | 1 | 12.50 | 12 | 36.37 |
| Total | 8 | 100 | 9 | 100 | 10 | 100 | 8 | 100 | 33 | 100 |

normal cognitive function (Table XIV). Statistical analysis showed the following:

$\chi^2$ calc. = 0.62 < $\chi^2$ = 7.814 $_{p > 0.05}$

Consequently, there is no relationship between place of residence and cognitive function measured with the AMTS (significance level $\alpha = 0.05$).

Rehabilitation performed in study patients included mainly kinesiotherapy procedures. A total of 25 patients (75.76%) underwent exercises with equipment in the form of an upper limb pedal exerciser and 13 patients (39.39%) performed exercises with a lower limb pedal exerciser. Gait training was performed in 15 study patients (45.45%) (Table XV).

## DISCUSSION

The results of the study confirmed that rehabilitation in patients staying at a nursing and care institution is difficult due to their reduced functional ability and due to somatic and mental comorbidities. Multimorbidity is the main problem in rehabilitation since it often requires treatment modifications [6,7,8,10].

Rehabilitation of the elderly should be tailored to the current functional status of the patient. According to Pasek et al., rehabilitation considerably improves motor performance in geriatric patients as well as their wellbeing and mental state [23]. Depending on the current condition of the patient, rehabilitation should be initially aimed at helping them maintain the ability to perform basic activities of daily living. Next, again based on the current functional status of the patient, rehabilitation should focus on the musculoskeletal system and improve those activities that will in turn improve the quality of life. Physical activity has significant and undervalued antidepressive effects [19,20].

Standardised ADL testing showed moderate disability in a considerable proportion of study patients (60%) at the age of 66–75 years, severe disability in 36.36% of patients over the age of 86 years and full function in 33.33% of patients aged 76–85 years. A study by Muszalik revealed a moderate or low functional ability level according to the Katz scale. The highest proportion of study patients (81.82%) needed assistance during urination and defecation, a large group of patients were completely dependent during bathing (78.79%) and considerable difficulties were associated with

**Table XIV.** Cognitive function assessment with AMTS versus place of residence

| AMTS | Place of residence | | | | | |
|---|---|---|---|---|---|---|
| | Rural area | | Urban area | | Overall | |
| | n | % | n | % | n | % |
| severe memory impairment | 6 | 28.57 | 2 | 16.67 | 8 | 24.24 |
| moderate memory impairment | 5 | 23.81 | 3 | 25.00 | 8 | 24.24 |
| mild memory impairment | 3 | 14.29 | 2 | 16.67 | 5 | 15.15 |
| normal memory | 7 | 33.33 | 5 | 41.66 | 12 | 36.36 |
| Total | 21 | 100 | 12 | 100 | 33 | 100 |

**Table XV.** Kinesiotherapy procedures used in study patients

| Kinesiotherapy procedure | Men | | Women | | Overall | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Passive verticalization | 3 | 9.09 | 2 | 6.06 | 5 | 15.15 |
| Active verticalization | 6 | 18.18 | 8 | 24.24 | 14 | 42.42 |
| Gait training | 7 | 21.21 | 8 | 24.24 | 15 | 45.45 |
| Locomotion | 5 | 15.15 | 7 | 21.21 | 12 | 36.36 |
| Exercises with equipment – upper limb pedal exerciser | 12 | 36.36 | 13 | 39.39 | 25 | 75.76 |
| Exercises with equipment – lower limb pedal exerciser | 7 | 21.21 | 6 | 18.18 | 13 | 39.39 |
| Upper limb free resistance exercises | 1 | 3.03 | - | - | 1 | 3.03 |
| Upper limb non-weight-bearing active exercises | - | - | 1 | 3.03 | 1 | 3.03 |
| Lower limb non-weight-bearing active exercises | 1 | 3.03 | 2 | 6.06 | 3 | 9.09 |
| Exercises with equipment – roller | - | - | 3 | 9.09 | 3 | 9.09 |
| Exercises with equipment – ankle joint training device | 2 | 6.06 | 4 | 12.12 | 6 | 18.18 |
| Upper limb non-weight-bearing exercises | 1 | 3.03 | 2 | 6.06 | 3 | 9.09 |
| Lower limb non-weight-bearing exercises | 2 | 6.06 | 3 | 9.09 | 5 | 15.15 |
| Upper limb self-assisted exercises | 5 | 15.15 | 8 | 24.24 | 13 | 39.39 |
| Lower limb self-assisted exercises | 2 | 6.06 | 1 | 3.03 | 3 | 9.09 |
| Isometric resistance exercises | 1 | 3.03 | - | - | 1 | 3.03 |
| General fitness exercises | 1 | 3.03 | 2 | 6.06 | 3 | 9.09 |
| Breathing exercises | 2 | 6.06 | 1 | 3.03 | 3 | 9.09 |
| Assisted exercises | 1 | 3.03 | 1 | 3.03 | 2 | 6.06 |
| Balance exercises | - | - | 2 | 6.06 | 2 | 6.06 |

Notes: Response percentages do not add up to 100% because study patients could undergo more than one procedure.

toileting (63.64%) and dressing (45.45%). In turn, a study by Kozik et al. indicated that a considerable group of their patients found the following basic activities of daily living to be difficult: dressing, bathing, urination and defecation. The empirical material collected by Adamek et al. showed that the most difficult activities were personal hygiene (49%), dressing (44%) and urination and defecation (61%) [11].

Standardised Lawton score testing performed in the study patients showed that the most difficult complex activities were home maintenance (96.97%), shopping (90.91%), cooking (87.88%), cleaning (87.88%) and doing laundry (78.79%). In their study, Rybka et al. found that the most difficult activities assessed according to the I-ADL score were preparing meals (17%), shopping (22%) and home repairs and doing laundry (6%). According to Adamek, the most difficult complex activities of daily living included home maintenance (88%), shopping (78%), cleaning and doing laundry (76%) and long walks (71%). A study by Błaszczyk-Bębenek et al. showed that the elderly had considerable difficulties with such activities as cooking, minor repairs, ambulation, taking medicines, handling finances and using the telephone [14].

The standardised Timed Up and Go Test showed that a large proportion of study patients (71.43%) aged 66–75 years had considerable functional mobility limitations and needed more than 30 seconds to complete the test, with patients using a cane or walking frame. A smaller group of study patients (27.27%) aged over 86 years had partial functional mobility limitations and completed the test in 20–29 seconds. Only few study patients (10%) aged 76–85 years completed the test in 10–19 seconds, showing independence.

The AMTS, which assesses the cognitive function, revealed that 36.36% of study patients had normal results, few patients (15.15%) had mild memory impairment and some patients (24.24%) had moderate or severe cognitive function impairment. According to Doroszkiewicz et al., a considerable proportion (42%) of elderly patients have cognitive function abnormalities and over a half (60%) show abnormalities with respect to emotions [11].

## CONCLUSIONS

1. Study patients had significant functional disability.
2. The patients' sex did not influence the ability to perform complex activities of daily living, such as home maintenance, shopping, cooking, cleaning and doing laundry.
3. Sociodemographic determinants did not influence cognitive functioning in study patients.
4. Physical therapy and rehabilitation in the elderly should be performed on a regular basis and in the entire society.

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**Conflict of interest:**

*The Authors declare no conflict of interest.*


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ORIGINAL ARTICLE

# ANXIETY DISORDERS IN CHILDREN SUFFERING FROM FUNCTIONAL AND ORGANIC RESPIRATORY DISORDERS

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## ABSTRACT

**The aim:** To determine the anxiety disorders in children suffering from organic diseases and functional disorders of the respiratory tract in the clinical settings of the pulmonology department, as well as to assess their impact on disease course and quality of life.

**Materials and methods:** 131 pediatric patients aged 6-17 years old have been studied. The patients were divided into three groups: the children with somatoform respiratory disorders (SRD) – 33,6 % (n = 44), those with bronchial asthma (BA) – 34,3 % (n = 45) and those with pneumonia - 32,1 % (n = 42). Spielberger-Khanin test questionnaire was used to study anxiety, and Nijmegen questionnaire was used to diagnose hyperventilation syndrome (HVS). Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) was used to determine the quality of life.

**Results:** Severe trait anxiety was observed more often in the subgroup of children with SRD (65,9 %) than in those with asthma (40,0 %) and pneumonia (21,5 %). HVS occurred in 19.1% of patients. Direct moderate correlations were found between Spielberger scale (trait anxiety, r = 0,426; p<0,0001), (state anxiety, r = 0,393; p<0,0001) and Nijmegen HVS questionnaire, as well as inverse moderate correlations between Spielberger scale (state anxiety, r = -0,321; p<0.0001), (trait anxiety, r = -0.429; p<0,0001) and Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q).

**Conclusions:** Severe trait and state anxiety was found in 42,8 % and 19,1 % of children, respectively. Severe state and trait anxiety was observed more often in patients with SRD (65,9 % and 27,3 %, respectively), being twice as common in girls as in boys (57,6 % versus 32,1 % for trait anxiety and 24,8 % versus 12,6 % for state anxiety, respectively). Anxiety disorders are supposed to be the basis for HVS development and the cause of low satisfaction with the quality of life in patients with pulmonary diseases.

**KEY WORDS:** anxiety, organic lung diseases, functional disorders of the respiratory tract, quality of life, children

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## INTRODUCTION

Anxiety disorders are one of the most common mental disorders in children and adolescents. Anxiety is characterized by unpleasant emotional experiences (e.g. uneasiness), cognitive (e.g. fear, helplessness), physiological (e.g. muscle tension) and behavioral (e.g. avoidance) changes [1].

In adolescence, anxiety disorders can be associated with significant functional impairment, significant decline in quality of life and higher levels of comorbidities [2].

Lifelong anxiety disorders are the only psychiatric disorders that are significantly associated with bronchial asthma (BA), with a possible bidirectional link, each of which may be caused by or be the consequence of another. Regression analysis has showed that the presence of lifelong anxiety disorder quadruples the risk of developing asthma, including the uncontrolled and severe one. Similarly, asthma makes the risk of anxiety disorder development higher than twice [3].

Bronchial asthma is one of the most common diseases included in the so-called Holyseven, i.e. childhood psychosomatosis. It is a classic example of a multifactorial disease pathogenetically caused by the interaction of numerous somatic and psychoemotional factors. The physiological characteristics of respiration are directly related to the emotional state of a child, and this correlation persists all lifelong. Asthma in children is accompanied by severe anxiety reactions with a layering on the anxious personality causing emotional discomfort that increases with higher severity of the disease and decreases with a greater control of the disease [4].

Asthma is often described as a classic psychosomatic disorder that has got common features of pathophysiological and psychological ways with anxiety and depression [5].

Anxiety disorders, somatoform disorders and stress disorders are usually classified under the same heading. Their common denominator is anxiety. Anxiety is quite often transformed into a number of somatic symptoms that imitate the dysfunction of various organs and systems. Such somatic manifestations of anxiety are commonly called somatoform disorders (SD) [6].

Somatoform disorders are characterized by recurrence of subjective experiencing physical symptoms that are not explained by any physical disease. They are accompanied by significant distress and deterioration in life quality. As a rule, SD is diagnosed by excluding organic causes [7].

SD in children and adolescents can have negative effects on their development and life quality. Thus, this disorder requires more attention [8].

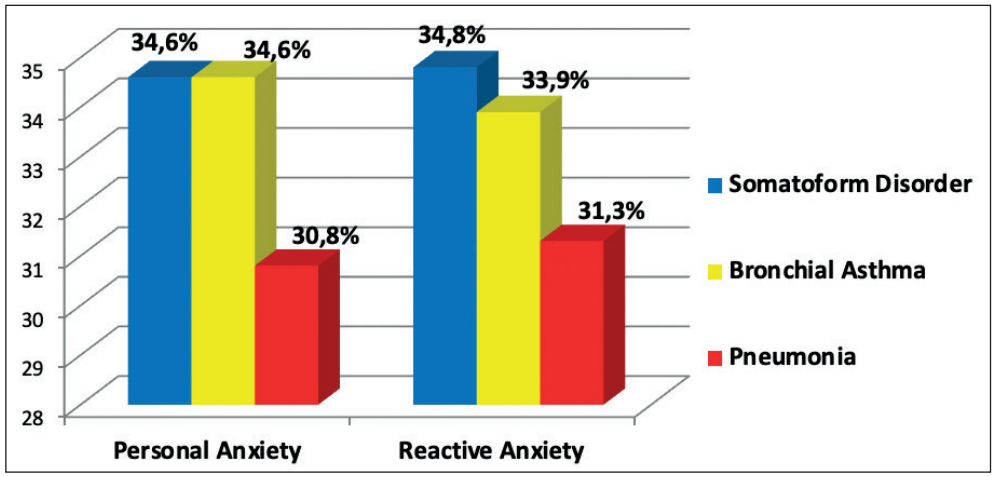


**Fig. 1.** Structure of anxiety in children with lung disease

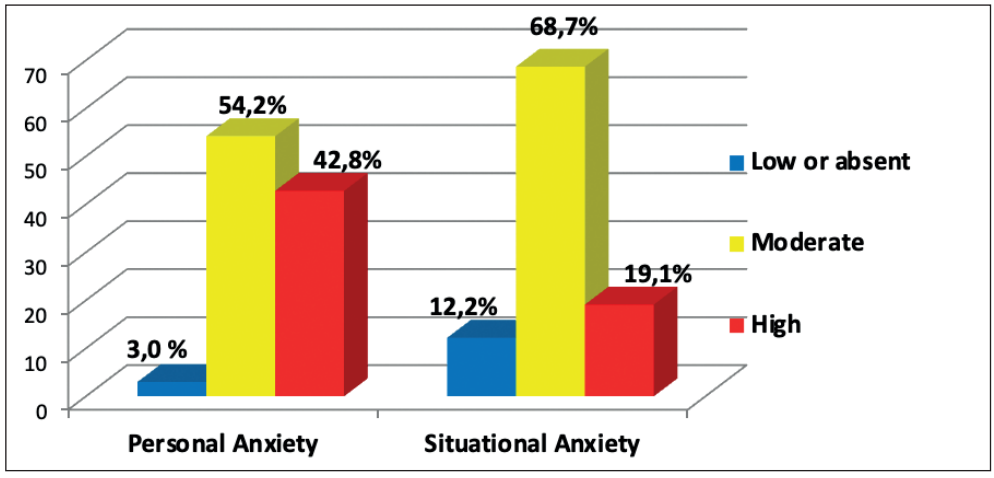


**Fig. 2.** Severity of anxiety in children with respiratory diseases

Furthermore, early diagnostics of anxiety disorders in children is important because most cases remain untreated. It causes suffering and hinders their social functioning [1].

## THE AIM

The objective of the study is to identify the anxiety disorders in sick children suffering from organic and functional lung pathologies at the pulmonology department and to assess their impact on the course of the disease and patients' life quality.

## MATERIALS AND METHODS

Having signed the informed consent of the parents and children, 131 patients aged 6-17 years old were involved in the study. 54,9 % counted boys (n = 72), and 45,1 % counted girls (n = 59). The children were divided into three groups. The first one included the patients suffering from asthma – 34,3 % (n = 45), the second one included those with SD from the respiratory system – 33,6% (n = 44), and the third group contained the patients suffering from pneumonia – 32,1 % (n = 42).

The selection of children and the diagnosis of SD were performed after their general clinical examination and according to the criteria of SD ICD-10. To study anxiety we used Spielberger's test (STAI - State - Trait Anxiety Inventory) modified by Yu. L. Khanin. It helped us detect the level of reactive and personal anxiety. The indicators are interpreted as the following: the anxiety is low up to 30 points, it is moderate according to 31- 44 points, and it is high according to 45 points and higher [9]. The Nijmegen Questionnaire (Nijmegen Questionnaire) was used to diagnose HVS as the main manifestation of SD. The sum of points according to the Nijmegen questionnaire > 23 has a sensitivity of 91 % and a specificity of 95 % for the diagnosis of HVS [10]. To determine life quality of the patients suffering from respiratory diseases and comorbidities Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) was used. The questionnaire was developed by Jean Endicott to assess the degree of satisfaction in various spheres of life of children aged 6-17 years old [11].

Statistical analysis was performed using the software package Statistica 8.0.360, MedCalc.7.4.4.1 and Excel (2007). The quantitative characteristics are given in the form of $M \pm \sigma$. The validity of differences was assessed using Student's two-sample t-test and constructing a 95% confidence interval (CI) for the difference between the means, as well as employing methods of correlation and regression analysis. The values at $p<0,05$ were considered reliable.

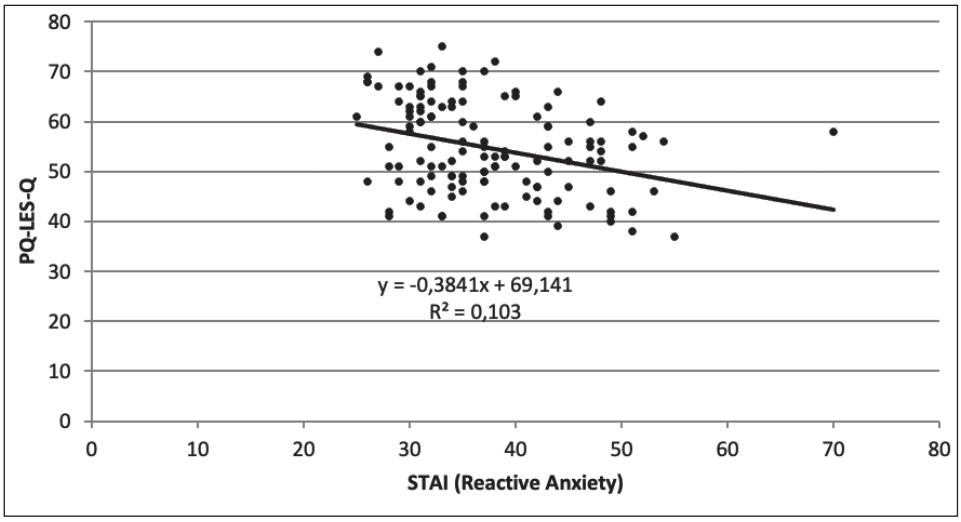


**Fig. 3.** Interrelationship between reactive anxiety according to the STAI scale and quality of life satisfaction according to the PQ-LES-Q questionnaire.

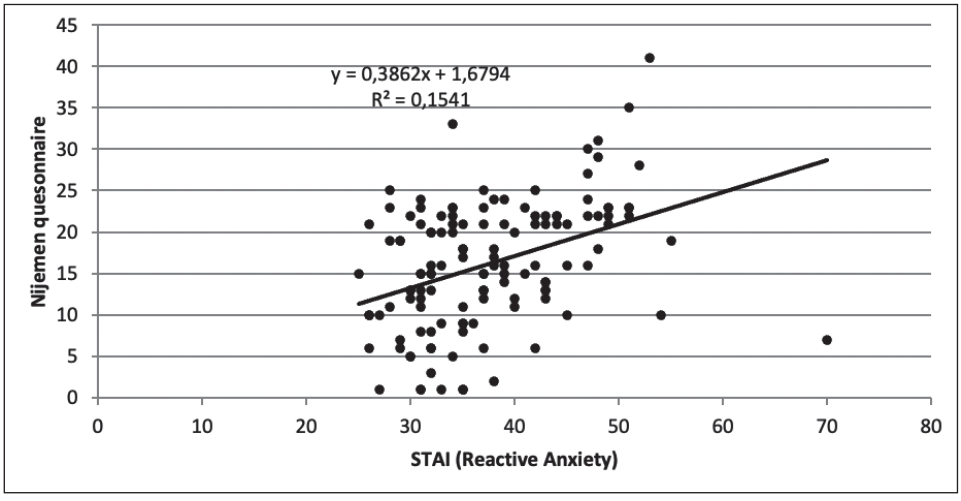


**Fig. 4.** Interrelationship between personal anxiety on the STAI scale and quality of life satisfaction according to the PQ-LES-Q questionnaire.

## RESULTS

The conducted study on the anxiety symptoms in children, both in general and in separate groups, has shown a high frequency of both personal and reactive anxiety.

The study of the entire cohort of children (n = 131) has revealed moderate or severe personal anxiety in 127 (96,9 %) patients, and reactive anxiety in 115 (87,7 %) ones.

The main structure of the personal anxiety numbered 44 (34,6 %) children suffering from functional respiratory disorders who met the criteria of SD; 44 (34,6 %) children with asthma, and 39 (30,8 %) children with pneumonia. Reactive anxiety was found in 40 (34,8 %) children with SD, in 39 (33,9 %) children with asthma and in 36 (31,3 %) children with pneumonia (Fig. 1).

The severity is an important indicator of anxiety. Thus, in the general structure of personal anxiety, the mild or no anxiety was determined in 4 (3,0 %) sick children, the moderate one was seen in 71 (54,2 %) sick children, and the severe anxiety was observed in 56 (42,8 %) children. In the general structure of the reactive anxiety a mild degree of anxiety or its absence was determined in 16 (12,2 %) sick children, the moderate one - in 90 (68,7 %) sick children, and the severe one - in 25 (19,1 %) children (Fig. 2).

The severity of both personal and reactive anxiety varied significantly depending on the pathology. The highest number of severe personal anxiety was observed in the subgroup with SD in 29 (65,9 %) children, slightly less in the subgroup with asthma, i.e. in 18 (40,0 %) children, and the lowest number was observed in the subgroup with pneumonia, i.e. in 9 (21,5 %) children. Similarly, the highest number of severe reactive anxiety was also observed in the subgroup with SD, i.e. in 12 (27,3 %) children, slightly less was observed in the subgroup with asthma, i.e. in 11 (24,4 %) children and the lowest number was observed in the subgroup with pneumonia, i.e. in 2 (4,8 %) children.

According to the questionnaire the largest number of children with severe personal anxiety occurred at the age period from 15 to 17 (19 out of 36 people, which accounted 52,7 %). Less frequently severe personal anxiety occurred at the age period from 11 to 14 (in 19 out of 47 children, which was 40,5 %), and the lowest frequency was observed in children aged 6-10 years old (in 17 children out of 48, which equaled 35,4 %). At the same time, the largest number of children with the severe reactive anxiety occurred at the age period from 11 to 14 years old (14 out of 47 people, which equaled 29,9 %). Slightly lower incidence of the severe reactive anxiety occurred at the age period from 6 to 10 years old (in 7 out of 48 children,

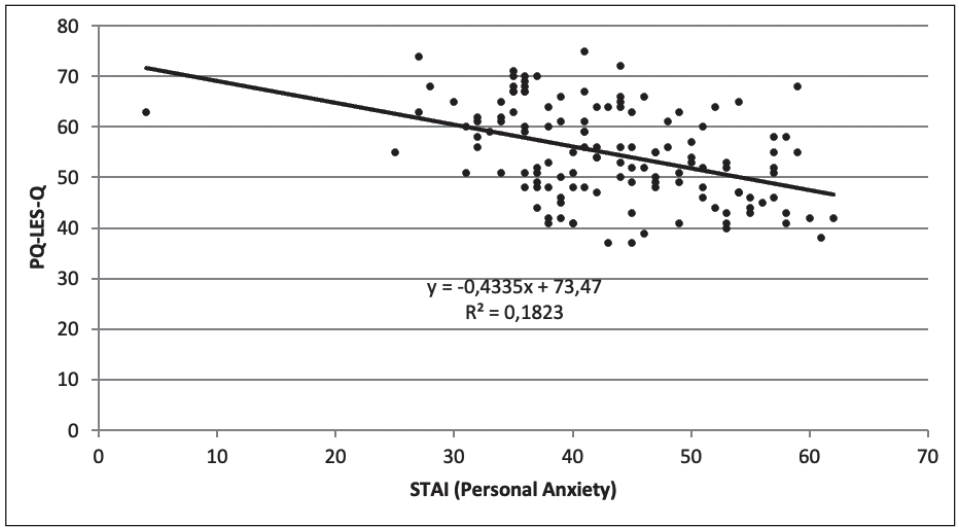


**Fig. 5.** Interrelationship between personal anxiety on the STAI scale and according to the Nijmegen HVS questionnaire.

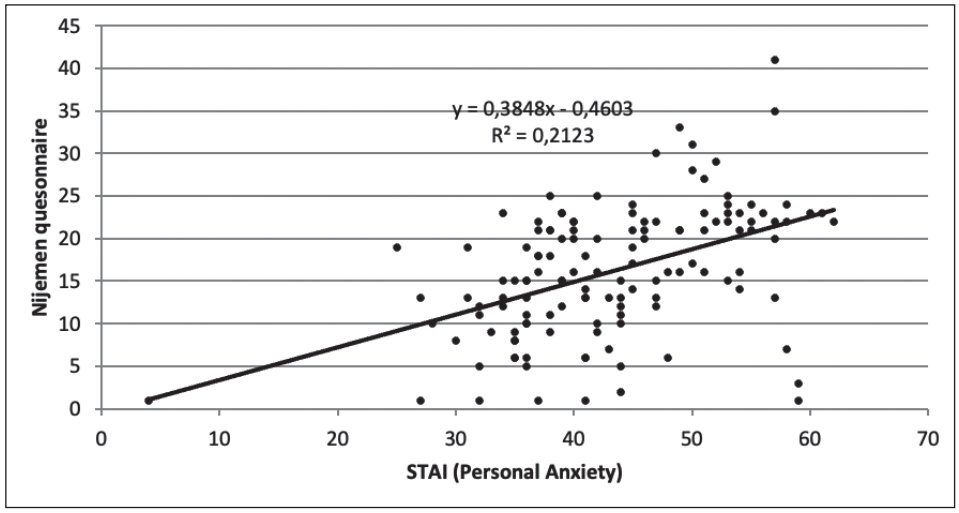


**Fig. 6.** The interrelationship between reactive anxiety results according to the STAI scale and according to the Nijmegen HVS questionnaire.

which was 14,7 %), and the least common in children aged 15-17 years old (in 5 children out of 36, which was 13,9 %).

Low levels of both personal and reactive anxiety, or its absence, were almost three times more common in boys than in girls (4,1 % vs. 1,7 % for personal anxiety, and 16,6 % vs. 5,0 % for reactive anxiety respectively). Severe levels of both personal and reactive anxiety were almost twice as common in girls as in boys (57,6 % vs. 32,1 % for personal anxiety, and 24,8 % vs. 12,6 % for reactive anxiety respectively).

The children suffering from the personal anxiety, the highest score on the Spielberger-Khanin scale was determined in the children with SD, much lower it was observed in the children with asthma, and the lowest one was found in the patients with pneumonia. The children with SD might demonstrate higher levels of the personal anxiety due to the presence of the pathology in its basis with somatic manifestations in the form of HVS and the comorbid development of depression or vice versa. Thus, the sick children with SD demonstrate the number of points according to the Spielberger-Khanin scale 47,3 ± 8,3, which significantly exceeded the number of points for the group of children with asthma, i.e. 43,9 ± 7,8 (95% CI: 0,01 – 6,8; $p<0,05$), and for the group of children with pneumonia, whose total score was 38,4 ± 9,3 (95 % CI: 5,1 – 12,7; $p<0,0001$). The number of points in the group of children with asthma also significantly exceeded the level in the group of children with pneumonia (95 % CI: 1,8 – 9,1; $p<0,003$).

Among the children suffering from the reactive anxiety, the highest score on the Spielberger-Khanin scale was determined for the children with asthma, slightly lower for the children with SD, and the lowest one was for the patients with pneumonia. The highest score of the reactive anxiety is expected in the group of patients with asthma, because the presence of background anxiety in combination with organic lung disease, accompanied by asthma attacks, can cause a significant increase in the exacerbation of the pathology. Similar changes can be observed in patients with SD, especially in the crisis course of HVS, which is accompanied by a significant feeling of shortness of breath. Thus, the number of points in the group of patients with asthma according to the Spielberger-Khanin scale was 39,1 ± 8,7, and it significantly exceeded the number of points in the group of children with pneumonia, which was 34,1 ± 5,8 (95 % CI: 1,8 – 8,2, $p<0,002$), and it was slightly different from the number of points in the group of children

with SD – 38,4 ± 9,2 (p>0,05). The number of points in the group children with SD also significantly exceeded its level in the group of children with pneumonia (95 % CI: 1,0 – 7,6; p<0,001).

Applying the Nijmegen questionnaire for 131 patients with respiratory disorders, 25 (19,1 %) children were diagnosed with hyperventilation syndrome (HVS). Its basic structure constituted 17 (68 %) children with SD, 5 (20 %) children with asthma and 3 (12 %) children with pneumonia. The combination of organic pathology and dysfunction of the respiratory tract in children has been observed in many studies, which must be considered for the management of such patients, since the presence of HVS or any other dysfunctional disorders can worsen the course of organic disease and mislead the doctor about the ineffectiveness of the treatment.

The children having HVS, the highest score according to the Nijmegen questionnaire was determined in the children with asthma, the children with pneumonia had slightly lower scores, and the patients with SD had the lowest ones. Probably, such a difference in manifestation may be due to the existing premorbid psycho-emotional background and autonomic dysregulation in the children with organic lung diseases. Occurring in the period of organic disease these factors lead to decompensation of autonomic regulation of the respiratory system, which come in combination with pathophysiological disorders due to the underlying disease and emotional stress, that may increase during the disease, and lead to increased shortness of breath and, thus, increased HVS. Thus, in the group of patients with asthma the number of points according to the Nijmegen questionnaire was 31,2 ± 3,0, which significantly exceeded the number of points in the group of children with respiratory tract SD, which was 24,1 ± 1,8 (95 % CI: 4,9 - 9.3, p<0,0001). Also, in the group of patients with pneumonia, the number of points was 29,7 ± 9,8, and it significantly exceeded the number of points in the group of children with SD (95 % CI: 0,7 – 10,4; p<0,02). The patients with asthma and the ones with pneumonia had no significant difference in the questionnaire results.

Having applied the pediatric quality of life questionnaire PQ-LES-Q, the lowest score was observed in the group of children with SD, significantly higher scores were noted in the group of sick children with organic lung disease (asthma and pneumonia). Thus, the total score on the PQ-LES-Q scale in the group of children with SD was 47,5 ± 6,6, and it was significantly lower than the overall score in the group of children with asthma, which was 57,5 ± 13,9 (95% CI: 5,4 – 14,6; p<0,0001), and in the group of children with pneumonia, whose total score was 56,9 ± 8,4 (95 % CI: 6,2 – 12,6; p<0,0001). There was no significant difference in scores between children with asthma and pneumonia.

Taking into account the obtained data, it is possible to suppose a certain link between the presence and severity of anxiety and the development of HVS. Also, it is presumable that the decline in life quality of the children with functional and organic lung diseases may be due not only to the underlying disease, but also to the emergence of both primary and secondary anxiety symptoms, associated with the underlying pathology. We used correlation and regression analyzes to establish this interrelationship.

The analysis of the diagram showed the peculiarities of the link between the growth of reactive anxiety and the life quality of the patients with pulmonary pathology (Fig. 3).

The calculated correlation coefficient r is -0,321 (p<0,0001). Thus, reliable feedback and moderate correlation were found according to the Chaddock scale, i.e. with the increased scores on the STAI scale (reactive anxiety), the score on the PQ-LES-Q scale decreases, which may indicate the role of the reactive anxiety in reducing life quality of the patients with the pulmonary pathology.

A similar significant feedback and moderate correlation was found between the personal anxiety on the STAI scale and according to the PQ-LES-Q questionnaire. The calculated correlation coefficient r was -0,429 (p<0,0001) (Fig. 4).

The analysis of the diagram showed certain features of the interrelationship between the growth of personal anxiety symptoms and the occurrence of HVS (Fig. 5).

The calculated correlation coefficient r is 0,426 (p<0.0001). Thus, a reliable direct and moderate correlation was found on the Chaddock scale between the values on the STAI scale (personal anxiety) and according to the Nijmegen Questionnaire HVS, i.e. with the increasing scores on the STAI scale (personal anxiety), the score on the Nijmegen Questionnaire increases too. It may indicate the role of the anxiety symptoms in the development of HVS.

A similar reliable direct and moderate correlation was found between the reactive anxiety results according to the STAI and according to the PQ-LES-Q questionnaire. The calculated correlation coefficient r was 0,393 (p<0,0001) (Fig. 6).

## DISCUSSION

Anxiety is an individual psychological feature that is an increased tendency to feel anxious in a variety of life situations. There are two types of anxiety, i.e. situational, or reactive, and personal. The reactive anxiety is an indicator of the intensity of experiences that occur in relation to typical events and is characterized by tension, anxiety, nervousness. The personal anxiety is a person's readiness (attitude) to experience fear and anxiety about a wide range of subjectively significant phenomena. The personal anxiety is a persistent condition. It characterizes a person's tendency to perceive a wide range of situations as threatening, to respond to such situations with anxiety [12].

In our study, almost every second examined child suffering from organic diseases and functional disorders of the respiratory tract has significant anxiety disorders, both personal and reactive, which may be a factor in the predisposition to comorbid depression, as well as its somatic manifestation (e.g. HVS) can worsen the course of the disease and the duration of rehabilitation. The obtained data indicate a significant prevalence of anxiety disorders in children with various pathologies of the respiratory tract, which may be a premorbid background; they may further

cause psychosomatic spectrum disorders, depression and predisposition to some somatic pathology. Similar trends were demonstrated in the study of L.V. Pypa et al. (2019), which revealed a high incidence of anxiety disorders, especially in adolescents who had a premorbid background and the social component of their occurrence (incomplete family, bad habits) [13].

In the structure of SD the anxiety can form the basis of the pathology itself and be determined at the primary level. But in the structure of the organic diseases anxiety can be comorbid pathology as a reaction to the development of the underlying disease, especially it concerns the reactive anxiety. However, it is possible that the personal anxiety in the patients with organic lung disease may have been present as a characteristic feature before the development of organic disease, and on the basis of which functional somatic disorders, including HVS, may occur simultaneously with the development of organic disease. Thus, the study by S.R. Del Giacco et al. (2016), demonstrated a significant association between bronchial asthma and anxiety disorders (OR 3,03; p<0,003); no significant association with another psychiatric diagnosis was found. In addition, anxiety was associated with the severity of asthma (p<0,001). Asthma preceded anxiety in 48 % of cases, and in 52 % of cases anxiety preceded asthma [3].

According to T. Deraz1 et al. (2018), 34,4 % of the children with asthma had increased anxiety, and 33,3 % of the children had depression. Moreover, severe asthma, uncontrolled asthma and concomitant depression were independent risk factors for anxiety in the children with asthma [5].

The highest incidence of the severe, both personal and reactive, anxiety in the patients with SD, in comparison to other pulmonary pathologies, confirms its main component of the premorbid background, which further leads to psychosomatic spectrum diseases, as well as its role in clinical manifestations of HVS. The lowest incidence of the severe anxiety was observed in the patients with pneumonia, where functional respiratory disorders are much less common during the disease, and which contribute much less to the clinical symptoms of the disease, in comparison to the patients with asthma, where the main clinical symptoms are more often accompanied by the psychosomatic spectrum disorders, worsening the course of the disease and rehabilitation.

The predominance of the severe reactive anxiety at the age from 11 to 14 years old may be due to unstable emotional background, which occurs during puberty, which can lead to increased sensitivity to various stressors with the development, in response, anxious symptoms, including the background of organic lung disease. Completion of the formation of anxious personality occurs during the completion of puberty and the transition to adulthood, which, accordingly, determines the largest number of children with severe personal anxiety in the period between 15 to 17 years old.

Severe both personal and reactive anxiety were almost twice as common in girls as in boys. Relevant results may suggest that the female gender may be a risk factor for the development of anxiety disorders and related psychosomatic disorders, including HVS in the structure of SD and organic lung diseases.

Such dysfunctional respiratory disorders as HVS have been reported in all pulmonary pathologies, including asthma and pneumonia. However, the largest number of them occurred in the SR, which determines their affiliation to psychosomatic disorders as a somatic component of the anxiety. The dysfunctional respiratory disorders in the patients with organic diseases of the respiratory tract indicate the development of anxiety and depressive disorders in response to the underlying pathology or their existence before the development of organic disease. The premorbid psycho-emotional background and decompensation of autonomic respiratory dysregulation also contribute to the occurrence of HVS. In combination with pathophysiological disorders due to the underlying disease and emotional stress it leads to the increased shortness of breath.

According to the PQ-LES-Q scale, the lowest quality of life satisfaction was observed in the group of children with SD in comparison with other pulmonary pathologies. It is most likely that anxiety and depressive disorders, which are most revealed in this category of the patients and are the main symptoms of the disease, may play a significant role in low level of the life quality satisfaction of the sick children with SD in comparison with the patients suffering from organic diseases of the respiratory system. Thus, it is possible to suppose the existence of the primary relation of the life quality satisfaction of the child with the psycho-emotional state rather than with the organic disease, which requires further research.

## CONCLUSIONS

Among the children suffering from respiratory diseases, severe personal and reactive types of anxiety were observed in 42,8 % and 19,1 % respectively, being significantly predominant in the children with SD, i.e. the personal anxiety was found in 65,9 % of the children, the reactive one was in 27,3 % respectively). Severe both personal and reactive types of anxiety were almost twice as common in girls as in boys (57,6 % vs. 32,1 % for the personal anxiety, and 24,8% vs. 12,6 % for the reactive anxiety respectively).

The HVS occurs in 19,1 % of pediatric patients having airway pathology. The anxiety premorbid background may be the cause of HVS, and its clinical manifestations may be a somatic one of anxiety, as evidenced by the existing direct and moderate correlations between the STAI scale (personal anxiety, r = 0,426; p<0,0001), (reactive anxiety, r = 0,393; p<0,0001) and the Nijmegen HVS questionnaire.

The reason of the low life quality satisfaction of the children suffering from respiratory diseases may be anxiety disorders, as evidenced by the available inverse and moderate correlations between the STAI scale (reactive anxiety, r = -0,321; p<0,0001), (personal anxiety, r = -0,429; p<0,0001) and the PQ-LES-Q.

To optimize the ways of treatment of pulmonary pathologies in children, it is necessary to consider not only

the main mechanisms of disease development but also the psycho-emotional state of the patient. Early detection of emotional disorders, especially anxiety and depression, can increase the effectiveness of treatment, improve the course of the disease and social adaptation, and reduce the frequency of relapses, especially in children suffering from asthma.

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**Conflict of interest:**

*The Authors declare no conflict of interest.*



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ORIGINAL ARTICLE

# PERIACETABULAR BONE CHANGES AFTER TOTAL HIP ARTHROPLASTY WITH HIGHLY POROUS TITANIUM CUPS IN PATIENTS WITH LOW BONE MASS

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## ABSTRACT

**The aim:** To assess the bone remodeling around highly porous titanium cups TTM in patients with low bone mass one year after total hip arthroplasty (THA).

**Materials and methods:** In this prospective study were included 18 patients (18 hips), whom was performed primary THA with the use of TTM cups. According to T-score of Lumbar Spine, patients were divided into 2 groups: normal bone mineral density (BMD) (n=9) if T-score ≥ –1, and low BMD (n=9) if T-score < –1. According to DeLee and Charnley's model BMD in 3 periacetabular regions were evaluated 1 week and 1 year after THA.

**Results**: One year after primary THA, BMD of all 3 periacetabular regions did not differ in patients of both groups comparing with initial data. One week after THA, it was found that BMD R1 and BMD R3 in low BMD group were lower by 1.4 times (p=0.035) and 1.5 times (p=0.001) respectively, BMD R2 did not differ from the normal BMD group. One year after THA it was found that in low BMD group BMD R1 and BMD R2 were lower by 1.5 times (p=0.005) and 1.3 times (p=0.050) respectively, BMD R3 did not differ from the group with normal BMD.

**Conclusions**: The use of highly porous titanium cups TTM in patients with low bone mass did not lead to a bone loss in DeLee and Charnley periacetabular zones one year after THA. Consequently, the use of these cups in patients with low bone mass undergoing THA is a valuable treatment option.

**KEY WORDS:** Bone density, hip replacement, bone remodeling, osteoporosis, cementless

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## INTRODUCTION

Osteoporosis and osteopenia are found in 21-32% of patients requiring total hip arthroplasty (THA) [1]. Low bone mass affects the occurrence of intraoperative (periprosthetic fractures, acetabular fractures) and postoperative complications [2]. In patients with low bone mass, the remodeling of bone tissue with increased resorption and inhibition of bone formation around the components of the prosthesis can lead to an increase in their micromobility, the formation of fibrous tissue, and a decrease in the survival of the implant [3, 4].

Dual-energy x-ray absorptiometry (DEXA) in modern orthopedics is considered as a good clinical indicator of bone tissue response after arthroplasty. Based on DEXA data, bone remodeling in the DeLee and Charnley zones was studied after the installation of the porous titanium acetabular components [5], but there is no data on changes in the structure of the acetabular bone after THA with low bone mass.

## THE AIM

The aim of the study was to assess the bone remodeling around highly porous titanium cups TTM in patients with low bone mass one year after THA.

## MATERIALS AND METHODS

The study was approved by the Local Bioethics Committee (Protocol No. 182 dated 9 July 2018). All patients signed informed consent forms for participating in the study.

### PATIENTS

In the period 2018-2019, primary THA was performed on 57 patients in one health facility. Patients were chosen based on these criteria: men and women, age 30-75 years, body mass index (BMI) ≤40 kg/m$^2$, with different bone mass according to DEXA of the lumbar spine.

The exclusion criteria were age <30 years, BMI >40 kg/m$^2$, severe kidney failure, type 1 diabetes mellitus, hypo- or hyperthyroidism, hip fracture, tumors.

Out of the 57 patients, 18 agreed to continue participating in the study. The age of the patients was between 34 and 75 years, average BMI 30.2 (±5.9) kg/m$^2$, average bone mineral density (BMD) of the lumbar spine 0,990 (±0,197) g/cm$^2$. There were 9 (50%) women, with ages between 34 and 75 years, and 9 (50%) men, with ages between 35 and 61 years. BMI was 31.06 (±3.51) kg/m$^2$ for the women and 29,38 (±7,77) kg/cm$^2$ for the men. Diagnosis: osteoarthritis

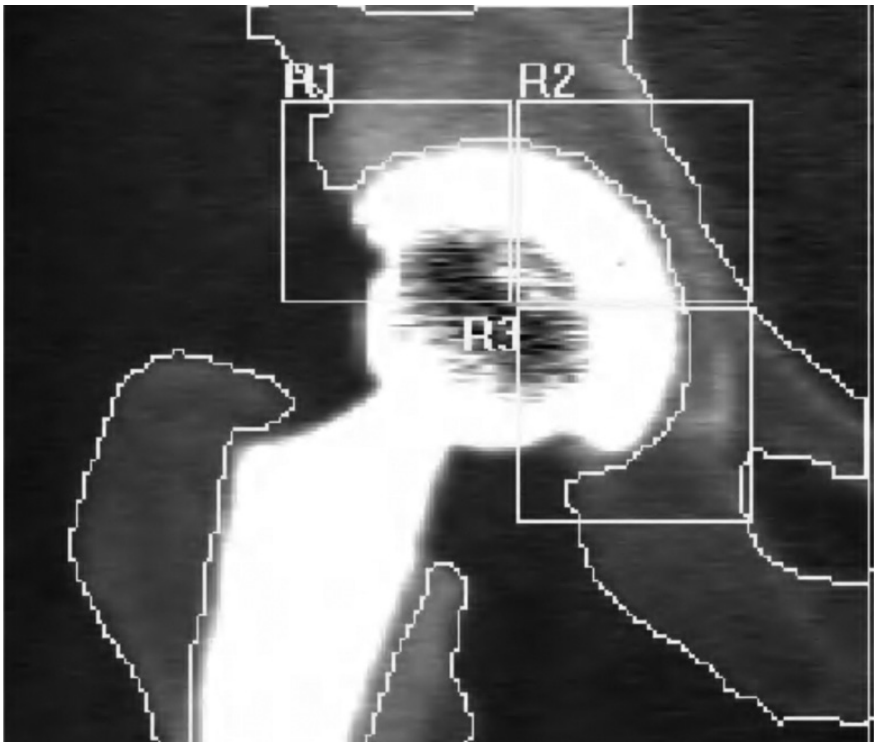


**Fig. 1.** Arrangement of three zones (R1, R2, R3) according to DeLee and Charnley's model on the right hip DEXA scan after placement of an prosthesis with highly porous titanium cups TTM

(12 patients), rheumatoid arthritis (4 patients), femoral neck nonunion (2 patients).

### SURGERY

All 18 patients (18 hips) underwent cementless THA using the prosthesis AK Medical (Beijing, China) with highly porous titanium cup TTM. THA was performed with the use modified lateral approach to the hip by one senior surgeon in one hospital. Clinical and radiological evaluation of patients was conducted preoperatively, at 7 days, 2 months, 6 months and one year postoperatively.

Harris Hip Score (HHS) was used to assess the outcome of the patients after THA. Complications (intra and postoperative) were also taken into account.

### DEXA ANALYSIS

BMD of the lumbar spine, and, after THA, the lower extremity, was analyzed for all patients. BMD was measured using the Explorer QDR 4500 (Hologic, USA) bone densitometer. Before THA, the lumbar spine examination was conducted in the Lumbar Spine mode (APEX ver. 3.3.0.1). Both one week and one year after THA, the proximal femur with the prosthesis was examined using the Metal Removal mode. The images with the implant were analyzed in 3 regions of interest (R1, R2, R3) around the cup according to a DeLee and Charnley's model [6] (Figure 1).

According to T-scores of the lumbar spine, patients were divided into 2 groups: Normal BMD group (n=9, 4 females, 5 males) with T-score ≥ –1, and Low BMD group (n=9, 5 females, 4 males) with T-score < –1.

### STATISTICAL ANALYSIS

Statistical analysis was completed by using IBM Statistics SPSS 23 software. All values were assessed with the use of Kolmogorov-Smirnov test to ensure the normality of the distribution. Values were presented as mean ± standard deviation (± SD), except for Hip Harris Score values, which were reported as median and percentiles (25th and 75th). Differences between the Normal BMD and Low BMD groups, male and female groups were evaluated by using an unpaired t-test. The paired t-test was used to compare BMD values right after THA with BMD values one year later. HHS changes were evaluated in different periods of follow-up by using Wilcoxon signed-rank test, and intergroup comparisons were performed by using Mann-Whitney U-test. The correlations between the preoperative lumbar spine BMD, age, BMI, and the BMD of R1, R2 and R3 one week and one year after the THA were evaluated with the calculation of the Pearson correlation coefficient. Spearman rank correlation was used to assess correlation with gender. Differences were considered statistically significant if $p<0.05$.

## RESULTS

### CLINICAL OUTCOMES

In the term of follow-up, no radiological or clinical signs of acetabular loosening or osteolysis were found. In both groups of patients, HHS increased a week after THA up to 6 months of follow-up, after which it stabilized (Table I). In Low BMD group, HHS preoperatively was significantly lower, but after THA, it did not differ from Normal BMD group at all follow-up periods. All 18 patients achieved excellent results one year after THA (HHS ≥90).

**Table I.** Hip Harris Score (HHS) in patients with different bone mineral density (BMD) preoperatively, at 2 months, 6 months and one year after total hip arthroplasty

| Variable | Normal BMD group (n=9) | | | Low BMD group (n=9) | | | |
|---|---|---|---|---|---|---|---|
| | HHS | [1]p-value | [2]p-value | HHS | [1]p-value | [2]p-value | [3]p-value |
| preop. | 44.0 (41.5-47.0) | – | – | 35.0 (33.0-39.5) | – | – | <0.001 |
| 1 week | 53.0 (49.0-55.5) | 0.016 | – | 52.0 (48.5-57.5) | 0,008 | – | 1.000 |
| 2 month | 78.0 (75.5-83.5) | 0.008 | 0.008 | 81.0 (76.0-85.5) | 0.008 | 0.008 | 0.730 |
| 6 month | 94.0 (88.0-95.5) | 0.008 | 0.008 | 94.0 (90.0-95.0) | 0.008 | 0.007 | 0.931 |
| 1 year | 97.0 (91.5-98.0) | 0.008 | 0.312 | 93.0 (91.5-97.0) | 0.008 | 0.573 | 0.489 |

[1,2]Wilcoxon signed-rank test; [1]comparison with preoperatively values, [2]comparison with previous term; [3]Mann–Whitney U-test; comparison with Normal BMD group. Differences are significant if $p<0.05$. Data presented as median and percentiles.

**Table II.** Bone mineral density (BMD; g/cm2) values one year after total hip arthroplasty

| Variable | Normal BMD group (n=9) | | Low BMD group (n=9) | |
|---|---|---|---|---|
| | 1 week | 1 year | 1 week | 1 year |
| BMD R1 | 1.612±0.414 | 1.678±0.257<br>$p_1$=0.502 | 1.127±0.479<br>$p_2$=0.035 | 1.136±0.431<br>$p_1$=0.889<br>$p_2$=0.005 |
| BMD R2 | 1.547±0.323 | 1.586±0.415<br>$p_1$=0.729 | 1.175±0.503<br>$p_2$=0.080 | 1.212±0.329<br>$p_1$=0.749<br>$p_2$=0.050 |
| BMD R3 | 1.290±0.279 | 1.228±0.259<br>$p_1$=0.243 | 0.829±0.226<br>$p_2$=0.001 | 0.995±0.259<br>$p_1$=0.099<br>$p_2$=0.074 |

$p_1$–paired t-test; comparison with 1 week; $p_2$–unpaired t-test; comparison with normal BMD group. Differences are significant if $p<0.05$. Data presented as mean ± SD.

**Table III.** Correlation (r) between bone mineral density (BMD) of R1, R2 and R3 for both periods of observation and with age, body mass index, gender

| Variable | 1 week | | | 1 year | | |
|---|---|---|---|---|---|---|
| | BMD R1 | BMD R2 | BMD R3 | BMD R1 | BMD R2 | BMD R3 |
| Age[1] | 0.413<br>p=0,089 | 0.553<br>p=0.017* | 0.481<br>p=0.043* | 0.505<br>p=0.032* | 0.331<br>p=0.179 | 0.138<br>p=0.585 |
| Body mass index[1] | 0,500<br>p=0,035* | 0.638<br>p=0.004* | 0.743<br>p<0.001* | 0.588<br>p=0.010* | 0.571<br>p=0.013* | 0.588<br>p=0.010* |
| Gender[2] | -0,155<br>p=0,540 | -0.160<br>p=0.527 | 0.081<br>p=0.749 | -0.009<br>p=0.973 | 0.196<br>p=0.436 | 0.488<br>p=0.040* |
| BMD lumbar spine[1] | 0.502<br>p=0.040* | 0.702<br>p=0.002* | 0.830<br>p<0.001* | 0.714<br>p=0.001* | 0.753<br>p<0.001* | 0.719<br>p=0.001* |

[1]Pearcon correlation method; [2]Spearman rank correlation; *statistically significant if $p<0.05$.

## DEXA MEASUREMENTS

Age (55.6±6.0 vs. 51.8±12.9 years; p=0.444) and BMI (32.67±5.29 vs. 27.77±5.72 kg/m$^2$; p=0.078) in Normal BMD group and Low BMD group were not differ, but BMD was significantly higher in Normal BMD group (1.123±0.121 vs. 0.863±0.161 g/cm$^2$; p=0.001) comparison with the Low BMD group.

One year after THA, BMD values in all three regions of interest (R1, R2, R3) did not differ significantly from the initial values for both the normal and low BMD groups (Table II). One week after the operation, it was determined that BMD values in R1 and R3 were lower by 1.4 times (p=0.035) and 1.5 times (p=0.001) respectively in the Low BMD group in comparison with the Normal BMD group, while R2 values did not differ between the groups. One year after the operation, lower BMD values in R1 (1.5 times, p=0.005) and R2 (1.3 times, p=0.050) were found in the Low BMD group, while BMD values in R3 did not differ in comparison with the Normal BMD group.

A significant correlation between age and BMD R2 and BMD R3 was found one week after THA. One year after THA, there was a significant correlation only between age and BMD R1 (Table III). A correlation between BMD in all three regions and BMI was found for both periods of observation. BMD of the lumbar spine correlated with BMD values of all three regions for both periods of observation.

The only parameter that correlated with gender was the BMD R3 value one year after the operation (Table III). After patients were separated based on gender, it was determined that the two groups did not differ in age, BMI, BMD of the lumbar spine, BMD of all three regions one week after THA. One year after THA, BMD values in R1 and R2 did not differ significantly, although BMD R3 values were higher by 1.3 times (p=0.040) in men (1.244±0.313) than in women (0.979±0.166).

## DISCUSSION

In our study, changes in BMD in DeLee and Charnley's zones one year after THA using porous TTM cups were evaluated in comparison with initial BMD values in the periacetabular zone and the lumbar spine. It was discovered that, independent of initial bone mass of the patients, who were divided into groups with low and normal BMD using T-scores of the lumbar spine, one year after THA, BMD values in all regions (DeLee and Charnley's model) did not change. However, one week after THA, BMD values in R1 and R3 were significantly lower in the Low BMD group than in the Normal BMD group. One year later, similar differences from the Normal BMD group were found in R1 and R2 of the Low BMD group, while BMD values for R3 did not differ from the Normal BMD group. Clinical results of patients with Low BMD group according to HHS were comparable to Normal BMD group in all periods of follow-up after THA.

It is known that a decrease in BMD in the acetabular zone could be connected with stress-shielding syndrome after installation of the prosthesis during THA [7], as a result of which there is an increase in bone resorption around the stem [8]. However, the influence of the patient's initial BMD on bone remodeling around the cup is unknown. In our study, one year after THA, a decrease in BMD R2 was discovered in the Low BMD group, despite the fact that initially the value was not different from the same region in the Normal BMD group. During computer modeling using the finite element model of the pelvis, it was likewise found that the largest bone loss was in R2, in comparison with R1 and R3 [9]. In clinical trials, one year after cementless THA using a porous Tritanium cup, X-ray examinations of the patients showed that in R2 contact with the bone was worse than in R1 and R3 [10]. This probably signifies a negative bone remodeling and can explain the decrease in BMD R2 one year after THA in our study. During the examination of the periacetabular zone, based on the texture analysis of X-ray films, on the contrary, an increase in the density of R2 was found, one year after cementless THA with the RM-Pressfit® cup, although the authors did not evaluate the initial bone mass of the patients [11].

We discovered that, in the Low BMD group, BMD R3 increased one year after the operation, reaching the level of the Normal BMD group. Such changes in BMD R3 after THA are linked with an increase in load on the leg while walking as a result of improved function [5].

Low BMD R1 in patients in the Low BMD group in comparison with the Normal BMD group both one week and one year after THA can be an important clinical sign, as after cement THA radiolucency in this zone is connected with acetabular loosening in nearly 30% of all cases [12].

As a result of correlational analysis, we found that BMD of the lumbar spine is correlated with BMD in three acetabular zones, both one week and one year after THA. These results confirm the importance of evaluating BMD of the lumbar spine to predict changes in the pelvis after THA and the survivability of the implant [13].

Moreover, a correlation between age and BMD R2 and R3 was established one week after THA, and between age and BMD R1 one year later. There is also a correlation between BMD in all three regions of interest both one week and one year after THA. This data matches the obtained results, according to which BMD R1 was correlated with BMI one year after THA in patients with BMI≥25 [5].

We discovered a correlation between gender and only BMD R3 values. BMD R3 values were higher in men than in women one year after THA, even though one week after THA there were not significant differences. The influence of gender on BMD values of the acetabular zone after THA was also shown by other researchers [5, 14]. Bone restoration in men can occur faster in comparison to women as a result of more physical activity after THA. For example, it was shown that in the year after THA, men covered longer distances than women [15].

The high survivability of porous cups was confirmed by long-term studies [16, 17]. However, low BMD before THA increased the possibility of a migration of the cup in comparison to patients with normal BMD for three months, without any further development [3, 4]. One year after THA, we also did not discover X-ray signs of cup migration in patients from the Low BMD group.

One limit of our study is the low number of patients, although both groups were similar in gender, age, and BMI. Considering the small number of studies that evaluated THA results in connection with initial bone mass and had a control group, our results can be useful for further trials with patients that have low bone mass.

## CONCLUSIONS

The use of highly porous titanium cups TTM in patients with low bone mass did not lead to a bone loss in DeLee and Charnley periacetabular zones one year after THA. A good clinical result was achieved in all patients who underwent primary THA with the application of TTM cups, regardless of initial bone mass. Consequently, the use of these cups in patients with low bone mass undergoing THA is a valuable treatment option.

ABBREVIATIONS

BMD – bone mineral density
BMI – body mass index
DEXA – dual-energy x-ray absorptiometry
HHS – Harris Hip Score
THA – total hip arthroplasty

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ORIGINAL ARTICLE

# INFECTIONS ASSOCIATED WITH OBSTETRIC AND GYNECOLOGICAL SURGERIES AS A CAUSE OF FEMALE INFERTILITY IN UKRAINE

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## ABSTRACT

**The aim:** To assess the role of surgical site infections types associated with obstetric and gynecological surgeries as a cause of infertility among women reproductive age in Ukraine.

**Materials and methods:** We conducted a retrospective multicentre cohort study was based on reproductive health surveillance data among women reproductive age from 2019 to 2021. Definitions of infertility were used from the WHO and surgical site infections were used CDC/ NHSN.

**Results:** Among all the 3,825 of infertility women in this study, the prevalence of surgical site infection (SSI) was 67.9%. The prevalence of SSI among primary infertility group and secondary infertility group women was 67.5% and 71.4%, respectively. There were differences among SSI type associated with infertility, primary infertility and secondary infertility. In logistic multivariate regression analyses, infertility was associated history of induced abortion ($p < 0.001$), history of obstetric and gynecological surgeries ($p < 0.001$), Salpingitis ($p < 0.001$), Oophoritis ($p < 0.001$), Endometritis ($p < 0.001$), Adnexa utery ($p=0.009$), and Pelvic abscess or cellulitis ($p=0.043$). The main factors associated with primary infertility were history of Salpingitis (33.6%) and Oophoritis (28.2%) after gynecological surgery. A factors associated with secondary infertility were history of Endometritis (27.2%), Pelvic abscess or cellulitis (11.2%), Salpingitis (10.1%), Adnexa utery (9.4%), Oophoritis (4.8%), and Chorioamnionitis (3.9%).

**Conclusions:** One of the main causes of infertility in women of reproductive age in Ukraine are SSIs after obstetric and gynecological surgeries, and induced abortion. This applies to both primary and secondary infertility group women's in this cohort study.

**KEY WORDS:** reproductive health, primary and secondary infertility, obstetric and gynecological surgery, induced abortion, risk factors, surgical site infection, Ukraine

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## INTRODUCTION

Infertility is a global socio-demographic, economic and clinical issue worldwide. Its consequences are manifested in many ways in our society, including the monetary costs of its investigation, diagnosis, and treatment as well as the psychosocial stresses it imposes on this portion of the population. Available data suggests that between 48 million couples [1] and 186 million individuals have infertility globally [2]. Infertility is estimated to affect half a million of reproductive age women attempting to conceive in the Ukraine.

One of the causes of female infertility is a history of infections after obstetric and gynecological surgeries [3-7]. The most common infections after these procedures are Endometritis, Pelvic abscess or cellulitis, Episiotomy, Vaginal cuff infection, Adnexa utery, Salpingitis, Oophoritis, Parametritis, Chorioamnionitis, and Bacterial Vaginitis. The prevalence of reproductive tract infection (RTI) after gynecological surgery varies from country to country and ranges from 1.8% [8] to 37.8% [7, 9]. Incidence rate of SSI after obstetric and gynecological surgeries were highest in Ukraine. According to a variety of sources, rates of RTI among women in Ukraine varied from 4.6% to 38.8% [3,7,8,10]. In the United States, 1 million women are diagnosed with RTI each year and the cost of their treatment is estimated at $4.2 billion [11].

Over the past three decades, the problem of infertility in Ukraine has not been given due attention, although increase fertility level has been a priority task for in the country. The decline of fertility level in Ukraine is increasing social interests about infertility as one of priority areas to be addressed not only to respond a potential population aging but also to improve reproductive health. The introduction of family planning programs in the face

of deteriorating economic dynamics in Ukraine did not contribute to a permanent and significant increase in the total fertility rate to the level of among most European countries. Despite the availability of new technologies for diagnosing and treating patients, the number of infertile men and women does not decrease.

Despite of significant socio-demographic, economic and clinical meaning of childlessness, there has been less scientific focuses on causes of infertility in Ukraine. To our knowledge, only a few studies were conducted to study infertility within narrow clinical features, showing that the percentage of infertile women seeking infertility treatment services has grown increasingly in Ukraine. Also, several studies have been conducted to study the prevalence of SSIs after obstetric and gynecological surgeries [3, 7, 12, 13]. The results of studies showed high prevalence and incidence rate of surgical site infections after these surgeries. In addition, there has been no attempt to study focused on female infertility in the context of surgical site infections after obstetric and gynecological surgeries based on surveillance data. Therefore, it is clearly important to understand infertility dynamics for its current level and health-care associated infections as a cause of female infertility, to not only effectively respond to fertility decrease but also ensure reproductive health rights of residents in Ukraine.

## THE AIM

The aim of this study was to assess the role of surgical site infections types associated with obstetric and gynecological surgeries as a cause of infertility among women reproductive age in Ukraine.

## MATERIALS AND METHODS

### DESIGN AND STUDY POPULATION

We conducted a retrospective multicentre cohort study was based on reproductive health surveillance data among women reproductive age from January 1st, 2019 to December 31st, 2021 in Ukraine. We compiled list of the 17 medical centers for family planning and reproductive health. Of these, only 12 medical centers from 8 regions (Lviv, Ivano-Frankivsk, Vinnytsia, Kyiv, Sumy, Kherson, Dnipropetrovsk, and Odessa) of Ukraine agreed to take part in our study. The study population included women who had experienced infertility had sought medical or professional help for the problem. The inclusion criteria in this study for participants were as follows: 20–49 years old; married or cohabitational; local residents. Te exclusion criteria: not a local resident of the selected regions; cancer; Chlamydial infections; positive serological test for syphilis or other sexually transmitted bacterial infections. In addition, local women were excluded from the study if they did not regularly visit doctors and medical records were not properly executed. In total of 17 women were excluded from the study.

### DEFINITIONS

In our study infertility is defined as disease of the female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse [14]. In present study infertility among married women was classified as primary and secondary. In this study primary infertility is defined as a woman who has never been diagnosed with a clinical pregnancy and meets the criteria of being classified as being infertile, while secondary infertility is defined as a woman unable to establish a clinical pregnancy who has previously been diagnosed with a clinical pregnancy [15]. The CDC/NHSN (Centers for Disease Control and Prevention/National Healthcare Safety Network) definition [16] for SSI types after obstetric and gynecological surgeries was used.

### DATA COLLECTION

This study includes interviews, questionnaires, and examinations medical records. Information on Infertility was collected at baseline and each follow-up visit. Full text ambulatory medical records and relevant hospital records were reviewed for the all women's. All free-text notes were reviewed, and encounters for which the principal focus was the Infertility were identified. A standard data collection form was created to extract demographic and clinical data, and outcome information from routine patient records. Supervision and quality control were conducted throughout the entire study. In this study adopted double entry mode of paper questionnaire data and were analyzed anonymously. According to their history of pregnancy, child birth and contraception, the infertile women were divided into primary infertility and secondary infertility cohorts.

### ETHICS

Our study was performed in line with the principles of the Declaration of Helsinki. Also, the Shupyk National Healthcare University of Ukraine Ethics Committee approved this study. All participants signed an informed consent.

### STATISTICAL ANALYSIS

The prevalence of SSIs after obstetric and gynecological surgeries was reported as the percentage of the total number of infertile women's. Cases of SSIs were analysed by type of infection, which were mutually exclusive. The analysis of statistical data was performed using Excel (Microsoft Corp., Redmond, WA, USA). Results are expressed as median (range), mean standard deviation for continuous variables, and number and corresponding percentage for qualitative variables. Comparisons were undertaken using Student's t-test and Fisher's exact test for categorical variables. In this study we used binary logistic multivariate regression analysis, and for variable selection we used forward stepwise regression based on maximum likelihood estimation. Statistical significance was defined as $P<0.05$.

## RESULTS

### PREVALENCE SURGICAL SITE INFECTION AMONG INFERTILE WOMEN

In during study period (2019-2021) we sampled 3825 infertile women who were 20–49 years old in 12 medical centers of 8 regions in Ukraine. The prevalence of primary infertility and secondary infertility was about 88.6% (3,388/3,825) and 11.4% (437/3,825), respectively. The mean ± SD age was 32.97 ± 0.25 years for the primary infertility group and 34.95 ± 0.39 years for the secondary infertile group. The difference in mean age between these two groups was statistically significant (p< 0.001). As shown in Table I, the difference in the history of obstetric and gynecological surgery, procedure of induced abortion, and history of surgical site infection (SSI) between the two groups were statistically significant (p < 0.001). In total, 95.7% (3,661/3,825) of infertile women had a history of surgical procedures. The prevalence of SSIs in this study cohort of infertility women was 67.9% (2,599/3,825). The prevalence of SSI among primary infertility group and secondary infertility group women was 67.5% and 71.4%, respectively. Characteristics of infertile women who have a history of obstetric and gynecological surgery, procedure of induced abortion, and history of SSI are presented in Table I.

There were differences among SSI type associated with infertility, primary infertility and secondary infertility. The main factors associated with primary infertility were history of salpingitis (33.6%) and oophoritis (28.2%) after gynecological surgery. A factors associated with secondary infertility were history of Endometritis (27.2%), Pelvic abscess or cellulitis (11.2%), Salpingitis (10.1%), Adnexa utery (9.4%), Oophoritis (4.8%), and Chorioamnionitis (3.9%). Comparison of characteristics of primary and secondary infertile groups is shown in Table II.

### RISK FACTORS OF SSI ASSOCIATED WITH INFERTILITY

Table III showed the odds ratio (OR) and 95% confidence interval (CI) for the risk factors of SSI associated with infertility in logistic multivariate regression analyses. Unsurprisingly, infertility was associated with SSI after obstetric and gynecological surgery, and surgical procedure for induced abortion as shown in logistic regression analysis. Further, there were differences among risk factors of SSI associated with infertility, primary infertility and secondary infertility.

In Table IV, factors associated with primary infertility were Salpingitis (p< 0.001) and Oophoritis (p< 0.001) after gynecological surgery. In single-factor analysis, history of gynecological surgery (p< 0.001) and pelvic abscess or cellulitis (p = 0.043) might have association to primary infertility but all of them were excluded when binary logistic multivariate regression analyses were carried out.

In Table V, risk factors of SSI associated with secondary infertility were history of induced abortion (p < 0.001), gynecological surgery (p < 0.001), Cesarean section (p < 0.001), Endometritis (p < 0.001), Salpingitis (p < 0.001), Oophoritis (p < 0.001), Adnexa utery (p=0.009), and Pelvic abscess or cellulitis (p=0.043). In single-factor analyses, history of Chorioamnionitis (p < 0.001) might be associated with secondary infertility but it was excluded when binary logistic multivariate regression analyses were carried.

**Table I.** Characteristics of infertile women who have a history of surgery for delivery or elective gynecological surgery for benign reasons in Ukraine (2019-2021)

| Variables | Infertile women (n=3825) | | *p*-value | 95%CI[a] |
|---|---|---|---|---|
| | n | % | | |
| History of surgical procedure | | | | |
| Cesarean section | 335 | 8.8 | < 0.001 | 8.3 – 9.3 |
| Surgery for benign gynecological disease | 2971 | 77.7 | < 0.001 | 77.0 – 78.4 |
| Induced abortion | 355 | 9.3 | < 0.001 | 8.8 –9.8 |
| History of SSI[b] type | | | | |
| A pelvic abscess or cellulitis | 127 | 3.3 | < 0.001 | 3.0 – 3.6 |
| Adnexa utery | 70 | 1.8 | < 0.001 | 1.6 – 2.0 |
| Salpingitis | 1000 | 26.1 | < 0.001 | 25.9 – 28.8 |
| Oophoritis | 1160 | 30.3 | < 0.001 | 29.6 – 31.0 |
| Endometritis | 170 | 4.4 | < 0.001 | 4.1 – 4.7 |
| Chorioamnionitis | 17 | 0.4 | 0.043 | 0.3 – 0.5 |
| Vaginal cuff infection | 48 | 1.2 | 0.074 | 1.0 – 1.4 |
| Episiotomy | 7 | 0.2 | 0.087 | 0.13 – 0.3 |

[a]CI, confidence interval
[b]SSI, surgicai site infection

**Table II.** Characteristics of primary and secondary infertile groups among women's (n=3825) in Ukraine (2019-2021)

| Characteristics | Primary infertility (n = 3,388) | | Secondary infertility (n = 437) | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| History of surgical procedure | | | | | |
| Cesarean section | 0 | 0.0 | 335 | 76.7 | < 0.001 |
| Surgery for benign gynecological disease | 2909 | 85.9 | 62 | 14.2 | |
| Induced abortion | 0 | 0.0 | 355 | 81.2 | |
| History of pelvic abscess or cellulitis | | | | | |
| No | | | | | |
| Yes | 78 | 2.3 | 49 | 11.2 | < 0.001 |
| History of Adnexa utery | | | | | |
| No | | | | | < 0.001 |
| Yes | 29 | 0.9 | 41 | 9.4 | |
| History of Salpingitis | | | | | |
| No | | | | | < 0.001 |
| Yes | 1139 | 33.6 | 44 | 10.1 | |
| History of Oophoritis | | | | | |
| No | | | | | < 0.001 |
| Yes | 956 | 28.2 | 21 | 4.8 | |
| History of Endometritis | | | | | |
| No | | | | | < 0.001 |
| Yes | 48 | 1.4 | 122 | 27.9 | |
| History of Chorioamnionitis | | | | | |
| No | | | | | < 0.001 |
| Yes | 0 | 0.0 | 17 | 3.9 | |
| History of Vaginal cuff infection | | | | | |
| No | | | | | < 0.001 |
| Yes | 37 | 1.1 | 11 | 2.5 | |
| History of Episiotomy | | | | | |
| No | | | | | < 0.001 |
| Yes | 0 | 0.0 | 7 | 1,6 | |

## DISCUSSION

To the best of our knowledge, this is the first study examining surgical site infections associated with obstetric and gynecological surgeries as a cause of infertility among women reproductive age in Ukraine. We found that the prevalence of surgical site infection (SSI) among women with infertility was 67.9%. The prevalence of SSI among primary infertility group and secondary infertility group women was 67.5% and 71.4%, respectively. There were differences among SSI type associated with infertility, primary infertility and secondary infertility. In logistic multivariate regression analyses, infertility was associated history of induced abortion ($p < 0.001$), history of obstetric and gynecological surgeries ($p < 0.001$), Salpingitis ($p < 0.001$), Oophoritis ($p < 0.001$), Endometritis ($p < 0.001$), Adnexa utery ($p=0.009$), and Pelvic abscess or cellulitis ($p=0.043$). The main factors associated with primary infertility were history of Salpingitis (33.6%) and Oophoritis (28.2%) after gynecological surgery. A factors associated with secondary infertility were history of Endometritis (27.2%), Pelvic abscess or cellulitis (11.2%), Salpingitis (10.1%), Adnexa utery (9.4%), Oophoritis (4.8%), and Chorioamnionitis (3.9%).

The prevalence of SSIs after induced abortion, obstetric and gynecological surgeries varies greatly in different countries and regions, and change all the times. The SSI cases estimates use different definitions considering different periods, which make direct comparisons difficult between various studies. SSIs in Ukraine are among the most common healthcare-associated infections (HAIs) after, obstetric and gynecological surgeries, and induced abortion.

Over the past two decades, along with significant improvements in clinical obstetric care in many countries,

**Table III.** Logistic multivariate regression analyses of risk factors associated with infertility women in Ukraine (2019-2021)

| Characteristics | *p*-value | Unadjusted OR[a] (95% CI[b]) | *p*-value | Adjusted OR (95% CI) |
|---|---|---|---|---|
| History of Cesarean section | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 0.557 (0.344–0.902) | 0.008 | 0.494 (0.294–0.830) |
| History of gynecological surgery | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 3.611 (2.235–5.832) | < 0.001 | 3.063 (1.819–5.159) |
| History of induced abortion | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 6.618(1.549–28.274) | 0.031 | 5.031 (1.163–21.830) |
| History of pelvic abscess or cellulitis | | | | |
| No | | Ref | | Ref |
| Yes | 0.043 | 0.563 (0.386–0.822) | 0.012 | 0.517 (0.342–0.781) |
| History of Adnexa utery | | | | |
| No | | Ref | | Ref |
| Yes | 0.009 | 0.557 (0.344–0.902) | 0.008 | 0.494 (0.294–0.830) |
| Histiry of Salpingitis | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 5.131 (2.662–9.889) | < 0.001 | 3.835 (1.908–7.711) |
| History of Oophoritis | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 9.379 (2.165–40.622) | 0.011 | 6.862 (1.557–30.248) |
| History of Endometritis | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 6.618(1.549–28.274) | 0.031 | 5.031 (1.163–21.830) |
| Constant | | | 0.003 | 0.109 |

[a]OR, Odd Ratio
[b]CI, confidence interval

the incidence rate of SSI after CSEC remains an important issue. According to literature data, the incidence of SSI after CSEC was 7-10% [17, 18]. Previous studies have shown that prevalence of SSI after Cesarean section (CSEC) in Ukraine was 14.2% [12]. In European Union Member States for CSEC operations, the percentage of SSIs was 2.2%, with an inter-country range from 0.6% to 7.7% [19]. The percentages of SSIs for CSEC operations in the Ukraine were significantly higher than those reported from EU for 2014–2016 [19] and other countries [17, 18].

Healthcare-associated reproductive tract infections (RTIs) after gynecological surgery include Endometritis, Episiotomy, Vaginal cuff infections and other infections of the female reproductive tract. Other infection of the female reproductive tract involves the Deep pelvic tissue infection or other infection of the female reproductive tract (for example, vagina, ovaries, uterus) including chorioamnionitis. The prevalence of healthcare-associated deep pelvic tissue infection and other infections of the female reproductive tract after gynecologic surgery in Ukraine was 26.3%. Incidence of infection was: 13.3% Pelvic abscess or cellulitis, 14.6% Adnexa utery, 9.5% Salpingitis, 7.1% Oophoritis, 12.2% Parametritis, 4.6% Chorioamnionitis, and 38.8% Bacterial Vaginitis [7]. The prevalence of RTIs varies from country to country and ranges from 1.8% [8] to 48% [20, 21]. In the United States, 1 million women are diagnosed with RTI each year [11]. Available literatures there are no epidemiologic studies (prevalence or incidence) of different types of healthcare-associated deep pelvic tissue infection and other infections of the female reproductive tract. Therefore, we were unable to compare our results with other studies in other countries.

Induced abortion is one of the most common surgical procedures in the world. In Ukraine, USA, most European and other countries, the law allows abortion on request or on broad social grounds. One of the major complications resulting from the unsafe abortions is RTIs. The reported of SSI rate following first trimester induced abortion ranges widely due to various clinical practices and degrees of ascertainment and diagnostic biases. According to literature, SSI after induced abortion, the rates were very variable between studies (from 0.7% to 3.6% with

**Table IV.** Logistic multivariate regression analyses of factors associated with primary infertility among women in Ukraine (2019-2021)

| Characteristics | *p*-value | Unadjusted OR[a] (95% CI[b]) | p-value | Adjusted OR (95% CI) |
|---|---|---|---|---|
| History of gynecological surgery | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 2.937 (1.772–4.870) | < 0.001 | 2.695 (1.548–4.695) |
| Histiry of Salpingitis | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 4.175(2.357–7.394) | < 0.001 | 3.359 (1.827–6.174) |
| History of Oophoritis | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 7.117 (2.651–19.107) | 0.002 | 6.258 (1.962–19.956) |
| Constant | | | < 0.001 | 0.095 |

[a]OR, Odd Ratio
[b]CI, confidence interval

**Table V.** Logistic multivariate regression analyses of factors associated with secondary infertility among women in Ukraine (2019-2021)

| Characteristics | *p*-value | Unadjusted OR[a] (95% CI[b]) | *p*-value | Adjusted OR (95% CI) |
|---|---|---|---|---|
| History of Cesarean section | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 0.637(0.428–0.950) | 0.043 | 0.650 (0.428–0.987) |
| History of Induced abortion | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 4.175(2.357–7.394) | < 0.001 | 3.359 (1.827–6.174) |
| History of gynecological surgery | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 3.611 (2.23–5.83) | < 0.001 | 3.063 (1.819–5.159) |
| History of pelvic abscess or cellulitis | | | | |
| No | | Ref | | Ref |
| Yes | 0.043 | 0.637(0.428–0.950) | 0.049 | 0.650 (0.428–0.987) |
| Histiry of Adnexa utery | | | | |
| No | | Ref | | Ref |
| Yes | 0.009 | 2.924(1.481–5.773 | 0.036 | 2.170 (1.052–4.479) |
| Histiry of Salpingitis | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 3.690 (1.913–7.114) | < 0.002 | 3.145 (1.532–6.455) |
| History of Oophoritis | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 2.937 (1.772–4.870) | < 0.001 | 2.695 (1.548–4.695) |
| History of Endometritis | | | | |
| No | | Ref | | Ref |
| Yes | < 0.001 | 2.924(1.481–5.773 | 0.036 | 2.170 (1.052–4.479) |
| Constant | | | < 0.001 | 0.039 |

[a]OR, Odd Ratio
[b]CI, confidence interval

one study reporting 8%) [22-24]. This rate in Ukraine was significantly higher than the rate observed in other country after terminated pregnancy but probably is a reflection of the variable abortion practices and definition

of SSIs used in these different countries. The prevalence of SSI after induced abortion in Ukraine was 25.9%. Of these SSIs, 25.9 were Endometritis, 21.8% Bacterial Vaginitis, 14.3% Parametritis, 13.1% Cervicitis, 9.9% Adnexa utery, 7.8% Salpingitis, 6.3% Chorioamnionitis, and 0.9% other reproductive tract infections [3].

According to literature data, the role of reproductive surgery is declining due to the widespread availability of assisted reproductive technology, but an evidence-based fundament for this decline is lacking. Worldwide assisted reproductive technology (ART) has replaced reproductive surgery for tubal factor infertility, limiting its role as first-line treatment [25]. However, it is not clear whether this change in clinical practice is due to the higher cost-effectiveness of ART compared to reproductive surgery or caused by other factors such as a lack of surgical expertise, patient's desires to achieve results rapidly or the concern to protect patients from procedure-related complications. In addition, the shift away from reproductive laparoscopic surgery favoring ART is not supported by solid evidence. The position of hysteroscopy in current fertility practice is similarly unclear.

Finally, our study showed that SSI remains the most common complication of gynecologic procedures. Despite the introduction into medical practice of new diagnostic technologies and treatment, as well as broad-spectrum antibiotics, the number of SSI after induced abortion, obstetric and gynecological surgeries is not decreasing. Implementing programs to reduce SSI requires a collaborative approach that involves clinicians, nurses, and staff.

## STRENGTH AND LIMITATION

The main advantage of this study is that we conducted a multicentre cohort study was based on women reproductive health surveillance data. This investigation provides valuable data as a first study for national surveillance of SSI associated with induced abortion, obstetric and gynecological surgeries as a cause of infertility among women reproductive age in Ukraine and potential comparison with data from other countries. In addition, this study included all types of SSIs after operations in the reproductive tract of women according to the CDC/NHSN definition. A limitation of this study is its retrospective design.

## CONCLUSIONS

One of the main causes of infertility in women of reproductive age is surgical site infections (SSIs) after obstetric and gynecological surgeries, and induced abortion. The results of this study revealed high level the prevalence rate of SSI among infertile women of reproductive age in Ukraine is high. This applies to both primary and secondary infertility group women's in this cohort study. This study provides the newest data of SSIs after obstetric and gynecological surgeries, and induced abortion in Ukraine and finds some predictors of SSI. The data presented in our study can be a tool to develop optimal preventive measures and improve surgical quality in Ukraine. The most of the risk factors identified are amendable through interventions of infection control. Surveillance is a key component in the prevention of healthcare-associated infections and an important tool for monitoring the effectiveness of prevention and control measures. Optimizing the management and empirical antimicrobial therapy may reduce the burden of SSIs, but prevention is the key element.

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**Conflict of interest:**
*The Authors declare no conflict of interest*

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ORIGINAL ARTICLE

# FACTORS INFLUENCING THE FORMATION OF THE PROXIMAL FEMUR IN PATIENTS WITH CEREBRAL PALSY

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**ABSTRACT**

**The aim:** Establishment of the factors influencing the formation of femoral neck-shaft angles and femoral torsions indices among the patients with cerebral palsy.

**Materials and methods:** The total number of patients was 46 persons (84 joints). We have examined patients using our method (patent №137567), obtained the true parameters of the femoral neck-shaft angle and femoral torsion, and conducted a statistical analysis of factors that might influence their formation.

**Results:** A statistically significant influence of factors of age, Gross Motor Function Classification System (GMFCS) level, ambulatory status, adductor myotomy and lack of statistical significance concerning the influence of factors such as level of lesion and developmental dysplasia of the hip upon the indices of neck-shaft angle. Femoral torsion's parameters were in statistically significant fashion affected by GMFCS levels, ambulatory status, level of lesion, and did not display statistical significance of factors of age, adductor myotomy, developmental dysplasia of the hip.

**Conclusions:** Our research shows that gait function, as well as GMFCS level, are the important factors in the formation of the proximal femur in patients with cerebral palsy.

**KEY WORDS:** cerebral palsy, hip joint, femoral torsion, neck-shaft angle, X-ray indices

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## INTRODUCTION

In the opinion of some authors, impaired development of the proximal femur (PF) in patients with cerebral palsy (CP) is a principal factor contributing to the pathology of the hip joint. [1] A stable and painless hip joint with a sufficient range of motion is considered not only as an important requirement for gait but also as a necessary condition for favorable sitting among the non-ambulating population groups. [2] Establishment of true parameters, as well as factors influencing the formation of pathological changes of the femoral neck-shaft angle (NSA) and femoral torsion (FT) in patients with cerebral palsy, who can ambulate independently or with crutches, and among those persons who can not ambulate independently, should be the objective of modern orthopedics.

Clinical evaluation of movements often does not allow assessing objectively the anatomical and functional condition of the hip joints in patients with CP. Restriction of external rotation in the hip joint cannot be used as a principal marker for the clinical evaluation of increased FT in these patients. [3] At the same time, excessive internal rotation of the thigh can be determined in the underdeveloped posterior edge of the acetabulum, which is often observed in CP. [3]

The method of femoral torsion's clinical evaluation is a simple, easily reproducible one and correlates well with intraoperative data. [4] This technique is used for the clinical evaluation of FT in patients with CP. [3]

It is the method of femoral torsion's clinical evaluation according to Ruwe [4] that forms the basis of our method for the determination of the clinical and radiographic parameters of the hip joint in patients with diseases of the latter (Fig. 1). [5]

Examination of the hip joints showed significant differences in the femoral NSA and FT among different groups of patients with CP, which prompted us to study the factors that might affect the formation of the PF more profoundly, as well as to analyze true parameters of femoral NSA and FT, obtained with our method referring to the age norms.

## THE AIM

The study aimed to establish the factors influencing the formation of femoral neck-shaft angles and femoral torsion indices among the patients with CP.

## MATERIALS AND METHODS

Presented data is based upon the study of clinical cases of 46 patients (84 joints) treated due to diseases of the hip joints in CP in the SI "Institute of Traumatology and Orthopedics of the National Academy of Medical Sciences of Ukraine" (Kyiv, Ukraine) during 2018-2020. The gender of the patients was not taken into account, as previous studies did not report significant inter-gender differences. [6] No patient had a history of bone surgery. We have studied various factors that may affect the formation of PF parameters: age, Gross Motor Function Classification System (GMFCS) [7], the level of lesion (paraparesis, tetraparesis, hemiparesis),

**Table I.** Normal age-related parameters of neck-shaft angle (NSA) and femoral torsion (FT) according to Kutsenok Ya.B. (1992)

| Age | Up to 4 years | 4-6 years | 7-9 years | 10-12 years | 13-15 years |
|---|---|---|---|---|---|
| Neck-shaft angle (degrees) | 137.16 ± 1.52 | 134.96 ± 0.86 | 132.54 ± 0.98 | 131.23 ± 1.09 | 128.61 ± 1.98 |
| Femoral torsion (degrees) | 37.6 ± 1.44 | 36.67 ± 0.98 | 33.23 ± 1.53 | 27,11 ± 2.09 | 19.86 ± 1.37 |

**Table II.** Age-related parameters of neck-shaft angle (NSA) and femoral torsion (FT) (Mean ± SE, N=84)

| Age groups, years | Neck-shaft angle, degrees | Femoral torsion, degrees |
|---|---|---|
| Up to 4 | 141,92 ± 2,19* | 55,00 ± 2,11 |
| 4-6 | 138,69 ± 1,71** | 51,39 ± 2,05 |
| 7-9 | 137,55 ± 1,23*** | 50,00 ± 2,05 |
| 10-12 | 137,37 ± 1,25 | 52,69 ± 2.98 |
| 13-15 | 132,50 ± 1,12 | 52,71 ± 1,16 |

Note. * P<0.05, ** P<0.01, *** P<0.001 comparing to the 13-15 years (one-way analysis of variance ANOVA with subsequent Tukey's HSD test).

**Table III.** Parameters of neck-shaft angle NSA and femoral torsion (FT) (Mean ± SE, N=84)

| Factor | Neck-shaft angle, degrees | Femoral torsion, degrees |
|---|---|---|
| GMFCS, level | | |
| 2 | 131,84 ± 0,96 | 50,25 ± 2,13 |
| 3 | 136,63 ± 1,08* | 52,50 ± 1,19 |
| 4 | 141,44 ± 1,23*** ## | 56,04 ± 1,28* |
| Ambulatory status | | |
| non-ambulating | 141,87 ± 1,08 | 55,18 ± 1,19 |
| ambulating | 134,33 ± 0,73*** | 50,54 ± 1,14* |
| Adductor myotomy (AM) | | |
| No AM | 137,84 ± 0,77 | 52,27 ± 1,05 |
| AM | 133,94 ± 1,59* | 51,56 ± 1,69 |
| DDH | | |
| DDH in the medical history | 140,29 ± 1,73 | 53,33 ± 2,11 |
| healthy joints at birth | 137,98 ± 1,81 | 49,58 ± 2,50 |
| Level of lesion | | |
| tetraparesis | 137,76 ± 0,87 | 53,19 ± 1,06 |
| paraparesis | 134,09 ± 1,50 | 52,50 ± 1,47 |
| hemiparesis | 136,43 ± 1,91 | 43,13 ± 2,49** # |

Note. * P < 0.05, ** P < 0.01, *** P < 0.001 comparing to the the first gradation of the factor # P < 0.05, comparing to the the second gradation of the factor ##P < 0.01 (one-way analysis of variance ANOVA with subsequent Tukey's HSD test).

ambulatory status (ambulating, non-ambulating), adductor myotomy and developmental dysplasia of the hip (DDH) in the medical history. The age of patients ranged between 3-15 years, in particular – up to 4 years (5 patients), 4-6 years (10 patients), 7-9 years (10 patients), 10-12 years (8 patients), 13-15 years (13 patients). Distribution according to the GMFCS – II level (10 patients), III level (16 patients), IV level (12 patients). The sample in this study included mainly patients with spastic tetraparesis (30 persons), spastic paraparesis (8 persons), and hemiparesis (8 persons). Each thigh was evaluated separately, in patients with hemiparesis only the affected side was taken into account. 32 of the patients were ambulating ones, 14 patients did not ambulate at the moment of examination, but were considered perspective in terms of verticalization, or their gait function was lost due to spastic hip dislocation. 8 patients had adductor myotomy in the medical history, performed in local medical settings. 15 patients had preserved X-ray images of the hip joints performed at the age of 3 months: 8 patients had a diagnosis of DDH, 7 patients were born with healthy hip joints. Data on whether DDH had been treated before the age of 1 year were not taken into account due to their absence. To avoid exposure of healthy children to irradiation, the reference normal parameters were taken from Kutsenok Ya.B. (Table I). [8] In our study, we analyzed two parameters of the hip joint: NSA and FT.

All patients underwent: clinical evaluation of femoral torsion according to Ruwe [4]; anteroposterior X-ray imaging of the hip joints using our method when true parameters of the hip joint were obtained. [5]

**Table IV.** Spearman Rank Order Correlations

| | Neck-shaft angle, degrees | | Femoral torsion, degrees | |
|---|---|---|---|---|
| **Factor** | **Spearman R** | **p-level** | **Spearman R** | **p-level** |
| Age groups | -0,44 | 0,0000 | 0,00 | 0,9643 |
| GMFCS | 0,54 | 0,0000 | 0,26 | 0,0250 |
| Ambulatory status | -0,55 | 0,0000 | -0,25 | 0,0220 |
| Adductor myotomy (AM) | -0,25 | 0,0237 | -0,04 | 0,7048 |
| DDH | -0,19 | 0,3513 | -0,23 | 0,2414 |
| Level of lesion | -0,20 | 0,0729 | -0,27 | 0,0124 |

Note. Significant correlations are highlighted in bold.

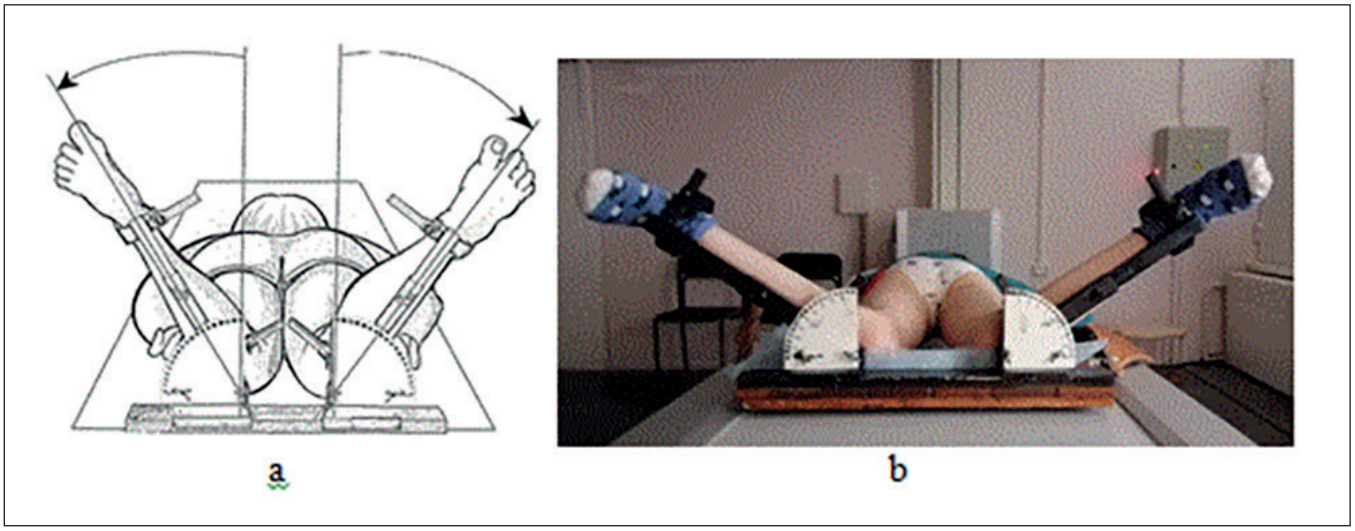


**Fig 1. a, b.** The method of determining the clinical and radiographic parameters of the hip joint in patients with diseases of the latter (prone position of the patient and fixation with an orthopedic console).

Formula: the method involves a combination of clinical and radiological methods and their interrelationship, which makes it possible to obtain radiographic indicators that exist in different planes when performing only one X-ray imaging of the hip joints (anterior-posterior projection) of the patient in a prone position. In a pronation position patient's knee joints are flexed at an angle of 90°, both thighs are exposed to the internal rotation so that neck of the femur is positioned parallel to the table. To do this, the left hand of the doctor was used to palpate the greater trochanter, and with the right hand, he performed the internal rotation of the thigh. At a certain point of rotation, the doctor with his left hand noted the maximum palpation of the greater trochanter, which indicates its most lateral position. Fixation of limbs with internal rotation of the thighs and measurement of femoral torsion were performed using developed by authors orthopedic console (patent for the invention №122629 and patent for utility model №140346). [9, 10] Clinical evaluations of femoral torsion were recorded. The X-ray imaging of hip joints in the described above position was carried out so that we could establish the true parameters of a hip joint. [5]

All data were analyzed using Statistics software version 7.0 (Statistics Inc., USA). One-way analysis of variance (ANOVA) with repeated measures followed by Tukey's HSD post hoc test was performed to determine group main effect. The level of statistical significance was set at $P<0.05$. All data are presented as mean values ± SE within text, figures and tables. Spearman's correlation coefficient was used to estimate the relationship between radiographometric parameters and other factors.

## RESULTS

The subject of this study was the parameters of the hip joint in patients with CP. We have analyzed the true indices of NSA and FT depending on various factors to demonstrate how they affect their development. Most patients had stable hips and were able to ambulate. 30 thighs had a migration rate >33%.

According to the results of one factor analysis of variance, statistically significant influence of the next factors upon the variance of NSA was revealed: age (Table II), GMFCS level (II, III, IV), ambulatory status (ambulating, non-ambulating), adductor myotomy in medical history (Table III). The variance of the FT has been affected in statistically significant fashion by GMFCS level (II, III, IV), ambulatory (ambulating, non-ambulating), the level

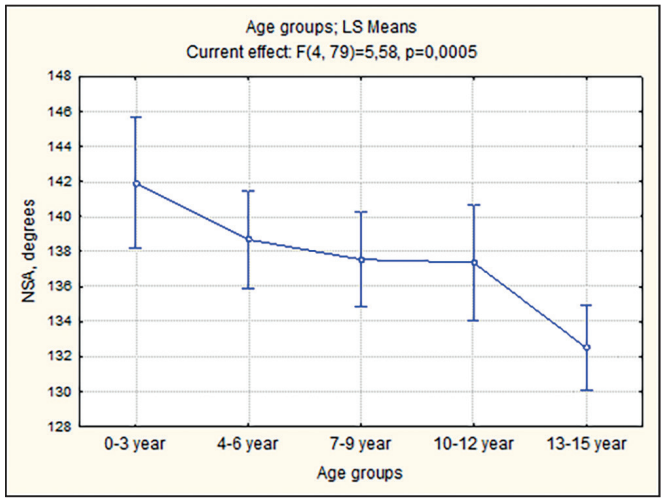


**Fig. 2.** The influence of age (years) upon the variance of NSA (degrees).

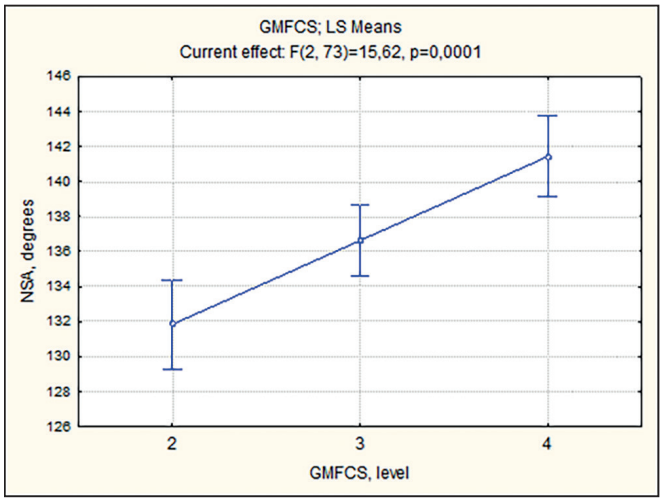


**Fig. 3.** Influence of GMFCS (levels II, III, IV) upon the variance of NSA (degrees).

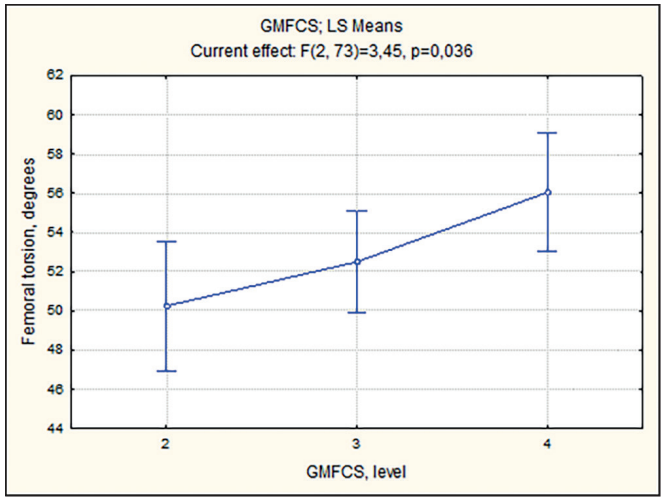


**Fig. 4.** Influence of GMFCS (levels II, III, IV) upon the variance of the femoral torsion (degrees).

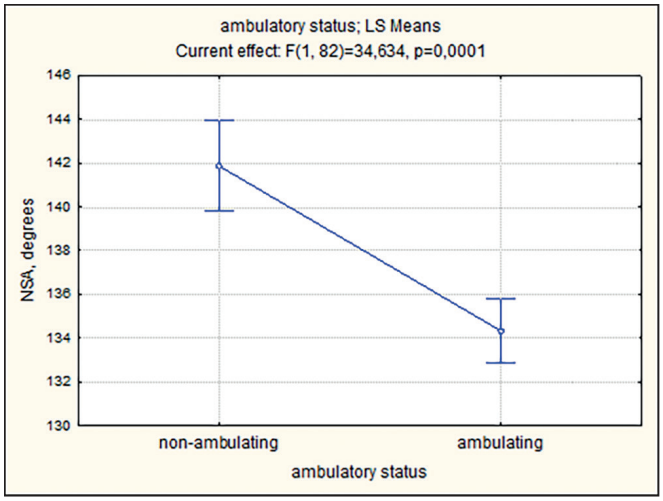


**Fig. 5.** Influence of the ambulatory status (ambulating, non-ambulating) upon the variance of NSA (degrees).

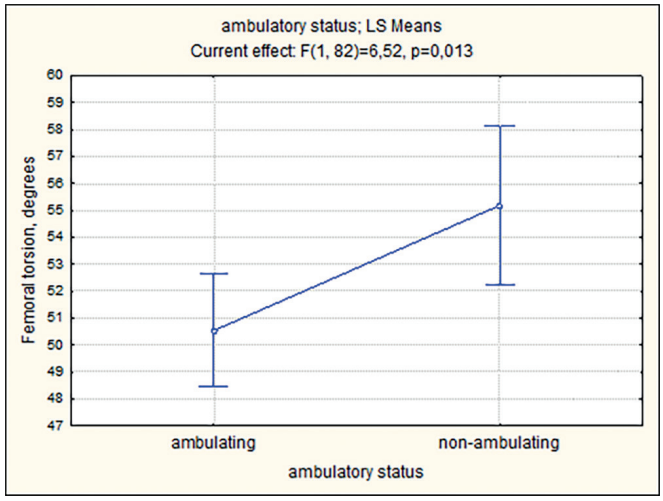


**Fig. 6.** Influence of the ambulatory status (ambulating, non-ambulating) upon the variance of the femoral torsion (degrees).

of lesion (tetraparesis, paraparesis, hemiparesis) (Table III). Similar results were obtained using Spearman correlation coefficient (Table IV). There is a complete correspondence between the results of two statistical research methods regarding the NSA and FT variance.

## DISCUSSION

The main objective of the study was to establish the influence of different factors upon NSA and FT that was achieved in full scale with two statistical methods. Difficulties in determining the FT among patients with CP have been described by many researchers and pose many questions about what factors may influence its formation. The accuracy of our own method of measuring FT and NSA among patients with CP comparing to intraoperative data was described in our previous studies. [11] In mild forms of CP pathological changes of PF were insignificant.

No statistically significant effect of age factor upon the variance of the FT was found. This confirms the hypothesis that FT in patients with cerebral palsy does not change with age. [1] A significant increase of this parameter in younger patients indicates that pathological FT in CP appears quite early – at the age 2.5-3 years. The same average values of FT indicate that in each age group there were patients

with a slight of pronounced increase in this parameter. Comparing to age groups, the NSA is significantly higher in the age 3-9 years comparing to the age 13-15 years. We found a statistically significant effect of age upon NSA (Fig. 2). As children with CP grow the NSA decreases, what is typical also for healthy children. It should be noted that we did not conduct a total screening of the hip joints among patients with CP. Patients who were referred to our clinic for medical care, were subjects of examination, so all persons from the older age groups were ambulating ones. This explains the fact that NSA was within the age-matched norms among the studied patients aged 13-15 years.

There were no differences between groups of patients referring the influence of level of lesion's factor (tetraparesis, paraparesis, hemiparesis) upon NSA, but one observed statistically significant differences between groups of patients concerning influence of level of lesion's factor upon the increased FT.

There was a statistically significant effect of GMFCS levels (II, III, IV) upon NSA (Fig. 3) and FT (Fig. 4). Some of our younger patients with GMFCS levels (II, III) did not ambulate at the moment of the examination, so it was decided to consider the factor of ambulatory status (ambulating, non-ambulating) separately.

Comparing the groups of patients on the ambulatory status' factor (ambulating, non-ambulating) one observed statistically significant differences between the groups of patients on NSA (Fig. 5) and FT (Fig. 6). In our opinion, the function of gait, and therefore the load upon the hip joints has a tremendous impact on the formation of PF. In the joints, loaded during ambulation, the NSA was within the age-matched range or slightly increased, while in all non-ambulating patients there was a significant increase of NSA, except for one of our female patients who had spastic dislocation and lost gait function. Mean FT indices in non-ambulating patients were also higher than among the ambulating ones. FT was increased in all non-ambulating persons. We examined in detail the ambulating patients with elevated NSA and found that they were either children who just started ambulating and, accordingly, loaded the joints, or children who had phenotypic signs of connective tissue dysplasia. This allows us to say that in ambulating patients with CP, NSA is within the age-matched limit, and increased NSA (coxa valga) among them is formed in the absence of gait function and in connective tissue dysplasia in ambulating patients. The age, when children with CP start ambulating, also matters.

Analyzing the factor of adductors myotomy in the medical history we revealed its statistically significant effect upon NSA and no statistically significant effect upon the FT. The lack of a standardized approach and a clear protocol for the examination of patients with CP, the usage of exclusively clinical indications for adductor myotomy without taking into account the bone pathology of the hip joint often leads to impaired lower extremity function in ambulating patients. Although the change in the balance of forces in the hip joint due to the weakening of the adductor muscles still had an influence on the formation of NSA.

Unexpectedly, there was no difference in NSA and FT indices in groups of patients with DDH and patients born with healthy hip joints confirmed by hip joints' radiographs of the in infancy. That is why we believe that the factor of DDH does not affect the formation of PF in patients with CP. These data may lead to controversy due to the small sample's size, as well as the lack of data on whether DDH was treated before the age 1 year.

Given that 3 joints had normal FT according to age in patients with CP, we analyzed them in detail and found no hallmarks and nothing in common. Pathological FT is observed in most patients with CP.

Data on the influence of different factors upon PF can be used in the planning of surgical interventions on the hip joint. Since no increased NSA was observed in ambulating patients, attention should be paid to increased FT, which in turn gives a projectional misconception of NSA pathology in the standard anterior-posterior radiograph of the hip joints and can lead to diagnostic errors.

## CONCLUSIONS

We have revealed a statistically significant influence of factors of age ($F = 5.58$, $p = 0.0005$), GMFCS level ($F = 15.62$, $p = 0.0001$), ambulatory status ($F = 34.63$, $p = 0.0001$), adductor myotomy ($F = 4.95$, $p = 0.028$) and lack of statistical significance concerning the influence of factors such as level of lesion ($F = 2.23$, $p = 0.11$) and developmental dysplasia of the hip ($F = 0.84$, $p = 0.36$) upon the indices of NSA. Femoral torsion's parameters were in statistically significant fashion affected by GMFCS levels ($F = 3.45$, $p = 0.036$), ambulatory status ($F = 6.52$, $p = 0.013$), level of lesion ($F = 6.11$, $p = 0.003$), and did not display statistical significance of factors of age ($F = 0.71$, $p = 0.59$), adductor myotomy ($F = 0.095$, $p = 0.75$), developmental dysplasia of the hip ($F = 1.33$, $p = 0.25$).

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ORIGINAL ARTICLE

# ANATOMICAL VARIATIONS OF THE PARIETAL FORAMEN AND ITS RELATIONS TO THE CALVARIAL LANDMARKS: A CROSS-SECTIONAL CADAVERIC STUDY

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## ABSTRACT

**The aim:** Estimate the prevalence of the parietal foramen in the adult human skulls of Ukrainian origin, and study its morphology and relationships to main anatomical landmarks of the skull.

**Materials and methods:** A cross-sectional observational study of PF was conducted with 42 random cadaveric adult human skull roofs (calvaria) collected from the laboratory and museum of Human Anatomy Department, Kharkiv National Medical University, Ukraine. The patency and the length of the PF canal were determined, and PF external/internal diameters and the distance to the calvarial landmarks from PF were measured using the caliper. Mean and standard deviation were calculated to compare with the existing data.

**Results:** In the present study 85.7% (n = 36) of the calvaria had the PF, 54.8% (n = 23) had bilateral location of PF, 30.9% (n = 13) had unilateral presence of PF (right side: 23.8%, n=10 and left side: 7.1%, n=3), and 14.3 % (n = 6) demonstrated bilateral absence of PF.

**Conclusions:** An anatomical variation in parietal foramen is not uncommon, and the differences can be based on multiple factors like geography and race. It is important to have detailed information on anatomical variations in different population groups to facilitate surgical and radiological interventions.

**KEY WORDS:** Parietal Foramen, Parietal Bone, Skull, Calvaria, Anatomical Variations

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## INTRODUCTION

Gaining new knowledge and establishing patterns of variability in cranial foramina, especially those that are small in size and significantly variable in their topography, their presence, and content, is important in areas such as neurosurgery, maxillofacial surgery, three-dimensional diagnosis, and minimally invasive interventions [1, 2].

It is known that the calvaria and the skull base contain numerous openings permeated with vital vascular or nerve formations. Detailed knowledge of the anatomy of these holes is important not only for understanding the local topography but also for the differentiation of normal and potentially anomalous structures [1, 3, 4]. Many researchers believe that misunderstanding variations in such formations leads to frequent damage to blood vessels or nerves during active manipulation of tools around the areas with cranial foramina [5, 6]. Detailed anatomy of the emissary foramina is important for understanding epilepsy and risk factors for seizure development [7, 8].

Particularly important and vulnerable in such cases are the foramina of the skull, through which the emissary veins pass, connecting the dural venous sinuses, diploic canals, and extracranial veins of the head [9]. Also in such openings, the arterial branches participating in the blood supply of the dura mater can pass [10].

The parietal foramen (PF) is one of these important emissary openings that have practical significance. The PF contains the emissary vein, which connects the superficial veins of the head and superior sagittal sinus and has a bilateral drainage function, which in pathological conditions can be a way for infection [11]. In addition, there is a vessel that forms an arterial anastomosis with the middle meningeal artery and branches of the superficial temporal artery [11, 12]. This arterial anastomosis can be a source of significant bleeding in case of a craniotomy in the parietal area [13].

## THE AIM

To estimate the prevalence of PF in the adult human skulls of Ukrainian origin, and to study their morphology and relationships to main anatomical landmarks of the skull.

## MATERIALS AND METHODS

We aim to estimate the prevalence of PF in the adult human skulls of Ukrainian origin, study their morphological varia-

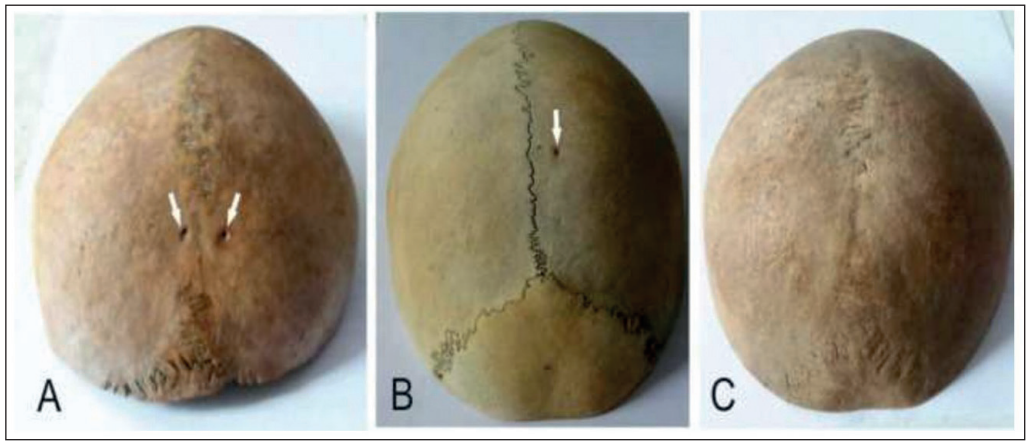


**Fig. 1.** Picture showing the dry cranial roofs in the present study (A) The bilateral location of the parietal foramen. (B) The unilateral location of the parietal foramen. (C) The cranium without the parietal foramen.

**Table I.** Table showing the morphological characteristics of the parietal foramina (PF) in the cadaveric adult human skull roofs (calvaria) of the Ukrainian origin

| PF (Physical attributes) | Side | Samples | Mean ± Standard Deviation (mm) | Range (mm) | Confidence Interval (95%) | p-value |
|---|---|---|---|---|---|---|
| External Diameter | Right | 33 | 1.7±0.6 | 0.5 - 3.0 | 1.49 to 1.91 | P < 0.0001 (t= 6.830) |
| | Left | 26 | 2.7±0.5 | 1.0 - 2.7 | 2.51 to 2.89 | |
| Internal Diameter | Right | 33 | 1.0±0.6 | 0.4 - 2.5 | 0.795 to 1.21 | P = 0.4679 (t= 0.731) |
| | Left | 26 | 1.1±0.4 | 0.5 - 1.8 | 0.946 to 1.25 | |
| Length of the canal | Right | 33 | 5.4±1.7 | 2.0 - 8.0 | 4.75 to 6.05 | P = 0.0429 (t= 2.071) |
| | Left | 26 | 6.3±1.6 | 3.0 -10.0 | 5.68 to 6.92 | |

**Table II.** Table summarizing the distance between parietal emissary foramina (PF) and main calvarial landmarks in the cadaveric adult human skull roofs (calvaria) of the Ukrainian origin

| PF-main calvarial landmarks | Side | Samples | Mean ± Standard Deviation (mm) | Range (mm) | Confidence Interval (95%) | p-value |
|---|---|---|---|---|---|---|
| PF-bregma | Right | 33 | 86.3±8.5 | 70-99 | 83.4 to 89.2 | P = 0.7043 (t= 0.381) |
| | Left | 26 | 87.2±9.6 | 62-99 | 83.5 to 90.9 | |
| PF-vertex | Right | 33 | 43.7±12.9 | 20-65 | 39.3 to 48.1 | P = 0.6635 (t= 0.437) |
| | Left | 26 | 45.2±13.3 | 21-77.5 | 40.1 to 50.3 | |
| PF-lambda | Right | 33 | 35.7±11.1 | 22.5-62 | 31.9 to 39.5 | P = 0.8890 (t= 0.140) |
| | Left | 26 | 36.1±10.6 | 24-61 | 32.5 to 39.7 | |
| PF-obelion | Right | 23 | 7.2±3.2 | 1.0-12.5 | 5.89 to 8.51 | P=0.966031 (t= 0.04) |
| | Left | 23 | 7.4±3.4 | 1.0-14.0 | 6.01 to 8.79 | |

tions, and establish anatomical relationships to other major landmarks. A cross-sectional observational study was conducted for this purpose taking 42 random cadaveric adult human skull roofs (calvaria) of Ukrainian origin collected from the laboratory and museum of Human Anatomy Department, Kharkiv National Medical University, Ukraine. The exact gender and age of the specimens were not determined. The skulls and bones with visible pathological changes and apparent deformities at the cranial roof were excluded from the study.

The specimens were examined, and the presence of PF was described. The patency and the length of the canal were determined with a standard metal probe. The external and internal diameters of the foramina were measured with the caliper, and the distance from PF to the important calvarial landmarks – craniometrical points obelion, bregma, lambda, and vertex were additionally measured. Mean and standard deviation were calculated to compare with the existing data.

## RESULTS

Among 42 calvaria, 85.7% (n = 36) of the calvaria had visible PF located close to the posterior 1/2 of the sagittal suture. Out of all specimens, 54.8% (n = 23) had bilateral location of PF, 30.9% (n = 13) had unilateral presence of PF (right side: 23.8%, n=10 and left side: 7.1%, n=3), and 14.3 % (n = 6) demonstrated bilateral absence of PF (Fig.1).

The external and internal diameters and length of the PF were measured both on the right and left sides (Table I).

**Table III.** Table summarizing the incidence of the parietal foramen in different populations as observed and reported by various authors and the present study

| Authors | Incidence (%) | | |
|---|---|---|---|
| | Overall | Unilateral | Bilateral |
| Boyd, 1930, [21]. | 60.4 | 35.9 | 19.9 |
| Wysocki et al., 2006, [14]. | 60 | - | - |
| Yoshioka et al., 2006, [15]. | 50 | 20 | 40 |
| Mann et al., 2009, [16]. | 79.6 | 34.3 | 45.3 |
| Murlimanju et al., 2015, [12]. | 71.5 | 32.7 | 55.2 |
| Gangmei et al., 2018 [17] | 91.7 | 29.2 | 62.5 |
| Naidoo et al., 2020 [22] | 68 | 35 | 32 |
| Liu et al., 2021, [23]. | 82.86 | - | - |
| de Souza Ferreira et al., 2021, [25]. | 84.3 | 39.0 (in females)<br>30.0 (in males) | 44.7 (in females)<br>54.9 (in males) |
| Present study | 85.7 | 30.9 | 54.8 |

The range of the external diameter was 0.5-2.7 mm, and the mean was 1.7±0.6 mm and 2.7±0.5 on the right and on the left sides respectively. The internal diameter was from 0.4 mm to 2.5 mm with the mean of 1.0±0.6 mm on the right and 1.1±0.4 mm on the left. The mean external diameter was greater than the internal diameter in both the right ($p<0.0001$) and left ($p < 0.0001$). Both the external and internal diameters appeared to be larger on the left than on the right, but only the differences in the external diameters were significant ($P < 0.0001$, $t= 6.830$).

The length of the canal was established with a wide range of 2.0-10.0 mm with the mean 5.4±1.7 mm on the right and 6.3±1.6 mm on the left side. Also, the length of the PF canals was significantly higher in the left than the right halves of the calvaria ($P = 0.0429$, $t= 2.071$).

We also estimated the amplitude of the distance between the main landmarks of the calvaria and the PF. The distance from the PF to obelion was measured among the group of specimens with the bilateral presence of the PF ($n = 23$). This dimension had a wide range from 1.0 mm to 14.0 mm without significant difference on the sides (7.2±3.2 mm on the right and 7.4±3.4 on the left side, $P=0.966031$, $t= 0.04$). The range of distance between PF and bregma was 62.0-99.0 mm and the mean distance from PF to bregma was 86.3±8.5 mm and 87.2±9.6 mm on the right and on the left respectively. The distance of the PF from lambda ranged 22.5-62.0 mm with an established mean of 35.7±11.1 mm on the right and 36.1±10.6 mm on the left side. And the distance from the PF to the vertex had a range from 20.0 mm to 77.5 mm and the mean distance between the PF and vertex was 43.7±12.9 mm on the right and 45.2±13.3 mm on the left side. There was no significant difference between the PF and mentioned cranial landmarks depending on the right or left side (Table II).

## DISCUSSION

Evaluating the prevalence of PF we have to take into account existing data that parietal foramen is found in more than half of the population and variations in these foramina is based on multiple factors like geography and race [14, 15]. In the present study, more than 4/5 of samples (85.7%) had PF, comparable to the prevalence observed by Mann [16] and Gangmei et al., [17], but other researchers reported significantly lesser prevalence (Table III). These foramina were located alongside the sagittal suture at its middle or posterior third. Bilateral localizations were the most common, although they may be present on either side or sometimes completely absent [18]. Slightly more than half (54.8%) of our samples had bilateral foramen similar to the study reported by Murlimanju et al., [12]. As we can see from different reports, bilateral localization is more common than unilateral (Table III). It is believed, that the diversity in the location of PF can be attributed to the differences in the process of ossification of the anterior fontanels [19, 12].

Different study populations had reported variable PF diameter, but the abnormally large diameter is uncommon and rarely reported [13, 20]. Diameters are usually found to be larger in people from Australia and New Zealand [21]. Similarly, the shape of the parietal foramina may be round, oval, or slit-like [13, 14]. The dimensions of the foramen and its distance from the sagittal midline affect the shape of the foramina in the relevant area [19]. Variability can be explained by differences in the ossifications as mentioned earlier.

In the present study, we observed the diameter of PF ranging 0.5 – 3.0 mm which is similar to earlier reports. Boyd has found the average size of the PF about 0.5 mm with rare cases larger than 1.5 mm [21]. In the other study, reported by Wysocki et al., the average size found was twice as major in female skulls (3 mm) than in males (1.5 mm) and a range was from 0.38 to 16.8 mm, and sexual dimorphism in the parietal ossification was suggested [14]. The study of Naidoo et al., recorded a mean diameter of 1.55 mm, with a range of 0.74–3.08 mm [22]. Similarly, Liu et al. reported that the mean diameter of the PF on the left and right sides were 1.02±0.72 mm and 1.07±0.67 mm, respectively, and the diameter of the PF on the sagittal suture was 1.77±0.44 mm [23].

The canal between the external and internal openings of the PF was found to have a twisted course. In our samples, the length of the canal on the left was also greater, especially when it followed the inclined course. There is a lack of data regarding this parameter in the literature.

PF is usually enlarged by intracranial space-occupying lesions as they behave like a safety valve to maintain the internal pressure [12]. The practical significance of PF foramina is important because of the emissary vein, which passes through it and connects superficial veins of the head and superior sagittal sinus. Although not frequently present, this vein basically functions as drainage and is a potential pathway for the inward spread of the infection [21, 16, 24]. In addition, they also transmit blood vessels that form an arterial anastomosis between the middle meningeal artery and branches of the superficial temporal artery [10]. It is important to remember that in the case of the parietal craniotomy these blood vessels can cause significant bleeding leading to high morbidity and mortality [6].

Regarding the topography of the PF, our study showed that the most common location of the PF was at the sides of the sagittal suture, middle of the distance between the craniometric points vertex and lambda (Table II). The maximum distance was observed between the PF and the point of bregma (86.3±8.5 mm on the right and 87.2±9.6 mm on the left), and the minimal distance was between PF and the obelion (7.2±3.2 mm on the right and 7.4±3.4 mm on the left) (Table II). Similar data were published by de Souza Ferreira et al., which stated that parietal foramina are located in the proximity of the sagittal suture (male 7.1 ± 2.5 mm vs. female, 7.4 ± 2.7 mm) [25].

This relevant information and characteristics can be used to determine the zone of possible localization of the emissary vessels to avoid accidental damage to these structures and prevent subsequent complications during surgical interventions. Unfortunately, we couldn't make a sufficient comparison as there was a dearth of literature. We believe that our data helps to complement this gap, prove useful in further study, and provide practical application.

## CONCLUSIONS

An anatomical variation in parietal foramen is not uncommon, and the differences can be based on multiple factors like geography and race. Detailed anatomical knowledge based on the accumulation and comparison of a large amount of data from different populations for a comprehensive study of the emissary foramina will certainly improve the diagnosis, treatment, and prevention of various pathological conditions of the scalp region. We recommend that regional studies and information be collected and analyzed to incorporate them into different clinical procedures for optimal patient outcomes.

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ORIGINAL ARTICLE

# INDICATORS OF ENDOTHELIAL DYSFUNCTION, MARKERS OF INFLAMMATION AND LIPID METABOLISM IN PATIENTS WITH HYPERTENSION WITH THE ADMINISTRATION OF QUERCETIN

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## ABSTRACT

**The aim:** To improve the effectiveness of treatment of patients with hypertension using metabolic therapy based on the evaluation of endothelial dysfunction indicators, markers of inflammation, and blood lipid spectrum.

**Materials and methods:** A clinical study was performed with 72 patients (34 male and 38 female) with stage 2 arterial hypertension of 2-3 degrees, admitted to the cardiology department of the municipal non-profit enterprise "Lviv Emergency Clinical Hospital". The mean age of patients was 44.8±8.5 years. Patients were divided into 2 groups: Group I was taking quercetin in addition to basic therapy (Ramipril/Amlodipine in individually adjusted dose); Group II – had basic therapy following the clinical protocol. The level of nitric oxide, IL-1, IL-6, TNF-a, CRP, seromucoid, blood lipid spectrum was determined.

**Results:** There is a significant decrease in the NO and CRP levels. There is a decrease in the TNF-a level by 31.27±2.13 ($p<0.01$) after the treatment of patients with hypertension. The TNF-a level decreased by 22.2±1.13 ($p<0.01$) with the use of basic therapy. IL-1 decreased significantly in the two groups, but it was more pronounced in group I, by 40.68±1.67 ($p<0.01$) and 21.4±2.1 in group II ($p<0.05$). There is a positive change in the blood lipid spectrum, but the changes were more pronounced in the group of patients receiving metabolic therapy.

**Conclusions:** The use of quercetin (Corvitin, Quertin) in combination therapy with the combined antihypertensive drug containing ramipril/amlodipine (Egis-Hungary) significantly reduces the levels of nitric oxide, CRP, IL-1, and blood lipid spectrum, which reduces the incidence of complications and progression of hypertension.

**KEY WORDS:** endothelial dysfunction, TNF-a, IL-1, IL-6, CRP, lipid spectrum, hypertension, amlodipine, ramipril, quercetin

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## INTRODUCTION

Systemic endothelial dysfunction (ED) is a risk factor of cardiovascular complications in various diseases. There is a stable relationship between indicators of endothelial damage and coagulation disorders, atherogenesis, and the level of proinflammatory cytokines [1-4]. Arterial hypertension is one of the most important factors of atherosclerosis, the inalienable conditions of which are oxidative stress, endothelial dysfunction, and low-grade inflammation, which remains a leading cause of death all over the world [5].

ED is considered as the main mechanism of formation of hypertension and its complications [6]; it is involved in the pathological process in the earliest stages of hypertension [7]. The term "endothelial dysfunction" should primarily be understood as changes in the functional state of the endothelium, which is a response to external stimuli and have protective functions [8]. However, prolonged exposure to pathogenic factors leads to a gradual development of endothelial dysfunction, which is expressed in an imbalance between mediators, which normally provide the optimal course of all endothelium-dependent processes [9] between hypertension and atherothrombotic cardiovascular complications.

The endothelium is one of the systemic "target organs" in hypertension, damage to which plays an important role in the development of cardiovascular complications. The mechanism of endothelial involvement in the onset and development of various pathological conditions is many-sided and associated not only with the regulation of vascular tone but also with participation in the process of atherogenesis, thrombosis, protection of the vascular wall integrity. The endothelium performs a barrier function to maintain homeostasis by maintaining a dynamic balance among several multidirectional processes of vascular tone regulation (vasodilation/vasoconstriction), anatomical structure and remodeling of blood vessels (synthesis/inhibition of proliferation factors), local inflammation (production of anti-inflammatory factors, regulation of vascular permeability, leukocyte adhesion processes), hemostatic and thrombolytic processes (synthesis and inhibition of platelet aggregation factors and fibrinolysis) [10].

Depletion and changes in endothelial function occur with prolonged exposure to various factors (hemodynamic overload, hypoxia, intoxication, inflammation). Decreased nitric oxide concentration causes vasocon-

striction, stimulation of platelet aggregation, adhesion of platelets and leukocytes, growth and proliferation of smooth muscle cells [11]. In this case, the intensive production of peroxide radicals disturbs the balance between protective and damaging effects on the vessel wall, which realize their harmful effects due to the intensification of oxidative stress processes. The formation of superoxide anion and endothelin-1 is the consequence of this [12]. All these changes provoke the development of local and systemic complications that contribute to the accumulation of lipids in the subendothelial space, where chemical modification of low-density lipoprotein (LDL) can occur.

Modified LDL attract monocytes into the vascular wall, where they turn into macrophages, absorb modified lipoproteins. Unregulated uptake of modified LDL leads to the formation of large foam cells characteristic of fatty streaks, which subsequently lead to the progression of atherosclerosis [13].

The failure of the hemostasis system plays a certain role in a complex system of mechanisms that contribute to the development of atherosclerotic changes in blood vessels [10]. Atherosclerotic and associated inflammatory vascular lesions increase platelet activity, their readiness for aggregation and adhesion, activate plasma coagulation factors such as fibrinogen, and inhibit the anticoagulant system and fibrinolysis [14].

NO deficiency is one of the defining elements of endothelial dysfunction. NO is a signaling molecule involved in the regulation of several physiological processes, such as vasodilation, transmission of nerve impulses, and the immune response. NO affects vascular tone, proliferation and apoptosis, regulation of oxidative processes. NO has angioprotective properties [15], is responsible for anti-inflammatory effects, such as inhibition of the expression of cell adhesion molecules ICAM-1 (intercellular adhesion molecules-1), VCAM-1 (vascular cellular adhesion molecules-1), and tissue factor; inhibition of the chemokine release, such as MCP-1 (monocyte chemoattractant protein-1). NO blocks platelet aggregation and has a fibrinolytic effect [16].

The substrate for NO synthesis is a flavonoid – quercetin, which can reduce the activation and adhesion of leukocytes and platelets to the vascular endothelium, inhibits the synthesis of VCAM-1 and MCP-1 adhesion proteins, thus preventing the formation and development of atherosclerotic plaques, inhibits the synthesis of endothelin-1, which is a powerful vasoconstrictor and stimulator of proliferation and migration of smooth myocytes of the vascular wall. It has pronounced antioxidant, antiradical, membrane-stabilizing properties, antiplatelet effect, prevents an increase of potassium level in cells, has a vasoprotective effect, inhibits protein kinase, has a pronounced cardioprotective activity [17].

## THE AIM

To improve the effectiveness of treatment of patients with stage 2 arterial hypertension, 2-3 degrees using metabolic therapy based on the evaluation of endothelial dysfunction indicators, inflammatory activity, and lipid metabolism.

## MATERIALS AND METHODS

A clinical study was performed with 72 patients with stage 2 arterial hypertension of 2-3 degrees, admitted to the cardiology department of the municipal non-profit enterprise "Lviv Emergency Clinical Hospital". Randomization was performed using random numbers. The results of NO concentration, CRP, seromucoid, IL-1, IL-6, TNF-α levels, and lipid spectrum in blood and serum of patients with stage 2 hypertension of 2-3 degrees are presented. 72 patients (34 male and 38 female) were examined. The mean age of patients was 44.8±8.5 years. The study groups did not differ in age composition, severity of disease and other outcomes that could affect the final results of the study. The study did not include patients with severe cardiac, hepatic, and renal failure, cancer, alcoholism, or drug addiction. The study was approved by the local bioethics committee and conducted in accordance with the principles of the Declaration of Helsinki. The patients were given general clinical and instrumental examination methods, they were determined the indicators of proinflammatory cytokines (interleukin-1β (IL-1β), interleukin-6 (IL-6), necrosis factor of alpha tumors (TNF- α)), C-reactive protein (CRP), nitrogen oxide (NO) and seromucoid. Examination of patients was performed on entry to the hospital.

Hypertensive patients received basic combination antihypertensive therapy using ramipril/amlodipine in individually adjusted doses: 5/5; 5/10; 10/5; 10/10, in combination with metabolic therapy with quercetin – corvitin at a dose of 0.5 g dissolved in 50 ml of isotonic sodium chloride solution IV b.i.d. after 12 hours for 5 days; the following 30 days of outpatient treatment, patients received quertin 40 mg t.i.d. orally.

Patients were divided into 2 groups: Group I (study) including 39 patients with stage 2 hypertension of 2-3 degree taking quercetin in addition to basic therapy; Group II (comparison) including 33 hypertensive patients who received basic therapy following existing standards. The study was performed three times: 1st time – on admission; 2nd time – on the day of discharge (on 10th – 12th day of inpatient treatment), 3rd time – on 30th day after the end of treatment with quertin.

Evaluation of total cholesterol and lipid fractions was performed using the enzyme-linked immunosorbent assay (ELISA) on the FP-900 analyzer (Finland), latex turbidimetric immunoassay was used in the laboratory of MNE "LECH" to study the CRP, seromucoid levels. A set of BMS810F reagents, manufactured by MedSystems GmbH – Austria, was used for ELISA of the IL-1; IL-6, TNF-a levels.

Statistical processing of the results was performed using Microsoft Office Excel 2007 and "Statistica 10.0". The reliability of the results was assessed using nonparametric and Student's t-test. The difference was considered significant ($p<0.05$).

**Table I.** Dynamics of changes in TNF-α, IL-1, IL-6, CRP, NO, and seromucoid in patients with hypertension.

| Indicator | Patients receiving basic and metabolic therapy, n=39 | | Patients receiving basic therapy, n=33 | |
|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment |
| TNF-α, pg/ml | 52.56±1.23 | 36.41±1.17 ** | 51.72±1.21 | 40.35±1.18* |
| IL-1, pg/ml | 76.14±3.93 | 45.16±2.78 * | 75.6±3.2 | 59.40±3.5 |
| IL-6, pg/ml | 19.41±1.35 | 14.03±1.2 | 19.67±1.4 | 17.31±1.3 |
| CRP, mg/L | 8.2±0.21 | 5.1±0.18 * | 9.3±0.34 | 7.4±0.326* |
| Seromucoid, g/L | 0.48±0.12 | 0.36±0.08 | 0.54±0.15 | 0.47±0.04 |
| NO | 50.04±15.1 | 34.51±13.75 * | 48.97±29.84 | 33.79 ± 11.12 |

Note: * — p<0.05, ** p<0.01

**Table II.** Changes in blood lipid spectrum in patients with hypertension

| Indicators, mol/L | Patients receiving basic and metabolic therapy, n=39 | | Patients receiving basic therapy, n=33 | |
|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment |
| Total cholesterol | 6.89±0.82 | 5.39±0.85 | 6.73±0.73 | 5.66±0.73 |
| HDL | 1.15±0.34 | 1.12±0.41 | 1.18±0.4 | 1.16±0.31 |
| LDL | 4.43±0.63 | 3.4±0.64 | 4.24±0.29 | 3.58±0.43 |
| VLDL | 0.97±0.081 | 0.67±0.088 * | 0.95±0.079 | 0.85±0.089* |
| Triglycerides | 2.89±0.38 | 1.92±0.41 | 2.89±0.42 | 2.04±0.39 |
| AI | 4.99±0.95 | 3.81±0.84 | 4.70±0.30 | 3.87±0.38 |

Note: * — p<0.05, ** p<0.01

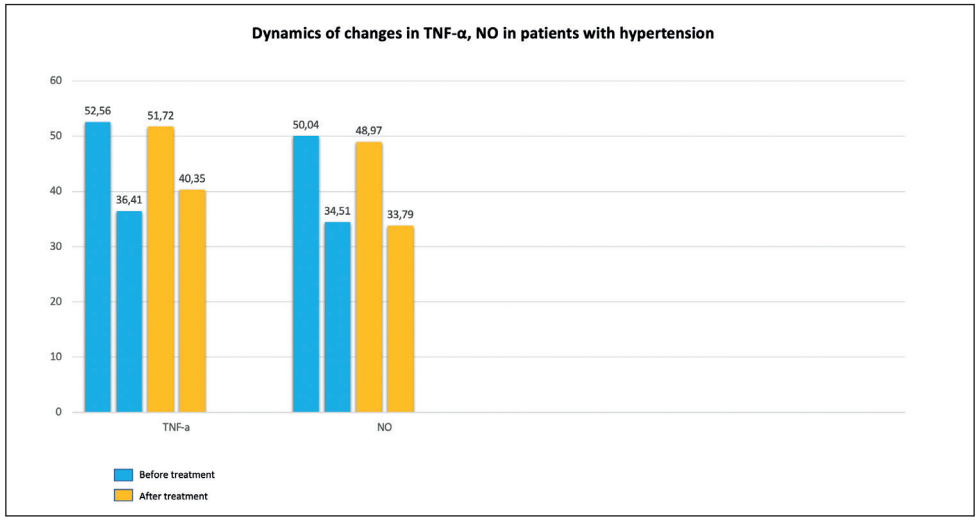


**Fig. 1.** Dynamics of changes in TNF-α. NO in patients with hypertension

## RESULTS

According to the study, patients receiving metabolic therapy have decreased TNF-a level by 31.27±2.13 (p<0.01), while the TNF-a level decreased by 22.2±1.13 using basic therapy (p<0.01). IL-1 decreased significantly in the two groups but it is more pronounced in group I, by 40.68±1.67 (p<0.01) and 21.4±2.1 (p<0.05), respectively. There was a significant decrease in CRP and NO levels, (Tabl. I, fig. 1).

Positive changes were detected in lipid profile after treatment of patients with hypertension, but they were more pronounced in the group of patients who received additional metabolic therapy: the total cholesterol level decreased during treatment by 21.6% (5.29±0.85 after treatment), vs. 13.6% (5.81±0.89) and 15.8% (5.66±0.73) in patients receiving only basic therapy. The LDL level in both groups decreased; in group I, it decreased by 23.6% (3.41±0.56), in group II – by 15.6% (3.59±0.31).

LDL rates decreased significantly by 30.9% (0.67±0.088) compared with the results before treatment in group I, in contrast to group II, where the value decreased by only 10.5% (0.85±0.089).

The triglyceride level tended to decrease in the group of patients who were prescribed metabolic therapy by 33.5% (1.92±0.41); the decrease in triglycerides was less pronounced in the comparison group (group II) – 29.4% (2.04±0.39).

In the evaluation of HDL – significant differences between the indicators of both groups of patients were not observed; HDL increased by 2.5% (1.18±0.28) in the study group of patients taking quercetin, and the HDL level was 1.11±0.32 in the group with basic therapy.

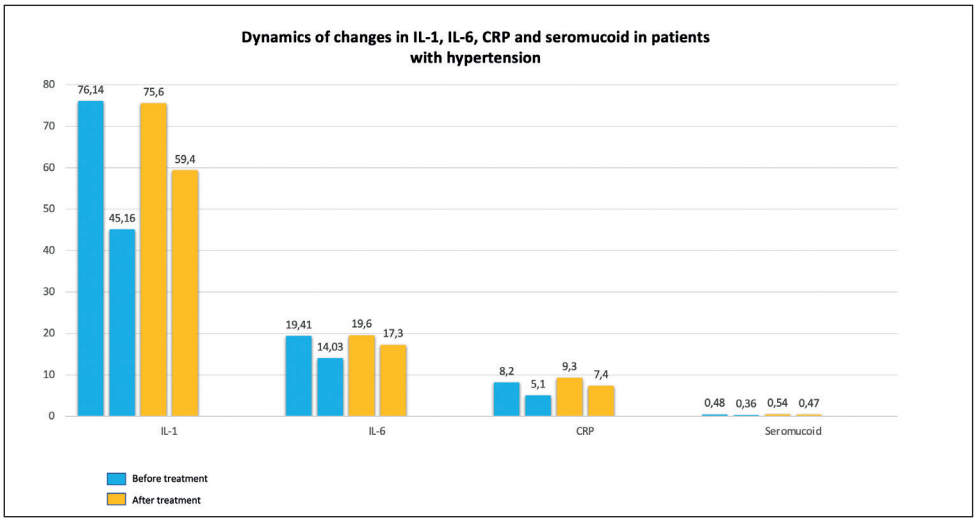


**Fig. 2.** Dynamics of changes in IL-1, IL-6, CRP and seromucoid in patients with hypertension

After the course of treatment, the atherogenic index (AI) decreased by 23.6% (3.81±0.84) and 17.6% (3.87±0.38) in the comparison group, but the level of atherogenic index remained elevated in both groups of patients, (Tabl. II, fig. 2).

## DISCUSSION

Endothelial dysfunction is characterized by inadequate (increased or decreased) formation in the endothelium of various biologically active substances. One of the methods of assessing the severity of endothelial dysfunction is to determine blood factors that damage the endothelium, the level of which correlates with endothelial dysfunction. Such factors include hypercholesterolemia, cytokines (interleukins, tumour necrosis factor (TNF). [18].

ED is the initial stage in the pathogenesis of atherosclerosis. In vitro, a decrease in the N0 production in endothelial cells in hypercholesterolemia. Insufficient N0 synthesis contributes to free radical damage of cell membranes. Oxidized LDL enhance the expression of adhesion molecules on the surface of endothelial cells, promoting monocytic infiltration of the subendothelium. In turn, adequate N0 synthesis inhibits processes in the nucleus of atherosclerotic lesions, including platelet aggregation, monocyte adhesion and migration, vascular smooth muscle cell proliferation, and vasoconstriction [19].

It has been found experimentally that quercetin can directly inhibit major inflammatory mediators by inhibiting histamine secretion and the activity of alloantigen-specific cytotoxic T lymphocytes, IL-8 interleukin, and tumour necrosis factor (TNF-α). High antihistaminic quercetin activity has been clinically confirmed. Quercetin may interact with the calcium-mobilizing polyphosphoinositide system and other elements of this signalling cascade. It modulates many intracellular responses, including the formation and secretion of inflammatory mediators, blood clotting processes, smooth muscle contraction, some immune responses etc.. In preclinical in vitro studies, quercetin showed a significant decrease in the level of inflammatory markers (NO-synthase, COX-2 and C-reactive protein in human hepatocyte cell culture) [20].

Studies have shown that quercetin can act as an arterial vasodilator, particularly in the coronary arteries, by increasing cAMP levels in endothelial cells and inhibiting platelet aggregation [20].

Interest in quercetin as a means of prevention and treatment of COVID-19 has already found a response from many experts taking into account the urgency of the problem. In particular, Dr P. Marik recommends an updated (April 15, 2020) treatment protocol for COVID-19 patients called "Critical Care COVID-19 Management Protocol" (evmc.edu/covidcare) [21].

The use of quercetin in the treatment of patients with hypertension helps to restore the functional state of the endothelium, as it has antihypoxic, membrane-stabilizing, antioxidant properties. Its positive effects are shown in patients with coronary artery disease, hypertension, metabolic syndrome, and associated cardiac conditions, as well as in almost all components of the cardiovascular continuum [2, 4, 6, 7].

## CONCLUSIONS

1. The use of quercetin (corvitin, quertin) in combination therapy with the combined antihypertensive drug containing ramipril/amlodipine significantly reduces the level of nitric oxide, CRP, IL-1, and blood lipid spectrum, which reduces the incidence of complications and progression of hypertension.
2. Quercetin in therapeutic doses has proven efficacy, high safety, and good tolerability, with the absence of severe side effects, which enhances the effectiveness of combination antihypertensive therapy.
3. The use of quercetin (corvitin, quertin) in combination with conventional antihypertensive therapy improves the performance of the endothelium and its NO-synthesizing ability.

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ORIGINAL ARTICLE

# EVALUATION OF THE PATIENTS' SATISFACTION WITH PRIVATE DENTAL CLINICS SERVICES: A QUESTIONNAIRE-BASED STUDY

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## ABSTRACT

**The aim:** To evaluate patient satisfaction with dental care services at Iraqi private dental units

**Materials and methods:** Online questionnaires were sent to 1600 Iraqi people. The questionnaires were composed of four sections: the first section was involved with gathering the demographic information of the participants, and the remaining three sections consisted of twenty-one questions to evaluate the responders' satisfaction with regard to the dentist, treatment, and the dental clinic.

**Results:** The final total of responses was 427 after using the inclusion and exclusion criteria. The distribution of the participants according to the obtained demographic data was as follows: (male 45.4% and female 54.6%), (above 40y 41.7% and less or equal to 40y 58.3%), (employed 52.9% and not employed 47.1%), (postgraduate 29.3%, college graduate 55.7%, and undergraduate 15%), and (enough and exceeding income 4.9%, enough income 51.8%, and less than enough income 43.3%). Only the educational level and the income level appeared to have an effect on the degree of patient satisfaction. Most of the participants complained about the high treatment fees and the long wait in the clinic before receiving treatment.

**Conclusions:** The current study is the first conducted in Iraq to assess dental patient satisfaction. The satisfaction levels differed among the participants, which indicates the need to benefit from the evaluation of patients to improve the quality of treatment service in dental clinics. Future research should be conducted to precisely identify the factors that lead to increased satisfaction of dental patients with their treatment experiences.

**KEY WORDS:** patient satisfaction, Iraq, dental care

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## INTRODUCTION

The dental patient satisfaction expresses the experience during his presence in dental units to receive treatment within or exceeds his expectations [1, 2]. Dental service providers are placing great attention on evaluating patient satisfaction. Dental clinics are interested in the patient's feedback to improve the quality of services to make them among the patient's first choices when treatments are needed and sustain the continuity of appointments with the same dentist and clinic [3, 4]. Multiple factors have been documented to affect patient satisfaction [5]. The dentist's conduct and professionalism play a vital role in the patients' satisfaction. Providing high standard treatment, communicating professionally with the patient to reduce the tension and fear generated before taking the treatment, identifying the patient's complaint, clarifying the appropriate choices for treatment regarding the condition, and providing subsequent follow-up. These points were seen as having an effective role in obtaining a positive feedback evaluation from the patient [6-9]. The management and design of dental clinics are essential factors for patient satisfaction. Providing multiple ways of communication with the clinic for arranging appointments to avoid the long waiting for of the patient, and the comfortable environment of the clinic with safety and privacy measurements, all of these criteria have a great impact on maintaining the patient's interest in receiving clinic services [10-12]. Despite the different cultural, socioeconomic, and educational levels among individuals, several studies have been made to assess the satisfaction regarding dental services among patients and define the aspects that the clinic needs to enhance and develop [13, 14].

## THE AIM

The study aimed to evaluate the degree of satisfaction with dental care among dental patients at Iraqi private dental clinics and determine the factors associated with the level of satisfaction.

## MATERIALS AND METHODS

### STUDY DESIGN

The cross-sectional study was based on an online questionnaire. The study was approved by the ethical committee of Dijhla university of college and carried out for three weeks (3/9/2021 to 18/9/2021). The constriction of the

**Table I.** Questions to evaluate the satisfaction of the participants with the dentist, treatment, and clinic.

| No. | Question |
|---|---|
| **Section two: The responders opinion about the dentists.** | |
| Q1 | The Dentist was professional. |
| Q2 | The dentist was friendly with me. |
| Q3 | The dentist tried to limit my fear and anxiety. |
| Q4 | The dentist listen to my complain carefully. |
| Q5 | You was gave all the treatment choice alternatives. |
| Q6 | The selected procedure of the treatment was explained by the dentist. |
| Q7 | The dentist did not ask me the personal question during offering care. |
| Q8 | The dentist gave me the required instructions after the treatment. |
| **Section three: The responders opinion about the treatments.** | |
| Q9 | The treatment was not painful. |
| Q10 | I was received good quality treatment. |
| Q11 | The Dental instruments were sterilized. |
| Q12 | The treatment time in each appointment was suitable and acceptable. |
| Q13 | The fees of the treatments were acceptable. |
| **Section two: The responders opinion about the clinic management and design.** | |
| Q14 | The working hours of the clinic were suitable for me. |
| Q15 | The communication with the clinic was easy and various. |
| Q16 | I did not wait for long time to have an appointment. |
| Q17 | Short waiting time inside the clinic to get the treatment. |
| Q18 | The Clinic geographic location was easy to access. |
| Q19 | The waiting area was comfortable and clean. |
| Q20 | The clinic design was insured the privacy during the treatment |
| Q21 | The safety instruction and measurements were found within the clinic |

**Table II.** The responders' demographic information

| Variable | |
|---|---|
| **Gender** | |
| Male | 194 (45.4)a |
| Female | 233 (54.6)a |
| **Age** | |
| Above 40 y | 178 (41.7)a |
| Less or equal 40 | 249 (58.3)a |
| Mean age (y)± SD | 39.01y ± 13,14 |
| Age range | 18y- 76y |
| **Employ status** | |
| Employed | 226 (52.9)a |
| Unemployed | 201 (47.1)a |
| **Educational level** | |
| Postgraduate | 125 (29.3)a |
| college graduate | 233 (55.7)a |
| Undergraduate | 64 (15) |
| **Income level** | |
| Enough and exceed | 21 (4.9)a |
| Enough | 221 (51.8)a |
| Less than enough | 185 (43.3)a |

(a) Frequency (percentage)

questionnaire was based on utilizing the Google platform and the link shared online on Facebook using sponsored ads. The questionnaire was answered anonymously by all responders. The explanation of the aim of the study and the consent section was added to the form before the questionnaire. The agreement to participate was required to accept the response.

## STUDY SAMPLE

The study targeted Iraqi individuals aged over 18 years. The criteria of inclusion were any person with a defined age group. The neglected answers belong to people under 18 and working as dentists. Incomplete answers or those who did not give consent to participate in the study were also excluded. According to official statistics, the number of Iraqi people within the target age group was 20,900,753 [15]. The study sample was calculated by using the following equations:

- Sample Size

(Distribution of 50%) divided by (Margin of Error%/Confidence Level Score) 2

- Confidence level

1.96 (for confidence level of 95%), margin of error=0.05

- True Sample

**Table III.** The distribution of the responses to each question and the overall satisfaction score.

| | Question | Mean ± SD | Strong agree [a] | Agree [a] | Neutral [a] | Disagree [a] | Strong disagree [a] |
|---|---|---|---|---|---|---|---|
| Responders' satisfaction with dentist | Q1 | 3.47 ± 1 | 54 (12.6) | 180 (42.2) | 125 (29.3) | 48 (11.2) | 20 (4.4) |
| | Q2 | 3.77 ± 0.91 | 88 (20.6) | 201 (47.1) | 93 (21.8) | 42 (9.8) | 3 (7) |
| | Q3 | 3.63 ± 0.96 | 69 (16.2) | 197 (46.1) | 103 (24.1) | 48 (11.2) | 10 (2.3) |
| | Q4 | 3.69 ± 0.97 | 70 (16.4) | 232 54.3 | 59 13.8 | 56 13.1 | 10 (2.3) |
| | Q5 | 3.39 ± 1.14 | 58 (13.6) | 186 43.6 | 78 18.3 | 73 17.1 | 32 (7.5) |
| | Q6 | 3.44 ± 1.12 | 59 (13.8) | 198 (46.4) | 64 (15) | 82 (19.2) | 24 (5.6) |
| | Q7 | 3.66 ± 1.1 | 95(22.2) | 192(45.0) | 55 (12.9) | 71 (16.6) | 14 (3.3) |
| | Q8 | 3.81 ± 0.96 | 88 (20.6) | 234 (54.8) | 58 (13.6) | 32 (7.5) | 15 (3.5) |
| Responders' satisfaction with treatment | Q9 | 3.40 ± 1.02 | 40 (9.4) | 198 (46.4) | 102 (23.9) | 66 (15.5) | 21 (4.9) |
| | Q10 | 3.50 ± 1.02 | 49 (11.5) | 216 (50.6) | 78 (18.3) | 67 (15.7) | 17 (4.0) |
| | Q11 | 3.95 ± 0.94 | 116 (27.2) | 222 (52.0) | 52 (12.2) | 24 (5.6) | 13 (3.0) |
| | Q12 | 3.59 ± 1.06 | 70 (16.4) | 211 (49.4) | 69 (16.2) | 57 (13.3) | 20 (4.7) |
| | Q13 | 2.41 ± 1.24 | 30 (7.0) | 65 (15.2) | 73 (17.1) | 141 (33) | 118 (27.6) |
| Responders' satisfaction with administration and environment of the clinic | Q14 | 3.45 ± 1.1 | 59 (13.8) | 193 (45.2) | 84 (19.7) | 64 (15.0) | 27 (6.3) |
| | Q15 | 3.31 ± 1.25 | 63 (14.8) | 182 (42.6) | 60 (14.1) | 70 (16.4) | 52 (12.2) |
| | Q16 | 3.42 ± 1.12 | 55 (12.9) | 202 (47.3) | 65 (15.2) | 77 (18.0) | 28 (6.6) |
| | Q17 | 2.77 ± 1.2 | 30 (7.0) | 108 (25.3) | 95 (22.2) | 121 (28.3) | 73 (17.1) |
| | Q18 | 3.76 ± 0.97 | 78 (18.3) | 237 (55.5) | 63 (14.8) | 31 (7.3) | 18 (4.2) |
| | Q19 | 3.39 ± 1.14 | 58 (13.6) | 193 (45.2) | 64 (15.0) | 83 (19.4) | 29 (6.8) |
| | Q20 | 3.56 ± 1.09 | 69 (16.2) | 209 (48.9) | 60 (14.1) | 68 (15.9) | 21 (4.9) |
| | Q21 | 3.19 ± 1.12 | 35 (8.2) | 177 (41.5) | 78 (18.3) | 106 (24.8) | 31 (7.3) |
| The total satisfaction score (Mean ± SD) | | | | | 3.44 ± 0.68 | | |

(a) Frequency (percentage)

(Sample Size ×Population) divided by (Sample Size+Population−1)

The obtaining finding determined that the study sample was 385 people. The sample population was multiplied by 4 to enable a 25% response rate and avoid the drop back. The final number of the sample included in the study was about 1600 persons.

The questionnaires' design and the scoring system

The online questionnaire was adapted and modified from previous studies [14, 16]. The questionnaire template was translated into the native (Arabic) language. A pilot study was conducted on a group of people (n = 25) of both sexes and of different ages. The goal was to assess the population's understanding of the translated copy and the time needed to finish the questionnaire before conducting the study.

The questionnaire (table I) consisted of four sections: Section one represented the demographic information: age, gender, employment status, education level, and income level. The second section (questions 1–8) aimed to evaluate the degree of satisfaction with the dentist. The third section (question 9–13) was formatted to evaluate the satisfaction degree of treatment. The fourth section (questions 14–21) was designed to evaluate the satisfaction degree regarding the clinic's management and design. The study participants were asked to answer the questions within the last three sections using a five-point Likert scale: (5 = strong agree), (4 = agree), (3 = neutral), (2 = disagree), and (1 = strongly disagree). The sum of the total replies for each question was used to compute the mean for each question, followed by comparing the means of the answers between the demographic variables.

## STATISTICAL ANALYSIS

Descriptive statistics were used to analyze the demographic variables and the responses to each question; the results were shown as mean/standard deviation and frequency/percentage. The inferential statistics included the Mann-Whitney and Kruskal-Wallis tests followed by post hoc; both tests were used to compare the variable with the responders' satisfaction. The statistical significance level was defined at $P < .05$. All statistical analysis was conducted using SPSS software (IBM Corp., SPSS Statistics for Windows, version 23.0).

## RESULTS

A total of 3162 Facebook users viewed the online link for the questionnaire. The total responses were 551 with the inclusion and exclusion criteria; the final dependent responses were 427 over the calculated study sample. Table II summarizes the demographic records. The analysis of each response is presented in Table III. According to responders' satisfaction with the section

**Table IV.** Comparison of the total satisfaction mean score of the responders with the demographic data

| Variable | Mean ± SD | P-value* | |
|---|---|---|---|
| Gender | | | |
| Male | 3.4 ± 0.76 | 0.271 | |
| Female | 3.49 ± 0.61 | | |
| | | | |
| Age | | | |
| < 40 | 3.5 ± 0.69 | 0.205 | |
| ≥ 40 | 3.4 ± 0.68 | | |
| | | | |
| Employ status | | | |
| Employed | 3.4 ± 0.64 | 0.967 | |
| Not employed | 3.4 ± 0.73 | | |
| | | | |
| | | **Comparisons** | **P-value**** |
| Educational level | | | |
| Postgraduate | 3.6 ± 0.59 | (Postgraduate) vs (College) | 0.010 |
| College | 3.4 ± 0.65 | (College) vs (Undergraduate) | 0.611 |
| Undergraduate | 3.3 ± 0.9 | (Postgraduate) vs (Undergraduate) | 0.003 |
| | | | |
| Income level | | | |
| Enough and exceed | 3.7 ± 1.03 | (Enough and exceed) vs (Enough) | 1.00 |
| Enough | 3.6 ± 0.59 | (Enough) vs (Not enough) | 0.00 |
| Not enough | 3.3 ± 0.70 | (Enough and exceed) vs (Not enough) | 0.039 |

*Significant at P < .05 by Mann-Whitney test
**Significant at P < .05 by Kruskal-Wallis test followed by post hoc

that regards the dentist, the dentist's instruction (Q8) had the highest mean score (3.81), and the dentist's professionalism (Q1) appeared to have the lowest mean (3.47). The questions to evaluate the responders' satisfaction with treatment showed that the sterilization of the instruments and equipment (Q11) was registered with the highest mean score (3.95); meanwhile, the cost of the intervention (Q13) had the lowest satisfaction (2.41). Satisfaction with the geographic location of the clinic (Q18) was 3.76, and satisfaction with waiting time (Q17) was 2.77. Both (Q18) and (Q17) are the highest and lowest score meanings for the clinic's satisfaction criteria.

There was no difference in satisfaction between men and women, between employed and unemployed people, or between age groups (<40y and ≥ 40y). A significant difference regarding satisfaction was found between the responders with high and enough income levels and those who mentioned the income was not enough. The postgraduate respondents showed a higher satisfaction degree than the other educational levels. In table IV, the comparison between all variables and the mean score of satisfaction was presented.

## DISCUSSION

Patient feedback is crucial for improving dental services. Patient satisfaction did not depend on the treatment alone, but several aspects played important roles in how the patient described his experience, good or bad [7, 17]. A good dentist's behavior, clinical experience, and communication skills will build continuous and positive dentist-patient relations [18]. The high standards of treatment, which extend from the diagnosis to dentist instructions, always serve the reputation of the clinic among the patients and the community [19]. Although many patients appreciate the afforded services, they are still seeking to minimize the cost of the treatments [20]. Patients always desire the clinic to be easily accessible and its management to be at a high level in terms of the attitude of the dental staff, the reception, and the scheduling of appointments. Patients demand the clinic's infrastructure to be comfortable with attention to safety measurements [21]. The present study was the first to evaluate Iraqi dental patients' satisfaction with private clinics. A series of questions was designed to evaluate the impact of the sociodemographic variables on the participants' perceptions of dental care services. Age groups in the present study showed no satisfaction difference. This finding agrees with previous studies [22-24], although the outcomes of other studies were not agreed with our results. Lahti and his collogues found that older patients were less satisfied with dental care services than younger patients [25]. An alternative study held in the United Kingdom showed that the satisfaction degree was high in the older

group [26]. More studies were needed to evaluate the impact of age on the patients' perception. The satisfaction of both gender in the present study showed no statistical satisfaction difference. The comparison findings of the satisfaction between males and females within previous studies varied. A Group of studies were mentioned that females were more satisfied than male [21, 27], another group of studies showed that no difference was between males and females, this group agreed with our finding [28, 29].The answers related to the job situation were found to have no effect on the difference in satisfaction among the respondents. The educational level and the income level were registered in the current study to affect the satisfaction differences among the participants. The education level was classified into three levels: undergraduate, college, and postgraduate. The present study showed that the increase in the educational level is associated with the raising the degree of satisfaction. The perceptions of the postgraduate group toward dental services at the private clinic were more good than the college and undergraduate groups with a significant difference. People who hold higher degrees after the college certificate may appreciate the treatment services provided and the efforts of the dentist and the clinic staff, the comparison between the educational level groups is similar to the finding of the previous studies [30-32]. The present comparison of the satisfaction between the responders according to the income level showed that the people with sufficient or exceeded salaries were more satisfied than those with insufficient monthly income; this finding was the same in other studies [33, 34]. People whose financial situation is less than acceptable may not have the freedom to choose all the appropriate treatments. Their submission to elective cosmetic treatments may be limited due to the high prices of such treatments. The twenty-one questions of the present study were attempted to assess participants' satisfaction with a dentist, treatment, clinic design and management. These three elements could have an important role on the perception of the patient and affect their decision regarding if they keep the appointment or move to choose another clinic. Two-thirds or more of the respondents agreed or strongly agreed about the tools used within a treatment were sterilized (Q11), and the dentist was listened to the patient complain (Q4) and gave clear instruction after the treatment session (Q8). Only twenty percent of the responders showed a satisfied feeling about the cost of the treatment (Q13). The continued development of the treatments technique requires a new generation of the material and the equipment; consequently, the cost of intervention may raise. The comparison between the private clinic and governed hospitals regarding the fees of the treatment could be found and impact the patients' point of view. The waiting time before moving to the treatment zone appeared in the present study with low satisfaction; about 40% of the responders were given their agreement (Q17). The long waiting time could be attributed to the increase of the appointments and miscalculation of the treatment duration required for each case. The negative opinion of the responders regarding the cost and the waiting time agrees with several studies [24, 35, 36]. The limitations of the current study were that the questionnaire did not reach people who were not on social media during the study period, and in addition, the study did not present open-ended questions to find out if there were other factors not mentioned in the current study that may affect the opinion of the dental patient about the service provided to him.

## CONCLUSIONS

The evaluation of the patient's feedback was essential in the review and measuring the quality of the service provided by private dental care units. The present study showed various satisfaction degrees among the responders. The cost of the treatment and the patient's delay in the waiting room had a bad impression on the patients. Diversifying the treatments in terms of their type and prices may give people with limited income more options to solve their oral problems. Developing the appointment system and a good estimation of the required period for each case, with the development of waiting areas and providing the means to make waiting less weary and boring. The staff at the clinic must do everything they can to make sure all of their patients are satisfied, no matter how well-educated and regardless of their financial circumstances.

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ORIGINAL ARTICLE

# SUBSTANTION OF THE NEED FOR MONITORING IN ENVIRONMENTAL OBJECTS OF INSECTICIDES FROM THE CLASS OF TETRAMIC AND TETRONIC ACID DERIVATIVES TAKING INTO ACCOUNT THEIR SPECIFIC INFLUENCE ON THE HUMAN ORGANISM

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## ABSTRACT

**The aim:** Substantiation of the need for monitoring in environmental objects of spiromesifen, spirodiclofen and spirotetramat, taking into account their specific impact on the human organism to reduce the risk of their negative influence on public health and the environment.

**Materials and methods:** The subject was insecticides, the class of tetramic and tetronic acids derivatives, spiromesifen, spirodiclofen and spirotetramate. Physico-chemical, toxicological and hygienic evaluation of the results was performed according to the literature data. Selection criteria were used to substantiate the needs in monitoring of these insecticides.

**Results:** Spiromesifen, spirodiclofen and spirotetramate according to the Hygienic classification of pesticides by the limiting criterion of hazard belong to 1 class (strong allergen), 2 (carcinogen) and 3 classes (inhalation toxicity), respectively. The value of ADD (allowable daily dose) for human of spiromesifen, approved in Europe is 0.03 mg•kg-1. According to the assessment of hazards for professional contingents and the coefficient of possible inhalation poisoning (CPIP) and the coefficient of selective action (CSA), spiromesifen may pose a risk. We can conclude about the safety of the compound according to GUS, SCI-GROW, LEACH indices, and hence the absence of risk of potential entry of the substance into the human body with contaminated water or food. According to persistence in the environment, these insecticides are law and moderately persistent. Direct effect on the thyroid gland is absent.

**Conclusions:** Monitoring of spiromesifen and spirotetramate in water, soil and agricultural raw materials is not obligatory, and for spirodiclofen is desirable.

**KEY WORDS:** Insecticides, Toxicology, Monitoring, Risk

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## INTRODUCTION

The application of pesticides in agriculture in all countries of the world is now a necessary part of successful crop production and profits with minimal losses [1]. However, the question of uncontrolled and mass chemical plant protection products usage is very acute, given their accumulation and the studied toxic effects on the environment and the human organism [2, 3].

Every year, new modern, more effective formulations appear on the chemical market [4]. Insecticides derived from tetramic and tetronic acids – spiromesifen, spirotetramat and spirodiclofen are among those that have proven themselves in the effective control of pests and are widely used in Ukraine and Europe [5]. This new chemical class combines two mechanisms of action on the warm-blooded animals and humans: induction of liver microsomal enzymes and inhibition of 4-hydroxyphenylpyruvate dioxygenase [5].

Monitoring and risk assessment for the population and professional contingents when consuming and working directly with pesticides is used by all European countries and the United States [6, 7]. However, the vast majority of monitoring models do not take into account specific indices for pesticides that can affect the thyroid gland, cause endocrine disorders and increase the already high level of endocrine pathology, including the thyroid gland, in the world [8].

Therefore, the introduction of monitoring methods is quite relevant, necessary and timely to reduce the risk of adverse effects of the above insecticides on the environment and the human organism.

## THE AIM

The aim – substantiation of the need for monitoring in environmental objects of spiromesifen, spirodiclofen and spirotetramat, taking into account their specific impact on the human organism to reduce the risk of their negative influence on public health and the environment.

## MATERIALS AND METHODS

Representatives of insecticides of tetramic and tetronic acids derivates class were selected for the study: spiromesifen, spirodiclofen and spirotetramate.

**Table I.** Physico-chemical properties of spiromesifen, spirodiclofen and spirotetramate [9, 14, 15]

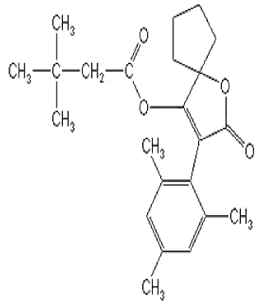
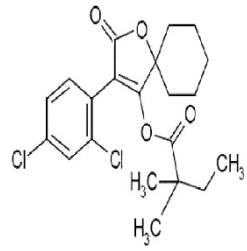
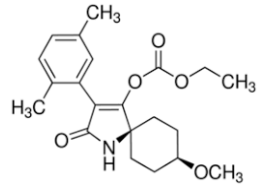
| Index | Spiromesifen | Spirodiclofen | Spirotetramate |
|---|---|---|---|
| Empirical formula | C23H30O4 | C21H24Cl2O4 | C21H27NO5 |
| Relative molecular weight | 370.48 | 411.32 | 373.48 |
| Vapor pressure (at 20 ° C), mPa | 7×10-3 | 3×10-4 | 5,6×10-6 |
| Melting point, °C | 98.0 | 94.8 | 142.0 |
| Solubility in water (at 20 °C), mg·l-1 | 0.13 | 0.05 | 30.0 |
| Partition coefficient n-octanol / water (logKo/w) | 4.55 | 5.83 | 2.51 |
| Chemical formula |  |  |  |
| Solubility in organic solvents, g·l-1 | heptane - 23, acetone, xylene, ethyl acetate - 250 | heptane - 20, acetone, xylene, ethyl acetate -> 250 | ethanol - 44, toluene - 60, acetone -, 100-120, ethyl acetate - 67 |

**Table II.** Selection criteria for monitoring of insecticides

| Index of hazard | Selection criteria | Object for controle | | | |
|---|---|---|---|---|---|
| | | air | water | soil | food products |
| Physico-chemical properties | | | | | |
| Vapor pressure, mPa | >1×10-4 | + | - | - | - |
| Solubility in water, mg·l-1 | >100 | - | + | - | - |
| Soil sorption coefficient (Koc) | <75/>500 | - | + | + | - |
| Toxicological danger | | | | | |
| Class of hazard | I-II клас | + | + | + | + |
| Allowable daily dose (ADD), mg·kg-1 | <0,01 | + | + | + | + |
| Coefficient of possibility of inhalation poisoning (CPIP) | >2,0 | + | - | - | - |
| Selective action coefficient (SAC) | <99 | + | - | - | - |
| Occupational risk (complex, combined) | >1 | + | - | - | - |
| Persistence in the environment and ecotoxicological hazard | | | | | |
| Half-life period (DT50) in soil, day | >30 | - | - | + | - |
| Ecotoxicological hazard (Ecotox) | >0,4 | - | - | + | - |
| DT95 in water, day | >10 | - | + | - | - |
| Ground ubiquity score (GUS) | >1,8 | - | + | - | - |
| Risk of pesticides intake with water in case of their leaching from soil to groundwater | >1 | - | + | - | - |
| DT50 in agricultural raw materials, day | >14 | - | - | - | + |

The main physical and chemical properties are given in the Table I [9].

The criteria proposed in [10, 11, 12] for fungicides and adapted for insecticidal compounds were used to preliminarily assess the need to monitor the proposed substances in the environment.

The selection criteria for monitoring insecticides (on example of spiromesifen) include the physicochemical properties of the compound, toxicological and ecotoxicological hazards, and, of course, stability in the environment (Table II).

The coefficient of sorption (Koc) of spiromesifen in the soil is 30,900, the allowable daily dose (ADI) is 0.03 $mg \cdot kg^{-1}$ [9].

According to the literature [9], the half-life period ($DT_{50}$) in the soil of spiromesifen is 4.1 days, $DT_{50}$ in water – 0.3,

**Table III.** Selection of investigated insecticides for hygienic monitoring [5, 9, 14, 15, 18]

| Compound | Index name and value (score in points) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Allowable daily dose (ADD), mg/kg | Class of hazard according to State Standards 8.8.1.002-98 | Impact on the thyroid gland as a target organ | The severity of pesticide-induced tyrosinemia (plasma tyrosine levels, nmol/ml) | Half-life period (DT50) in soil, day | Half-life period (DT50) in water, day | Half-life period (DT50) in plants, day | the Groundwater and Surface Water Pollution Index (LEACH), units | Screening of maximum pesticide concentration in groundwater (SCI-GROW), μg·l-1 | Integrated index of pesticides contaminated water consumption (IIPCWC) | Integrated index of pesticides contaminated food consumption (IIPCFC) | Total score |
| Spiromesifen | 0,03 (1) | 1 (4) | Weak effect in animal experiments (2) | <300 (1) | 4,1 (1) | 0,15 (1) | 2,0 (1) | 0,00002 (1) | 5,35×10-3 (2) | 3 (1) | 4 (1) | 16 |
| Spirodiclofen | 0,001 (4) | 2 (3) | Weak effect in animal experiments (2) | <300 (1) | 7,0 (1) | 0,7 (1) | 10,1 (2) | 0,00001 (1) | 5,35×10-3 (2) | 6 (2) | 8 (3) | 20 |
| Spirotetramate | 0,05 (1) | 3 (2) | Weak effect in animal experiments (2) | <300 (1) | 0,19 (1) | 0,78 (1) | 3,0 (1) | 0,01972 (2) | 2,05×10-4 (2) | 4 (1) | 4 (1) | 15 |

$DT_{50}$ in agricultural raw materials is 2.0 days. The value of GUS (ground ubiquity score) is equal to 0.06.

Given that compounds of this class can affect the functioning of the thyroid gland [5], an assessment of the need for their monitoring was carried out taking into account this feature according to the criteria given in [13].

## RESULTS

According to the generalized data of the literature [5, 14, 15] new chemical compounds – insecticides of the tetramic and tetronic acids derivates class – spiromesifen, spirotetramat and spirodiclofen have two types of effects on warm-blooded animals and humans: induction of microsomal liver enzymes and inhibition of 4-hydroxypyruvate dioxygenase.

All three active substances, according to the Hygienic classification of pesticides according to the degree of hazard (StateStandard 8.8.1.002-98) [16], by the acute oral and dermal toxicity belong to the 4th class of hazard, and inhalation toxicity – to the 3rd class of hazard [5, 14, 15]. Spiromesifen, same as spirodiclofen, is not an irritant to the skin and mucous membranes of the eyes – hazard class 4. Spirotetramate [5, 14, 15] by irritating effect on the skin also belongs to the 4th class of hazard, but by irritating effect on mucous membranes belongs to the 3rd class (slightly irritating). Spiromesifen, in contrast to spirodiclofen (hazard class 2) and spirotetramate (hazard class 3), is a strong allergen – hazard class 1. According to mutagenic activity, all substances belong to the 4th hazard class. Spirotetramate [5, 14, 15]is not a carcinogen – hazard class 4, in contrast to spiromesifen – hazard class 3 and spirodiclofen – hazard class 2. According to embryo- and reproductive toxicity, spiromesifen, spirodiclofen and spirotetramate belong to the 3rd class of hazard [5, 14, 15].

According to the limiting criteria of toxicity, spiromesifen is the most toxic and belongs to the 1st class of hazard – a strong allergen, spirodiclofen [5, 14, 15] belongs to the 2nd class by carcinogenic effect, and spirotetramate – to the 3rd class of hazard (acute inhalation toxicity).

According to the physicochemical properties, spiromesifen has a low sorption capacity (Koc), is not mobile and is moderately soluble in water (Table I). The value of the allowable daily dose (ADI) characterizes it as a low-risk compound for the human body [5].

The test compounds does not have high possibility of inhalation poisoning (according to CPIP) and the coefficient of selective action (CSA), and have allowable occupational risk level (complex and combined). So, according to Table II there is no need for their obligatory monitoring in air.

Spiromesifen is not stable in environmental conditions and is characterized by an extremely low possibility of leaching into groundwater by the value of GUS [5], so it does not pose a potential risk when using contaminated food and water. However, according to Table II its ecotoxicological hazard, and the existing risk of the pesticide entering the water, which washes the chemical from the soil into the groundwater, should be taken into account.

Monitoring of pesticides in Ukraine and Europe with an increased risk of thyroid disease is necessary and relevant [6, 11]. For example, the incidence of thyroid pathology among the population of Ukraine is the highest in Kyiv region [17], but regions that are intensively engaged in agriculture, and therefore actively use chemical plant protection products, also need such control and scientific substantiation of norms and regulations for pesticides application and their further monitoring.

According to the scale proposed [18], each criterion was evaluated in points and their total amount was calculated for each studied insecticide and analyzed by us (Table III).

Assessing the toxicological effects of tetramic and tetronic acids derivatives, namely spiromesifen, spirodiclofen, and spirotetramate on the thyroid gland, it can be concluded that the effect in animal experiments is weak; tyrosinemia induced by these pesticides is absent.

When studying the stability of spiromesifen in various environmental objects, it, like spirodiclofen and spirotetramate, is unstable in soil and water (class 4). According to stability in plants, spiromesifen is an unstable compound, same as spirotetramate (class 4), spirodiclofen is moderately stable (class 3).

According to the integrated index of pesticides contaminated water consumption (IIPCWC) and integrated index of pesticides contaminated food consumption (IIPCFC), spiromesifen and spirotetramate have as low-risk for humans (class 4), and spirodiclofen is moderately dangerous (class 3).

Analyzing the screening of the maximum concentration of pesticides in groundwater (SCI-GROW) of spiromesifen, spirodiclofen and spirotetramate, we can talk about insignificant and much lower than the permissible concentrations of pollution. The index of potential contamination of groundwater and surface water (LEACH) for all investigated insecticides (spiromesifen, spirodiclofen, spirotetramat) in different soil and climatic conditions is low.

From obtained results we can assess the need to monitor these pesticides of tetramic and tetronic acids derivatives class for the total score: spiromesifen and spirotetramate are insecticides for which monitoring in environmental objects is not obligatory (16 and 15 points, respectively), and spirodiclofen is subject to the desired monitoring (20 points) in water, soil and agricultural raw materials.

## DISCUSSION

Among other classes of pesticides, insecticides have proven to be safer chemical plant protection products according to above assessed indices [19].

Comparing with literature data [20] insecticides of the tetramic and tetronic acids derivatives class, spiromesifen, spirotetramat and spirodiclofen, are safer in assessing groundwater pollution than previously studied herbicides dicamba, sulfoniculfonyl sequinilicin, pyraclostrobin, which are characterized by a high risk of contamination and may pose a risk to humans if they potentially enter the water through agricultural raw materials that have been treated with formulations with these active ingredients.

The fact that their monitoring in the air is not required and in water, soil and food is optional also testifies to the lesser danger of the studied compounds. In contrast, for most fungicides, monitoring in soil and food is mandatory; in water – also desirable [11-13].

Also, studied insecticides are lower or on the same level with a very widespread today SDHI fungicides in term of needs in monitoring, taking into account their possible effect on thyroid gland. For example, SDHI fungicides from the chemical class of pyrazolecarboxamides (isopyrazam, pentiopyrad, sedaxan, fluxapyroxad) are assigned to the second pesticide group, hygienic monitoring of which is desirable but not required [18]. This is due, to low environmental sustainability (same as for spiromesifen, spirodiclofen, spirotetramat) and to their low toxicity (despite of spiromesifen, spirodiclofen).

## CONCLUSIONS

Based on the results obtained, spiromesifen and spirotetramate, can be classified as the first group of pesticides, hygienic monitoring of which in environmental objects is not obligatory, spirodiclofen – to the second group of pesticides, hygienic monitoring of which in water, soil and agricultural raw materials is desirable, in air is not required.

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**Conflict of interest:**
*The Authors declare no conflict of interest.*

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ORIGINAL ARTICLE

# ANATOMIC AND TOPOGRAPHIC CHANGES OF ANTERIOR SEGMENT STRUCTURES IN EHLERS-DANLOS SYNDROME PATIENTS WITH MYOPIA

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## ABSTRACT

**The aim:** Determination of anatomical and topographical relationships of the eyeball anterior segment structures to assess possible glaucoma development risk factors in SED patients with myopic refraction.

**Materials and methods:** Patients, aged from 10 to 34, have been examined since 2009. All the patients have undergone required medic and genetic examination as well as generally accepted ophthalmological one. Ultrasound biomicroscopy (UBM) has been performed using the VuMax II apparatus (Sonomed, USA) with a sensor frequency of 50 MHz.

**Results:** Biomicroscopy found no symptoms such as pigment dispersion on the iris stroma, in the chamber anterior angle, iris transillumination and "Krukenberg's Spindle", which are characteristic for the ultrasound picture in pigment dispersion syndrome.

**Conclusions:** 1. Clinical and functional study with the eyeballs mandatory ultrasound biomicroscopy have revealed functional space limitations for the structures of the iridociliary zone in patients with myopic type of eye structure in SED. 2. Detected congenital changes in the anterior segment structures (iridociliary cystic formations and residual mesodermal tissue) can lead to the emergence of intraocular blocks. 3. The research has identified conducive anatomical and topographic changes, which are likely to induce pigment dispersion syndrome or lead to the development of pigmentary glaucoma. 4. In our opinion, the UBM role in the early diagnosing and monitoring patients with SED syndrome is quite significant in terms of assessing the stability or dynamics of the changes received and possible complications. Ultrasound biomicroscopic scanning should be added to the list of necessary early diagnostic examinations to determine the markers and features of structures in SED.

**KEY WORDS:** Ehlers-Danlos Syndrome (SED), ultrasonic biomicroscopic (UBM), iridociliary cysts

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## INTRODUCTION

Ehlers-Danlos Syndrome, (ICD code - 10: Q79.6) is a group of hereditary diseases caused by disorder of collagen metabolism, the myomatrix structure and function, proteoglycans synthesis [1]. It is characterized by multiple organ lesions (musculoskeletal, joint, eye, etc.) and belongs to heterogeneous connective tissue diseases. Currently SED organic symptoms are known and widely described whereas the research focusing on early diagnosis, detection and prevention of possible complications in such patients is highly promising. Ongoing technical progress of modern diagnostic equipment enables to detect functional changes at much earlier stages of the disease. Identification of early diagnosis markers, their comprehensive combination, analysis and assessment of the complications risk could facilitate the complete understanding of this pathology specifics.

## THE AIM

The objective of our study has become the identification of anatomical and topographical relationships of the eyeball anterior segment structures to assess possible glaucoma development risk factors in SED patients with myopic refraction

## MATERIALS AND METHODS

22 patients of Kharkiv specialized medical and genetic center of rare (orphan) diseases, aged from 10 to 34, have been examined since 2009. All the patients have undergone required medical and genetic examination (according to the accepted standards (Order of the Ministry of Health and the Academy of Medical Sciences of Ukraine dated 31.12.03 № 641/84) and protocols). Alongside, a generally accepted ophthalmological examination that included visometry, corneal topography, tonometry, perimetry, determination of A-P axis (Aladdin), and ophthalmoscopy has been done. Ultrasound biomicroscopy (UBM) of the anterior segment has been performed using the VuMax II apparatus (Sonomed, USA) with a sensor frequency of 50 MHz. Applying epibulbar anesthesia, a funnel-shaped eyelid dilator has been placed in the patients' conjunctival

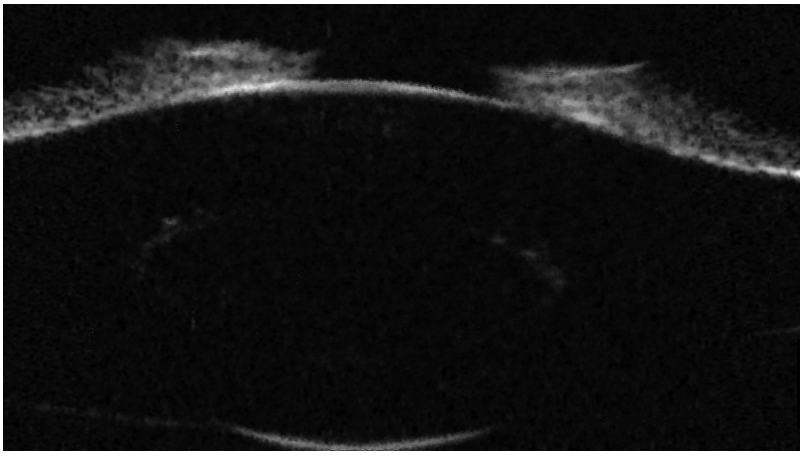

**Fig.1.** Fine-grained hyperreflective lenticular shape inclusions in the lens nucleus area

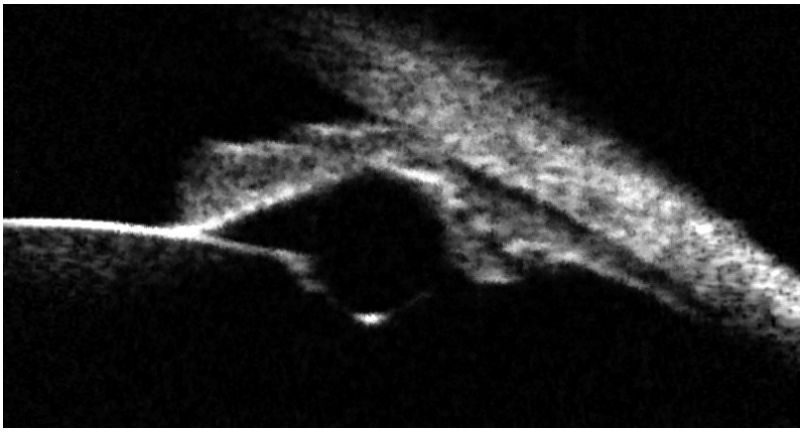

**Fig.2.** Cystic formation, which is localized in the iridociliary sulcus and causes angular block

cavity and filled with saline. Three scanning algorithms (axial, longitudinal and tangential) in grayscale and color modes have been used. The patients have been observed in the dynamics 1-2 times a year including the comparison of qualitative and quantitative (linear and angular parameters) characteristics with previous studies, which allowed to control the stability of the detected changes. The study group had no patients with keratitis, scleritis, uveitis, trauma and surgery in the anamnesis.

## RESULTS

In the focus of the research there have been SED patients with myopic refraction from -0.5 D to -6.0 D. During the bio microscopic examination and ultrasound scan of the eyeballs, different variants of residual embryonic pupil membranes in the form of thin inhomogeneous "filamentous" structures, fixed to the "iris collarette" or mobile, have been identified. In isolated cases, hyperreflective dot pigment inclusions "kite's tail" have been observed on the anterior capsule of the lens. Opacity in the form of fine-grained hyperreflective inclusions of a lenticular shape in the area of the nucleus has been detected in 9% of cases, as well as opacity in the form of focal hyperreflective zones in the subcapsular layers has been detected in 27.3% of cases (Fig. 1). The lens average thickness was 3.32 ± 0.28 mm

In the iridociliary zone, the research has found single or multiple spheroidal benign cystic formations with relatively clear boundaries and homogeneous anechogenic fluid content, with no change in dynamic. The diameter of the cysts varied from 0.17 mm to 1.48 mm. With the increase in their size to 0.9 - 1.48 mm, the forward iris displacement was determined, which induced a local angular block (Fig. 2). According to the pachymetry, our subjects' intraocular pressure was within normal limits. Glaucoma optic neuropathy was not detected.

In 19 cases (86.4%) single iridociliary cysts were found in the ciliary body, in other cases, multiple cysts of the iridociliary zone were detected. (Fig. 3).

In 40.9% of cases the patients had the plateau configuration of the iris. The concave configuration was observed less often (in 22.7%). In 36.4%, the iris configuration was defined as convex. The iris typical position was posterior; the ciliary processes were directed forward, to the center and back.

The depth of the anterior chamber averaged 3.28 ± 0.34 mm with a range of 2.65 - 3.79 mm. The anterior chamber depths indicators had a correlation dependence on the largest angle of the anterior chamber, which averaged 28.5 ± 1.1 degrees. In 9% of cases in the anterior chamber angle drainage zone in 1-2 meridians in both eyes residual mesodermal tissue was determined in the form of thin hyperreflective bridges fixed to the trabecular zone and the iris root part.

We determined such linear parameters as the distance "trabecular-iris" in 250 μm and 500 μm from the scleral spur as well as the distance "trabecular-ciliary processes" which equal 0.26 ± 0.07 mm (250 μm from the scleral

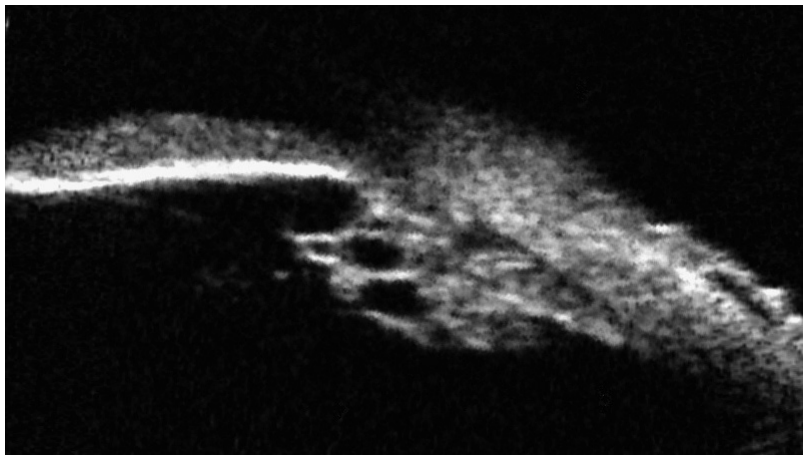

**Fig.3.** Multiple cysts of the iridociliary zone

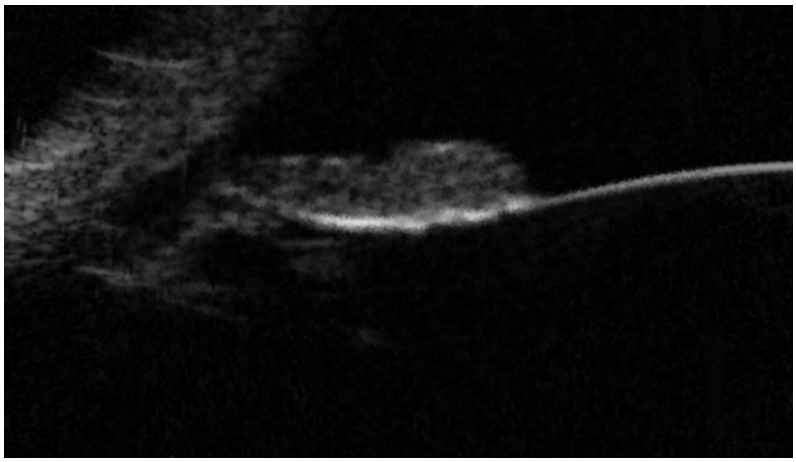

**Fig.4.** Iris backward prolapse, changed configuration of the posterior chamber, segmental contact of the ciliary processes with the iris pigmented leaf, cyst of the iridociliary zone

spur) and 0.39 ± 0.05 mm (500 μm from the scleral spur) and 1.1 ± 0.09 mm respectively.

The posterior chamber depth averaged 0.56 ± 0.05 mm, but there was a wide range of fluctuations of its values from 0.22 mm to 1.5 mm. In 18.2% of cases there was a backward prolapse of the iris, change in the posterior chamber configuration, contact of the ciliary processes and fibers of the zonule ciliaris with the iris pigmented leaf at the anterior chamber depth more than 3.2 mm (from the corneal endothelium). The posterior camera lost the correct triangular configuration; there was a decrease of its depth to 0.22 mm. There was also an expansion of the anterior chamber angle, an increase in the distance "trabecular-iris" and "trabecular-ciliary processes", and in 13.6% of cases there were cystic formations of the iridociliary zone (Fig. 4).

Biomicroscopy found no symptoms such as pigment dispersion on the iris stroma, in the chamber anterior angle, iris transillumination and "Krukenberg's Spindle", which are characteristic for the ultrasound picture in pigment dispersion syndrome.

## DISCUSSION

The cystic formations found in the iridociliary zone were more often thin-walled, according to the authors' data [4], they can be classified as cysts of neuroepithelial origin, but single cysts had a thickened capsule. During the whole research period the cysts did not change their content and form.

However, the risk factor is that cystic formations of big size can cause changes in iris configuration and induce secondary glaucoma [5,6]. Referring to some resources similar formations are characteristic of iridociliary dystrophies [7]. Iridociliary complex is an important structure to perform the function of accommodation and hydrodynamics of the eye therefor it demands local careful observation.

Taking into account the changes in the anatomical and topographic parameters of the eyeball anterior segment structures in this group of patients with myopic refraction, we can consider the factor of pigmentary glaucoma possible development [2].

In our opinion, it is important that the contact of the iris pigment leaf with the zonule ciliaris and the lens anterior surface can mechanically provoke the release of pigment granules into the anterior chamber and imbibition of the eyeball anterior segment anatomical structures with pigment.

No changes in anatomical and topographic parameters in the dynamics of the observations were found. As well as no correlation between changes in the studied parameters with the degree of myopia were discovered. Despite the fact that in no cases of the research were found any glaucomatous lesions of the optic nerve, it is necessary to add

the following to the list of methods of ophthalmological examination in patients with myopic refraction with SED: Optical Coherence Tomography or HRT of the optic nerve, corneal topography, and 30-2 or 32 program computer perimetry.

With these changes found, SED patients are highly recommended to undergo the standard ophthalmological examination in combination with ultrasound eyes scanning and a careful optic nerve observation to take preventive measures in time.

## CONCLUSIONS

1. Clinical and functional study with the eyeballs mandatory ultrasound biomicroscopy have revealed functional space limitations for the structures of the iridociliary zone in patients with myopic type of eye structure in SED.
2. Detected congenital changes in the anterior segment structures (iridociliary cystic formations and residual mesodermal tissue) can lead to the emergence of intraocular blocks.
3. The research has identified conducive anatomical and topographic changes, which are likely to induce pigment dispersion syndrome or lead to the development of pigmentary glaucoma.
4. In our opinion, the UBM role in the early diagnosing and monitoring patients with SED syndrome is quite significant in terms of assessing the stability or dynamics of the changes received and possible complications. Ultrasound biomicroscopic scanning should be added to the list of necessary early diagnostic examinations to determine the markers and features of structures in SED.

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ORIGINAL ARTICLE

# AN INTEGRATED APPROACH TO THE MORPHOLOGICAL DIAGNOSIS OF DIFFERENT TYPES OF PLEOMORPHIC ADENOMAS OF THE SALIVARY GLAND: LONG-TERM RESEARCH RESULTS

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## ABSTRACT

**The aim:** To describe an integrated approach to the morphological diagnosis of different types of pleomorphic adenomas of the salivary gland.

**Materials and methods:** Surgical and biopsy material from 30 patients with pleomorphic adenomas of epithelial, mixed and mesenchymal variants was studied using histological, immunohistochemical, genetic, morphometric and statistical methods.

**Results:** The results of research allowed us to identify methods for determination the pleomorphic adenomas types. The first method requires an immunohistochemical reaction with a monoclonal antibody to human papillomavirus type 16, followed by counting the percentage of positively stained cells in the tumor. Thus, the mesenchymal variant of the tumor is diagnosed when the percentage of positively stained cells is < 40%. In the mixed variant, this indicator is ≥ 40%, but ≤ 70%, and in epithelial variant – > 70%. The second method was based on the multivariate discriminant analysis. Three formulae were derived to determine the tumor types ($F_{mesenchymal} = - 41.03 + 4.96X_1 + 1.11X_2$, $F_{epithelial} = - 22.27 + 3.46X_1 + 0.85X_2$, $F_{mixed} = - 122.25 + 5.63X_1 + 3.2X_2$, here $X_1$ - number of vessels, $X_2$ – specific volume of parenchyma).

**Conclusions**: The authors identified several methods for determining the histological variants of pleomorphic adenomas. These methods will improve the morphological diagnosis of pleomorphic adenomas variants in the preoperative and postoperative periods.

**KEY WORDS:** diagnosis, morphology, pleomorphic adenomas types, salivary gland

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## INTRODUCTION

Salivary gland neoplasms are a heterogeneous group of tumors, accounting for only 3 to 10% of all head and neck neoplastic processes [1, 2].

Pleomorphic adenoma is the most common benign tumor of the salivary glands with an incidence rate between 4.2-4.9/100,000 person-years [3]. The frequency of pleomorphic adenoma among all salivary gland tumors ranges from 32.6 to 78.6% [4].

Pleomorphic adenoma is more often localized in parotid glands (85%), minor salivary glands (10%) and submandibular glands (5%). It can also be located in the lip, cheek, tongue, floor of the mouth, etc. This tumor definitely shows a female predilection with male-female ratio of 8:13 (5). Pleomorphic adenoma may be diagnosed at any age, with a maximum incidence in the 4th life decade [1].

The histogenesis of pleomorphic adenoma continues to be a controversial subject. Thus, while some authors suggest that the two tumor components (parenchyma and stroma) originate from different sources, mesenchymal and epithelial, others support the unicellular origin of this tumor [1]. Some scientists explain the development of pleomorphic adenoma by the presence of reserve cells in the tumor that can transform into different directions [2].

The risk of malignant transformation of pleomorphic adenomas is rare. Only 3% recur at 12.5-year follow-up, of which 6% seem to show malignant transformation (carcinoma ex pleomorphic adenoma) [6].

The diagnosis of pleomorphic adenoma is crucial in the choice of the tactics of patient treatment, preventing the development of complications and recurrences. The diagnosis cannot be established only on clinical history and simple physical examination, and requires complementary diagnostic methods [7].

Morphological research methods play an important role in the diagnosis of pleomorphic adenoma in the preoperative and postoperative periods [8]. Pleomorphic adenoma is histologically extremely heterogenous and has a complex structure [9], which sometimes causes certain difficulties and misdiagnosis for pathologists in the morphological

diagnosis of this tumor and its histological variant determination. Pathologists emphasize that pleomorphic adenoma may be confused with myoepithelioma, adenoid cystic carcinoma, mucoepidermoid carcinoma, basal cell adenoma because of its varied histopathological presentation [5]. The results of our own long-term research [10-15] allow us to identify certain morphological features of various pleomorphic adenomas and, on their basis, to formulate an integrated approach to the morphological diagnosis of these tumor variants.

## THE AIM

The aim of the study is to describe an integrated approach to the morphological diagnosis of different types of pleomorphic adenomas of the salivary gland.

## MATERIALS AND METHODS

In this study we used surgical and biopsy material from 30 patients with pleomorphic adenomas of the salivary glands. The patients underwent treatment in Kyiv City Clinical Hospital No. 12 (Ukraine, Kiev) from 2018 to 2019. The Ethics and Bioethics Commission of Kharkiv National Medical University approved the study, all the participants signed an informed consent in accordance with data protection regulation and the Declaration of Helsinki.

Morphological study of biopsy and surgical material was carried out at the Alpern Department of General and Clinical Pathological Physiology of Kharkiv National Medical University (Kharkiv, Ukraine), Department of Pathologic and Topographic Anatomy of Shupyk National Healthcare University of Ukraine (Kyiv, Ukraine). Among all cases of pleomorphic adenomas, we found a mesenchymal variant in 15 cases, a mixed variant in 10 cases, and an epithelial variant in 5 cases.

Surgical and biopsy material was fixed in a 10% solution of neutral buffered formalin, carried out according to the generally accepted method and embedded in paraffin. Serial sections of 3-4 μm thick were made from paraffin blocks. Microspecimens stained with hematoxylin and eosin were studied, using an Olympus BX-41 microscope (Japan) with subsequent processing with the Olympus DP-soft version 3.1 software, which was used to conduct a morphometric study. By morphometry in the tumor tissue, the specific volumes (%) of the parenchyma and stroma, the number of vessels in the field of view of the microscope at × 100 magnification was counted.

Using mouse monoclonal antibody (MCA) to human papillomavirus (HPV) type 16 (clone CAMVIR-1, «Diagnostic BioSystems», USA), the authors have carried out an immunohistochemical study. Brown staining of cell nuclei characterized positive expression of the marker. Visualization was performed, using an EnVision™ FLEX detection system (Dako, Denmark). Antigen was unmasked in citrate buffer pH 6.0 at 95 °C. Primary antibodies were incubated at room temperature for 30 min, secondary – for 20 min. Sections were counterstained with Gill hematoxylin. The authors assessed the immunohistochemical reaction by a semi-quantitative method, counting the percentage of positively stained cells in the field of view of a microscope × 400.

The expression of microRNA-34a, microRNA-29a was assessed by reverse transcription and quantitative polymerase chain reaction (PCR) in real time. Reverse transcription was performed using a set of TaqMan MicroRNA reagents (Applied Biosystems, USA) with a specific primer for microRNA and 10 ng of total RNA. Real-time qPCR microRNA assays TaqMan (Applied Biosystems, USA) were used: U6 snRNA, ID001973 (as endogenous control), hsa-microRNA-34a, hsa-microRNA-29a, ID000426, ID002447 (Applied Biosystems, USA). Temperature cycles were as follows: initial denaturation step 95°C 10 min; 50 cycles of 95°C – 15 s and 60°C – 60 s. The level of microRNA expression was normalized to U6 snRNA and was presented in relative units (RU). Amplification was performed using real-time PCR 7500Fast (Applied Biosystems, USA).

The authors used the following methods of descriptive statistics in the study: means, errors of the mean, confidence interval (CI). The nonparametric Mann-Whitney U test was used to compare the means in the groups [16, 17]. Differences were considered significant at $p<0.05$. Methods of multivariate discriminant analysis were used to predict the type of the tumor [18]. In all calculations, we used Microsoft Excel. Statistical analysis was performed using IBM SPSS software Statistics 28 (license No. Z125-3301-14).

## RESULTS

The results of long-term research allowed us to identify an integrated approach to the morphological diagnosis of different types of pleomorphic adenomas of the salivary gland, which gives us several methods of their determination.

The first method requires an immunohistochemical reaction with a MCA to HPV type 16, followed by counting the percentage of positively stained cells in the tumor tissue. This MCA was expressed by the epithelial cells of the nests and strands, solid, trabecular, cystic, glandular, ductal and tubular structures; some myoepithelial cells; fibroblast cells, immune cells, vascular endotheliocytes, cellular elements of myxoid and mucoid zones. The percentage of positively stained cells significantly ($p<0.05$) varied in different pleomorphic adenomas (Table I).

Table I shows the values of CI for the means, allowing us to determine the histological variants of pleomorphic adenomas. Thus, the mesenchymal variant of the tumor is diagnosed in cases when the percentage of positively stained cells is < 40%. In the mixed variant of the tumor, this indicator is ≥ 40%, but ≤ 70%, and in epithelial variant – > 70%.

The second method for determining the histological variants of pleomorphic adenomas was not as simple as the first one, based on the multivariate discriminant analysis. The purpose of the latter was to determine two discriminant functions (canonical roots), which divided all objects into three groups depending on the histological variant of the tumor. These two discriminant functions are two hyperplanes, which divide the

**Table I.** The percentage of positively stained cells in pleomorphic adenomas of various histological variants in an immunohistochemical reaction with a MCA to HPV type 16.

| Pleomorphic adenomas variants | M±m | CI (95%) |
|---|---|---|
| Mesenchymal | 27.2±0.69 | (25.72; 28.63) |
| Epithelial | 75.8±0.75 [1] | (73.71; 77.89) |
| Mixed | 56.9±1.70 [2,3] | (53.06; 60.74) |

[1] – significant (p<0.05) differences of indicators in mesenchymal and epithelial variants of the tumor; [2] – significant (p<0.05) differences of indicators in epithelial and mixed variants of the tumor; [3] – significant (p<0.05) differences of indicators in mesenchymal and mixed variants of the tumor

**Table II.** Morphometric parameters of pleomorphic adenomas variants.

| Name of parameter | Pleomorphic adenomas variants | | |
|---|---|---|---|
| | Mesenchymal | Epithelial | Mixed |
| Specific volume of parenchyma, % | 15.50±4.44 | 87.86±2.16 [1] | 53.67±1.49 [2,3] |
| Specific volume of stroma, % | 84.50±4.41 | 12.14±2.18 [1] | 46.33±1.48 [2,3] |
| Number of vessels, absolute quantity | 12.83±1.02 | 8.86±1.02 [1] | 12.50±0.84 [2] |
| Expression level of microRNA-34a, RU | 630.29±98.51 | 838.62±82.23 [1] | 305.59±57.18 [2,3] |
| Expression level of microRNA-29a, RU | 120.62±24.47 | 78.40±19.73 [1] | 22.23±3.55 [2,3] |

[1] – significant differences (p<0.05) of indicators in mesenchymal and epithelial variants of the tumor; [2] – significant differences (p<0.05) of indicators in epithelial and mixed variants of the tumor; [3] – significant differences (p<0.05) of indicators in mesenchymal and mixed variants of the tumor

**Table III.** Factor structure matrix

| Name of parameter | Canonical root 1 | Canonical root 2 |
|---|---|---|
| Specific volume of parenchyma | -0,063 | -0,998 |
| Number of vessels | -0,978 | 0,205 |

**Table IV.** Matrix of aposteriori classification.

| Pleomorphic adenomas variants | Rows: observed groups Columns: stipulated groups | | | |
|---|---|---|---|---|
| | Percentage of faithful | Mesenchymal | Epithelial | Mixed |
| Mesenchymal | 100% | 15 | 0 | 0 |
| Epithelial | 100% | 0 | 5 | 0 |
| Mixed | 100% | 0 | 0 | 10 |
| Total | 100% | 15 | 5 | 10 |

entire n-dimensional space of indicators into three regions corresponding to three tumor variants.

The authors determined the indicators for discriminant functions by the method of sequential selection of 5 parameters (specific volume of the parenchyma and stroma; number of vessels in the microscope field of view × 100; expression level of microRNA-34a and microRNA-29a (Table II)) (10, 11). We obtained these parameters by the morphometric study. The values of the specific volume of parenchyma, specific volume of stroma, expression level of microRNA-34a, expression level of microRNA-29a were significantly (p<0.05) different in pleomorphic adenomas types. The absolute number of vessels was large (p<0.05) in the mesenchymal and mixed variants compared with the epithelial variant. The absolute number of vessels did not differ (p>0.05) in mesenchymal and mixed variants of the tumor (Table II).

The authors took into account statistical significance of each parameter and its redundancy for classification. Thus, the discriminant functions contained only two parameters: "specific volume of parenchyma" and "number of vessels".

The statistical significance and quality of the resulting discriminant model were evaluated based on Wilks' Λ-statistics and amounted to Λ=0.026 at F (4.52) = 67.5 (p<0.000).

The contribution of each parameter to the discriminant function was evaluated using the factor structure matrix (Table III). Table III shows that the highest correlation with the first discriminant function (canonical root) was the indicator "number of vessels", and with the second – the indicator "specific volume of parenchyma".

Thus, three formulae were derived to determine the histological variants of pleomorphic adenomas ($F_{mesenchymal}$, $F_{epithelial}$ and $F_{mixed}$). We can determine the type of tumor with the highest value according to the classification function:

$F_{mesenchymal} = - 41.03 + 4.96X_1 + 1.11X_2$,

$F_{epithelial} = - 22.27 + 3.46X_1 + 0.85X_2$,

$F_{mixed} = - 122.25 + 5.63X_1 + 3.2X_2$,

here $X_1$ - number of vessels, $X_2$ – specific volume of parenchyma.

The accuracy of determining the histological variant of the tumor using classification functions was assessed based on aposteriori classification. This model showed 100% accuracy (Table IV).

## DISCUSSION

The most common benign salivary gland tumor is pleomorphic adenoma [19]. In order to minimize the incidence of this neoplasm, the etiological factors causing it should be well known [20].

Pleomorphic adenoma is a polyetiological tumor. Viruses play a certain role in its development. The etiological role of HPV type 16 in the genesis of this tumor development is a debatable issue [21]. HPV type 16 is a high-risk oncogenic virus [22, 23].

A comprehensive immunohistochemical study with a MCA to HPV type 16 allowed us to reveal a causal relationship between the infection of a patient with HPV type 16 and development of pleomorphic adenoma of the salivary gland in him [12]. The MCA to HPV type 16 was expressed by the parenchyma and stroma cells of pleomorphic adenomas, consistent with the literature data [20]. Calculating the percentage of positively stained cells in various pleomorphic adenomas variants, we found that the maximum, moderate and minimum values, respectively, were in epithelial, mixed and mesenchymal tumor variants. Analyzing the mean CI of positively stained cells percentage, we identified the method for determining the histological variants of pleomorphic adenomas while morphologically studying the biopsy or surgical material.

In our previous studies [10] and literature data [1], it was noted that pleomorphic adenomas were characterized by a morphological heterogeneity, the presence of parenchymal (epithelial) and stromal (mesenchymal) components. Some scientists separate the myoepithelial cell component [5]. The ratio of parenchymal and stromal components can be different, which made it possible for us to distinguish mesenchymal, epithelial and mixed variants of this tumor during morphometric study. It was noted that the maximum, moderate and minimum values of the specific volume of parenchyma were in epithelial, mixed and mesenchymal tumor variants. The maximum, moderate and minimum values of the specific volume of stroma were in mesenchymal, mixed and epithelial tumor variants.

Vascularization has rarely been studied in pleomorphic adenomas. Some scientists have noted that pleomorphic adenoma is a poorly vascularized tumor [24].

Swelam W. et al. suggest that pleomorphic adenoma cells produce vascular endothelial growth factor (VEGF) in several functional forms for their own proliferation or differentiation, and that the VEGF expression is controlled by hypoxic circumstances of poorly vascularized pleomorphic adenomas [25].

There is no information in the literature about the vascularization features in different histological variants of pleomorphic adenomas. In our study, we noted that the mesenchymal and mixed variants were characterized by a large number of vessels compared to the epithelial variant.

Angiogenesis activation was found in carcinoma ex pleomorphic adenoma compared to pleomorphic adenoma. This process is necessary for tumor growth, invasion and metastasis [6, 24, 25].

The modern genetic direction in the tumors diagnosis is the study of microRNAs role. MicroRNAs are a group of endogenous 21-25 nucleotide noncoding RNAs which target gene coding in the posttranscriptional level. They are involved in various important biological processes such as development, differentiation, proliferation and apoptosis [26]. MicroRNAs appear to be new promising biomarkers for tumor diagnosis and prognosis [27]. Among all microRNAs, molecules responsible for apoptosis controlling (proapoptotic) (microRNA-29a, microRNA-34a) are of considerable interest.

In our study, we determined the expression level of microRNA-34a, microRNA-29a in various histological variants of pleomorphic adenomas. In all tumor variants, the expression of these microRNAs was increased compared to the physiological norm. We obtained the physiological norm of microRNA-34a, microRNA-29a expression level earlier and it amounted to 47.72±28.83 and 8.12±4.40, respectively [11].

Analyzing the expression level of microRNA-34a, we found that the maximum, moderate and minimum values were in epithelial, mesenchymal and mixed tumor variants, respectively. The maximum, moderate and minimum values of the expression level of microRNA-29a were in mesenchymal, epithelial and mixed tumor variants.

The statistical analysis of the above 5 indicators ("specific volume of parenchyma", "specific volume of stroma", "number of vessels", "expression level of microRNA-34a", "expression level of microRNA-29a") allowed us to identify two indicators ("number of vessels", "specific volume of parenchyma") which were used in determining the discriminant functions (formulas). These formulae help us to identify the histological variants of pleomorphic adenomas.

## CONCLUSIONS

In consequence of a comprehensive study, the authors identified several methods for determining the histological variants of pleomorphic adenomas. These methods will improve the morphological diagnosis of pleomorphic adenomas variants in the preoperative and postoperative periods.

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ORIGINAL ARTICLE

# A STUDY OF THE NOVEL WU AND KI POLYOMAVIRUSES, BOCAVIRUS ADENOVIRUS IN CHILDREN WITH UPPER RESPIRATORY TRACT INFECTIONS

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## ABSTRACT

**The aim**: To find out the frequency of WU and KI polyomaviruses, and Human Boca and Adenoviruses infections among children with different types of acute upper respiratory tract infections and to compare the frequency of these viruses among immune-competent and immune compromised patients.

**Materials and methods**: A case-control study conducted in children aged 3-18 years with acute upper respiratory tract infections. The samples were taken from: Group 1: 100 immuno competent children with acute upper respiratory tract infections. Group 2: 100 immuno compromised children (Leukemic, cancer, Nephrotic syndrome, chronic renal failure and children with renal transplant) with acute upper respiratory tract infections. Group 3: 100 apparently healthy children without respiratory infections as control group. Nasal swap samples were collected from children and then viral DNA extracted from these samples. Then detection of WU, KI polyomaviruses HBoV and HAdv was done by using real time PCR.

**Results**: All of 300 samples were negative for WU and KI polyomaviruses. However, human Bocavirus was detected in the three groups (immunocompromised, immunocompetent and control group) and the positivity rates were 61.61%, 37.37% and 18.18%, respectively. While human adenovirus was found only in 2% of immunocompromised patients and 1.1% of immunocompetent patients also there were cases positive for both HBoV and HAdv in 5.5% of immunocompromised patients, and 8.8% of immunocompetent patients.

**Conclusions**: High frequency of HBoV especially in immunocompromised patients while low number of positive cases for HAdv by using nasal swab samples, WU and KI polyomaviruses could not be detected in samples.

**KEY WORDS:** novel WU, KI polyomaviruses, Bocavirus Adenovirus

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## INTRODUCTION

Upper respiratory tract infections (URIs) are common and important. Although rarely fatal, they are a source of significant morbidity and carry a considerable economic burden. URIs are the most common infectious diseases. They include rhinitis (common cold), sinusitis, ear infections, acute pharyngitis or tonsillopharyngitis, epiglottises, and laryngitis, the vast majority of URIs have a viral etiology. The viral causes of URIs are rhinoviruses, human adenoviruses HAdv, parainfluenza viruses, respiratory syncytial virus (RSV), influenza viruses, human metapneumoviruses, and human bocaviruses (HBoV) [1]. In 2007, two novel human polyomaviruses HPyV were reported, the Karolinska Institute polyomaviruses KIPyV and the Washington University polyomaviruses WUPyV, both were discovered in respiratory tract samples from individuals with acute respiratory tract infections, and they were categorized among Polyomaviridae family. They are non-enveloped double-stranded DNA viruses [2-3].

Serological studies have shown that infection with KIPyV and WUPyV is common in general population. Primary infection probably occurs early in childhood [4]. KIPyV and WUPyV have been detected in respiratory samples from children and adult patients with acute respiratory symptoms from around the world [5]. The human adenovirus (HAdv) is another common virus in acute upper respiratory tract infections; it is also being non-enveloped double-stranded DNA virus [6]. It accounts for at least 5 to 10% of pediatric and 1 to 7% of adult respiratory tract infections [7-8], typical symptoms of HAdv respiratory tract infections include fever, pharyngitis, tonsillitis, cough, and sore throat [9]. Human Bocavirus (HBoV) was first described in 2005, as non-enveloped single-stranded DNA virus of Parvoviridae family [10]. Several studies have shown the association between HBoV and the upper and lower respiratory tract. In this regard, the most frequently described clinical presentation of HBoV1 infection includes cough, fever, rhino rhea, asthma exacerbation, bronchiolitis, acute wheezing and pneumonia [10-12].

## THE AIM

To find out the frequency of WU and KI polyomaviruses, and Human Boca and Adenoviruses infections among children with different types of acute upper respiratory tract infections and to compare the frequency of these viruses among immune-competent and immune compromised patients.

**Table I.** Nucleotides sequences of Primers and probes

| Virus | Sequence | Target gene | Reference |
|---|---|---|---|
| WU-F | AACCAGGAAGGTCACCAAGAAG | VP1 | [41] |
| WU-R | TCTACCCCTCCTTTTCTGACTTGT | | |
| WU-Probe | HEX-CAACCCACAAGAGTGCAAAGCCTTCC-BHQ-1 | | |
| KI-F | GAGCCCACCCCTCATTACTG | VP1 | [42] |
| KI-R | CTTGAACCGCTTTCCTTGTCA | | |
| KI-Probe | FAM-TCAATTAGCTCTGCCATTG-MGB | | |

**Table II.** Thermal profile for detection of WU, KI, Hadv and HBoV by real time PCR

| Step | Temp/C° | Time | Cycles | Virus |
|---|---|---|---|---|
| 1 | 95 | 10 min | 1 | WU and KI |
| 2 | 95 | 20 sec | 45 | |
| | 60 | 60 sec* | | |
| | 72 | 72 sec | | |
| 1 | 95 | 15 min | 1 | HAdv and HBoV |
| 2 | 95 | 10 sec | 10 | |
| | 54 | 25 sec | | |
| | 72 | 72 sec | | |
| 3 | 95 | 10 sec | 35 | |
| | 54 | 25 sec* | | |
| | 72 | 72 sec | | |

**Table III.** Distribution of patients according to sex type, HBoV and HAdv infection

| | Male | Female | +ve HBoV | +ve HAdv | +ve both |
|---|---|---|---|---|---|
| Immunocompromised | 57 (57%) | 43 (43%) | 61 (61%) | 2 (2%) | 5 (5%) |
| Immunocompetent | 62 (62%) | 38 (38%) | 37 (37%) | 1 (1%) | 8(8%) |
| Control | 57(57%) | 43 (43%) | 18 (18%) | 0 | 0 |

## MATERIALS AND METHODS

A case-control study was conducted in children aged 3-18 years with acute upper respiratory tract infections admitted to Al Imamein Al Kadhimein Medical City, Central Teaching Hospital of Pediatric, Children Welfare Teaching Hospital at (Baghdad Medical City), and AL-Karama Teaching Hospital, Baghdad. Nasal swabs were collected during January, February, October, November and December of 2020 and January of 2021. This study was approved by the Institutional review board IRB of the College of Medicine- Al-Nahrain University (approval no. 327 in 24 /12 /2019). The samples were taken from 3 groups of children: 100 immuno-competent children with acute upper respiratory tract infections, 100 immunocompromised children (with leukemia, cancer, nephrotic syndrome, chronic kidney disease and children with renal transplant) with acute upper respiratory tract infections and 100 apparently healthy children without respiratory infections as control group. Nasal swabs were placed in 1 ml virus transport media VTM tube (Heinz Herenz, Germany), provided with the swab and stored at -20 C° and the DNA extraction was done by using Viral Gene-spin™ Viral DNA/RNA Extraction Kit (Intron, Cat No 17151, Korea). Each sample was analyzed for the presence of WU and KI polyomaviruses DNA by the use of duplex real-time PCR procedure. The PCR procedure for WU and KI was previously designed and described, table I. The PCR mix (total volume 20 µl) composed of a master mix kit (Go taq green master mix, Promega) 10 µl, primers (0.5 µl each), Probes (0.5 µl each), sample (7µl each). The detection of HAdv and HBoV was done by using ARVI-screen-FRT PCR kit (R-V57-100-F) (Ampli Sens, Russia). This kit is an in vitro nucleic acid amplification test for multiplex detection and identification of specific nucleic acid fragments of pathogens that cause acute respiratory viral infections. In this study, only reagents of human B, C, and E Adenovirus (hAdv) and human Bocavirus hBov were used. The PCR mix (total volume 25 µl) composed of 10 µl of PCR-mix-1-FL-F, 5 µl of PCR-mix-2-FRT, Polymerase TaqF (0.5 µl3, µl were added of internal control IC, from this mixture, 15 µl is taken and 10 µl of the sample or positive control was added to it. PCR procedures were performed on a real-time PCR detection system (Sa-cycler-96, Italy). Analysis of the PCR data was performed with computer software provided

**Table IV.** The association between age groups and HBoV infection

| | (3-5) years | (5-10) years | (10-18) years | P value |
|---|---|---|---|---|
| Immunocompromised | 13 (19.7%) | 30 (45.5%) | 23 (34.8%) | 0.369 |
| Immunocompetent | 15 (33.3%) | 18 (40%) | 12 (26.7%) | 0.23 |
| Control | 2 (11.1%) | 10 (55.6%) | 6 (33.3%) | 0.79 |

**Table V.** The association between clinical presentation and HBoV infection

| | Common cold | P value | Flu | P value | Pharyngitis | P value | Croup | P value |
|---|---|---|---|---|---|---|---|---|
| Immunocompromised | 49 (74.2%) | 0.043 | 14 (21.2%) | 0.021 | 22 (33.3%) | 0.649 | 1 (1.5%) | 1 |
| Immunocompetent | 31 (68.9%) | 0.831 | 14 (31.3%) | 0.361 | 38 (84.4%) | 0.004 | 0 (0%) | 1 |

by the instruments company (Sa-cycler-96, Italy), cycling conditions for the real time-PCR procedures for WU, KI, HAdv and HBoV as shown in table II.

### STATISTICAL ANALYSIS

The data were processed using SPSS version 16.0.0, Microsoft Excel 2010, and Graph pad Prism version 7.04. The data of the current study were scrutinized carefully in terms of being parametric or non-parametric using normality tests. Accordingly, the proper statistical tests were used. Student t-test and ANOVA test were used for parametric data to measure the significance of difference in means taking into account whether variables of analysis sharing different or equal variance. For qualitative nominal data, Pearson's chi-square test, with or without Yate's correction, Fisher Exact test, and McNemar test were used to measure significance of hypothesis for association. In addition, for qualitative nominal variables dictating the occurrence of a bad outcome, odds ratio was calculated. Correlation coefficient tests or, r, among variables were used to assess the nature of correlation in terms of positive, negative or indifference.

## RESULTS

The age of immunocompromised patients ranged from 3-18 years, their mean age was 8.5±2.1 years, while the age of immunocompetent patients ranged from 3-13 years, with a mean of 6.21±2.5 years. The age of apparently healthy control group ranged from 3-18 years, with a mean of 8.5±2.2. Males were more numerous than females in all three groups (immunocompromised, immunocompetent and control) with percentage (57%,43%), (62%,38%) and (57%,43%) respectively. All the samples were negative for WU and KI polyomaviruses; however, among immunocompromised patients (61,61%) were positive for HBoV only, (5,5%) positive for both of HBoV/HAdv and (2, 2%) positive for HAdv only. On the other hand, among immunocompetent patients; (37,37%) were positive for HBoV only, (8,8%) positive for both HBoV/HAdv and (1,1%) positive for HAdv only. In addition, only (18,18%) of the control group samples were positive for HBoV, and all of them were negative for HAdv as shown in table III. Among the immunocompromised patients, the highest number positive cases for HBoV were in the age group of 5-10 years, 30 of 66 cases positive for HBoV, which represent 62.5% in this age group and 45.5% of all positive cases for HBoV. Regarding immunocompetent patients, the most of positive cases for HBoV were in the age group 5-10 years, 18 of 45 cases positive for HBoV, which represent 48.6% in this age group and 40 % in all positive cases for HBoV as shown in table IV. Common cold was the most typical (51.45%) among immunocompromised children followed by pharyngitis (23.85%) and flu (22.31%). Pharyngitis was the most typical 41.32% in immunocompetent patients followed by common cold 67 (40.12%), while only 1(0.6%) case had croup. Forty-nine of 66 immunocompromised patients with common cold had HBoV infection, 74.2% of all HBoV positive cases and was statistically significant. On the other hand, among the immunocompetent children, 38 of 45 cases positive for HBoV had pharyngitis and this represented 84.4% of all HBoV positive cases in this group, which was statistically significant as shown in table V. Human adenovirus infection was found in 7 immunocompromised patients, distributed as 5 cases with common cold and 2 cases with flu, and there was no statistically significant association, while among immunocompetent children 8 of 9 cases positive for HAdy had pharyngitis, yet, it was statistically insignificant.

## DISCUSSION

To the best of our knowledge, this is the first study in Iraq for detection of novel WU and KI polyomaviruses in respiratory tract infection. All samples were negative for WU and KI polyomaviruses; there are several possible reasons for this result linked to several factors. The first factor is age of the patients, as this study was based on age of more than 3 years. Rockett RJ et al., 2015, while analyzing samples from nasal swabs, found that children at the age under 12 months have the most positive cases for these two viruses [13]. There are other studies that found that the most positive cases were at the same age as mentioned above [14].

The other factor is the type of disease. These viruses could be associated with lower respiratory tract infection and many researches noticed increased viral loads among patients with more severe illness [15-16]. The final factor is

the type of sample, the sample that was used in this study was nasal swab, other studies have used nasopharyngeal aspirate or swab and bronchoalveolar lavage (BAL) and mainly with lower respiratory tract infection [17-18]. Other studies found these viruses in tonsils tissue and this may suggest persistence of WU and KI polyomaviruses in lymphoid tissues [19]; also, WU and KI polyomaviruses were detected in lung tissue by molecular and immunohistochemical techniques [20-21].

After reviewing the difference in these studies on different types of samples, age groups and even the type of disease, one or more than one or all of three factors could be the reason of the negative result of current study. Human Bocavirus is a common virus detected alone or in combination with other respiratory viruses in upper respiratory tract infections [22]. In the current study, there was a noticeable increase in the number of positive cases in the immunocompromised group 61% compared to the other groups. Different findings were reported by Koskenvuo M. et al 2008 and Baptista ER et al., 2012, in which their reported the positive cases 5.6% and 2.44% respectively [23-24]. At the same time, there are a few cases with HBoV infection in the control group (18%), and this is not the first time this virus has been found in normal asymptomatic children and the expected reasons for it may be able to persist at low levels in the setting of an efficient immune system, thus, making its detection difficult unless an immunocompromised status and/or coinfection with other viruses and subsequent increased replication occur. Exposure to HBoV during immunosuppression can lead to persistent infection and prolonged viral shedding [25]. In immunocompetent patients, the positive cases of HBoV were 37%, similar findings were reported by Yaseen ZT et al., 2020, and different findings were reported by Rasheed et al., 2019, who reported 6% of positive cases [26-27]. According to HAdv index, there were few positive cases in both groups (2% in immunocompromised and 1% in immunocompetent) and there were no positive cases in the control group, similar findings were reported by Lee SJ et al., 2017 [28]. Also, there were some cases with co-infection of HBoV and HAdv (5% in immunocompromised and 8% in immunocompetent) and several studies have shown the same [29-30]. The reason of the small number of positive samples of the HAdv was probably because of the type of the sample, or pharyngeal swabs being more sensitive than nasopharyngeal swabs, as the major site of initial replication of adenoviruses is non-ciliated respiratory epithelium of the or pharynx [31-32]. Most of the positive cases with HBoV were located within the age group 5-10 years in both immunocompromised (30 of 48) and immunocompetent (18 of 37) patients. This may be due to children in this age group were at school-age and upper respiratory infections are prevalent within these children because of the different activities within the school [33].

Also, more than 80% of immunocompromised children within age group less than 5 years were positive for HBoV, the high prevalence rate in young children led to the hypothesis that HBoV may be an endemic virus with high attack rates in those susceptible. Similar findings were reported by Tabl HA, et al. 2012 [34]. There were 66.7% of all the cases with HAdv infection in immunocompetent patients, in the age group less than 5 years with borderline significance. This could be explained with immunity to HAdv infection increased in children older than 5 years [35]. In both patients' groups (immunocompromised and immunocompetent), common cold is the most typical disease presentation, followed by pharyngitis. Common cold is a conventional term for a mild upper respiratory illness, the hallmark symptoms of which are nasal stuffiness and discharge, sneezing, and cough; the pharyngitis is most often being caused by direct infection of the pharynx, primarily by viruses or bacteria [36-37]. In the current study, common cold and pharyngitis are the most common among the children, who were HBoV positive, which is in agreement with Bharaj P, et al. 2010 [38]. More than 90% of immunocompetent children who were positive for HAdv had pharyngitis. HAdv infections are identified as etiologic agent in up to 25% of cases in children and in 3% of ambulatory adults with pharyngitis [39]. Similar findings were reported by Dominguez O et al 2005 [40].

In conclusion, HBoV was significantly high in immunocompromised children with acute upper respiratory infection, while HAdv had relatively low rates in the nasal swabs of children with acute upper respiratory tract infection. Common cold was most common among HBoV infected children, and pharyngitis was most common among HAdv infected children. However, this study could not detect WU and KI polyomaviruses in the nasal swabs in children with or without upper respiratory infections.

## CONCLUSIONS

High frequency of HBoV especially in immunocompromised patients, with low number of positive cases for HAdv by using nasal swab samples, WU and KI polyomaviruses could not be detected in such samples.

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ORIGINAL ARTICLE

# EXPERIMENTAL STUDY OF CHANGES IN THE CHEMICAL COMPOSITION OF TOOTH ENAMEL WHEN USING HYDROGEN PEROXIDE AS THE MAIN CHEMICAL COMPONENT IN PROFESSIONAL BLEACHING

DOI: 10.36740/WLek202207114

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## ABSTRACT

**The aim:** To study changes in the chemical composition of the tooth enamel surface when using hydrogen peroxide as a chemical component of the whitening system in combination with professional oral hygiene.

**Materials and methods:** To achieve this goal, during the study, we studied the enamel of the teeth of the frontal area, which was removed for orthodontic and orthopedic indications. The age of the patients whose teeth were examined ranged from 18 to 44 years. In the experiment, we studied the chemical structure of enamel by a method thatcovered the selection of the study area, with the designation of areas for microanalysis, and subsequent elemental analysis in selected areas of the enamel.

**Results and conclusions:** Analyzing the results of this study, we can make assumptions about the impact of professional dental hygiene on the procedure of photo-whitening teeth based on 35% hydrogen peroxide gel and its subsequent impact on theother clinical indicators, which will depend on the characteristics of functional and structural resistance of the enamel.

**KEY WORDS:** teeth whitening, tooth color, aesthetics, chemical composition of enamel, hydrogen peroxide

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## INTRODUCTION

The aesthetics of a smile needs further study and improvement. This is confirmed by scientific studies, which were published based on the results of social surveys [1,2].

74% of respondents believe that an imperfect smile has a negative impact on their career, and 92% believe that it contributes to success in personal life. The desire of patients to have an aesthetically perfect smile has always aroused great interest of dentists and led to the active development of such a direction in aesthetic dentistry as restoration and teeth whitening [3].

Much attention in this aspect is paid to the issue of tooth color in connection with the increased aesthetic requirements of patients to restore or reconstruct their smile [4]. The procedure of professional whitening in modern dentistry is quite a popular method. Various clinical and experimental aspects of the effect of whitening systems on the structure of tooth hard tissues are reflected in the modern literature. Teeth whitening is a chemical oxidation process in which free radicals of hydrogen peroxide are released, which leads to the lightening of the hard tissues of the tooth. Currently, teeth whitening is popular as a non-invasive way to improve the aesthetics of dentitions[5,6].

Methods of correction of tooth discoloration are quite diverse. Modern bleaching systems are based on the use of hydrogen peroxide or urea peroxide in combination with activating factors [7]. Bleaching substances are applied externally or placed internally in the tooth cavity during whitening depulped teeth. In both cases there is a tendency to whiten the chromogens inside the dentin, thus changing the basic color of the tooth [8,9].

## THE AIM

The purpose of this study became a study changes in the chemical composition of the tooth enamel surface when using hydrogen peroxide as a chemical component of the whitening system in combination with professional oral hygiene.

## MATERIALS AND METHODS

To achieve this goal, during the study, we studied the enamel of the teeth of the frontal area, which was removed for orthodontic and orthopedic indications. The age of the patients whose teeth were examined ranged from 18 to 44 years according to the WHO classification (2018).

In the experiment, we studied the chemical structure of enamel by specially preparing teeth and establishing areas for chemical microanalysis.

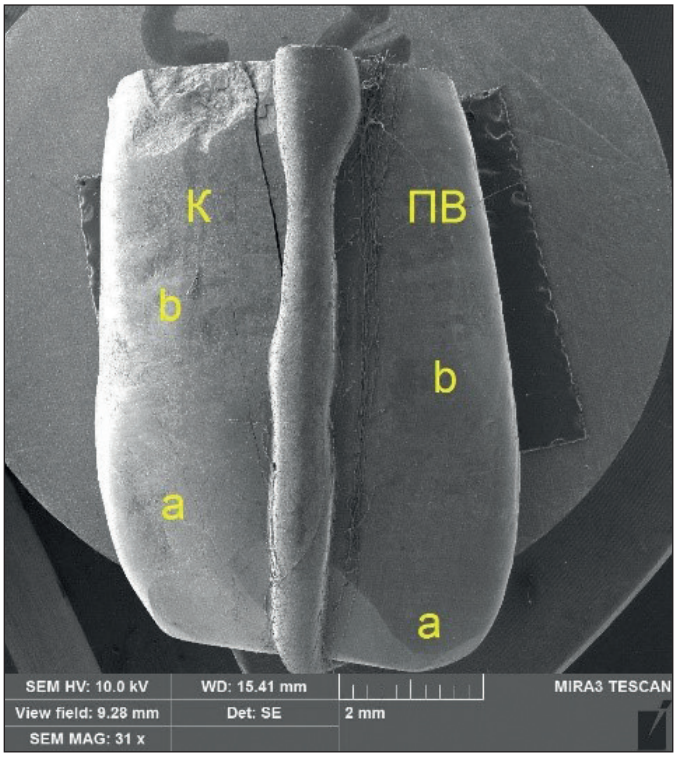


**Fig. 1.** Photo of the examined tooth 21 from group II with the applied distribution line (control - right, left - application of hydrogen peroxide without prior professional hygiene).

The study was performed using an energy-dispersive spectrometer "X-max 80mm2" ("Oxford Instruments", UK), which was integrated into a scanning electron microscope. The research was conducted on the basis of the Paton's Institute, Department of Nanomedical Technology (Kyiv).

The proposed research system allowed to determine the chemical structure of the enamel without the traditional procedure for dielectric samples to cover the surface with a thin layer of conductive material (C, Au, Pt). It was possible to prevent surface charge due to the significant reduction of the probe current and the high sensitivity of the detectors. The study of the elemental composition using an energy-dispersive spectrometer allows to detect chemical elements in the sample with atomic numbers from 4 to 92 and to quantify their composition.

To analyze and compare the composition and characteristics of the samples, an algorithm for their evaluation was developed, the same for all samples studied.

The method included the selection of the studied area with the designation of areas for microanalysis, followed by elemental analysis in selected areas of the enamel. Areas of microanalysis were zoned, depending on the effect of the chemical agent on the enamel surface.

The peculiarity was that the study areas differed from the right and left sides of the tooth, due to the fact that the left side in the examined teeth was the control area, and the right side allowed us to conduct and compare changes in the chemical component of enamel in each tooth. , by comparing indicators with each other.

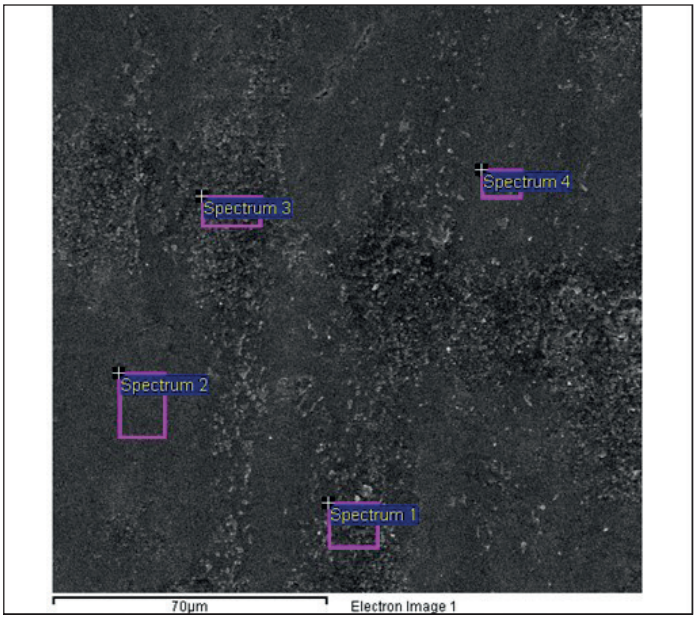


**Fig. 2.** Areas for studying the micronutrient composition of tooth 21 from the II research group (right).

To carry out laboratory methods of research, the studied teeth were divided into two groups, the vestibular surface of the teeth under study was conditionally divided into two sides - one of which served as a control, and the other was used to apply whitening chemicals:

Group I - teeth, without prior professional hygiene, for whitening which used the method of photobleaching using 35% concentration of hydrogen peroxide.

Group II - teeth with previous professional hygiene, for whitening which used the method of photobleaching using 35% concentration of hydrogen peroxide.

The technique of professional oral hygiene included the following stages:

1. Removal of hard and soft dental plaque with an ultrasonic tip.
2. Polishing enamel with a medium-hard nylon brush and polishing paste Cleanic (Kerr) RDA 27.

Next, a professional bleaching procedure was performed using a cold light lamp (Philips ZOOM! White Speed) and gels based on 35% hydrogen peroxide.

## RESULTS AND DISCUSSION

Description. Teeth taken for the experiment were to be removed from orthodontic and orthopedic indications. The tooth to be examined (Fig. 1) was divided into 2 parts using a liquid rubber dam.

Markings were made: K-left side of the control, PV-right side, the area that was subject to professional hygiene (or without) and professional bleaching with 35% hydrogen peroxide, and b - areas that were taken for the study of enamel.

Next, the analysis of micro-plots was performed and data were obtained. In fig. 2 we can see the selected areas (spectrum 1,2,3,4) for the analysis of the chemical composition of the enamel. The results obtained are shown in

**Table I.** Quantitative indicators of the chemical composition of the tooth 11 (group I)

| Spectrum | In stats. | C | N | Oh | On | P | Cl | Ca | Total |
|---|---|---|---|---|---|---|---|---|---|
| Spectrum 1 | Yes | 45.52 | 11.75 | 26.59 | | 6.20 | 0.78 | 9.17 | 100.00 |
| Spectrum 2 | Yes | 26.39 | | 36.50 | 0.38 | 13.86 | | 22.86 | 100.00 |
| Spectrum 3 | Yes | 56.23 | 16.00 | 23.97 | | 1.67 | | 2.13 | 100.00 |
| Spectrum 4 | Yes | 24.29 | | 38.29 | | 13.77 | 0.88 | 22.78 | 100.00 |
| Max. | | 56.23 | 16.00 | 38.29 | 0.38 | 13.86 | 0.88 | 22.86 | |
| Min. | | 24.29 | 11.75 | 23.97 | 0.38 | 1.67 | 0.78 | 2.13 | |

Processing option: All elements analyzed (Normalized)
All results in weight%

**Table II.** Quantitative indicators of the chemical composition of tooth 21 (group II)

| Spectrum | In stats. | C | Oh | On | P | Cl | Ca | Total |
|---|---|---|---|---|---|---|---|---|
| Spectrum 1 | Yes | 27.79 | 30.43 | 0.64 | 15.41 | 1.12 | 24.61 | 100.00 |
| Spectrum 2 | Yes | 49.78 | 30.10 | 1.70 | 7.11 | | 11.31 | 100.00 |
| Spectrum 3 | Yes | 28.55 | 31.49 | 0.51 | 14.64 | 1.20 | 23.62 | 100.00 |
| Spectrum 4 | Yes | 46.95 | 31.17 | 1.37 | 8.21 | | 12.31 | 100.00 |
| Max. | | 49.78 | 31.49 | 1.70 | 15.41 | 1.20 | 24.61 | |
| Min. | | 27.79 | 30.10 | 0.51 | 7.11 | 1.12 | 11.31 | |

Processing option: All elements analyzed (Normalized)
All results in weight%

**Table III.** Comparison of the chemical composition of tooth enamel in the norm and with the use of bleaching agents from hydrogen peroxide 35% without prior professional dental hygiene (at $p < 0.05$) between the indicators research

| Chemical element | Control | Group I | P |
|---|---|---|---|
| | N = 56 | N = 56 | |
| C | 45.91 ± 1.20 | 42.46 ± 1.74 | 0.128 |
| O | 23.03 ± 0.63 | 26.18 ± 0.81 | 0.007 |
| Na | 0.38 ± 0.03 | 0.57 ± 0.05 | 0.006 |
| P | 9.77 ± 0.39 | 9.56 ± 0.75 | 0.792 |
| Cl | 0.14 ± 0.03 | 0.16 ± 0.53 | 0.654 |
| Ca | 15.96 ± 0.64 | 15.21 ± 1.22 | 0.570 |
| Si | 0.37 ± 0.10 | 0.68 ± 0.30 | 0.213 |
| N | 2.89 ± 0.40 | 4.35 ± 0.76 | 0.075 |
| Mg | 0.07 ± 0.01 | 0.01 ± 0.01 | 0.034 |
| Al | 0.06 ± 0.02 | 0.09 ± 0.04 | 0.475 |
| Au | 1.37 ± 0.56 | 0.00 ± 0.00 | 0.143 |
| F | 0.00 ± 0.00 | 0.02 ± 0.01 | 0.004 |
| Ba | 0.00 ± 0.00 | 0.45 ± 0.25 | 0.004 |

tables I and II. Next, a study was conducted to determine the average values.

As a result of statistical data processing, we have the indications shown in tables III and IV.

When comparing the indicators relating to the chemical composition of the enamel in the norm and when using bleaching agents in the form of 35% hydrogen peroxide should be noted the following data indicators that have sig-

**Table IV.** Comparison of the chemical composition of tooth enamel in the norm and with the use of bleaching agents from hydrogen peroxide 35% with previous professional teeth cleaning (at p <0.05) between the indicators of the study

| Chemical element | Control Group N = 56 | Group II N = 56 | P |
|---|---|---|---|
| O | 36.32 ± 0.63 | 31.53 ± 0.81 | 0.000 |
| Na | 0.48 ± 0.02 | 0.51 ± 0.05 | 0.578 |
| P | 14.7 ± 0.30 | 14.18 ± 0.52 | 0.369 |
| Cl | 0.82 ± 0.05 | 0.83 ± 0.07 | 0.853 |
| Ca | 23.95 ± 0.49 | 23.41 ± 0.96 | 0.601 |
| Si | 0.05 ± 0.04 | 0.00 ± 0.00 | 0.257 |
| N | 0.00 ± 0.00 | 0.28 ± 0.28 | 0.262 |
| Mg | 0.00 ± 0.00 | 0.02 ± 0.01 | 0.114 |
| Al | 0.01 ± 0.01 | 0.00 ± 0.00 | 0.211 |
| Au | 1.25 ± 0.61 | 0.00 ± 0.00 | 0.071 |
| F | 0.05 ± 0.03 | 0.05 ± 0.03 | 0.979 |
| C | 28.55 ± 0.55 | 27.79 ± 0.08 | 0.543 |

nificant differences. Differences between indicators relate to carbon, sodium, chlorine, magnesium and nitrogen. At research significant decrease is noted amounts of carbon, sodium, silicon, magnesium and gold.

When conducting a comparative analysis between areas where professional cleaning was used and where it was not used, it should be noted that a significant difference between the indicators according to the results of the study was observed for nitrogen, sodium, silicon, aluminum and carbon, at p <0.05.

Elements such as sodium, phosphorus and calcium play a special role in the structure of enamel, the change in the number of which causes changes in the structure of the hard tissues of the teeth, which is directly related to the morphological features of their structure.

If we adopt as an standard enamel with the ideal formula Ca5 (PO4) 3OH, it is possible to assume changes in the ideal formula of hydroxyapatite with the possibility of replacing calcium ions with magnesium or sodium ions or exchange in $PO^{3-}_4$ for $CO^{2-}_3$ and $HPO^{2-}_4$. We can make assumptions about the substitution of carbon in the hydroxy group for compounds with oxygen, fluorine, chlorine or water molecules.

Comparing comparisons of indicators in the experimental groups statistically obtained a difference in carbon levels with changes from 42.46 on the surface, which was subject to professional bleaching with hydrogen peroxide 35% without professional cleaning to 27.79 using bleach based on hydrogen peroxide 35% and previous professional cleaning. There is also a decrease in the amount of nitrogen from 4.35 to 0.28 and the amount of silicon from 0.68 to 0.00, aluminum from 0.09 to 0.00. As well as reducing sodium from 0.57 to 0.51. Decreased levels of these micronutrients may indicate that when performing a protocol that includes professional brushing, the number of the above micronutrients may be reduced. It is their reduction, in our opinion, can lead to increased sensitivity in the rehabilitation period during the restoration of the chemical composition of the enamel.

All other indicators increase slightly, which may be due to the impact on the surface layer of enamel and the exposure of the subsurface layer, which has a slightly different structure and therefore a different trace element composition. The change of all these indicators will significantly affect the clinical indicators, which, in turn, will depend on the characteristics of functional and structural resistance of the enamel.

## CONCLUSIONS

Therefore, the results of the evaluation of the experiment in two groups show a decrease in elements such as carbon, sodium, silicon, nitrogen and aluminum.

We can conclude that professional hygiene can affect the trace element composition of the enamel in combination with professional clinical whitening.

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ORIGINAL ARTICLE

# LYMPHOTROPIC ADMINISTRATION OF ANTIBACTERIAL DRUGS – A METHOD OF RATIONAL ANTIBIOTIC THERAPY

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## ABSTRACT

**The aim:** To explore the possibilities of rationalizing antibacterial therapy by comparative analysis of the accumulation of ceftriaxone administered lymphotropically and intramuscularly.

**Materials and methods:** The research used a method of studying the sensitivity of microorganisms to antibacterial drugs, which is based on the diffusion of antibacterial drugs from the carrier (homogenate of the test organ) in a dense nutrient medium, which, depending on the sensitivity of microorganisms, inhibits the growth of the studied culture and is accompanied by the formation of a growth inhibition zone (GIZ) in the nutrient medium. For control purposes, a commercial disk with ceftriaxone was used, which caused GIZ of microorganisms at the level of 27.05 ± 0.9 mm.

**Results:** The homogenate of organ samples obtained from rabbits administered with the antibiotic lymphotropically, inhibited the growth of test cultures around the discs in all cases. The inhibition was slightly less than the control inoculation, but the result clearly indicated the presence of antibiotics in the test material in the quantity sufficient to inhibit the growth of the pathogen. Concurrently, after intramuscular administration of the antibiotic, biopsy specimens from various growth inhibition organs of test cultures were either not induced at all or were induced in small amounts, which was certainly insufficient for the inhibitory action of the drug administered by this method.

**Conclusions:** The administration of the antibiotic lymphotropically promotes its accumulation in all organs in the quantity sufficient for antibacterial action, which allows us to recommend lymphotropic therapy as a rational method of antibiotic therapy.

**KEY WORDS:** lymphotropic therapy, antibiotic therapy, ceftriaxone

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## INTRODUCTION

Recently, the issue of optimizing antibacterial therapy has become acute. This is primarily due to the growing number of infectious and suppurative and inflammatory diseases and their complications, as well as increasing the resistance of pathogenic microflora to antibiotics accompanied by a decrease in the effectiveness of the latter and the growth of various complications [1]. Unfortunately, it becomes clear that the development of new antibiotics does not solve this problem. Therefore, to achieve the desired result, the antibacterial drug dose should be increased, which, accordingly, increases the number of toxic and allergic manifestations. Complications mostly occur with the use of expensive most advanced antibacterial drugs, which, among other things, are not available to all patients [1]. Given the above, the issue of rational antibiotic therapy, which can reliably maintain a sufficient inhibitory antibiotic concentration in the body (bacteriostatic or bactericidal), without causing toxic stress and other adverse effects in the patient is very important, raises many questions.

Many authors, in particular, R. T. Panchenkov, Yu. E. Vyrenkov and I. V. Yarema [2] highlighted the role of the lymphatic system in the pathogenesis of suppurative and inflammatory diseases. The authors emphasize that the lymphatic system is the first to react to any «regional» aggression, including the inflammatory process of any localization [3, 4]. The hemolymphatic barrier in each region of the human body is represented by a system of blood and lymph vessels and lymph nodes, which create mechanical, physicochemical, and biological protection of organs and tissues of this region due to the active functioning of the endothelium of blood vessels, capillaries, and interstitial layers from the penetration of pathogens into the relevant organs. Metabolic processes between blood, interstitial fluid, and lymph, as well as cells of organs and systems, are in close active interaction. The change in the intercellular substance during inflammation affects its permeability and changes according to the course of pathological processes [5-7]. Spasm in the microvascular bed, slowing of blood flow, and inhibition of metabolic processes, which results in the accumulation of acidic metabolic products in the interstitium and leads to reduced outflow on the background of dilatation of precapillary sphincter mechanisms and, consequently, increased hypoxia and acidosis accompanied by tissue edema and dysfunction of cellular structures [5, 8]. Disruption of blood flow in the region helps to go beyond the vascular bed of fluid and blood-formed elements leading to increased blood viscosity, activation of adhesion, and aggregation of formed elements. The above-mentioned is accompanied by sludge formation and causes

tissue necrosis of varying prevalence. The pressure in the affected tissues and lymph nodes increases, which blocks capillary blood flow and the entry of anti-inflammatory and antibacterial drugs into the area of inflammation, as well as the excretion of products of pathological metabolism. Considering this, the leading role in maintaining the proper functional level of homeostasis in the inflammation zone should be played by the regional lymphatic system, which is also affected [8, 9]. Taking this into account, it becomes obvious that by influencing the physiological state of the lymphatic system and its rehabilitation, it is possible to prevent homeostasis in the relevant part of the human body, which is identical to the prevention or reversal of the inflammatory process.

It has been studied that the current method of lymphotropic antibiotic therapy can be used for targeted delivery of antibiotics to the affected organ against the background of effective rehabilitation of the lymphatic system [10, 11]. At the same time, a stable therapeutic concentration of the antibiotic in the relevant tissues is maintained for a long time, even when used in small doses. Given this, we believe that there are all prerequisites for studying the targeted supply of antibacterial drugs to the selected region or diseased organ by applying our proposed method of lymphotropic supply of antibiotics and other anti-inflammatory drugs to various organs, which determines the relevance of the issue.

## THE AIM

To explore the possibilities of rationalizing antibacterial therapy by comparative analysis of the accumulation of ceftriaxone administered lymphotropically compared to intramuscular administration of the drug to specific organs.

## MATERIALS AND METHODS

We experimentally studied the accumulation of the antibiotic in the tissues of various organs after its lymphotropic administration in comparison with the accumulation of the drug after intramuscular administration. The antibiotic ceftriaxone was chosen for the study, which according to the literature is most often used in surgical hospitals and has a fairly high (59%) inhibitory capacity for intra-abdominal microflora, including the microflora of the pancreas and retroperitoneal tissue with resistance to 32% [12].

## RESULTS

In the course of the research, the method of studying the sensitivity of microorganisms to antibacterial drugs was used according to the order of the Ministry of Health of Ukraine № 167 of 05.04.2007 «On the approval of guidelines of «The determination of the sensitivity of microorganisms to antibacterial drugs».

During the experiment, ceftriaxone was lymphotropically administered in experimental rabbits regionally in five different parts of the body according to the organ to be studied: in the right iliac region, left iliac region, right paravertebral region, left paravertebral region. The essence of the lymphotropic method of antibiotic administration was the regional sequential administration of drugs that stimulate lymph secretion to antispasmodics, anticoagulants, anti-inflammatory drugs, and antibiotics.

The drug was injected intramuscularly into the posterior-upper quadrant of the left gluteal muscle. One hour after the drug administration, the animals were removed from the experiment after overdosing on the analgesic drug.

Eight tissue samples were obtained from different abdominal organs from each rabbit: the body of the stomach, the middle part of the small intestine, blind intestine, sigmoid intestine, omentum, the body of the pancreas, parietal peritoneum in the right hypochondrium, liver.

The weight of each sample was determined on electronic scales AD – 200. Their weight ranged from 0.152 g. to 0.354 g. The homogenate was then prepared from the samples and pipetted into an Eppendorf tube using an automatic pipette, where a similar volume of saline was added, that is a 1:1 dilution was obtained. The study of the presence of the antibiotic was performed by the diffusion method based on the diffusion of the antibacterial drug (ABD) from the carrier (homogenate of the studied organ) into a dense nutrient medium that inhibits the growth of the studied laboratory culture. The formation of a growth inhibition zone (GIZ) was due to the diffusion of ABD from the homogenate of the test organ into the nutrient medium – Mueller-Hinton agar, prepared from a dry preparation of industrial production following the manufacturer's instructions. 90 mm diameter Petri dishes were used in the research. 20 $cm^3$ of the prepared medium was added to each cup, which allowed obtaining a layer of agar with a 4 mm thickness. The plates were then left at room temperature to solidify the agar. Before the inoculation of the laboratory culture of Escherichia coli, the plates were dried in a thermostat at 35 °C with the lid open for 10–20 minutes to ensure the absence of liquid condensation on the inner surface of the lids. Then, a suspension of the microorganism *Escherichia coli* ATCC 25922 was prepared using a densilameter, the concentration of the microorganism was 1.5 x $10^8$ colony-forming units / $cm^3$, which at visual inspection corresponded to a turbidity standard of 0.5 according to McFarland. The standard inoculum was pipetted onto the surface of a Petri dish with a nutrient medium in a volume of 1–2 $cm^3$, distributing it evenly over the surface by shaking. The excess inoculum was removed with a pipette. The opened Petri dishes were dried at room temperature for 10–15 minutes. As a control, a standardized commercial disk with ceftriaxone was applied to each plate, which caused a zone of growth retardation on Petri dishes at the level of 27.05 ± 0.9 mm.

In the preparation of the carrier (antibacterial drug) (antibiotic), cardboard disks were immersed in the homogenate of the corresponding organ, after which sterile tweezers were applied to the agar surface. The distance between the discs and the edge of the cup was 15–20 mm. To ensure equal contact with the agar surface, the discs were gently pressed with tweezers. On each plate, 5 disks

**Table I.** The dynamics of growth inhibition zones of test culture

| № | Samples | Growth inhibition zone (mm) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Intramuscular administration n=10 | Lymphotropic administration | | | | Control n=10 |
| | | | Right iliac n=10 | Left iliac n=10 | Right paravertebral n=10 | Left paravertebral n=10 | |
| 1 | Stomach | Absent<br>* | 11,95±1,79<br>*# | 13,7±1,59<br>*# | 15,05±1,61<br>*# | 15,65±1,66<br>*# | 27,05±0,9<br># |
| 2 | Small intestine | 2,7±1,03<br>* | 19,25±1,62<br># | 18,3±1,66<br>*# | 10,55±1,85<br>* | 13,3±1,69<br>*# | 27,05±0,9<br># |
| 3 | Blind intestine | 1,95±1,1<br>* | 19,15±2,03<br># | 14,8±1,74<br>*# | 11,65±1,9<br>*# | 9,4±1,64<br>* | 27,05±0,9<br># |
| 4 | Sigmoid intestine | 2,2±1,11<br>* | 14,25±1,97<br>*# | 18,45±1,85<br># | 9,25±1,37<br>* | 9,75±1,48<br>*# | 27,05±0,9<br># |
| 5 | Omentum | 2,4±1,19<br>* | 14,6±1,76<br># | 13,6±1,67<br>*# | 12,45±1,61<br>*# | 11,5±1,15<br>* | 27,05±0,9<br># |
| 6 | Pancreas | Absent<br>* | 9,65±1,84<br>*# | 10±1,75<br>*# | 17,1±1,68<br>*# | 18,1±1,86<br>*# | 27,05±0,9<br># |
| 7 | Parietal peritoneum | 2,85±1,04<br>* | 13,85±1,93<br># | 11,8±2,12<br>*# | 12,45±1,79<br>*# | 10,7±1,69<br>*# | 27,05±0,9<br># |
| 8 | Liver | Absent<br>* | 7,65±1,63<br>*# | 5,8±1,79<br>*# | 9,6±1,73<br>*# | 8,75±1,74<br>*# | 27,05±0,9<br># |

Note: *- the probability of difference from the values of the control group (p <0,05),
# - probability of difference from the values of the comparison group (intramuscular injection) (p <0,05)

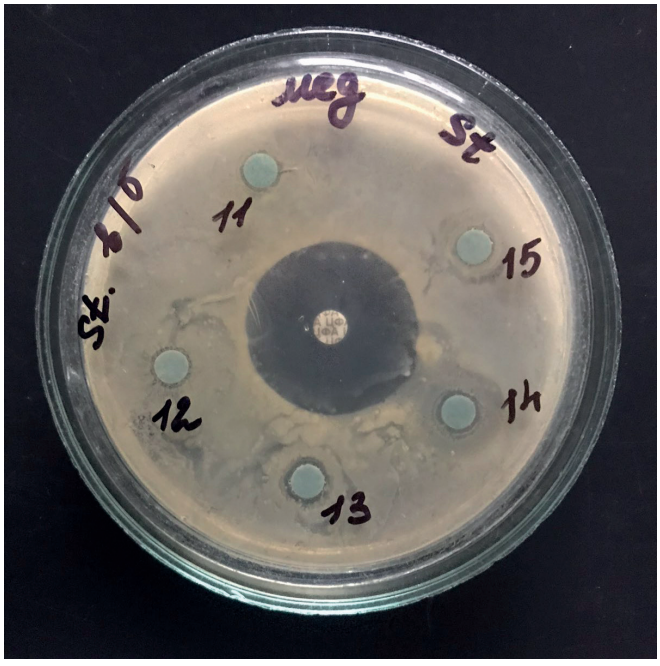


**Fig. 1.** Growth inhibition zones of the laboratory culture one hour after the intramuscular administration of the antibiotic

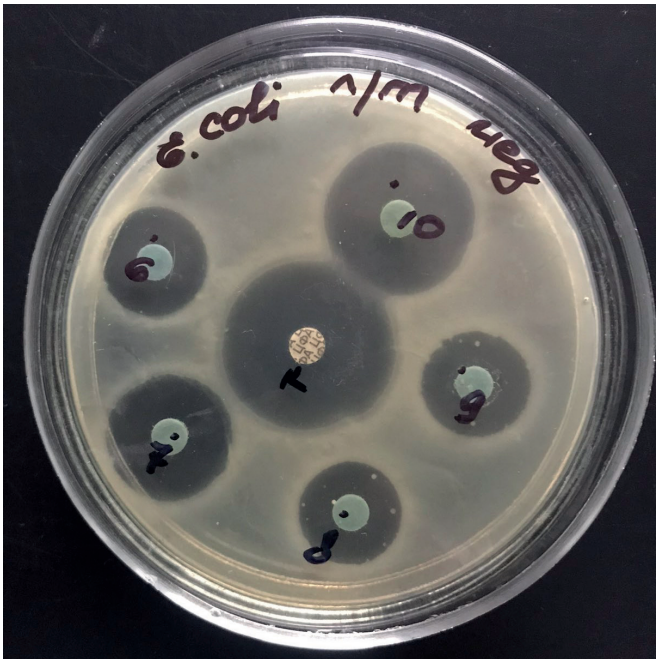


**Fig. 2.** Growth inhibition zones of the laboratory culture influenced by lymphotropic therapy 1 hour after the antibiotic administration

with samples of the studied organs and a control disk with ceftriaxone were placed. Immediately after the application of disks, the Petri dishes were placed in a thermostat upside down and incubated at 35 °C for 24 hours.

After the incubation, the results were determined. For this purpose, the cups were placed upside down on a dark matte surface so that light fell on them at an angle of 45°. The diameter of the growth retardation zones was measured around the disks with the investigated material to the nearest 1 mm using a caliper.

The obtained data were statistically processed according to standard formulas. Continuous data are presented as

mean ± standard deviation (M ± SD). Differences between the two groups in continuous variables were analyzed using the nonparametric Kruskal-Wallis H test. Values of $P<0.05$ were considered statistically significant.

The results are shown in Table I.

The table shows that the homogenate of the samples of the studied organs obtained from the studied animals to which the antibiotic was administered lymphotropically inhibited the growth of *Escherichia coli* in the discs' zones in all cases. The growth of the test culture under the action of homogenates of tissues obtained from animals after lymphotropic administration of ceftriaxone was inhibited slightly less than the control seeding. However, the result indicates the presence of antibiotics in the test material in a quantity sufficient to inhibit the growth of the pathogen (*Escherichia coli*).

However, after the intramuscular administration of the antibiotic, biopsy specimens from various organs did not inhibit the growth of *Escherichia coli* at all or caused a negligible amount, which was insufficient for the inhibitory effect of the drug administered in this way.

Thus, the table shows the complete absence of growth inhibition zones after intramuscular administration of ceftriaxone in the wall of the stomach, pancreas, and liver, indicating the absence of drug accumulation in these organs. In other organs (small, blind, and sigmoid intestines, omentum, parietal peritoneum) the growth inhibition zones of laboratory test culture *Escherichia coli* were in the range of 1.9–2.8 mm, which is 7.2–10.4% of the control effect of pure antibiotic (standardized disc with the drug). After the lymphotropic administration of the antibiotic, the small intestine homogenate caused GIZ in the test culture of *Escherichia coli* in the range of 71.2–67.7% to the action of pure antibiotic; the appendix homogenate caused GIZ at the level of 70.8–54.7% to the control; sigmoid intestine homogenate caused GIZ at the level of 68.2–51.8% to the control; the homogenate of the omentum caused GIZ at the level of 54–50.3% to the control; parietal peritoneal homogenate caused GIZ at the level of 51.2–46% to the control; liver homogenate caused GIZ at the level of 35.5–32.4% compared to the control. The given sizes of GIZ of *Escherichia coli* are taken by us on their maximum values at various regional zones of lymphotropic administration of the drug.

## DISCUSSION

Thus, the maximum inhibitory effect of the homogenate of samples of small, blind, and sigmoid intestines, omentum, and parietal peritoneum was manifested maximally by lymphotropic administration of the antibiotic in the right iliac region, approaching the control effect of the pure antibiotic. However, the most intense inhibitory effect of homogenates of the stomach, pancreas, and liver was observed after lymphotropic administration on the drug in the right or left paravertebral zone. An example of the clinical effectiveness of the results is our first attempt to treat acute pancreatitis by lymphotropic administration of antibiotics and anti-inflammatory drugs [12]. From the above, it can be assumed that in diseases and injuries of the abdominal cavity in case of traffic and military explosive and shooting injuries, the selective area for the lymphotropic administration of ceftriaxone should be the right or left iliac zones, and in acute pancreatitis and retroperitoneal injuries – the right or left paravertebral zones.

Because of this, it is clear that there is no or insufficient therapeutic effect under the influence of standard methods of antibiotic administration, accompanied by significant mortality, which, for example, in acute infected pancreatitis reaches 70-80% [13], because according to the data antibiotic (ceftriaxone) in these methods injection into the pancreas does not

## CONCLUSIONS

1) 1 hour after the intramuscular administration of ceftriaxone in experimental animals, its accumulation is not observed in the wall of the stomach, pancreas, and liver. In other organs (small, blind, sigmoid intestines, omentum, parietal peritoneum), the antibiotic accumulates in the quantity insufficient for the inhibitory effect of the drug on the growth of *Escherichia coli*.
2) The administration of the antibiotic lymphotropically promotes its accumulation in all organs in an amount sufficient for antibacterial action.
3) Given the lymphatic link in the pathogenesis of acute inflammation of any organ, empirical rehabilitation of the area should be carried out by the lymphotropic administration of antibiotics.
4) This method of administration of antibacterial drugs should be rationally used as a preparation for surgery, starting their administration 1–2 hours before surgery and continuing in the postoperative period, or as an independent method in conservative treatment. This administration of antibiotics in the presence of retroperitoneal hematoma is especially important. In infected pancreatitis, the method of lymphotropic therapy is considered the major [12].

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*The Authors declare no conflict of interest.*

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ORIGINAL ARTICLE

# COMPARISON OF FREE RADICAL LIPID PEROXIDATION PROCESSES IN PATIENTS WITH PRIMARY AND SECONDARY GLAUCOMA

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## ABSTRACT

**The aim:** To investigate and compare the effects of free radical lipid peroxidation, antioxidant supply and the state of hydro- and hemodynamics of the eye on the course and progression of the glaucoma process in patients with primary and secondary glaucoma.

**Materials and methods**: We observed 123 patients with primary and secondary glaucoma and 58 apparently healthy individuals, constituting the control group. The first group included 62 patients diagnosed with primary compensated glaucoma. The remaining 61 patients, who constituted the second group of subjects, were included in the study with a diagnosis of secondary compensated glaucoma.

**Results**: Clinical examination of patients with primary compensated glaucoma in winter demonstrates a statistically significant decrease in intraocular fluid production, decreased outflow and reduced actual intraocular pressure, whereas in summer and autumn these figures were less pronounced. Observations of patients with secondary compensated glaucoma also showed a statically significant decrease in the production of chamber fluid and a decrease in the coefficient of outflow in winter. Similar tendencies were confirmed by hemodynamic changes. During this period, the relative pulse volume of the blood entering the eye is significantly reduced, in the summer and autumn period, the deficit of blood supply to the eye is less pronounced.

**Conclusions**: The results of the research indicate the proliferative form of peroxide mechanisms in the pathogenesis of glaucoma of both types, which is the basis for using inhibitors of free radical lipid oxidation – antioxidant preparations – in the comprehensive therapy of these diseases. The identified features of clinical and biochemical disorders, based on the season of examination, are the basis for the development of differentiated regimens for the use of antioxidants in the treatment of glaucoma.

**KEY WORDS:** free radical lipid peroxidation, primary and secondary glaucoma

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## INTRODUCTION

Glaucoma is a multifactorial disease, therefore, many factors of its pathogenesis are currently known. The causes of the development of primary open-angle glaucoma (POAG) are genetic factors, hydrodynamic, neurovascular and immunological changes, but a special role belongs to metabolic disorders [1,2]. The basis for the formation and progression of many pathological diseases and conditions and glaucoma in particular, as well as their unfavorable prognosis, is the activation of free radical peroxidation in organs and systems of the body against the background of reduced functionality of antioxidant defense [3,4]. Imbalance due to the stimulation of free radical oxidation (FRO) and decreased antioxidant activity (AA), often leads to the accumulation of FRO products, which have extremely high reactivity, inducing the modification of the structure of lipids, proteins and nucleoproteins, and other important molecules. This subsequently leads to the induction and progression of various pathological processes in humans. At present, glaucoma is also considered a neurodegenerative disease, since the development of degenerative changes is observed not only in retinal ganglion cells and healthy nerve fibers, but also in the tissues of the conduction tracts of the visual analyzer and cerebral cortex [5]. Also common to neurodegenerative diseases and POAG are selective death of nerve cells of a certain type by apoptosis, elderly age of patients, increasing incidence with age, genetic determinism and long latency. Therefore, determining the impact of metabolic disorders on the progression and course of glaucoma is a very important issue in modern ophthalmic practice.

## THE AIM

The aim of the research is to investigate and compare the effects of free radical lipid peroxidation, antioxidant supply and the state of hydro- and hemodynamics of the eye on the course and progression of the glaucoma process in patients with primary and secondary glaucoma.

## MATERIALS AND METHODS

We observed 123 patients with primary and secondary glaucoma and 58 apparently healthy individuals, of whom 30 were examined in the winter and spring period, and 28 – in summer and autumn, constituting the control

**Table I.** Biochemical parameters in healthy individuals depending on the seasonality of observation

| Parameters | Number of observervations | Winter-spring | Number of observervations | Summer-autumn |
|---|---|---|---|---|
| β- and pre-β-lipoproteins, g / l | 30 | 5.67 ± 0.20 | 28 | 5.20 ± 0.2<br>p<0.01 |
| TBA reactants, units / ml | 30 | 0.15±0.01 | 28 | 0.07±0.0001<br>p<0.001 |
| AHP content, units / ml | 30 | 4.79±0.40 | 28 | 3.59±0.5<br>p<0.01 |
| SHE,% | 30 | 11.77±1.04 | 28 | 8.82±0.41<br>p<0.02 |

**Table II.** The state of hydro- and hemodynamics of the eye in healthy individuals depending on the seasonality of observation

| Parameters | Winter-spring n=30 | Summer-autumn n=28 |
|---|---|---|
| P0, mmHg | 17.50±0.30 | 18.40±0.40<br>p<0.01 |
| C, mm3/min | 0.42±0.006 | 0.44±0.004<br>p<0.01 |
| F, mm3/min | 3.45±0.08 | 3.50±0.08<br>p<0.1 |
| RQ, % | 3.40±0.08 | 3.50±0.03<br>p<0.1 |
| PV, mm3 | 13.90±0.40 | 13.50±0.10<br>p<0.01 |

group. The first group included 62 patients diagnosed with primary compensated glaucoma, 32 patients in this group were examined in the winter and spring period, and 30 patients – in the summer and autumn period. The remaining 61 patients, who constituted the second group of subjects, were included in the study with a diagnosis of secondary compensated glaucoma, of which 31 patients were examined in the winter and spring period, and 30 patients – in the summer and autumn period. All patients received traditional antiglaucoma therapy. The mean age of patients was 64.7 ± 8.43, from 54 to 81 years. All patients underwent general clinical and ophthalmological examinations, namely: visometry, tonometry, perimetry. To assess the hydrodynamics of the eye, we studied tonography according to A.P. Nesterov. The actual intraocular pressure (P0), the coefficient of outflow (C), the production of chamber fluid (F), and the Becker coefficient (BC) were determined. To assess the hemodynamics of the eye, ophthalmorheography was performed using a rheographic device 4RG-1A and an electroencephalograph according to the method of L.A. Katznelson. The obtained data were evaluated by the rheographic coefficient (RC) and pulse volume of the blood (PV). Along with ophthalmological examination, additional research methods were applied, namely: biochemical analysis of blood with the study of acylhydroperoxides (AHP) in the fraction of β- and pre-β-lipoproteins, 2-thiobarbituric acid (TBA-reactants), superoxide dismutase (SOD) and spontaneous hemolysis of erythrocytes (SHE). All results of biochemical studies and clinical observations were statistically processed using the software «Statistica for Windows».

## RESULTS AND DISCUSSION

When observing patients of the control group (58 apparently healthy individuals), in whom the somatic status corresponded to the age norm, the following average indicators of biochemical examination were revealed: β- and pre-β-lipoproteins 4.94 ± 0.16 g / l, SHE 12.20 ± 0.49%, catalase activity 1.79 ± 0.03 units / $10^6$ erythr., SOD – 2.36 ± 0.11 units / ml, ceruloplasmin 36.0 ± 0.63 units / ml, content of TBA reactants 16.63 ± 1.90 units extr / ml, AHP content 4.82 ± 0.33 units extr / ml.

Due to the seasonality of alimentary antioxidants, we analyzed biochemical parameters in this group of subjects in different seasons of the year (Table I).

Comparing the activity of antioxidant enzymes, we found that in the winter and spring period, the activity of SOD and catalase (p<0.001) in apparently healthy individuals is lower. We found a pattern of rising levels of β- and pre-β-lipoproteins in the winter and spring period (p<0.01). The results were interpreted as the norm. Hydro- and hemodynamic values in the control group, which were examined in different seasons, are given in Table II. We found no statistically significant difference in the values observed in this group by sex, age, and in different seasons.

During the examination of patients of group 1 (32 patients) with primary compensated glaucoma in the winter and spring period, significant changes in the hemodynamics of the eye were revealed. There was a decrease in the rheographic coefficient in patients with primary glaucoma, examined in the winter and spring period, as compared to the control group: in healthy individuals, this figure was 3.47 ± 0.06%, in patients of group 1 – 2.2 ± 0.04 %

**Table III.** The state of hydro- and hemodynamics of the eye in patients with primary glaucoma, examined in the winter and spring period

| Parameters | Control group n=30 | Group 1 n=32 |
|---|---|---|
| P0, mmHg | 17.50±0.30 | 16.00±0.08<br>p<0.001 |
| C, mm3/min | 0.42±0.006 | 0.52±0.004<br>p<0.1 |
| F, mm3/min | 3.45±0.08 | 5.60±0.08<br>p<0.1 |
| RQ, % | 3.40±0.08 | 2.20±0.04<br>p<0.01 |
| PV, mm3 | 13.90±0.40 | 12.30±0.60<br>p<0.01 |

**Table IV.** Biochemical parameters in patients with primary compensated glaucoma, examined in the winter and spring period

| Parameters | Control group n=30 | Patients of group 1<br>n = 32 |
|---|---|---|
| β- and pre-β-lipoproteins, g / l | 5.67±0.20 | 6.49±0.38<br>p<0.05 |
| TBA reactants, units / ml | 0.15±0.01 | 1.01±0.03<br>p<0.001 |
| AHP content, units / ml | 4.79±0.40 | 15.40±0.10<br>p<0.001 |
| SHE,% | 11.77±1.04 | 14.50±1.10<br>p<0.02 |

**Table V.** The state of hydro- and hemodynamics in patients with primary compensated glaucoma, examined in the summer and autumn period

| Parameters | Control group n=28 | Patients of group 1<br>n=30 |
|---|---|---|
| P0, mmHg | 18.40±0.40 | 23.60±0.30<br>p<0.001 |
| C, mm3/min | 0.44±0.004 | 0.50±0.04<br>p<0.001 |
| F, mm3/min | 3.50±0.08 | 4.48±0.05<br>p<0.001 |
| RQ, % | 3.50±0.03 | 2.70±0.04<br>p<0.001 |
| PV, mm3 | 13.50±0.10 | 12.30±0.90<br>p<0.5 |

(p<0.001), there was also a decrease in the relative pulse volume of the blood entering the eye (Table III).

Analyzing biochemical parameters in patients with primary compensated glaucoma, examined in the winter and spring period, we revealed moderate hyperlipidemia. The content of atherogenic fractions of lipoproteins reliably exceeded the same values in the subjects of the control group (p<0.05) (Table IV). In patients of group 1, there is a sharp intensification of free radical lipid oxidation, which indicates a slightly higher level of TBA reactants and AHP in lipoproteins as compared to the same indicators of the control group, which were examined in the winter and spring period.

The examination of patients of group 1 (30 patients) in the summer and autumn period also revealed significant changes. The rheographic coefficient decreased statistically significantly in comparison with apparently healthy individuals of the control group (p<0.001), a similar situation was observed with the indicators of minute blood volume in patients of this group (Table V).

When evaluating the results of functional methods of examination in patients of group 1 in the summer and autumn period, there is a statistically reliable and significant increase in the production of chamber fluid, as compared with those of the control group (p<0.001). These changes were observed against the background of a decrease in the coefficient of outflow (p<0.001), as well as an increase in actual IOP (Table 5). When analyzing the biochemical parameters in patients with primary compensated glaucoma, who were examined in the summer and autumn period, moderate changes in lipid metabolism were identified (Table VI). Intensification of free radical lipid oxidation

**Table VI.** Biochemical parameters in patients with primary compensated glaucoma, examined in the summer and autumn period

| Parameters | Control group n=28 | Patients of group 1 n=30 |
|---|---|---|
| β- and pre-β-lipoproteins, g / l | 5.20±0.2 | 11.70±0.08 p<0.001 |
| TBA reactants, units / ml | 0.07±0.0001 | 0.80±0.001 p<0.001 |
| AHP content, units / ml | 3.59±0.5 | 8.34±0.05 p<0.001 |
| SHE,% | 8.82±0.41 | 12.40±0.03 p<0.001 |

**Table VII.** The state of hydro- and hemodynamics in patients with secondary compensated glaucoma, examined in the winter and spring period

| Parameters | Control group n=30 | Patients of group 2 n=31 |
|---|---|---|
| P0, mmHg | 17.50±0.30 | 25.70±0.04 p<0.001 |
| C, mm3/min | 0.42±0.006 | 0.52±0.002 p<0.001 |
| F, mm3/min | 3.45±0.08 | 7.12±0.08 p<0.001 |
| RQ, % | 3.40±0.08 | 1.43±0.08 p<0.001 |
| PV, mm3 | 13.90±0.40 | 11.20±0.60 p<0.001 |

**Table VII.** Biochemical parameters in patients with secondary compensated glaucoma, examined in the winter and spring period

| Parameters | Control group n=30 | Patients of group 2 n=32 |
|---|---|---|
| β- and pre-β-lipoproteins, g / l | 5.67±0.20 | 8.5±1.20 p<0.05 |
| TBA reactants, units / ml | 0.15±0.01 | 1.1±0.01 p<0.001 |
| AHP content, units / ml | 4.79±0.40 | 15.43±0.20 p<0.001 |
| SHE,% | 11.77±1.04 | 23.60±1.02 p<0.001 |

(FRLO) was detected in patients of this group, the level of TBA reactants and AHP was statistically significantly higher than in the control group (p<0.001). The above changes occurred against the background of declining antioxidant levels.

Observing the change in biochemical parameters in patients of group 1 depending on the season, we noted the stability of the level of lipid metabolism. In the winter and spring period in patients with primary compensated glaucoma, there was a significant intensification of FRLO. Therefore, the content of TBA reactants in patients examined in the winter and spring period was 1.01 ± 0.03 units extr / ml, while in the summer and autumn period – 0.80 ± 0.001, respectively (p<0.001). Similar changes were observed in relation to the content of AHP, which was equal to 15.40 ± 0.1 units / ml in the winter and spring period, and 8.34 ± 0.05 units / ml in the summer and autumn period (p<0.001). The intensity of free radical reactions in the winter and spring period is twice as high as the same values in patients examined in the summer and autumn seasons. There is a tendency of reduced antioxidant activity in the winter and spring period (14.50 ± 1.10) as compared to the summer and autumn (12.40 ± 0.03) (p<0.1). When comparing the activity of antioxidant enzymes, it was found that in the winter and spring period, their activity was statistically significantly higher (Tables 4 and 6).

When observing patients of the **second group** with secondary compensated glaucoma in the winter and spring period, it was found that the indicators of hydrodynamics are statistically significantly different from the control group. First of all, this concerns the increase in the production of chamber fluid, which in turn led to a compensatory decrease in the coefficient of outflow (p<0.0001). We also found a statistically significant increase in actual IOP (Table VII).

Significant intensification of FRLO was observed in

patients of this group, which is indicated by a higher level of TBA reactants ($p<0.001$) and AHP in lipoproteins ($p<0.001$) when compared with the values of the control group, which were examined in the same period. However, we noted a high degree of intensity of free radical reactions, about 5 times higher than in the control group. The increase in the level of autooxidation detected by us was observed against the background of lower antioxidant activity (Table VIII).

After analyzing antioxidant enzymes in patients of group 2, we found a progressive increase in the activity of catalase, SOD and ceruloplasmin ($p<0.001$). Data from functional examination methods showed significant changes in eye hydrodynamics in patients of group 2 in the winter and spring period. The production of chamber fluid in patients of this group increased in the summer and autumn period in comparison with the control group, $3.50 \pm 0.08$ and $8.16 \pm 0.02$, respectively ($p<0.001$). There was a significant decrease in the coefficient of fluid outflow ($p<0.001$). Significant changes were also found in the hemodynamics of the eye in patients with compensated secondary glaucoma examined in the summer and autumn period. Patients had a statistically significant reduction in rheographic ratio as compared to healthy individuals, which leads to a decrease in the relative pulse volume of the blood, and thus to a deterioration in the blood supply to the eye. In healthy individuals, this figure was $4.0 \pm 0.08\%$ versus $1.0 \pm 0.05\%$ in patients with secondary glaucoma ($p<0.001$).

When observing the biochemical changes in patients of group 2 in the summer and spring period, changes were found that are similar to those patients who were examined in the winter and spring period. In patients, there was an intensification of FRLO, an increase in the level of TBA reactants and AHP, respectively, which exceeded these values in the control group. The intensity of free radical reactions was also statistically significantly higher. These changes were observed against the background of reduced antioxidant supply of patients with secondary compensated glaucoma, as evidenced by a higher level of spontaneous hemolysis of erythrocytes ($p<0.01$). Analysis of the activity of antioxidant enzymes in patients of group 2, examined in summer and autumn, showed that the activity of superoxide dismutase was statistically significantly lower than in the control group, whereas the activity of catalase and ceruloplasmin did not differ significantly.

When comparing clinical and biochemical parameters in patients of group 2 in different seasons, it was found that in the winter and spring period, there is a moderate decrease in chamber fluid production as compared to the summer and autumn period ($0.61 \pm 0.003$ and $0.52 \pm 0.002$, respectively) ($p<0.001$). Patients in group 2 in the winter and autumn period had a statistically significant deterioration in the blood supply to the eye ($1.30 \pm 0.08\%$ and $1.90 \pm 0.05\%$ $p<0.001$) as compared to the group of patients examined in the summer and autumn period.

Analysis of biochemical parameters in patients of group 2 depending on the season showed that in the winter and spring period, there is an increase in the level of AHP ($15.43 \pm 0.07$ units extr / ml and $9.54 \pm 0.01$ units extr / ml $p<0.001$). The intensity of free radical reactions in the winter and spring period is almost 2 times higher than in patients of group 2 in the summer and autumn period ($p<0.001$). We found a decrease in antioxidant supply in patients of group 2 in the winter and spring period as compared to summer and autumn ($23.6 \pm 0.20\%$ and $12.45 \pm 0.12\%$, respectively) ($p<0.001$). Comparison of the activity of antioxidant enzymes showed that in the winter and spring period, the activity of all of the above was statistically significantly higher.

## CONCLUSIONS

Clinical examination of patients with primary compensated glaucoma in winter demonstrates a statistically significant decrease in intraocular fluid production, decreased outflow and reduced actual IOP, whereas in summer and autumn these figures were less pronounced. Observations of patients with secondary compensated glaucoma also showed a statically significant decrease in the production of chamber fluid and a decrease in the coefficient of outflow in winter. Similar tendencies were confirmed by hemodynamic changes. During this period, the relative pulse volume of the blood entering the eye is significantly reduced, in the summer and autumn period, the deficit of blood supply to the eye is less pronounced. This is confirmed by the established close correlations between the level of blood supply to the eye and the content of intermediates of FRLO – TBA reactants and AHP.

The results of clinical observations were also confirmed by biochemical changes. Estimation of FRLO levels in patients with primary and secondary compensated glaucoma provides evidence of a proliferative form and a significant increase in the level of autooxidation intermediates. Intensification of FRLO occurred against the background of decreased antioxidant supply of patients. It is necessary to admit the greater intensity of free radical reactions in patients with secondary glaucoma. In terms of the influence of seasonal factors on the development of changes in different types of glaucoma, we analyzed seasonal differences in biochemical parameters. In patients with glaucoma in the summer and autumn period, there is a lower intensity of FRLO and a higher antioxidant supply of hydrophobic and hydrophilic antioxidants. The activity of all studied antioxidant enzymes in the summer and autumn period was compared to the winter and spring period. The greater intensity of autooxidation in glaucoma patients in the winter and spring period of the year against the background of low antioxidant supply and, consequently, more pronounced clinical manifestations and biochemical changes are due to nutritional deficiency of natural biologically active substances with antioxidant action. Their lack leads to disruption of the antioxidant defense system of the vascular wall in patients with glaucoma, thus creating conditions for increased reactions of FRLO and damage to the structures of the vascular wall, which leads to morphofunctional changes characteristic of glaucoma.

Thus, the results of the research indicate the proliferative form of peroxide mechanisms in the pathogenesis of glaucoma of both types, which is the basis for using inhibitors of FRLO – antioxidant preparations – in the comprehensive therapy of these diseases. The identified features of clinical and biochemical disorders, based on the season of examination, are the basis for the development of differentiated regimens for the use of antioxidants in the treatment of glaucoma.

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ORIGINAL ARTICLE

# LEGAL AND SOCIAL CHALLENGES OF COVID-19 VACCINATION BEFORE AND AFTER THE 2022 RUSSIAN INVASION OF UKRAINE

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## ABSTRACT

**The aim**: The study aims to develop ways of solving the social and legal problems of vaccination against COVID-19, showing them the example of Ukraine before and after the beginning of the active phase of Russian aggression.

**Materials and methods**: The study is based on international documents and legal acts adopted to combat the COVID-19 epidemic, the survey results of 165 ordinary Ukrainians on vaccination, interviewing health care organizers; statistical information, and content analysis of the media on vaccination, as well as ways of avoiding it. Dialectical, analytical-synthetic, system-structural methods, as well as methods of content analysis, questionnaires, interviews, and included observation, were used.

**Results**: Legal restrictions on the realization of persons' rights who have not been vaccinated against COVID-19 are an acceptable remedy, as they aim to protect human rights to life and health. Restrictions on the realization of labor and other rights of unvaccinated persons introduced in Ukraine have caused the following related social-legal problems: a) negative attitude of some persons to human rights' restrictions due to mandatory vaccination for workers, related fears of the population; c) stratification of the population according to the availability of vaccine of a particular manufacturer; d) background phenomenon in the form of imitation of vaccination with subsequent forgery of certificates. These restrictions have been lifted during the martial law, and anti-epidemic measures are recommendatory. Despite the availability of vaccinations throughout the non-occupied territory, the pace of vaccination has been significantly reduced.

**Conclusions**: Ways of overcoming the adverse socio-legal problems of vaccination and related background phenomena are to conduct quality information campaigns to inform the public about the benefits and safety of vaccination, counter misinformation, increase the availability of vaccines with a choice of vaccines from different manufacturers, and increase the effectiveness of criminal legal counteraction to forgery of documents confirming vaccination. After the imposition of martial law in Ukraine, there has been a change in the focus of public attention to solving vital problems, which, along with the transfer of anti-coronavirus restrictions to the status of recommendatory, creates danger of significant reduction in vaccination.

**KEY WORDS:** COVID-19 vaccination, legal regulation, the social impact of vaccination, forgery of vaccination certificate

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## INTRODUCTION

Vaccination is traditionally considered one of the most effective ways to prevent infectious diseases. Once again, humanity was able to assess the validity of this conclusion with the spread of the SARS-CoV-2 virus in the world. The World Health Organization (WHO) has recognized that vaccination is essential to ending the COVID-19 pandemic and stressed the importance of ensuring fair access to safe and effective vaccines for each country [1]. According to its recommendations, most countries are actively implementing COVID-19 vaccination in their national practice through government mechanisms. The Government of Ukraine has also taken several measures to combat the disease, one of which was vaccination, which began on February 24, 2021.

The National Security and Defense Council of Ukraine "On the National Plan for vaccination and prevention of acute respiratory disease COVID-19 caused by coronavirus SARS-CoV-2" (02.04.2021) declared the goal of vaccinating the majority of the adult population in Ukraine against COVID-19 disease. However, according to official data, the Ministry of Health of Ukraine (from now on – the Ministry of Health), as of February 23, 2022 (the last date of their publication) in Ukraine, the number of people vaccinated with the first dose amounted to more than 15.7 million; 96.7% of them (over 15.2 million people) received a second dose [2]. Given that the country's population was 41.5 million before the beginning of the active phase of Russian aggression (until February 24, 2022), the amount of vaccinated people exceeds a third (approximately 37.8%).

Ukraine is using five vaccines approved by the WHO. [3]. According to official data, no deaths have been registered in Ukraine or globally due to vaccination against COVID-19 [4]. However, the global vaccination campaign against COVID-19 has polarized society between proponents of such vaccinations and their opponents (anti-vaccines), the debate which sometimes takes aggressive forms.

It should also be noted that after February 24, 2022, when the Russian Federation launched a full-scale offensive on the entire territory of Ukraine, the vaccination state changed dramatically. The prevention of COVID-19 has receded into the background compared to defending the country, saving lives due to the constant threat of missile strikes and air strikes throughout Ukraine, mass extermination during the aggressor's attack, and in the occupied territories, destruction of housing and infrastructure, unemployment, and others.

In this regard, the issues related to the legal regulation of vaccination and the practice of its implementation in peace and war, the background social phenomena caused by vaccination, deserve attention. At the same time, the scientific literature lacks a comprehensive study of these issues based on sociological data.

## THE AIM

The study aims to develop proposals for solving social-legal problems and minimizing the background phenomena that have arisen in society after the introduction of many countries restricting the rights of unvaccinated persons from COVID-19 and further vaccination, taking into account changes in legal awareness and living conditions in Ukraine after the beginning of the active phase of Russia's armed aggression against Ukraine.

## MATERIALS AND METHODS

The study was launched in 2021, and most of it was conducted before the start of a full-scale attack by the Russian Federation on Ukraine, which took place on February 24, 2022. In October-November 2021, a survey of 165 people living in the Kharkiv region (Ukraine) who did not belong to medical professionals was conducted.

The study, conducted after the start of a full-scale Russian attack on Ukraine, is a pilot. It was conducted for a short time (from February 24 to May 6, 2022) and in conditions of limited capacity. It used interviews with four health care organizers from Kyiv, Poltava, and Kharkiv (Ukraine), analysis of media reports, as well as the method of included observation, as some authors of the study after February 24, 2022, for some time were in the zone of active hostilities in Kharkiv, as well as in Poltava, where at that time there was no direct combat.

The WHO documents, normative legal acts of Ukraine, and decisions of the European Court of Human Rights (total of 45 laws and papers) for 2020-2022, which concerned the implementation of vaccination against COVID-19, were analyzed. Statistical information from the WHO and the Ministry of Health of Ukraine and media reports were used.

The research used dialectical, analytical-synthetic, and system-structural, as well as methods of content analysis, questionnaires, interviews, and included observation.

## RESULTS AND DISCUSSION

COVID-19 vaccines are generally considered the only way to address the challenges posed by the current pandemic. Vaccination policies vary widely around the world. According to V. Horodovenko, etc., this is due to the lack of unambiguous answers about the need for vaccination in international legal instruments on human rights. In most countries, vaccination against COVID-19 is voluntary. However, the complication of the epidemiological situation has led to the fact that some countries have introduced mandatory vaccination for specific categories of citizens (France, Greece) and the general population (Tajikistan, Turkmenistan) [5 ].

In this regard, the primary challenge facing each state is *the choice of vaccination policy*. Regarding Ukraine in general, different approaches are discussed: compulsory vaccination, voluntary vaccination, and mixed (voluntary, combined with a system of specific restrictions with elements of indirect coercion) [6; 7; 8]. As a result, the Government of Ukraine has chosen a moderate vaccination campaign. It is possible to distinguish between the universal vector of vaccination and the vector of vaccination in the professional sphere.

Regarding the *universal vector of vaccination*, it should be noted that at the level of the Law of Ukraine "On Protection of the Population from Infectious Diseases" from 06.04.2000 № 1645-III (from now on - the Law № 1645-III) established voluntary vaccination. At the same time, in Ukraine, there are measures: 1) *restriction of the rights and opportunities of unvaccinated people*, which is manifested in the spheres of services and transport: only in the presence of vaccination certificates allowed interregional public transport, visiting non-food stores, restaurants, etc.; 2) *incentives for vaccinated people*, for which the state program "eSupport" was introduced on December 19, 2021, providing each vaccinated citizen with funds for UAH 1,000 (approximately EUR 30) with the opportunity to spend them in areas most affected by quarantine restrictions: travel, theater, cinema, fitness, buying books, and others. In the first month of its operation, more than 7.35 million people (about half of all vaccinated citizens) took part in the program, to whom about 7.35 billion hryvnias (about 230 million euros) were transferred [9].

Regarding *the vector in the professional sphere*, Law № 1645-III in Art. 12 provides for the possibility of introducing mandatory vaccination for employees of certain professions, industries, and organizations (the list of which is set by the Ministry of Health of Ukraine), whose activities can lead to infection of these employees and (or) the spread of infectious diseases. In case of refusal or evasion of obligatory preventive vaccinations in the order established by the law, these workers are suspended from performing the specified types of work.

These vectors of the Government's policy are related to the gradual trend toward compulsory vaccination, in which *restrictions on the rights of unvaccinated persons*, including the right to work, freedom of movement, etc., can be considered a priority socio-legal problem. Foreign scholars also note this problem and point out that public opinion about vaccines has become polarized, and discussions about compulsory vaccination, which are often

based on arguments on fundamental rights, are intensifying [10]. In this regard, the European Court of Human Rights in Vavřička and Others v. the Czech Republic "noted that compulsory vaccination is a permissible restriction of law, as it is necessary to protect public health and human rights and freedoms [11].

In general, considering the issue of compulsory vaccination from the point of view of justice, it is necessary to consider the balance of its positive (especially public health) and negative (restriction of the rights of unvaccinated and bringing them to justice) manifestations. In this context, the protection of public health is, of course, the dominant good, the achievement of which determines the permissibility of restricting the rights of individuals. However, such admissibility must be clearly defined by law.

The authors' survey confirmed that Ukrainian citizens are vaccinated not only voluntarily but also to prevent the established restrictions on their rights. Yes, to the question "*If you were vaccinated, what prompted you to do so?*" answer "under the threat of negative consequences at work, at the place of study, etc." 11.5% of respondents were provided[1]It should be borne in mind that some citizens perceive the obligation to be vaccinated as a violation of their rights, regardless of the regulations on compulsory vaccination [12]. At the same time, in some organizations, there is a negative practice of forcing workers who are not included in the categories of compulsory vaccination by the Ministry of Health to be vaccinated under threat of dismissal or dismissal. Such cases go beyond the scope of Ukrainian law and constitute a violation of individual rights.

Despite the Government's efforts, the vaccination level of the Ukraine population against SARS-CoV-2 remains low; the main reason is *the rejection of vaccinat*ion. In 2019, this phenomenon was included in the WHO list of ten global threats to humanity. Its leading causes are carelessness, distrust of vaccines, and lack convenient access to vaccination services [13]. These factors can also be traced in Ukraine to a greater or lesser extent. The survey revealed the following socio-legal preconditions for refusing vaccination.

*Distrust of vaccines*. Respondents' answers to the question "*If you have NOT been vaccinated and do not plan to do so, then why?*" were: "I am afraid of side effects" - 49.5%; "I do not believe in the effectiveness of the vaccine" - 33.6%; "I do not trust producers due to the probability of collective bargaining" – 21.7%; "I recently recovered"– 12.8%; "I do not have the opportunity to be vaccinated with the vaccine I want"– 9.9%; "I am not afraid of the disease" – 8.9%; "I have contraindications"– 6.9%; other answers – 5.9%. Thus, people's refusal to get vaccinated is mainly due to disbelief in the vaccine's effectiveness. Based on these results, it is seen that intensifying the educational campaign for promoting personal health and collective immunity could increase the population's desire to be vaccinated. It should be based on objectively validated information on the effectiveness of vaccination against various strains of SARS-CoV-2.

*Public fears about vaccination* are another major factor hindering its spread. Such fears can be caused by negative personal experiences, the advice of others (primarily relatives or acquaintances), and negative information campaign about vaccines. It is based on: *myths about vaccines* related to side effects from vaccination (anaphylactic shock, infertility, multiple sclerosis); the relationship between quality and country of production of the vaccine (European vaccine is better than Indian); vaccine mortality; by changing the mRNA vaccine of human DNA, etc. Some people are afraid to get vaccinated because of fantastic ideas about chipping, establishing external control over their consciousness and/or biometric data, zombies, etc.

Myths influence both people's decision to vaccinate and the choice of a particular vaccine and generally hurt the vaccination process, reducing its rate. This conclusion is confirmed by the respondents' answers to several of the above questions. In the fight against false information, the WHO's practice, authorities, non-governmental organizations, media, social networks, and other entities to disseminate explanatory information to answer common questions and refute established fakes is beneficial [4; 14; 15; 16]. Also, according to the WHO, the most authoritative advisers on vaccination, especially in small communities, are health workers, and the WHO helps them provide verified information about vaccines [14].

As more and more people become vaccinated, they will pass on their positive personal experiences to relatives, friends, and acquaintances, which will help overcome myths. It is significant that the question "*How did the vaccination affect you?"* the following answers were received: "I experienced minor side effects" – 40.3%; "I have no way" - 35.4%; "I felt confident that I would not get sick, but continue to follow the rules of quarantine" – 24.1%; "I began to lead a more active way of social life (visiting public places, cultural events, traveling, meeting friends, etc.)" – 14.5%; "I experienced serious side effects" – 4.8%; "I received more opportunities in work, the study" – 3.2%; "I felt confident that I would not get sick, and stopped following the quarantine rules"– 1.6%. Thus, vaccination is a positive or neutral experience for most people. Therefore, it is seen that the dissemination of information about the vaccination results will contribute to the final favorable decision of unvaccinated citizens in this regard.

Due to several WHO-recognized SARS-CoV-2 vaccines, vaccination selection may be a *prerequisite for the vaccination*, which may also slow vaccination rates due to people's preference for one vaccine over another and reluctance to vaccinate the latter. Respondents' answers regarding the personal choice of vaccine to the question "*Do you consider this or that vaccine a priority for yourself? If so, by what criteria?*" were distributed as follows: "Yes, I think, according to the criterion of the least side effects" – 37%; "Yes, I think, according to the criterion of efficiency"– 36.4%; "No, I do not think so"– 23.6%; "Yes, I think, according to the criterion of trust in the manufacturer" – 17.6%; "I did not think" – 11.5%; "Yes, I think, according to the criterion of limited access for the general public, prestige" – 4.8%.

To the question *"If you were vaccinated (plan to be vaccinated), how did you choose (plan to choose) the vaccine?"*

respondents answered: "I was waiting for the vaccine, about which I collected the most positive information from specialized sources (medical forums, professional publications, etc.)" – 33.3%; "I waited (will wait) for the vaccine, which I consider the best" – 19.6%; "I waited (will wait) for a specific vaccine recommended by a doctor" – 18.8%; "I used the one that was (will be) available" – 17%; "I waited (will wait) for the vaccine, about which I collected the most positive information from the media, Youtube, social networks and other widely available sources" – 15.3%; "I was waiting (will wait) for a specific vaccine, which was recommended to me by friends/relatives/colleagues" – 13.6%.

Thus, a person's vaccine choice is influenced by both the actual availability of the vaccine (for example, its availability in the medical facility of the locality where the person lives) and the criterion of its effectiveness and the least side effects. The latter, in turn, is often perceived subjectively under the influence of the myths described above. At the same time, citizens are actively searching for information about the vaccine and are mostly conscious of their choice, making inquiries in information sources and communicating with doctors. The solution to this problem is facilitated, on the one hand, by broad coverage of the results of clinical trials of vaccines with an objective assessment of their effectiveness and, on the other, by the Government's focus on purchasing those vaccines that are most in demand.

Due to the choice of a particular vaccine, which is not always available due to the limited number of doses, there is *a problem of stratification of the population according to the availability of a vaccine from a particular manufacturer*. Unfortunately, vaccination has become one of the factors dividing society into groups according to the prestige of the vaccine. One of the notions is that one vaccine is intended only for society's elite, and the other is for ordinary citizens. This hypothesis was confirmed by a survey, in which 52.1% said that a particular vaccine is the most prestigious, while other vaccines received less than 16% each; 18.2% do not consider any vaccine prestigious; 10.9% did not think about it. A negative consequence of this approach is the refusal of people to be vaccinated with a "non-prestigious" vaccine or the spread of corrupt practices to obtain the desired vaccine. Overcoming this negative trend will be facilitated by transparent supply and distribution of vaccines at vaccination points, which will help people make informed choices about vaccines.

The veiled form of denial of vaccination *is the problem of imitation vaccination*, which can be considered a reaction to the Government's introduction of compulsory vaccination when it becomes a condition for people to exercise their rights and access to social benefits (opportunities to visit restaurants, museums, cinemas, travel, etc.). Imitation of vaccination is a socially dangerous phenomenon because, in addition to the risks of non-vaccination, it further distorts the statistics and creates a "shadow market" of services to legalize such activities.

Forgery of vaccination certificates has become a common phenomenon in 2021, in conditions of high demand, costs 50 –300 euros [17]. Both third parties and doctors are subject to forgery. Counterfeiting by third parties is easier to detect, particularly by scanning the QR code, as it is not entered in the vaccination register. Instead, the relevant actions of doctors are more socially dangerous because the vaccine is destroyed, and the person is given a certificate certifying his vaccination, with the necessary information in the register. The forged certificate has two negative consequences: first, it does not reduce the risk of disease; secondly, it gives a person more excellent opportunities for social communication and, consequently, contributes to the spread of the disease, "removing suspicion from it" as a possible source of infection. Another problem is that a person formally registered as vaccinated will not be able to get it when he or she needs a natural vaccination.

There are also schemes to falsify PCR test results, where attackers collude with private laboratory staff. At the same time, advertisements are placed on online resources about the organization of the issuance of urgent certificates with negative test results, the cost of which reaches 30 euros, depending on the urgency of issuing the certificate and [18].

This problem, common in other countries, is of concern to the world community. In particular, in the UK, there is a practice of fraudulent people sending social networks to sites that sell fake NHS-Covid passes designed to confirm the vaccination of persons for those who have not been vaccinated. According to the BBC, from December 2020 to July 2021, the number of channels on one of the social networks offering such a service increased from 10 to more than 1,000 [19]. In view of this, states are considering options to increase liability for both providers and consumers of such illegal services.

## VACCINATION IN WARTIME

With the beginning of the large-scale war of the Russian Federation against Ukraine on February 24, 2022, the vaccination campaign in the country was significantly slowed down. This is due to the de facto closure of vaccination centers and mobile brigades at the sites of hostilities [20], which are taking place in the most populated regions of Ukraine, and the disruption of vaccine distribution logistics across the country. In addition, the population has shifted its focus to other vital issues and has largely lost interest in coronavirus disease. On March 26, 2022, the Cabinet of Ministers of Ukraine adopted Resolution № 372 On Amendments to the Resolution of the Cabinet of Ministers of Ukraine of December 9, 2020, № 1236, which for martial law: 1) abolished existing restrictions on labor rights of unvaccinated persons of specific categories; 2) observance by persons and economic entities of anti-epidemic measures aimed at preventing the spread of COVID-19 is recommendatory only.

Health care organizers' interviews confirmed this conclusion. Yes, there are still enough vaccines against COVID-19 in Ukraine. However, according to the representative of the National Health Service of Ukraine, in the future, there may be logistical problems due to the lack of air services

in Ukraine and difficulties in other modes of transport due to war. New logistics chains are currently being developed to address this issue. There are some difficulties associated with changing the attitude toward vaccination. However, in medical institutions of Ukraine in the territory where there is no occupation, the possibility of vaccination against COVID-19 is, although at a slower pace, but it is carried out. There is no information about vaccination in the occupied territories; it is impossible to deliver vaccines there. An interview with the head of a health facility in Kharkiv, which was not occupied but has been active since the beginning of the full-scale attack, showed that although the city has vaccines against COVID-19, there is almost no demand for vaccination. The medical staff who remain in the city mainly assist the wounded and urgent patients in inpatient health care facilities. At the same time, a significant number of doctors consult patients online. The leaders of two health facilities in Poltava, where no active hostilities occurred, said they had the required number of COVID-19 vaccines. Still, most patients want to vaccinate because of planning to travel abroad and want to avoid certain legal restrictions. Vaccination is only available in health facilities, and vaccinations in shopping malls and other convenient places have stopped working.

This situation is of concern to physicians, as cases of COVID-19, including those with severe consequences, continue to be recorded. The exclusion of SARS-CoV-2 from the official information agenda of the state even created in people the illusion of the complete disappearance of this disease. Under such conditions, the risks of the spread of the COVID-19 pandemic increase significantly, which may further complicate the war-torn humanitarian crisis in Ukraine.

## CONCLUSIONS

Legal measures aimed at maximum population coverage with vaccination against COVID-19 include 1) establishing the obligation to vaccinate with liability for violation of this obligation; 2) restrictions of realization of labor and certain other rights of unvaccinated persons; 3) financial incentives for vaccinated persons.

The legislation of Ukraine does not establish a legal obligation to vaccinate against COVID-19. However, it provides material incentives for vaccinated persons and restrictions on realizing labor and certain other rights of unvaccinated persons.

The existence of these legal restrictions in Ukraine has created concomitant socio-legal problems, namely: a) negative attitude to human rights restrictions due to compulsory vaccination, b) refusal to vaccinate due to distrust of vaccines and related fears of the population; c) stratification of the population according to the availability of particular manufacturer's vaccine; d) background phenomenon in the form of imitation of vaccination with subsequent forgery of certificates. Ways to overcome these problems are to conduct quality information campaigns to inform the public about the benefits and safety of vaccination, counter misinformation, increase the availability of vaccines with a choice of vaccines from different manufacturers, and increase the effectiveness of criminal law against forgery of documents proving vaccination.

In Ukraine, after the beginning of the active phase of Russian aggression (after February 24, 2022), vaccination continues throughout the territory, which is not occupied, but its pace is significantly reduced. Legal restrictions on the exercise of certain rights of unvaccinated persons during wartime do not apply; the population of Ukraine does not pay much attention to the prevention of COVID-19, as it focuses on solving problems of survival in war. This situation poses a risk of further spread of coronavirus disease.

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ORIGINAL ARTICLE

# ECOLOGICAL CONSCIOUSNESS FORMATION AMONG STUDENTS AS RELEVANT AND GLOBAL PROBLEM OF THE PRESENT: UKRAINIAN AND POLISH EXPERIENCE

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## ABSTRACT

**The aim:** The purpose of the study is to develop a scientifically grounded methodology for the formation of ecological consciousness among students on the activity basis, taking into account the interdisciplinary approach in the process of extracurricular work.

**Materials and methods:** The research was conducted during 2016–2021 on the basis of pedagogical faculty of Vasyl Stefanyk Precarpathian National University (PNU, Ukraine) in several stages.At the theoretical and diagnostic stage, the state of problem development in the scientific literature was studied; international documents on environmental protection and sustainable development were studied; domestic pedagogical experience was analyzed and generalized; through interviews, questionnaires, observations, interviews a statement experiment was carried out, which resulted in initial data on the state of environmental knowledge of future professionals, study the results of students' acquisition of environmental knowledge in university, their attitude to environmental protection, willingness to improve their knowledge of nature. 200 students were involved in the experiment. Also, students from the Warsaw Medical University (WMU, Poland) were interviewed.

**Results:** The ecological consciousness formation among future specialists has to be done on the activity basis. It should be a purposeful and completely voluntary process, taking into account the students' interests on interdisciplinary basis, using traditional methods (narration, conversation, lecture, etc.), but with an emphasis on the activity basis. Environmental education in higher education institutions should gain the status of a strategic large-scale and high priority course, with expanded and updated content, form and methods of training, which are based on the activity basis.

**Conclusions:** Forms and methods of ecologic and humanistic nature forming the ecological consciousness of a person create a model of positive moral and social behavior; forming such a behavior among students will ensure the nature preservation on planet Earth.

**KEY WORDS:** formation of ecological consciousness, environmental education, students, Ukrainian students, Polish students

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## INTRODUCTION

At the beginning of the XXI century the problem of environmental education among children and youth has become particularly acute as the environmental situation in the world and in certain regions of Ukraine worsen. Therefore, specialists consider it as pan-European and all-planetary. Boys and girls who after graduating from a secondary school receive vocational education at universities, are obliged to be included in the system of educational influence at the appropriate level. Environmental education starts in the family and preschool, continues at school, naturally and logically should be continued in higher education institutions (HEI), and thus throughout life [1].

Complexity of this process is due to the fact that the youth starts an independent life in the era of not only rapid development of science, technology, but also of those challenges that are associated with risks. They are provoked by negative effects of the scientific and technological revolution, environmental disasters, etc. These challenges are of all-planet scale [2; 3].

We are currently monitoring serious steps taken by Ukraine at the legislative level: in 2019 the Law "On Basic Principles (Strategy) of the State Environmental Policy of Ukraine until 2030" was adopted, which is our country's response to the challenges of globalization and social transformation. Ukraine, on the one hand, has clearly declared the priority of environmental protection, ecologically balanced nature management, on the other hand, outlined the root causes of environmental problems, including the subordination of environmental priorities to economic feasibility; low level of understanding in the society of the priorities of environmental protection and the advantages of balanced (sustainable) development, imperfection of the system of ecological education and enlightenment; unsatisfactory level of compliance with environmental legislation and environmental rights and responsibilities of citizens, etc. [4].

The analysis of this Law gives grounds to assert that the Strategy of the State Environmental Policy of Ukraine until 2030 corresponds to the ideas of ecologically balanced nature management, in particular the Resolution of the United Nations General Assembly "Transforming our world: Sustainable Development Agenda until 2030" [4].

The drama and complexity of the situation, among other things, is that, according to the above state documents, the leading tasks of environmental education are the formation of environmental culture by means of formal and non-formal education of all segments of the population. At the same time, theoretical and methodological principles of environmental education in higher educational institutions require an in-depth analysis of the problem of specialist's training (teacher, ecologist, engineer, physician, diplomat, etc.) as a new type of personality who is able to develop environment-friendly society and solve problems of nature preservation.

## THE AIM

The purpose of the study is to develop a scientifically grounded methodology for the formation of ecological consciousness among students on the activity basis, taking into account the interdisciplinary approach in the process of extracurricular work.

## MATERIALS AND METHODS

The research was conducted during 2016–2021 on the basis of pedagogical faculty of Vasyl Stefanyk Precarpathian National University (PNU) in several stages.

At the theoretical and diagnostic stage, the state of problem development in the scientific literature was studied; international documents on environmental protection and sustainable development were studied; domestic pedagogical experience was analyzed and generalized; through interviews, questionnaires, observations, interviews a statement experiment was carried out, which resulted in initial data on the state of environmental knowledge of future professionals, study the results of students' acquisition of environmental knowledge in university, their attitude to environmental protection, willingness to improve their knowledge of nature.

200 students were involved in the experiment. Also, students from the Warsaw Medical University (WMU) were interviewed.

## RESULTS

Thus, the training a specialist with a high level of environmental knowledge, environmental awareness and culture on the basis of new criteria for assessing the relationship between human society and nature (not violence, but harmonious coexistence with it) should be one of the main levers in solving extremely acute environmental and socio-economic problems of modern Ukraine.

The main educational documents also stress on the importance of environmental education of the upcoming generation. The Concept of Environmental Education, adopted in 2001 in Ukraine, which is based on the Law of Ukraine "On Environmental Protection" (in particular Article 7 "Education and Upbringing in the Field of Environmental Protection") [5] emphasizes that the main purpose of ecological education is the formation of environmental culture of individuals in particular and society in general, the formation of skills, fundamental environmental knowledge, environmental thinking and consciousness, based on the attitude to nature as a universal, unique value [6].

Consequently, the young person of the XXI century needs a new philosophy of life, a high level of ecological culture and ecological consciousness, formed ecological conservation skills, nature preservation behavior. Ecological consciousness formation of the person is caused not only by the need of time, it is an important pedagogical problem. Environmental education is now one of the leading directions in professiogram formation of future specialists who study at a higher school institution. It is important that the student mastered the knowledge of general laws of nature and society development, properly understood relationship of the existence between human and nature, being able to subordinate their activities to the requirements of rational nature management. Under such conditions, it is possible to efficiently solve global environmental problems which face not only Ukraine but also the whole human civilization.

There are grounds to argue that the natural wealth of the present generation of Ukrainians, inherited from thousands of previous generations, is a testimony to the high level of their ecological consciousness. The knowledge of nature as a gift of God, that should be preserved and valued, has been transmitted for centuries from the great-grandfathers to the growing generations. Therefore, Ukrainian pedagogical knowledge in the field of nature conservation should be updated and virtually applied in higher education institutes.

Scientists believe that ecological consciousness is a higher level of people's mental perception of nature, a sphere of social and individual consciousness, which is inextricably linked with the reflection of nature as a part of human life, the image of place and role of a human in the environment, as well as self-regulation of this reflection. Under the ecological consciousness (according to opinion of the majority of scientists) we understand the totality of ideas of interaction in the system "human – nature" and in nature itself, attitude towards nature, as well as corresponding interaction strategies with it [7; 8; 9; 10].

According to anthropocentric approach, ecological consciousness is defined as human's knowledge and understanding of its possibilities of influence on nature. It may serve as a definition of the goals of such influence, the evaluation of options for predictable behavior in the eco-environment, taking into account the consequences of behavior and self-cognition as one of subsystems of the ecosystem [10].

The problem of the ecological consciousness forming among future specialists is multidimensional. The meth-

odological foundations of environmental education and upbringing in higher education institutes were considered in the studies of A. Slastionina, A. Nekos, A. Myronova, H. Tarasenko, N. Lysenko, H. Danylova, N. Hnylusha, and others. The works of these scientists reveal the methodological and theoretical foundations of environmental education and conditions for their implementation. In the dissertation works of L. Lukyanova, N. Hreyda, M. Shved the issues of the system of ecological culture components formation, consciousness and world outlook, were outlined. Formation of ecological consciousness of a person as a psychological problem was studied by S. Deriado, T. Ivanova, I. Kryazh, A. Lyovochkina, V. Yasvin and others. From the foregoing, it may be concluded that many scholars were engaged in the study of the problems of environmental education of future specialists, but in general, their researches were aimed at preparing future teachers for teaching various special courses (T. Hladiuk, M. Shved), determining the readiness level for environmental education (M. Boycheva, T. Ninova), formation of ecological culture (N. Hreyda, V. Krysachenko, H. Ponomaryova). At the same time, the problem of students' educational consciousness formation is not sufficiently disclosed in pedagogical and psychological aspects. In our opinion, more attention has to be paid to the issue of content-conceptual foundations of students' educational consciousness, foundations for development of this personal quality on the activity basis, taking into account the interdisciplinary approach.

Nowadays, there is ambiguity and variety of interpretation of content patterns of the concept of "educational consciousness", which is linked to numerous approaches to the study of this notion, which rely on different theories. Considering the ontology of the notion of "consciousness", we draw attention to the fact that from a psychological standpoint, it integrates into itself three interrelated categories: mental reproduction of the natural, social and artificial environment; mental expression of the personal "I" in this environment; self-reflection and self-relation of "I" to reality and to this environment.

From the pedagogical point of view, the ecological consciousness formation of a person is a complex and laborious process aimed at rethinking knowledge, transforming them into beliefs, which evoke value orientations and settings among boys and girls, their conscious and responsible attitude towards nature. Under such conditions, in the terms of ecological consciousness, nature is the highest value. Ecological consciousness is a category that depends on the level of development of such features as concern about the state of the environment, a sense of responsibility, a moral attitude towards nature, etc.

The purpose of the study is to develop a scientifically grounded methodology for the formation of ecological consciousness among students on the activity basis, taking into account the interdisciplinary approach in the process of extracurricular work.

In the course of research, the following methods were used: theoretical methods: specific search (analysis of scientific literature on researched problem) for systematization and synthesis of facts, information, subjects of research, materials on studied topic and definition of the essence of the basic concepts; structural and functional (tutorials, dictionaries, reference books, fiction, collections of oral folk art, etc.) to substantiate the structure, content, principles of constructing the methodology of forming the environmental consciousness of students; empirical methods: observation, conversation, interview with the aim of clarifying the level of ecological consciousness among students, identifying the attitude of students towards the implementation of environmental education.

The level of ecological consciousness of future specialists in higher education institutes will increase in case of: formation of environmental abilities and skills of students will be carried out on the activity basis by using the interdisciplinary approach; systematically work on the formation of ecological consciousness of future specialists, the expansion of their knowledge of nature, nature management, environmental conservation, the environment and its protection, etc.; formation of a value relation to nature preservation; to involve students in nature conservationand scientific research activities, to create an ecologically rich environment.

In the context of the concept of our study, the opinions of scientists from Europe, Great Britain, and the United States, who actualize the problem of ecological consciousness, fit harmoniously [11; 12]. The main message of these works is as follows: a human in its actions and relations with nature should be responsible for the decision making [13].The authors also emphasize the legal aspect of the environmentally appropriate behavior, value-oriented knowledge as an important component in the system of environmental training of children and youth.

For Ukrainian schoolchildren, students, as well as teachers and professors in higher education institutions, the manual book "Environmental Handbook 01 Environmental Education" [14] can become a table book on ecological education programs operating in the UK. This is an effective educational and methodological resource that answers the question "What is environmental education and how to implement it?" [15].

Let's pay attention to the research "Environmental Education and Student's Perception, for Sustainability" [16] conducted by Gratiela Dana Boca and Sinan Saraçlı. The authors surveyed 358 students at the Northern Center of the University of Baia Mare (Romania). They studied the state of environmental education of students of engineering and electrical, mechanical, economic specialties, their attitude to ecological problems, analyzed the participation of future specialists in environmental protection activities. It should be noted that Ukrainian scientists have not conducted a similar study.

The research was conducted during 2016–2021on the basis of pedagogical faculty of Vasyl Stefanyk Precarpathian National University in several stages.200 students were involved in the experiment, also, students from the Warsaw Medical Universitywere interviewed.

Theoretical and methodical basics of a technique of creation of the ecologically saturated ecological environ-

**Table I.** Participants of experimental study

| Name of the specialty | Number of respondents at the I – V years of Vasyl Stefanyk Precarpathian National University and Warsaw Medical University | | | | | Total number of respondents |
|---|---|---|---|---|---|---|
| | I year | II year | III year | IV year | V year | |
| engineering | 28 | 3 | 0 | 20 | 5 | 50 |
| biology | 3 | 3 | 10 | 22 | 12 | 50 |
| pedagogy | 2 | 26 | 0 | 16 | 6 | 50 |
| medicine | 0 | 0 | 0 | 25 | 25 | 50 |
| Total | 33 | 32 | 10 | 83 | 48 | 200 |

ment for formation of nature protection knowledge and ecologically expedient behavior of experts in educational process of high school and in out-of-class work were developed, conclusions were formulated and methodical recommendations were implemented.

The purpose of the survey is to find out the students' attitude towards environmental problems, the level of their ecological awareness and environmental activities.

The questionnaire was created on Google Forms and was used both as an online form and as the standard manual filling by the audience.

Among the respondents there were students acquiring engineering, biological, pedagogical, medical education. The participants were aged 18-22 years. The ratio of men and women at this stage of the experiment ranged as follows: 34.66% of males and 65.34% of females (total 200 people). The general characteristics of the sample of students are given in table I.

At the beginning of the experiment, 200 questionnaires were issued. The main purpose of the questionnaire was to determine the level of environmental awareness among students. The most active were fourth-year students (Table I). For various reasons, third-year students abstained from engineering, pedagogical and medical specialties. The answers of biology students (PNU), medical students (WMU) showed a sufficient level of theoretical knowledge about environmental issues, proved a high desire and goal setting for self-development and self-improvement. Pedagogy students showed better knowledge in a general culture. Students – future engineers – showed the lowest results and the least interest in this survey. About 31.33% of students did not want to identify themselves as "anonymous".

Let's analyze some data from the survey of fourth-year students, as they most actively participated in the study and in general almost the same number of students participated in the survey (25% of future physicians; 20 future engineers; 20 future biologists; 16 future teachers).

Ecological consciousness is an extremely complex, multifaceted, systemic phenomenon, which is inseparable from self-consciousness of an individual. In the "ecological consciousness" phenomenon the constructs that make up the basis of ecological self-consciousness are singled out. Ecological self-consciousness is one of the forms of ideological self-awareness of an individual.

The study of ecological consciousness and self-consciousness of an individual in the period of adolescence and adulthood has important scientific significance. It is at this age that a person is capable of active transformation of the environment, which in turn also has an effect on a person. Therefore, the level of consciousness development and an individual's self-awareness depends on how the interaction with the outside world would be subjected to the laws of morality and spirituality.

Ecological self-consciousness of the individual is self-awareness both as the part of the ecosystem, and as a unique personality; it is an activity that will not harm nature, but rather will be aimed at its preservation and accumulation. So, our methodology was aimed at creating a profound awareness among students of the necessity of environmental preservation, which is a common habitat for the whole humanity. One of the key pedagogical conditions of our methodology was the active approach. We believe that onlyby the means of specific ecological events the ecological consciousness of students can be developed. In this case ecological knowledge is not enough, because most of those who commit ecological barbarism towards nature and environment still possess some knowledge about nature, ecology, the importance of its conservation. But in real life they don't do it. In our opinion, it is real specific nature-conservation measures that can actually form the ecological consciousness among students.

Undoubtedly future specialists have to be provided with necessary ecological knowledge, in particular on the challenges facing not only Ukraine, but also humanity as a whole. Having acquired its independency, Ukraine entered a completely new historical phase of development. In terms of natural conditions, the country has great potential and prospects. Ukraine has an area of 603,628 km$^2$, about 95% of which is a plain part, and the share of mountain systems of the Carpathians and the Crimea accounts for only 5%. Forests occupy 19% of its area. However, Ukraine is considered as one of the most ecologically disadvantaged countries in Europe. These facts were taken into account, while developing the process of environmental education at Vasyl Stefanyk Precarpathian National University.

Here are the answers to some questions. To the question "What is the place of environmental knowledge in your professional profile?" we obtained the following results: 94% of future engineers, 100% of future biologists, 100% of future teachers, 90% of future physicians classify them as an important and necessary component of the professional

profile. This proves that respondents are aware of the importance of acquiring knowledge about nature protection and conservation.

## DISCUSSION

It is important to note that both Ukrainian and Polish students are aware of the significance of environmental activities.

According to the survey results, almost all respondents admit the importance of environmental conservation for humanity.

Polish students referred to environmental problems mainly as problems of environmental pollution, problems of nutrition and health care, waste utilization, safe technologies, demography, problems of morality and international relations. Such shift of emphasis is quite natural: ecology as a science transforms into a theoretical foundation of a broad field of medical, industrial and political management activities [9; 10]. According to Ukrainian students, environmental issues are environmental pollution (air, water, soil, etc.), deforestation of the Carpathian Mountains, nutrition problems. As we see, in the top ecological problems, as for Ukrainian students, there are the "regional" ones. On the other hand, the loss of the Carpathians may become a major ecological catastrophe for Europe; 76% of Ukrainian students consider this ecological problem to be global.

One of social factors that influenced actualization of the problems of environmental education at Ukrainian and Polish universities was the Chernobyl disaster (an accident at the Chernobyl nuclear power plant on the night of April 26, 1986). According to Ukrainian students, possible man-made disasters are ecological situation in the Eastern Ukraine, where military actions are taking place, which destroy environment, as well as in Crimea, where environmental problems are being squandered due to occupation of this territory by Russia. Also, Ukrainian students pointedout ecologically unstable areas – Donbas and Dnipro regions – as an example of excessive concentration of industry in the single area; they are one of the most contaminated regions in Europe. This region, which occupies 18% of the country's area where there are 28% of Ukraine's population, produces 40% of the total volume of industrial production. Thus, the Chernobyl disaster caused a rethinking of development of industry, power engineering, etc.

Students defined one of the causes for the emergence of environmental problems, which are low level of ecological consciousness of people who "caused this", the Soviet regime, the socialist planned economy, communist ideology, etc. Students noted that the path to high ecological consciousness lies through an effective environmental education.

Respondents' answers to the question "What do you know about organizations engaged in environmental activities? a) in your area; b) in Ukraine / Poland; c) in the world" showed that, on the one hand, almost all students are aware of the level of environmental protection in the global dimension (for example, both Ukrainian and Polish students named UNESCO, UNEP, WHO, IUCN as international organizations involved in environmental protection activities). Ukrainian students, apart from line ministries (76%), unfortunately could not name other institutions, 24% of respondents named "green parties"; the same situation is at the regional level. Thus, the Ukrainian students demonstrate higher level of knowledge about environmental activities of international organizations than their knowledge about such activities at the state and regional levels. Polish students, in contrast to Ukrainian respondents, are better acquainted with the activities of domestic environmental organizations, social movements, foundations, environmental programs (for example, the Polish Environmental Club, League of Nature Protection, Federation of Greens, Polish Society for the Protection of Wildlife, Nature Foundation, Natural Freedom Foundation, Green Freedom, For the Benefit of All Creatures, the All-Polish National Fund for Environmental Protection and Water Management of the Republic of Poland). This proves that the level of environmental awareness of Polish students, as well as of society as a whole, is higher.

The answers to the question "Are you ready to carry out environmental activities?" were important to us. All students gave positive response to this question. Therefore, it is natural that the preparation of future specialists who possess high level of environmental knowledge, ecological consciousness and culture, based on new criteria for evaluating human relations and nature, should become one of the cornerstones of solving extremely acute environmental and socio-economic issues not only in Ukraine, but in Europe as well. Among the principles of environmental education of students, we highlight the interdisciplinary approach on shaping the students' ecological consciousness; continuity of students' communication with the environment involving participation in different kinds of activities; the unity of intellectual and emotional aspects in students' activities regarding environmental improvement.

Given the limited scope of the article, we provide the examples ofenvironmental measures we carried out at Vasyl Stefanyk Precarpathian National University. They took into account all of the abovementioned pedagogical conditions for the ecological consciousness formation among future specialists. The choice of such ecological actions was caused by the common vision of the Ukrainian and Polish students on the importance of environmental conservation for humanity and future generations.

First of all, we involved students in ecological action on Earth Day. On the eve they prepared mini-performances about the first Earth Day celebration. Students noted that it took place in the United States on the day of the vernal equinox on April 22, 1970. The initiators were American activist and politician A. N. Nelson and the students of Harvard (Dennis Hayes, the activist). It is thanks to this action that in 1970, US President Richard Milhous Nixon passed The National Environmental Education Act.Environmental education was included to school curricula in order to enhance the knowledge level of the growing

generation. Environmental education was brought up on the international level at the United Nations Conference on the Human Environment in 1972 in Stockholm. The United Nations Environment Program (UNEP) was introduced to address the most global environmental problems, namely degradation of soils, deterioration of its quality, desertification, decreasing the amount of freshwater, pollution of the oceans.Coordination of international cooperation in the field of environmental protection is the main goal of this project. The students made the proper conclusions: Ukrainians are not aware enough of international events in the sphere of environmental education; it was the students and the university environment that pushed and initiated organization of environmental events and adoption of relevant vital international documents at the international level. As for Ukraine, there is the insufficient level of legislative provision of environmental education. Unfortunately, environmental education is still basing on the approach which considers nature as an inexhaustible resource, without taking into account catastrophic consequences of such an approach. Therefore, there is a growing need for new skilled personnel who will be able to provide an adequate level of technogenic and environmental safety.

Earth Day was held in the form of an ecological communal work in the city of Ivano-Frankivsk. Students gladly participate in this kind of events. Involvement of students in socially useful work on the preservation of clean environment contributes to the formation of their ecological consciousness, self-control over their own behavior towards nature, and the ability of making timely and weighted decisions on creating the safe environment. Students cleaned garbage not only near the university buildings, but also around the dormitories where they live, in the park areas of the city, at crowded downtown, near the bus station, etc. It was done in order to attract people's attention to the problems of soil pollution, as well as to encourage similar actions of city residents, especially to participation in the event "Let's make our Earth cleaner" to create a safe environment [17].

Students were involved in celebrating Earth Hour as well. During the last ten years, students along with teachers have been participating in the Earth Hour international movement. The purpose of the students' participation in these events is not only to have the light turned off for one hour, but also to turn it off every time we leave an audience, to switch off electrical appliances when not in use. In short, do not lose contact with planet Earth and take care of its conservation. It is also an event uniting Ukrainian and Polish students, and all humanity in general. It is an opportunity for educational events, when students become initiators of such movements in cities, towns, villages where they were born. For example, on March 24, 2018 (Saturday), this international event lasted from 20.30 to 21.30. We suggested those students who go home on weekends to arrange Earth Hour in a circle of their family or their friends. Those students from PNU living in a dormitory gathered in a separate room. At first they actualized ethical rules of behavior on Earth, which had been expressed by the German philosopher and ecologist E. Callenbach: love and respect Earth that blesses life and governs it; treat every day on Earth as sacred and celebrate the change of seasons; do not consider yourself superior in regard to other living beings and do not treat them so that they would disappear; be grateful to animals and plants for the food they give you; do not damage and spoil Earth's wealth by weapons and wars; do not gain profit from Earth's resources, but try to restore its exhausted forces; do not hide from yourself and from others consequences of your doings on Earth; do not steal from future generations by exhausting and polluting the Earth; consume the gifts of Earth moderately, because all of its inhabitants have equal rights to its wealth [18].

On March 28, 2020, from 8.30 pm to 9.30 pm, together with the students, we celebrated Earth Hour. Due to the COVID-19 pandemic all students stayed at home. Therefore, the format of this action was changed. Prior to the event we organized an online conference with students, where they made meaningful reports on its history, the experience of nature conservation in Ukraine and abroad, international and domestic environmental organizations. It was important that students not only had to learn about nature protection in their region (which NGOs operate there, about the activities of local authorities on environmental protection, environmental problems in their region, environmental actions, etc.) and talk about it, but also to involve their brothers, sisters and parents in the online conference. Thus, environmental education was carried out.

During Earth Hour (from 20.30 to 21.30) all the participants of the event were writing an essay "I love my Earth" and created poetic works by candlelight at home. They promote a deep love for the Earth as a place of life, a rethinking of life as such, a call to value every moment, to protect nature, because it is a creation of God. Thus, we see that the terrible disaster – the COVID-19 pandemic that befell humanity, prompted young men and women to think not only about the problems of nature conservation, but also to reassess life values and care for nature, the environment. This poetry is very life-affirming and optimistic.

Thenasongcontestwasarrangedbyus (forthebestperformanceofthesongaboutplants, thenatureofthe Carpathians, the earth, etc.) and a contest of poetryreaders devoted to nature and native land. Thus, we combined environmental education with artistic and aesthetic, moral and ethical one. It is interesting to note that students did not even feel themselves awkward being in a room with the lights turned off. On the contrary, they noted that the wax candles made by the girls at the master class, "added some romance and charm" to this event. Also, in accordance with the students' will, the Earth Hour event was prolonged for another 30 minutes.

Similar events were carried out at the Warsaw Medical University.

Great interest was caused by another movement "If we do not buy – they would not cut", which was held at the Faculty of Pedagogy on the eve of Christmas holidays, December 20, 2018. The goal of the event is to enhance the

ecological consciousness of children and young people, to highlight the problem of deforestation of the Carpathians, namely coniferous trees. Educational goal was to inform students and pupils about the harmful effects of cutting-out the Christmas trees. The main attraction of the event was a contest of New Year's compositions, which should become an alternative to a live Christmas tree. Various ideas were implemented. Christmas trees and New Year's compositions distinguished by their originality and ease of execution, and most importantly, they did not require a lot of money or time. In addition, students demonstrated their own created cartoons and video films on this topic, recited poems and played songs about Christmas trees [19].

Among the events on environmental issues, Polish students named the following: competitions, volunteering, "green" schools, actions with the distribution of leaflets, participation in environmental holidays and Ecology Days, which are held in the bosom of nature. They organize reception points for batteries, light bulbs , take part in all-Polish master classes "Know, appreciate and protect your nature", events dedicated to the International Day of Nature Protection, actions "Cleaning the world – Poland" (actions of cleaning garbage in public areas – forests, rivers, streets, parks), etc.

## CONCLUSIONS

Thus, these facts prove that Polish students are actively involved in environmental activities, are aware of public environmental movements and participate in them. For example, students noted the activities of the Polish Ecological Club, the League for Nature Conservation, the Federation of Greens, the Polish Society for Wildlife Conservation, etc., as providing environmental education among children and adults by promoting the dependence of quality of life on the rational use of natural resources and maintaining a balance between the environment and the development of civilization, formation caring attitude to nature among young men and women, promotion of knowledge about nature and its protection, encouragement of active environmental work, compliance with environmental laws. The analysis of the experience of environmental activities of Polish students shows that it is carried out at both national and regional levels, and is multifaceted. This has a significant impact on the formation of environmental awareness of boys and girls. This experience, in particular, participation in the public environmental movement, should be borrowed by Ukraine. The public ecological segment needs to be actualized under modern conditions of society development.

Since there is no separate class in ecology in the higher school of Ukraine today, the problem of formation of environmental knowledge and environmental awareness among students must be solved on an interdisciplinary basis and by extracurricular activities. There are following ways of enhancing the level of environmental awareness in a higher education institution: a) increasing the importance of environmental issues both in certain subjects and by establishing internal and interdisciplinary links; b) creation the appropriate educational and material base in educational institutions: departments of nature protection, etc.; c) improvement of forms and methods of ecological education, active involvement of students in environmental work; d) formation of motives for a responsible attitude to nature, the desire to know it more deeply, to increase its wealth. To this end, it is necessary to develop pedagogical conditions for cooperation between students and teachers in the context of environmental education. The leading methodological principles of ecological education are the principles of ecological imperative (ecological responsibility of the individual), scientific-theoretical (ecological thinking), humanitarian (ecological culture), economic and legal (ecological prudence, eco-expediency, ecological-legal expediency), applied (ecological safety) and pedagogical (environmental education). In other words, it is all about creating a rich environment on active basis (students' participation in environmental activities, their involvement in university, city, state, international environmental events, the ability to organize environmental activities with students, organizing environmental education for adults, etc.). An important condition for the effectiveness of this process is the introduction of innovative teaching methods, design technologies, game techniques, excursions to nature conservation facilities, the environmental activities of students, etc., participation in the public environmental movement, designed to develop cognitive interest of future professionals in nature preserving issues.

Consequently, the abovementioned particular measures confirm that the ecological consciousness formation among future specialists has to be done on the activity basis. It should be a purposeful and completely voluntary process, taking into account the students' interests on interdisciplinary basis, using traditional methods (narration, conversation, lecture, etc.), but with an emphasis on the activity basis. Environmental education in higher education institutions should gain the status of a strategic large-scale and high priority course, with expanded and updated content, form and methods of training, which are based on the activity basis. Forms and methods of ecologic and humanistic nature forming the ecological consciousness of a person create a model of positive moral and social behavior; forming such a behavior among students will ensure the nature preservation on planet Earth.

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ORIGINAL ARTICLE

# BUCCAL CELL MICRONUCLEI AMONG PATIENTS WITH ORAL LEUKOPLAKIA

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## ABSTRACT

**The aim:** The purpose of research was to evaluate the efficiency of micronucleus test in buccal cells for the diagnosis of oral leukoplakia.

**Materials and methods:** We have conducted a comprehensive clinical and laboratory examination of 155 patients with oral leukoplakia. It was conducted histological examination leukoplakia mucosal sites, to assess the buccal epithelium cell micronucleus test was carried out.

**Results:** Histological evaluation of the material was made according to the classification of leukoplakia WHO (2005). They are established 10 (14%) sites unmodified mucosa, 10 (14%) of the samples hyperkeratosis without atypia, 14 (19%) biopsies hyperkeratosis SIN1, 15 (21%) of hyperkeratosis SIN2, 10 (14%) -- SIN3 and 13 (18 %) of the cases of squamous cell carcinoma. Micronuclei, whose appearance is caused by violation of differentiation of epithelial cells, were found in patients with leukoplakia, the detection of micronuclei almost equally high as in patients with leukoplakia SIN2, and with SIN3 (a difference of 1.3 times ($p < 0,05$, $rxy = + 0.271$)), and consequently the probability of occurrence of tumoral diseases of the oral mucosa or malignancy existing large.

**Conclusions:** Thus, on the background of the general increase in proliferative activity of epithelial cells with increasing SIN, for each treatment group revealed the appearance of micronuclei in buccal cells. And the frequency of micronuclei and the fourth type of increases with hyperplasia, indicating an increase in the likelihood of malignancy and cancer of the oral mucosa in patients with leukoplakia SIN3.

**KEY WORDS:** Leukoplakia, hyperplasia, epithelial cells, micronuclei, buccal epithelium

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## INTRODUCTION

A timely and effective diagnostic of the oral mucosa neoplastic lesions remains a serious challenge of dentistry. Annually registered in the world are nearly 400,000 cases of malignant tumors in the oral cavity, Ukraine recording more than 4,000 new cases [1].

Apparently, an effective clinical diagnostic of the oral cavity malignant tumors based on tracing of precancerous diseases should not cause major difficulties, since the oral cavity is easily accessible for examination and palpation. However, in spite of this, 40-90% of patients begin the treatment in late stages (III - IV) of the disease and only about 20% - in early (I - II) stages. Accordingly, a 5-year survival of patients with cancer of the oral mucosa (stage I and II) by applying radiation, surgical and combined methods of treatment is attained in 65-85% of cases, while the ratio for stage III patients is of only 11-40%. Therefore, treatment results depend on an early detection of tumors, a timely diagnostic and treatment of precancerous diseases. The most frequent diagnostic errors occur in this stage of tumor development [1].

Leukoplakia is the most common precancerous lesion of the oral mucosa [1, 2]. It is a type of mucous keratosis, which is characterized by chronic course and lesions of the oral mucosa and red border of lips [3]. At pathologicoanatomic examination, in case of clinical diagnosis of «leukoplakia», in 80-85% of cases hyperkeratosis with hyperplasia of basal and spinous layers of the epithelium is detected, hyperkeratosis with different degree of dysplasia is detected in 5--15% of cases, while squamous cell carcinoma is detected in 2--5% of cases [4].

Development of leukoplakia is caused by various polyetiologic factors. Among them one can mention mechanical, chemical and thermal injuries. Approximately 70-90% of cases of oral leukoplakia lesions are associated with smoking. Also there is a direct correlation between the frequency, duration of smoking and the development of leukoplakia [5, 6].

In recent decades, active work has been carried out to study the factors influencing the stability of human genetic material using a micronucleus test in the buccal epithelium. Currently, the influence of gender, age, genotype, anthropogenic pollution of the environment, diseases of various etiologies, immunological status of a person, psychophysical characteristics on the incidence of disorders in exfoliating cells of the oral cavity has been investigated. The widespread use of this method of analysis is due to its relative simplicity, speed and low cost, as well as the lack of the need for special equipment for cell cultivation. In addition, the buccal epithelium is a kind of "mirror" reflecting the state of the whole organism [1].

## THE AIM

Objective of our study was to evaluate the effectiveness of the micronucleus test in buccal epithelial cells for the diagnosis of oral leukoplakia.

## MATERIALS AND METHODS

To achieve this goal, a comprehensive clinical and laboratory examination was carried out of 155 patients with leukoplakia of the oral cavity, who applied to the Department of Therapeutic Dentistry of the National Medical University named after A.A. Bogomolets, including 68 men (43.9%) and 87 women (56.1%). The age of the patients ranged from 25 to 70 years and averaged 46.6 ± 2.63 years.

The localization of leukoplakia was determined according to individual areas of the oral mucosa: 1) tongue, 2) floor of the mouth, 3) lip, 4) hard palate, 5) soft palate, 6) cheek, and 7) in several areas simultaneously.

The histological examination of leukoplakia areas of the mucous membrane was carried out to confirm the diagnosis. According to the WHO classification (2005), the following types were distinguished: squamous cell hyperplasia (leukoplakia without atypia), low degree of dysplasia, moderate degree of dysplasia and high degree of dysplasia. For the last three types of leukoplakia, the concept of Squamous Intraepithelial Neoplasia (SIN) was introduced from 1 to 3, depending on the severity of dysplasia [10,11].

The micronucleus test was performed to assess buccal epithelial cells. Before preparing smears, the patients rinsed their mouths with water twice. A sterile spatula was scraped from the mucous membrane of both cheeks above the line of closing of the teeth. The taken material was suspended on a defatted glass slide and smears were prepared. The prepared preparations of exfoliating epithelial cells of the oral mucosa were dried in air and fixed with a May-Grunwald fixative. After fixation, the smears were stained according to Pappenheim (azure-2-eosin). Analyzed under a microscope in transmitted light at a magnification of 900x. All cells on the glass were counted for the presence of micronuclei and the proportion of different types of micronuclei was estimated. Well-expanded, undamaged, separately lying epithelial cells were analyzed without overlap or with little overlap in the monolayer. Cells containing numerous microorganisms on the surface were excluded from the analysis. Micronuclei (MN) were counted in cells with nuclei with a distinct and continuously smooth border, implying the presence of an intact nuclear membrane. We counted the number of cells with micronuclei per 2000 cells satisfying the described characteristics. Micronuclei were identified as rounded chromatin bodies with a continuous smooth edge, lying in the cytoplasm separately from the nucleus in the same plane with it and having the same chromatin pattern and color intensity [1].

There were 4 types of micronuclei:

Type 1 - 1 small MN (1/40 of the size of the main nucleus), located at a short distance from the main nucleus, formed by a detached chromosome fragment.

Type 2 - 1 MN measuring 1 / 15–1 / 10 of the size of the main nucleus, consisting of small fragments detached from chromosomes, or of 1–2 large fragments of chromosomes.

Type 3 - MNs of this type are several small formations from 2 to 10 in number and the size of microkernels of types 1 and 2.

Type 4 is one large MN up to 1/4 of the main nucleus, consisting of several (1-3) whole chromosomes and / or many fragments of other chromosomes [1].

The data obtained in the course of the study were subjected to statistical processing. The reliability of the revealed differences in the studied parameters was assessed using the Mann-Whitney test for independent samples.

## RESULTS

In a complex clinical and laboratory study of 155 patients with a clinical diagnosis of leukoplakia of the oral mucosa.

Histological evaluation of the material has been performed according to the WHO (2005) classification of leukoplakia. 10 (14%) sites of unaltered mucosa, 10 (14%) samples of hyperkeratosis without atypia, 14 (19%) biopsy specimens of hyperkeratosis SIN1, 15 (21%) – hyperkeratosis SIN2, 10 (14%) - SIN3 and 13 (18%) cases of squamous cell carcinoma were evidenced.

Squamous hyperplasia was characterized by an increased number of cells in the basal and spinous layers. No sign of cellular and tissue atypia was revealed.

SIN1 leukoplakia was characterized by an intense proliferation of keratinocytes, with symptoms of minor cellular atypia and nuclear polymorphism in the lower third of the epithelium.

Characteristic to SIN2 leukoplakia was the location of the pathological process not only in the lower, but also in the middle third of the epithelial layer. Cellular and nuclear polymorphism was more pronounced, and hyperchromatism was observed, along with a higher nuclear-cytoplasmic coefficient and amount of mitosis in the basal layer. In some cases, changes in the tissue architectonics, appearing as epidermal "loop-shaped" outgrowths, hyperkeratosis, were revealed.

The SIN3 leukoplakia characteristic was the change of more than 2/3 of the epithelium height, expressed to a greater extent by all these signs of displasia, and the increased number of nucleoli in cells with nuclear hyperplasia. Cells polymorphism was determined, and sometimes parakeratosis with foci of erosion was observed. Inflammatory phenomena, accompanied by a dense infiltration of lymphocytes with an admixture of plasma cells, were intensified.

Histologic investigation of squamous cell carcinoma of the oral mucosa revealed disorderly arranged complexes of typical squamous cells with invasive growth in the deep lying layers of the submucosa. Manifested in varying degrees, characteristic for cellular atypia was the change in cell size and shape, in the nuclei, nuclear-cytoplasmic ratio, and the presence of polyploid forms of pathological mitosis.

When studying smears from the oral mucosa, the presence of micronuclei in epithelial cells was detected only in patients

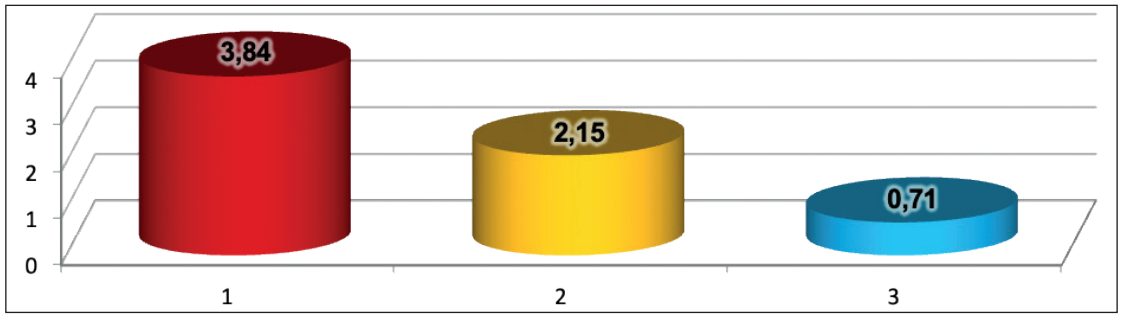


**Fig. 1.** The number of micronuclei in epithelial cells in patients with leukoplakia
1 – SIN1; 2 – SIN2; 3 – SIN3.

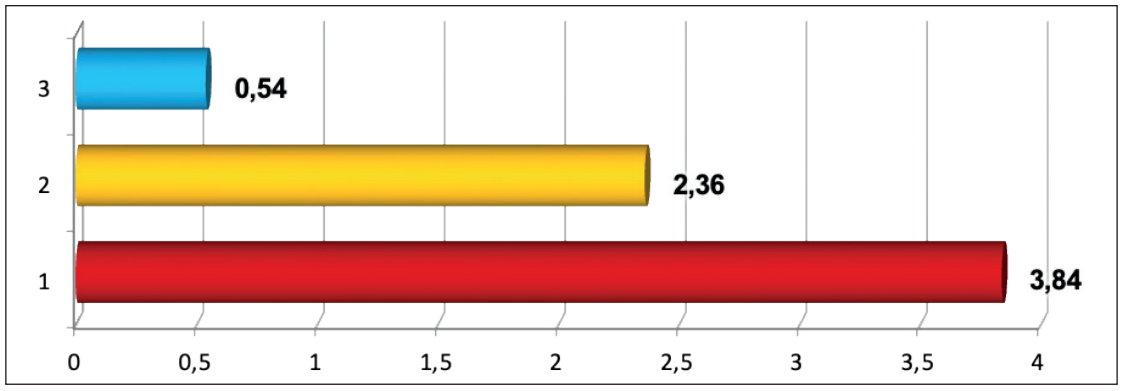


**Fig. 2.** Frequency of occurrence of micronuclei in epithelial cells in patients with leukoplakia
1 – Hyperplasia; 2 – SIN1; 3 – SIN3.

**Table I.** Frequency of micronuclei in epithelial cells of the oral mucosa in patients with leukoplakia

| Groups | Micronuclei,% | | | | |
|---|---|---|---|---|---|
| | 1 type | 2 type | 3 type | 4 type | Σ |
| SIN1 | - | - | - | - | - |
| SIN2 | 0,025±0,01 | - | - | 0,075±0,02 | 0,1±0,02 |
| SIN3 | 0,07±0,02 | 0,021±0,01 | 0,015±0,01 | 0,164±0,01 | 0,27±0,02 |
| Σ | 0,095±0,01 | 0,021±0,01 | 0,015±0,01 | 0,239±0,02 | 0,37±0,02 |

**Table II.** Frequency of micronuclei in epithelial cells of the oral mucosa in patients with leukoplakia

| Groups | Micronuclei,% | | | | |
|---|---|---|---|---|---|
| | 1 type | 2 type | 3 type | 4 type | Σ |
| SIN1 | 0,045±0,01 | 0,01±0,01 | 0,006±0,01 | 0,1±0,02 | 0,16±0,02 |
| SIN3 | 0,05±0,01 | 0,011±0,01 | 0,009±0,01 | 0,139±0,02 | 0,21±0,02 |

with leukoplakia of the SIN1, SIN2 and SIN3 groups. In 21.6 ± 5.3% of patients with SIN3 and SIN2 leukoplakia, micronuclei were found in the epithelial cells of the oral mucosa; in patients with squamous cell hyperplasia, this phenomenon was not found (rxy = + 0.737) (Fig. 1).

More often micronuclei were found in patients with SIN3 leukoplakia - 2.7 times more than in patients with SIN2 leukoplakia ($p < 0.001$, rxy = + 0.812). In patients with SIN2 and SIN3 leukoplakia, micronuclei were found 1.3 times more often than in patients with SIN1 leukoplakia ($p < 0.05$, rxy = + 0.271).

The analysis of the occurrence of various types of micronuclei (intensity) among all studied showed that the most common micronuclei of types 1 and 4 are found, with type 4 micronuclei (in total) 2.5 times more than type 1 micronuclei ( $p < 0.001$) (Fig. 2).

In patients with SIN3 leukoplakia, type 4 micronuclei were detected 3 times more often than all the others ($p < 0.01$), and in patients with SIN2 leukoplakia - 1.6 times as compared to the other three types of micronuclei combined (Table I).

The ratio of micronuclei types among patients with leukoplakia is as follows: type 4 micronuclei quantitatively prevails over all other types in patients with SIN2 leukoplakia by 1.6 times ($p < 0.05$), in patients with SIN3 leukoplakia - by 2 times ($p < 0.01$) (Table II).

## DISCUSSION

Many forms of oral mucosa diseases and red border of the lips characterized by chronic relapsing course, occur with severe clinical symptoms, can provoke the development of systemic diseases, and lead to a reduction of dental quality of life [5]. Many chronic diseases of the oral mucosa have a high oncogenic potential [4]. According to experts [5, 6], the share of oncological diseases of the maxillofacial

region is accounted for 2.4% of all malignant neoplasms, and «coarse» and standardized mortality rates from malignant tumors of the maxillofacial area (lip, tongue, salivary glands, other and unspecified parts of the oral cavity, oropharynx) in Ukraine are amounted to 8.88 and 5.64 per 100 000 population [7]. A high percentage of detection of malignant tumors of the maxillofacial region in the III and IV stages of cancer indicates a lack of alertness at the dentists. Early detection of precancerous lesions of the maxillofacial region should become an integral part of medical and dental checkups. [1].

The purpose of recent studies now is prevention and early diagnosis of malignant lesions because of expensive therapeutic and rehabilitating procedures of these lesions [8]. Buccal cells form the primary barrier for the ingestion and inhalation route. They are capable of metabolizing proximate carcinogens to reactive products [9].

Micronuclei are acentric chromosomal fragments and separate whole chromosomes that were lost during mitosis [10]. An indicator of genetic disorders in interphase nuclei can be the sum of the observed protrusions of the "broken egg" or "tongue" type [11]. The "broken egg" protrusion looks like a micronucleus connected to the nucleus by a nucleoplasm bridge, while a "tongue" protrusion is an egg on two nucleoplasm bridges [12,10]. Moreover, micronuclei in buccal epithelial cells can serve as adequate indicators for determining the level of xenogeneic intoxication and the adaptive status of an organism [13]. In another work, describes an increase in the frequency of occurrence of micronuclei in epithelial cells of the buccal mucosa as a result of the action of exogenous factors, that is, in areas with a high content of toxic substances in the air and soil [14]. The above changes in the epithelium of the oral cavity are cytogenetic disorders, and also indicate an inflammatory process in the body [15,16]. Moreover, in healthy individuals, all observed changes can be attributed to biological aging and natural death of epithelial cells of the oral cavity [17,18].

In our present study, analysis of the prevalence and frequency of micronuclei in patients by gender showed a significant difference (in men compared to women) for both indicators. The prevalence of micronuclei in epithelial cells of the oral mucosa in men is 2.4 times higher ($p < 0.01$, $rxy = + 0.571$), and the frequency is 3.2 times higher ($p < 0.01$, $rxy = + 0.658$), which may be indirectly related to the more common habit - tobacco smoking (smoking intensity, degree of tobacco strength, smoking culture, oral hygiene).

Comparison of the frequency of micronuclei among patients of different ages showed an insignificant difference (1.3 times), that is, the frequency of micronuclei slightly increases with increasing age ($p < 0.05$).

Thus, micronuclei, the appearance of which is caused by impaired differentiation of epithelial cells, were detected in patients with leukoplakia, and the detectability of micronuclei is almost equally high in both patients with SIN2 leukoplakia and SIN3 (the difference is only 1.3 times ($p < 0.05$, $rxy = + 0.271$)), and, consequently, the likelihood of neoplastic diseases of the oral mucosa or malignancy of the existing ones is high.

## CONCLUSIONS

Thus, against the background of a general increase in the proliferative activity of epithelial cells with an increase in SIN, the appearance of micronuclei in the cells of the buccal epithelium was revealed for each study group. Moreover, the frequency of occurrence of micronuclei and their fourth type increases with increasing hyperplasia, which indicates an increase in the likelihood of malignancy and the development of cancer of the oral mucosa in patients with SIN3 leukoplakia.

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ORIGINAL ARTICLE

# RISK ASSESSMENT OF NEW PESTICIDES TO PUBLIC HEALTH AS POTENTIAL CONTAMINANTS OF UNDERGROUND AND SURFACE WATER SOURCES

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## ABSTRACT

**The aim:** Risk assessment of amicarbazone, bicyclopyrone and pydiflumetofen to public health as potential contaminants of groundwater and surface water sources in soil and climatic conditions of Ukraine in comparison with other countries.

**Materials and methods:** Hazard assessment to public health was performed according to 3 methods: determination of integrated danger vector (R), integrated groundwater contamination hazard index (IGCHI), risk of adverse effects of studied pesticides to public health (RAEP).

**Results:** The assessment of R and IGCHI indicators showed that the highest level of potential danger to public health due to possible contamination of water sources in Ukraine and other countries (EU, USA, Australia) is inherent in bicyclopyrone. According to the vector R, the potential risk of groundwater contamination with amicarbazone is estimated from medium to high in different soil and climatic conditions; pydiflumetofen - as high; according to IGCHI amicarbazone is recognized as extremely hazardous for humans, while pydiflumetofen can be classified as both hazardous (particularly in Ukraine) and highly hazardous. At the same time, the comparison of potential and permissible exposures showed that the risk of harmful effects on the human body (RAEP) of all 3 substances is acceptable.

**Conclusions:** The risk of contamination of groundwater and surface water with amicarbazone and bicyclopyrone in Ukraine is quite high and coincides with that in other countries; pydiflumetofen in Ukraine shows less migration ability than in some soil and climatic conditions of other countries. Danger assessment of the studied pesticides to public health as potential contamination of water sources in Ukraine and other countries is generally identical.

**KEY WORDS:** public health, water sources, pesticides, pollution, risk assessment

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## INTRODUCTION

One of the urgent tasks of public health in the field of pesticides hygiene and toxicology is to minimize the risks arising from the widespread use of chemical plant protection products in modern agriculture. For people who do not have professional contact with pesticides, the main route of entry of the latter into the body is oral. In addition, 70–80% of the actual daily dose of the vast majority of pesticides enters the human body with a diet, and 20% – with drinking water. The entry of pesticides into the human body with drinking water is more likely in the context of decentralized water supply in rural areas, when the source is insufficiently protected groundwater, which the population receives from wells, catchments of springs, and individual wells. Therefore, predicting the likelihood of contamination of groundwater and surface water with new pesticides with a risk assessment of their impact on public health is very relevant today [1].

## THE AIM

The aim of this work is to assess the risk to public health of amicarbazone, bicyclopyrone and pydiflumetofen as a potential contaminant of groundwater and surface water in soil-climatic conditions of Ukraine in comparison with other countries.

## MATERIALS AND METHODS

The objects of the study were persistence and migration in the system "soil - groundwater and surface water" of two herbicides: amicarbazone from the chemical class of triazolinone compounds and bicyclopyrone from the class of tricetones, and the fungicide pydiflumetofen from the class of carboxamide. Amicarbazone – based preparations are used in lawns in the United States and Australia, including sports, ornamental plants, and sugar cane. Bicyclopyrone and pydiflumetofen are currently being evaluated for safety and efficacy in the EU; preparations based on them are used in Australia, Canada, USA and other countries: bicyclopyrone – on corn, sugar cane and cereals, including wheat and barley, pydiflumetofen – on a wide range of cereals, vegetables, fruits, and berries [2].

Risk assessment of contamination of groundwater and surface water sources by the studied pesticides was carried out based on the results of field studies conducted in Ukraine and data sources of information on the results of field research in different countries (EU, USA, Australia) with different soil-climatic conditions [2-9].

Field research in Ukraine was conducted during 2 growing seasons in Polissya, Forest-Steppe and Steppe climatic zones with preparations based on the studied active substances. Herbicides based on amicarbazone and bicyclopyrone were used to treat corn crops pre-emergence and post-emergence (in the phase of 1–2, 3–4 or 3–8 leaves of culture). The application rate was: amicarbazone – 0.14 kg/ha once, bicyclopyrone – 0.15 kg/ha once. These herbicides are not used on other crops in Ukraine because they are phytotoxic. Fungicides based on pydiflumetofen were treated in a wide range of crops including vegetables (onions, cucumbers), berries (strawberries), cereals (winter wheat), orchards (apple, peach) and vineyards. The application rate of pydiflumetofen on cereals was 0.075 kg/ha, once, on other crops was in range (0.05–0.18) kg/ha, twice.

During each growing season, the dynamics of residual amounts of test substances in soil were studied. Amicarbazone, bicyclopyrone and pydiflumetofen in soil samples were determined by high-performance liquid chromatography with limit of quantification (mg/kg) of 0.02; 0.01 and 0.02, respectively, and limit of detection (mg/kg) – 0.007; 0.005 and 0.007, respectively. The degradation of the studied pesticides in soil was described by first-order kinetics (SFO – Simple First-Order) [10]. According to the actual data, the degradation rate constant (k), the half-life ($DT_{50}$), the destruction periods of 95% ($DT_{95}$) and 99% ($DT_{99}$) of the initial amount of test substances in the soil were calculated.

Migration capacity assessment of amicarbazone, bicyclopyrone and pydiflumetofen in "soil - water" system and the probability of their entry into groundwater and surface water sources was performed by: leaching screening index (LIX) [11], leaching potential index (GUS) [12], leaching index to assess potential contamination of groundwater and river water ($LEACH_{mod}$) [13], maximum possible concentration of pesticide in groundwater at the application rate of 1 kg(l)/ha (SCI-GROW) [14]. Calculations of these indicators were performed using the parameters of persistence in soil in Ukraine (according to the results of our own research) and other countries (according to the literature).

Evaluation of hazard to public health of potential contamination of water supply sources with the studied pesticides was carried out according to 3 methods, which take into account not only the behavior of the substance in the «soil - water» system, but also link it to chronic toxicity criteria [15–17].

Methods [15, 17] provide an integrated assessment of 3 criteria: the migration rate of the substance in system "soil - water"; an indicator of the stability of the compound in the aqueous medium and an indicator of its toxicity and cumulative. The criterion for the stability of the substance in water in both methods is the half-life ($T_{50}$, day). The other two criteria in these methods differ, which led to the use of both in our study. In the method [17] as an indicator of the ability to vertical migration by soil profile used GUS, which we determined according to [12] including half-life period substances in soil in natural conditions ($DT_{50}$, day) and the sorption coefficient adjusted for organic carbon content ($K_{oc}$, ml/g ). The zone of biological effect ($Z_{biol.ef}$) was chosen as an indicator of chronic toxicity in the method [17], which we calculated as the ratio of the median lethal dose at a single injection of the substance into the stomach of rats ($LD_{50}$, mg/kg) to the threshold of chronic action at oral intake of the substance in the body of rats ($Lim_{ch}$, mg/kg). In the method [15] the index $LEACH_{mod}$ was used, in the determination of which according to [13] not only $DT_{50}$ and $K_{oc}$ were taken into account, but also the solubility of the substance in water ($S_w$, mg/l). As a criterion for the possibility of chronic intoxication in method [15] used the acceptable daily intake (ADI) of pesticide, which justified not only the results of chronic experiments on rats, but also the long-term effects (carcinogenicity, teratogenicity, reproductive, embryo- and fetotoxicity etc.), including on other, probably more sensitive than rats, animal species (mice, dogs, rabbits).

Data on stability and solubility in water, sorption in different soils and toxicometry parameters of test substances are taken from printed and electronic sources [2–9].

According to both methods, all three of the above indicators were translated into points and calculated the integrated danger vector (R) [17] or the integrated groundwater contamination hazard index (IGCHI) [15], which determined the hazard class.

Method [16] involves the calculation of the maximum possible daily intake of substance with water (PMDIW, μg/day) and its acceptable daily intake with water (PADIW, μg/day) with subsequent determination of the risk of adverse effects of pesticide (R) by comparing PMDIW and PADIW [16]. When determining PMDIW, the SCI-GROW index (μg/l) was taken into account, which was determined according to the screening model according to [14]; the maximum rate of pesticide consumption for the active substance, adjusted for the frequency of application during the growing season (kg (l)/ha), and the average daily consumption of water by human (3 l). Indicator PADIW was determined taking into account the ADI of the pesticide (mg/kg); average weight of a person (60 kg) and the proportion of ADI (20%) entering the body with drinking water. The risk of adverse effects of pesticides on human health was considered as acceptable if the value of RAEP ≤ 1; at RAEP > 1 the risk is not acceptable [16].

Mathematical processing of the results was performed using software products Microsoft Excel and MedCalc v.19.4.1 (MedCalc Software Inc, Broekstraat, Belgium, 1993–2020).

## RESULTS

The potential hazards to public health of chemical plant protection products are related to their toxic properties and behavior in the environment, namely stability and migration ability.

According to the actual data obtained during field research in Ukraine, we calculated the parameters of the persistence of the studied substances in the soil, which are shown in table I. According to the literature, the range of fluctuations (from the minimum to the maximum value) of

**Table I.** Stability of the studied substances in the soils of Ukraine to compare with other countries

| Indicator, units of measurement | Amicarbazone | Bicyclopyrone | Pydiflumetofen |
|---|---|---|---|
| k, day$^{-1}$ | 0.05131±0.00181 | 0.03850±0.00381 | 0.00928±0.00130 |
| $DT_{50}$, day | 13.5±0.5 | 18.3±1.9 | 103.3±16.4 |
| $DT_{95}$, day | 90.2±3.2 | 79.3±8.2 | 447.7±71.0 |
| $DT_{99}$, day | 58.7±2.1 | 122.0±12.6 | 688.7±109.3 |
| $DT_{50}$* (min – max), day | 4 – 87 | 1.7 – 36 | 29 – 8540 |
| k* (min – max), day$^{-1}$ | 0.00793 – 0.1725 | 0.01917 – 0.40588 | 0.00008 – 0.02379 |

Notes:
1. k – destruction rate constant, $DT_{50}$ – half-life period, $DT_{95}$ – the period of destruction of 95% of the original amount of the substance, $DT_{99}$ – the period of destruction of 99% of the original amount of the substance, or almost complete destruction;
2. * – $DT_{50}$ according to the results of field experiments in other countries [2–9]; k is calculated by the formula: $k = \ln 2 / DT_{50} = 0.69 / DT_{50}$.

**Table II.** Danger assessment of potential contamination by new pesticides of underground and surface water sources in Ukraine to compare with other countries

| Pesticide | | Values of indicators (min – max), units of measurement | | | |
|---|---|---|---|---|---|
| | | LIX | GUS | $LEACH_{mod}$ | SCI-GROW, µg/l |
| Amicarbazone | U | 0.105 – 0.425 | 2.66 – 3.14 | 1411.4 – 3718.6 | $1.05\times10^{-1}$ – $1.66\times10^{-1}$ |
| | OC | 0.001 – 0.876 | 1.42 – 5.39 | 418.2 – 9095.5 | $3.38\times10^{-3}$ – 6.60 |
| Bicyclopyrone | U | 0.000 – 0.794 | 1.64 – 4.07 | 435.5 – 36295.0 | $3.97\times10^{-2}$ – $5.47\times10^{-1}$ |
| | OC | 0.000 – 0.891 | 0.30 – 5.01 | 404.6 – 714000.0 | $6.41\times10^{-4}$ – 2.52 |
| Pydiflumetofen | U | 0.000 – 0.000 | 0.84 – 1.88 | 0.04 – 0.13 | $1.66\times10^{-2}$ – $6.96\times10^{-2}$ |
| | OC | 0.000 – 0.910 | 0.61 – 3.67 | 0.02 – 11.00 | $1.15\times10^{-2}$ – $3.27\times10^{-1}$ |

Notes:
1. LIX – Leachability Index, GUS (Groundwater Ubiquity Score) – leaching potential index, $LEACH_{mod}$ – leaching index to assess potential contamination of groundwater and river water, SCI-GROW – the maximum possible concentration in groundwater for the screening model.
2. U – according to the results of studies in Ukraine, OC – according to the results of studies in other countries.

**Table III.** Risk assessment to public health of potential contamination of groundwater and surface water sources by studied pesticides in Ukraine in comparison with other countries

| Pesticide | | Risk assessment by methods | | | | |
|---|---|---|---|---|---|---|
| | | [17] | | | [15] | [16] |
| | | R* | Level of hazard | IGCHI | Class, grade | RAEP * |
| Amicarbazone | U | 86.6 – 106.8 | medium – high | 11 | 1A (extremely hazardous) | $7.4\times10^{-4}$–$1.2\times10^{-3}$ |
| | OC | 76.8 – 122.5 | medium – high | 11 | 1A (extremely hazardous) | $2.3\times10^{-5}$ – $4.62\times10^{-2}$ |
| Bicyclopyrone | U | 144.6 – 173.2 | very high | 12 | 1A (extremely hazardous) | $5.0\times10^{-3}$–$6.8\times10^{-2}$ |
| | OC | 144.6 – 173.2 | very high | 12 | 1A (extremely hazardous) | $8.3\times10^{-5}$ – $3.2\times10^{-1}$ |
| Pydiflumetofen | U | 115.8 – 122.5 | high | 7/8 | 2, hazardous | $4.98\times10^{-5}$ – $2.09\times10^{-4}$ |
| | OC | 115.8 – 137.5 | high | 7/9 | 2, hazardous – 1B, highly hazardous | $3.4\times10^{-5}$ – $9.8\times10^{-4}$ |

Notes:
1. R – integral danger vector, IGCHI – integral groundwater contamination hazard index, RAEP – the risk of adverse effects of pesticides on public health; * – The range of oscillations from minimum to maximum value is given.
2. U – according to the results of studies in Ukraine, OC – according to the results of studies in other countries.

the studied substances half-life in soil-climatic conditions of other countries is determined and the corresponding rate constants of destruction are calculated (table I).

The persistence parameters of amicarbazone, bicyclopyrone and pydiflumetofen listed in the table 1 were used to calculate the LIX, GUS, $LEACH_{mod}$ and SCI-GROW

indices, which make it possible to predict the inflow of the substance into water and even predict the level of such inflow SCI-GROW (table II).

The results of the risk assessment to public health of potential contamination of underground and surface water sources due to the migration of the studied pesticides from the soil according to the methods [15–17] are shown in table III.

## DISCUSSION

It is established (table I ) that in soil-climatic conditions of Ukraine amicarbazone and bicyclopyrone are moderately persistent (III hazard class) in terms of soil persistent according to the hygienic classification of pesticides in Ukraine [18] and low persistent (IV class) according to international IUPAC classification [2]; pydiflumetofen is highly persistent (I hazard class) according to the national classification and moderately persistent (II class) according to the IUPAC classification. According to field studies in other countries, both herbicides are from low persistent to moderately persistent, pydiflumetofen – from low persistent to highly persistent.

According to the leaching screening index LIX (table II) amicarbazone in soil-climatic conditions of Ukraine can be classified as a leaching pesticide, pydiflumetofen – as nonleachable, while the LIX index of bicyclopyrone varies from 0 (minimum leaching potential, nonleachable pesticide) to almost 1 (maximum leaching potential) according to [11]. In general, the assessment of the leaching ability of amicarbazone and bicyclopyrone in Ukraine coincides with the assessment of the results of studies in other countries. As for pydiflumetofen, in Ukraine it is nonleachable, while according to the results of the study of dissipation in field studies conducted in the EU [4], its leaching potential varies from minimum to maximum (the LIX index calculated by us is in the range of 0.000–0.910).

The leaching ability of amicarbazone according to the GUS index (table II) was assessed in the soils of Ukraine from moderate (III class) to high (II class), bicyclopyrone – from low (IV class) to very high (I class), pydiflumetofen – from very low (V class) to low (IV class), while in general, according to the results of field research in other countries, the range of fluctuations is wider: amicarbazone – from low (IV class) to very high (I class), bicyclopyrone – from very low (V class) to very high (I class), pydiflumetofen – from very low (V class) to high (II class) according to the classificatio presented in [19]. With regard to pydiflumetofen, the assessment of its leaching ability in Ukraine by the GUS index (from very low to low) coincides with that of the LIX index (nonleachable pesticide) and also differs from the assessment by research in other countries.

The risk of potential contamination of surface and groundwater in Ukraine amicarbazone and bicyclopyrone according to the $LEACH_{mod}$ index (table II) is high (I class) according to the classification presented in [13], which generally coincides with the assessment of the results of studies in other countries. It should be noted that pydiflumetofen has a low risk of water pollution in Ukraine (III class), which coincides with previous estimates of the GUS and LIX indices.

The maximum possible concentration of test substances in the groundwater of Ukraine according to the screening model (SCI-GROW) [14] varies in a fairly narrow range and in the most unfavorable soil-climatic conditions will exceed the maximum permissible concentration of pesticide in drinking water (0.1 μg/dm3) only: amicarbazone – 1.7 times, bicyclopyrone – 5.5 times, pydiflumetofen – 0.7 times (ie will not actually exceed), while the study in other countries, the maximum excess is: amicarbazone – 66 times, bicyclopyrone – 25.2 times, pydiflumetofen – 3.3 times.

In soil-climatic conditions of Ukraine, the potential danger to public health of groundwater pollution by amicarbazone according to the integral vector R according to [17] is estimated from medium to high, bicyclopyrone – as very high, pydiflumetofen – as high and coincides with the assessment of the study in other countries (table III).

In accordance with the method [15] on the integrated groundwater contamination hazard index (IGCHI) amicarbazone and bicyclopyrone in Ukraine are considered extremely hazardous to health (1A class), which coincides with the assessment of studies in other countries (table III); pydiflumetofen is hazardous (2 class), which is better than in certain soil-climatic conditions of other areas.

Comprehensive assessment based on a comparison of potential exposure (maximum possible daily intake of pesticide with water) with the acceptable daily intake of studied pesticide with water by method [16] showed (table III) that the potential risk of adverse effects on human health (RAEP) of amicarbazone, bicyclopyrone and pydiflumetofen when washed into water is less than one, ie acceptable, both in Ukraine and in other countries.

Thus, despite the assessment of amicarbazone and bicyclopyrone as extremely hazardous (1A class), pydiflumetofen – as hazardous (2 class) for health on the integrated hazard indicator IGCHI; amicarbazone as moderately or highly dangerous, bicyclopyrone as highly dangerous, pydiflumetofen as dangerous for the integral vector R, comprehensive assessment showed that the potential risk of adverse effects on health (RAEP) of both substances is acceptable. Risk assessment of amicarbazone, bicyclopyrone and pydiflumetofen to public health as potential contaminants of groundwater and surface water in soil-climatic conditions in Ukraine coincides with the assessment of the results of studies in other countries.

## CONCLUSIONS

1. In soil-climatic conditions of Ukraine the most persistent in the soil is pydiflumetofen (II class, persistent); amicarbazone and bicyclopyrone are low persistent (IV class) according to the international IUPAC classification. According to field studies in other countries, both herbicides are from low persistent to moderately persistent, pydiflumetofen – from low persistent to highly persistent.

2. According to the LIX leaching screening index, amicarbazone in soil-climatic conditions of Ukraine can be classified as a leaching pesticide, while the leaching potential of bicyclopyrone varies from minimal to almost maximum; according to the GUS index, the leaching ability of amicarbazone is assessed from moderate to high, bicyclopyrone – from low to very high; According to the $LEACH_{mod}$ index, the risk of contamination of surface and groundwater of Ukraine with both herbicides is high. At the same time, pydiflumetofen is classified as a nonleachable pesticide with a very low to low leaching ability and a low risk of surface and groundwater contamination. In general, assessment of leaching ability of amicarbazone and bicyclopyrone in Ukraine coincides with the assessment of study results in other countries; pydiflumetofen in Ukraine shows less migration ability than in some soil-climatic conditions of other countries.
3. The maximum possible concentration of test substances in the groundwater in Ukraine according to the SCI-GROW screening model varies in a much narrower range than according to the generalized data in other countries. Under the most unfavorable soil-climatic conditions in Ukraine and other countries, multiplicity exceeding the maximum permissible concentration of pesticide in drinking water (0.1 μg/dm3) will be: amicarbazone – 1.7 and 66 times, respectively, bicyclopyrone – 5.5 and 25.2 times, pydiflumetofen – 0.7 and 3.3 times, respectively.
4. According to the integrated vector R and the IGCHI indicator, the highest level of danger to public health due to possible contamination of groundwater and surface water sources in Ukraine, as in other countries (EU, USA, Australia) is inherent in bicyclopyrone. According to the vector R, the potential danger to human body of groundwater contamination with amicarbazone is estimated from medium to high depending on soil-climatic conditions; pydiflumetofen – high; according to IGCHI, amicarbazone is recognized as extremely hazardous for health, in contrast to pydiflumetofen, which can be classified as both hazardous (including in Ukraine) and highly hazardous (1B class), depending on soil-climatic conditions.
5. A comprehensive assessment of the health hazards of the studied pesticides when they are leached into water sources by comparing the potential (PMDIW) and permissible (PADIW) exposures has shown that the risk of their harmful effects on human body (RAEP) is acceptable.

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ORIGINAL ARTICLE

# THE STATE OF TOXIN-RELEASING FUNCTION OF THE KIDNEYS IN THE SYNDROME OF ENDOGENOUS INTOXICATION OF PURULENT-SEPTIC ORIGIN IN PATIENTS WITH DIABETES MELLITUS

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## ABSTRACT

**The aim:** To investigate the state of renal toxin excretory function in EIS of purulent-septic genesis in patients with diabetes mellitus-2 under the condition of infusion load with low-volume Ringer's solution.

**Materials and methods:** The research belongs to the opened, randomized, prospective and controlled studies. The study group was consisted of patients with diabetes mellitus-2 complicated syndrome of endogenous intoxication of purulent-septic origin (CDSEI).

**Results:** However, their activity is different. In particular, renal toxin excretory function in patients with CDSEI by STPC clearance is characterized by an increase in activity by 165% (control - 282%; $p < 0.05$), and by MMM clearance - by 137% (control - 171%; $p < 0.05$). These data indicate the degree of depression of renal toxin function in patients with CDSEI and its compensatory capabilities.

**Conclusions:** The depression of the clearance of total blood plasma toxicity is a predictor of the predominance of toxin formation over the elimination of toxic substances in patients with diabetes mellitus 2 complicated by purulent-septic pathology. The low-volume infusion loads with Ringer's solution in terms of clearance of total blood plasma toxicity is a sensitive indicator of the degree of depression of toxin-releasing function of the kidneys and compensatory capabilities in diabetes mellitus 2 complicated by purulent-septic pathology.

**KEY WORDS:** diabetes mellitus, Ringer's solution, depression. predictor of the predominance

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## INTRODUCTION

The surgical practice of purulent-septic complications often has comorbid accompaniment, in particular diabetes mellitus [1]. In turn, the patients with diabetes are prone to this association [2]. These combinations are manifested by the development of a mutually aggravating course, the formation of endogenous intoxication syndrome (EIS) and multiorgan damage [3]. EIS can be polyetiological and polypathogenetic. It is characterized by the accumulation in tissues and biological fluids of endogenous toxins, which are formed due to an excess of metabolic products of normal or impaired metabolism or cellular response [3]. EIS includes the following components: the source of toxemia, where the endogenous toxins form; the biological barriers that prevent endotoxin from entering the source; the transport mechanisms that ensure the entry of endotoxins into the organs of biotransformation and excretion; the mechanisms of biotransformation and excretion; an effector responses to intoxication in the form of so-called secondary toxic aggression, as a result of which EIS significantly loses its specificity and requires long-term comprehensive treatment [4]. Among the priority measures of intensive care EIS are methods of activation of renal toxin function and nephroprotection [5]. In this regard, the methodology of monitoring the toxin-releasing function of the kidneys is gaining great importance in the formation of an arsenal of intensive care measures, needs elaboration and proposals.

## THE AIM

To investigate the state of renal toxin excretory function in EIS of purulent-septic genesis in patients with diabetes mellitus-2 under the condition of infusion load with low-volume Ringer's solution.

## MATERIALS AND METHODS

The research belongs to the opened, randomized, prospective and controlled studies. The study group was consisted of patients with diabetes mellitus-2 complicated syndrome of endogenous intoxication of purulent-septic origin (CDSEI). The inclusion criteria were CDSEI, age - 42-65 years, established experience of the disease 5-12 years; from the anamnesis: correction by diet, regimen, tableted hypoglycemic agents, insulin (9%); actual glycemia - 8-16 mmol / l, glycosylated hemoglobin > 7%, transient microalbuminuria (30-3000 mg / day); various clinical mani-

festations of angiopathy and neuropathy were registered without significant dysfunction of the affected organs and systems. The course of diabetes mellitus was complicated by the acute purulent surgical infection in the practice of surgical departments of abdominal, proctological, traumatological, otolaryngological, maxillofacial, obstetric and gynecological profiles after surgical remediation of the focus of different localization due to the association of aerobic sinusitis, the genesis on the scale of cell-humoral index of intoxication 20-50 points (moderate to severe intoxication) [6].

All patients had received the appropriate surgical rehabilitation and comprehensive standard intensive care. At hospital the glucose correction was performed with the insulin at blood glucose of > 10 mmol / l. The control group of the study included patients with systemic inflammatory response syndrome (SSRI), which corresponded to ICD-10: non-infectious etiology without organ failure - SIRS, ICD-10: R-65.2. The patients were divided into 4 groups: 1st gr. and 2nd gr. - control studies (SIRS, n = 30); 3nd gr. and 4th gr. - DEIS (n = 53). The patients of 2nd group and 4th group were studied in the fragment of infusion therapy with low-volume loads with Ringer's solution at the rate of 3 ml / kg / h for 3 hours, which was provided by the program. After increasing the volume of extracellular space (IVES) with Ringer's solution, the patients were examined in 4-hour interval, taking into account the time of infusion load. The indicators of values studied in biological media that total toxicity of blood plasma (urine) [7], the concentration of medium weight molecules in blood plasma or urine [8], cell-humoral index of intoxication [6], and procalcitonin [9] are given in the table. The T-test for dependent (Δ) and independent samples (statistical package Excell, trial version) was used to statistically process of these studies [10].

## RESULTS

The unicellular receptor systems are a sensitive indicator of total plasma toxicity (TPT) [7]. As a result of modification, it acquires informative content as criteria of toxin-releasing function of the kidneys (Table I). Under the condition of "inclusion" of TPT, in patients with diabetes mellitus complicated by EIS, the data of the control group prevail by 62% ($p < 0.05$). In this case, procalcitonin as an indicator of activity systemic inflammatory process of bacterial origin reaches 4.3 ± 0.095 ng / ml. The value of renal excretion of TPT components in patients with DEIS by 48% ($p < 0,05$) is higher than in SIRS (Table I) both due to higher figures of concentration of components of toxicity in urine (Table I) and the amount of diuresis (0, 98 ± 0.04 ml / min - SIRS; 1.22 ± 0.03 ml / min - DEIS; $p < 0.05$).

The calculation of the excretion of STPC components at a standardized glomerular filtration rate (load on active nephrons) confirms the degree of growth of activity and participation of nephrons in the processes of toxin elimination in patients with DEIS (Table). However, the consideration of renal function parameters such as excreted fraction, TPT clearance and toxicity release index (UT / PT: 2.9 ± 0.02 USD - SRIS; 2.1 ± 0.01 USD - $P < 0, 05$) indicates that in patients with DEIS toxin formation predominates over their removal from both the vascular bed and the extracellular sector.

Among the many factors of endogenous intoxication there are the part of TPT distinguish medium-mass molecules (MMM). They have high biological activity. In particular, they have neuro-, cardio-, hepato-, nephrotoxic activity. The organotropic action is based on the property of inhibiting the biosynthesis of protein and enzymes; separate oxidation and phosphorylation processes; to have a toxic effect on erythropoiesis, etc. The components of endotoxicosis in EIS are MMM (300-5000 Daltons). They are freely filtered by the glomeruli of the kidneys and create a high concentration in the ultrafiltrate of the proximal nephron. There, the major amount of MMM is metabolized by the nephrothelium peptidase system to reabsorbed amino acids. The part of the MMM is excreted by the kidneys. Therefore, the elimination activity of MMM depends on the magnitude of glomerular filtration rate and proximal metabolism. Given that MMM is one of the fractions that cause the development of EIS, consideration of the involvement of the kidneys in the elimination of the components of toxemia is an important issue for assessing the course of SEI and determining the tactics of infusion therapy. The degree of MMM production is indicated by their level in blood plasma. The concentration of MMM is 2.6 times higher in patients with DEIS than in patients with CVD. However, the increase in the values of renal elimination activity of MMM, namely UMSM, UMSMV, UMSMV / GFR · 100, EFMSM shows (Table; III gr. from MMM to the level of compensation (according to SMSM).

To elucidate the possibilities of renal detoxification function in the process of infusion therapy, a fragment (II group) was isolated, namely the period of application of low-volume infusion load with Ringer's solution (3 ml / kg / h, for 3 hours). The analysis of the results of these observations (Table; II gr., IV gr.) show that patients with SRIS and DEIS qualitatively respond equally to IVES, and vector changes are aimed at freeing the body from endogenous intoxication. However, their activity is different. In particular, renal toxin excretory function in patients with CDSEI by STPC clearance is characterized by an increase in activity by 165% (control - 282%; $p < 0.05$), and by MMM clearance - by 137% (control - 171%; $p < 0.05$). These data indicate the degree of depression of renal toxin function in patients with CDSEI and its compensatory capabilities.

The comparisons of the processes that serve the toxin-releasing function of the kidneys in the mode "before IVES and after" (II gr. and IV gr. of observation) showed that low-volume infusion loads of Ringer's solution in patients with CVD activate the mechanisms of detoxification potential in terms of RT 3.8%, $\Delta p < 0.05$), RMSM (decrease by 15 ± 5.9%, $\Delta p < 0.05$), KGII (decrease by 11 ± 4.3%, $\Delta p < 0.05$) , PKT (decrease by 14 ± 5.6%, $\Delta p < 0,05$). This is achieved by activating the detoxification function of the kidneys, in particular by increasing the CT by 2.8 times, SMSM - by 2.7 times ($\Delta p < 0,05$). Similar indicators, under the same condi-

**Table I.** Indicators of endogenous intoxication syndrome and renal detoxification function

| | SIRS (n=30) | | DEIS (n=53) | |
|---|---|---|---|---|
| | I gr. | II gr. (+ЗООП) | III gr. | IV gr. (+IVES) |
| Rt, y.o.т./ml | 103±3,9 | 91±4,1** | 167±3,6* | 156±3,7* ** |
| Ut, y.o.т./ml | 293±5,1 | 280±5,0** | 349±4,2* | 330±4,3* ** |
| UtV, y.o.т./m | 287±5,1 | 731±5,9** | 426±4,8* | 1070±7,3* ** |
| UtV/GFR·100, | 256±4,2 | 630±9,7** | 361±4,1* | 892±9,3* ** |
| EFT, % | 2,5±0,05 | 6,8±0,07** | 2,2±0,04* | 4,4±0,05* ** |
| Ст, ml/m | 2,8±0,06 | 7,9±0,14** | 2,6±0,05* | 6,9±0,11* ** |
| PMCM, ml | 0,27±0,010 | 0,23±0,012** | 0,71±0,019* | 0,64±0,021* ** |
| UMCM, ml | 5,0±0,13 | 4,4±0,12** | 11,7±0,21* | 9,4±0,19* ** |
| UMCMV, /m | 4,9±0,17 | 11,5±0,37** | 14,3±0,32* | 30,5±0,69* ** |
| UMCMV/GFR·100, m | 4,4±0,15 | 9,9±0,31** | 12,1±0,16* | 25,4±0,52* ** |
| EFMCM, % | 16,3±0,21 | 43,0±0,64** | 17,2±0,20* | 39,7±0,59* ** |
| CMCM, ml/m | 18,1±0,62 | 49,0±1,37** | 20,1±0,57* | 47,7±1,22** |
| CHII, points | 9±0,25 | 8±0,29** | 47±0,94* | 42±0,91* ** |
| PBP, ng/ml | 0,7±0,03 | 0,6±0,03** | 4,3±0,09* | 4,0±0,11* ** |

Note: I gr. and II gr. - systemic inflammatory response syndrome (SIRS); III gr. and IV gr. - diabetes mellitus (DM) combined with the syndrome of endogenous intoxication of purulent-septic genesis (EIS); IVES increases in the volume of extracellular space with Ringer's solution; * / P≤0,05 - reliability of indicators between I gr. and III gr., II gr. and IV gr., ** / P≤0,05 - reliability of indicators between I gr. and II gr.; III gr. and IV gr.
Rt - total toxicity of blood plasma;
Ut - total urine toxicity;
UtV - excretion of toxic substances;
UtV / GFR · 100 - excretion of toxic substances per 100 ml of GFR;
EFTS - excreted fraction of toxic substances;
RMSM - the concentration of MSM in blood plasma;
UMSM - concentration of MSM in urine;
UMSMV - excretion of MSM;
UMSMV / GFR · 100 - excretion of MSM per 100 ml of GFR;
EFMSM - excreted fraction of MSM;
SMSM - MSM clearance;
CHII - cell-humoral index of intoxication
PBP - procalcitonin of blood plasma.

tions in patients with CDSEI have the same orientation, but different absolute values. Thus, RT decreases by 7 ± 2.2%, (Δ, p <0,05), RMSM decreases by 10 ± 3,7%, Δ, p <0,05), KGII decreases in 11 ± 4,1 %, Δ, p <0,05), PKT decreases by 8 ± 3,2% (Δ, p <0,05) and is achieved by increasing CT by 2,6 times, SMSM - by 2,4 times (Δ, p <0.05); accordingly, indicates the level of depressed function.

## DISSCUSION

With the growth of experience and accumulation of facts during the second half of the twentieth century. there was a gradual transformation of understanding of the essence of this pathological process: from the leading and unique role of the infectious origin to the recognition of the determining importance of the reactivity of the macroorganism [2].

Sepsis can be diagnosed according to the criteria in the presence of a source of infection, as well as two or more signs of systemic inflammatory response syndrome. Severe sepsis is characterized by hypotension, organ dysfunction, tissue perfusion disorders, oliguria, including increased lactate concentration, acute disturbance of consciousness.

In the course of sepsis and the formation of multiorgan damage, the kidneys, as a homeostatic organ, are involved in the risks of the existence of biological integrity of the organism. The combined activity of the nephrons is the basis of the volumetric, osmo-, ion-regulatory, excretory, toxin-releasing functions of the kidneys. It is the state of these functions that ensures the stability of homeostasis, especially in severe sepsis. Damage to the enzyme systems of mitochondria - "mitochondrial distress syndrome" is attributed to, another cause of circulatory disorders and impaired oxygen consumption is considered. Mitochondrial dysfunction seriously affects the energy metabolism of cells and releases a large number of components into the cytosol or extracellular space, leading to a number of biochemical reactions such as apoptosis, necrosis and inflammation. According to the endosymbiotic theory of mitochondria, mitochondria may be derived from energy-producing bacteria [5].

Effective intensive care (IT) of sepsis is possible only with full surgical remediation of the source of infection and adequate antimicrobial therapy.

Thus, there are questions that are answered in the spectrum of special studies, in particular the effect of infusion load on the functional state of the kidneys and circulatory system with the use of polyhydric alcohols, which has not been previously studied. These observations have a practical orientation, pathogenetic direction, are to study, for example, the effects of basic crystalloid solution and solution of polyhydric alcohols on basic homeostatic systems (kidneys, circulatory system), the study of optimization of intensive care dopamine-dependent sepsis-induced sepsis. The conducted observations allow to offer a solution as a part of basic therapy of sepsis. It is recommended to use the scale of cell-humoral index of intoxication (CGII) to monitor endogenous intoxication (Ukrainian patent №112508) and clearance characteristics of MSM (Ukrainian patent № 97059). When preparing infusion therapy, it is recommended to take into account the results of studies on the effect of increasing extracellular space with Ringer's solution, reosorbilact on water-salt metabolism and renal function, central and peripheral hemodynamics, microcirculation in patients with sepsis in combination with diabetes.

## CONCLUSIONS

The depression of the clearance of total blood plasma toxicity is a predictor of the predominance of toxin formation over the elimination of toxic substances in patients with diabetes mellitus 2 complicated by purulent-septic pathology.

The low-volume infusion loads with Ringer's solution in terms of clearance of total blood plasma toxicity is a sensitive indicator of the degree of depression of toxin-releasing function of the kidneys and compensatory capabilities in diabetes mellitus 2 complicated by purulent-septic pathology.

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ORIGINAL ARTICLE

# ANALYSIS OF RISK FACTORS FOR DENTAL CARIES IN PATIENTS WITH DIABETES MELLITUS

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## ABSTRACT

**The aim:** To identify, structure and evaluate the degree of influence of risk factors on the intensity of dental caries in patients with type 1 diabetes mellitus to improve caries-preventive measures.

**Materials and methods:** 179 patients with type 1 diabetes mellitus aged 18 to 56 years with a disease duration from 1 to 50 years were examined. 157 patients had various chronic diabetic complications. In patients the prevalence and intensity of caries were determined according to the DMFT index and the DMFS index, as well as the state of oral hygiene according to the OHI- S index. To determine the risk factors for dental caries, patients were interviewed using the developed questionnaire "The state of dental health of a patient with diabetes mellitus."

**Results:** The most significant factors associated with indicators of the intensity of caries of the DMFT and the DMFS in patients with type 1 diabetes mellitus are xerostomia ($r=0.61$, $p<0.01$, and $r=0.66$, $p<0.01$), oral hygiene ($r=0.57$, $p<0.01$, and $r=0.58$, $p<0.01$), sharp fluctuations in blood glucose level ($r=0.54$, $p<0.05$, and $r=0.59$, $p<0.05$), frequent hypoglycemia ($r=0.53$, $p<0.05$, and $r=0.56$, $p<0.05$) and consumption of sweets ($r=0.52$, $p<0.01$, and $r=0.55$, $p<0.01$).

**Conclusions:** When introducing individualized caries prevention measures in patients with type 1 diabetes, it is necessary to take into account the identified leading cariogenic factors for their elimination or partial correction.

**KEY WORDS:** diabetes mellitus, caries, cariogenic factors

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## INTRODUCTION

The incidence of diabetes mellitus (DM) in the world is increasing every year. In the structure of this disease, type 2 reaches 85-90%, type 1 amounts to 10-15% [1]. Diabetes mellitus is characterized by disorders of all types of metabolism and the development of various complications [2]. Diabetes also affects the onset or progression of various dental diseases, the prevalence of which in patients with diabetes ranges from 89.1% to 100% [3-5]. The prevalence of dental caries in these patients is from 56.2% to 100%, while the intensity of carious lesions varies significantly [6, 7].

The development of dental caries in patients with type 1 and type 2 diabetes is influenced by a number of factors [8, 9]. The leading ones include dental biofilm bacteria, hyposalivation, changes in the qualitative and quantitative composition of the oral fluid, an increase in the number of cariogenic bacteria Str. mutans and Lactobaccillus, high levels of glucose in the oral and gingival fluid, impaired local immunity, that is, specific and nonspecific protective factors [10-12]. However, information on cariogenic factors and the degree of their influence on patients with type 1 diabetes mellitus has been described, to some extent, in a fragmentary and contradictory manner. There are still insufficiently studied and controversial issues of determining the primary risk factors for the development of caries in the adult population suffering from type 1 diabetes. Most of the factors are interrelated to the severity of diabetes, they require further study in order to develop and improve measures to prevent the development of dental caries in patients with type 1 diabetes.

## THE AIM

The aim of the study is to identify, structure and evaluate the degree of influence of risk factors on the intensity of dental caries in patients with type 1 diabetes mellitus to improve caries preventive measures.

## MATERIALS AND METHODS

Dental examination was carried out in 179 patients with type 1 diabetes aged 18 to 56 years, including 97 men (54.2% of the total number of patients examined) and 82 women (45.8%) in the clinic of the Department of Therapeutic Dentistry of the Private Higher Educational Institution "Kyiv Medical University" during 2018-2019. The duration of type 1 diabetes in all patients ranged from 1 to 50 years, in particular, the duration of up to 5 years was in 26 people (14.5%), from 5 to 10 years – in 40 patients (22.3%), more than 10 years – in 113 examined patients

(63.2%). Decompensation of type 1 diabetes was in 131 people (73.2%), while 61 patients had a labile course of diabetes with a predisposition to hypoglycemia or ketoacidosis. 25 people had a compensated diabetes mellitus (14.0%), and 23 people had a subcompensated DM (12.8%).

Various chronic diabetic complications were observed in 157 patients (87.7%), in particular, macroangiopathy – in 155 people (86.5%), microangiopathy – in 157 people (87.7%), moreover retinopathy and microangiopathy of the lower extremities were present in all patients who had microangiopathy, nephropathy was noted in 45 patients (25.1%), polyneuropathy – in 151 patients (84.3%), and osteoarthropathy – in 32 people (17.8%).

The exclusion criteria from the study were: the presence of type 2 diabetes in patients, gestational diabetes, metabolic syndrome, mental illness, blood diseases, cancer and infectious diseases, other concomitant autoimmune diseases, pregnancy, and age of patients under 18 years and over 60 years.

The study was conducted in compliance with the provisions of the Convention on Human Rights and Biomedicine developed by the Council of Europe, the World Medical Association Declaration of Helsinki on Ethical Principles for Scientific Medical Research involving Human Subjects, Ukrainian legislation and was approved by the Bioethics Commission of the Kyiv Medical University. Written informed consent was obtained from all patients to participate in the survey and research.

During the clinical examination the prevalence of dental caries and its intensity according to the DMFT index, which reflects the number of decayed (D), missing (M) and filled (F) permanent teeth, and the DMFS index, which reflects the number of affected tooth surfaces, as well as the state of oral hygiene by the simplified OHI-S index were determined in 179 patients [8].

To determine the risk factors for dental caries, all examined patients with type 1 diabetes were interviewed using a questionnaire "The state of dental health of a patient with diabetes mellitus", which included a number of questions that provide general information about the treatment and course of diabetes, diet, addressing the dentist, carrying out preventive and therapeutic measures for caries, determining the hygienic skills of the patient, etc. [13].

Statistical processing of indicators of the index assessment of the intensity of dental caries, as well as oral hygiene of patients was performed using the SPSS Statistics 23 (IBM SPSS, USA) and MS Excel 2019 software. A significant statistical difference was determined by Student's t-test. The results of the questionnaire were provided in absolute and relative values. The Pearson (r) parametric correlation criterion was calculated to establish correlations between the indicators.

## RESULTS

The prevalence of dental caries in the examined patients with type 1 diabetes was maximum and amounted to 100%. The intensity of dental caries in terms of the DMFT index was 14.1±0.43, which corresponds to a high level according to WHO criteria [14], in terms of the DMFS index it amounted to 30.7±1.53.

In individuals with a duration of type 1 diabetes up to 5 years, the intensity of caries was 9.84±0.94 according to the DMFT index, 14.8±1.73 according to the DMFS index, and by two indicators it was significantly ($p<0.05$) lower than in patients with duration of diabetes mellitus from 5 to 10 years and over 10 years (the DMFT index was 13.0±0.64 and 15.4±0.56, the DMFS index was 24.5±2.15 and 36.6±2.06, respectively). In patients without chronic diabetic complications, as well as in the presence of no more than 2 such complications, the intensity of caries was average, the DMFT index in these patients was 10.8±1.02 and 10.4±0.67, respectively, the DMFS index was 18.0±2.14 and 19.2±2.19, in patients with 3 complications, the intensity of carious lesions was high with the value of the DMFT index 14.2±0.62 and the DMFS index 32.6± 2.35 (the difference from the previous corresponding indices is significant, ($p<0.05$), in patients with 4 complications and more, the intensity significantly ($p<0.05$) increased to very high, the DMFT index was 17.6±0.78, and the DMFS index amounted to 41.8±3.12.

The index assessment of oral hygiene in all the surveyed showed that it was unsatisfactory with an average value of the OHI-S index of 2.25±0.04, while 44 people (24.6% of the total number of patients) had a satisfactory level of oral hygiene with an index of 1.42±0.02, 72 people (40.2%) had unsatisfactory condition with an indicator of 2.23±0.03, and 63 people (35.2%) had a poor level of hygiene with an index 2.85±0.03. No patient had a good level of oral hygiene.

According to the results of the interviewed patients, it was found that only 128 people (71.5% of the respondents) carry out daily monitoring of the blood glucose level (from 1 to 3 times a day), 27 patients (15.1%) monitor it once every few days, and 24 people (13.4%) – once a week. Sharp fluctuations in blood glucose level (from 2.5 mmol/l to 23 mmol/l) with varying frequency during the last month were noted by 112 patients (62.5%), and tendency to hypoglycemia was noticed by 109 patients (60.8%). HbA1c, which indicates the degree of diabetes compensation, is determined quarterly by 147 people (82.1%), 2 times a year – by 32 people (17.9%). This indicates, however, that some patients with type 1 diabetes do not sufficiently carry out any self-control of blood glucose level. Patients most often try to empirically calculate the required dose of insulin in order to correct glycemia, which, in turn, causes fluctuations in blood glucose levels, frequent hypoglycemia, especially at night, morning hyperglycemia, and leads to a decompensated state of the disease.

Data of the survey of patients on nutrition showed that only 59 people (33%) constantly followed the balanced diet recommended by an endocrinologist, 98 people (54.7%) partially followed a balanced diet, 22 patients (12.3%) did not follow recommendations at all. It should be noted that 140 people (78.2%) eat 3-4 times a day, 18 patients (10.1%) eat 1-2 times a day, and 21 people (11.7%) – 5-6 times a day.

The most often cause of fluctuations in blood glucose levels and decompensated diabetes is not following a balanced diet or violation of its regimen.

According to the survey data on the consumption of sweets, it was found that they are consumed by 133 people (74.3%). In addition, 11 respondents (6.2%) regularly consume sweets for diabetics, 26 patients (14.5%) use them periodically, and 142 people (79.3%) do not eat them at all.

Patients include sweets in their diet in different ways. During hypoglycemia, all patients (100%) eat sweets. Among the respondents, 83 people (46.3%) noted that they often eat sweets during the week, 10 people (5.6%) – several times a month. 21 people (11.7%) eat sweets after the main meal, 69 patients (38.5%) eat during snacks, and most respondents eat them in the evening, in particular, 154 people (86%). Sweet water is constantly consumed by 6 respondents (3.3%), 57 patients (31.8%) use it periodically, and 116 people do not use it at all (64.9%). Among the sweets that patients consume, including during hypoglycemia are lollipops, waffles, cookies, dried fruits, marshmallows, marmalade, much less often – sweet water ("Coca-Cola", "Pepsi") and juices.

According to the survey results, 132 people (73.7%) do not use sugar substitutes at all, but 24 people (13.4%) stated that they use them periodically, and 23 people (12.9%) constantly use sugar substitutes that contain stevia, cyclamate or xylitol.

Thus, the vast majority of patients only partially limit the consumption of sweets, a smaller proportion of patients continue to eat them uncontrollably, which negatively affects blood sugar level and the achievement of the state of diabetes compensation. In addition, sweets have a cariogenic effect, they are easily fermented by microorganisms with the formation of organic acids, which cause enamel demineralization.

The survey showed that the majority of the examined patients with type 1 diabetes, in particular, 134 patients (74.8%), visit a dentist only when necessary, 27 patients (15.1%) regularly visit the dentist once a year, and 18 people (10.1%) do it 2 times a year. The main reasons for going to the dentist were acute pain, which was noted by 33 people (18.4%), dental caries – 31 patients (17.3%), prosthetics – 27 people (15.1%), loss of fillings or their chipping – 24 patients (13.4%), tooth extraction – 22 people (12.3%), professional examination – 17 people (9.5%), bleeding gums – 13 patients (7.3%), professional oral hygiene – 12 people (6.7%).

108 interviewed patients (60.3%) periodically address for professional oral hygiene, among whom 43 people (39.8%) address 1-2 times a year, 65 patients (60.2%) – once for several years, however, 71 patients (39.7%) have never had professional oral hygiene. According to the questionnaire, the dentist conducted training and selection of means for individual oral hygiene and provided recommendations for the prevention of caries only to 73 patients (40.8%),

During the survey, 98 people (54.7%) had various dental complaints, namely regarding the presence of carious lesions of the teeth – 33 patients (33.7%), bleeding gums – 25 patients (25.5%), hypersensitivity of the hard tissues of the teeth of varying degrees – 98 people (54.7%), a combination of caries and bleeding gums – 14 patients (14.3%), missing teeth – 7 patients (7.1%). 136 people (76%) complained of dry mouth (xerostomia), in particular, permanent xerostomia was present in 17 patients (12.5%), periodic – in 119 patients (87.5%), but it was not noted at all in 44 patients (24%).

It is well known that maintaining oral hygiene is one of the most effective ways to prevent dental caries. According to the results of the survey, it was determined that 84 patients (47%) brush their teeth twice a day, 57 patients (31.8%) do it only once a day in the morning or evening, mainly before meals, and 38 patients (21.2 %) brush their teeth even once every few days. Only 79 people (44.2%) conduct interdental hygiene. Among the respondents, 95 patients (53.1%) brush their teeth for up to 1 minute, 69 patients (38.5%) – up to 2 minutes, and 15 patients (8.4%) – up to 3 minutes.

For individual oral hygiene, all interviewed 179 patients (100%) use toothpaste and toothbrush, in particular, manual toothbrush is used by 164 people (91.6%), and electric – by 15 people (8.4%). Toothpastes containing fluoride compounds are used daily by 87 patients (48.6%), without fluoride – by 35 patients (19.5%), and 62 people (34.6%) choose only fluoride or calcium-containing toothpastes containing plant components. Means for individual oral hygiene are chosen independently by 134 people (74.8%), another 15 people (8.5%) choose them on the recommendations of their acquaintances, and only 30 people (16.7%) do it according to the instructions of the dentist.

Thus, the violation by the vast majority of patients with type 1 diabetes of the basic principles of oral hygiene and the use of items and means of care besides the instructions and control of the dentist must certainly affect the hygienic condition of their oral cavity, which, in fact, is shown in the results of the index assessment of the dental status of these patients during a clinical study.

Based on the analysis of the obtained results, the indication and structuring of risk factors for dental caries in patients with type 1 diabetes were performed. The presence of correlations between risk factors and the intensity of dental caries in terms of the DMFT index and the DMFS index was established. The most significant cariogenic factors that cause an increase in the intensity of caries in patients with type 1 diabetes, according to the results of correlation analysis, are xerostomia (in accordance with the indicated indices, $r=0.61$, $p<0.01$, and $r=0.66$, $p<0.01$), oral hygiene ($r=0.57$, $p<0.01$, and $r=0.58$, $p<0.01$), sharp fluctuations in blood glucose level ($r=0.54$, $p<0.05$, and $r=0.59$, $p<0.05$), frequent hypoglycemia ($r=0.53$, $p<0.05$, and $r=0.56$, $p<0.05$) and consumption of sweets ($r=0.52$, $p<0.01$, and $r=0.55$, $p<0.01$) (Table I).

The influence of these general and local cariogenic factors manifests itself in different ways, therefore, the onset of caries is possible with different variants of their interaction. However, among these factors there are those that are subject to control with the possible complete elimination

**Table I.** The structure and influence of risk factors on the intensity of dental caries in patients with type 1 diabetes according to the results of correlation analysis

| Factors | Indicator of caries intensity | Pearson correlation coefficient (r) | Correlation significance |
|---|---|---|---|
| Xerostomia | DMFT index | 0.61 | p<0.01 |
| | DMFS index | 0.66 | p<0.01 |
| Oral hygiene | DMFT index | 0.57 | p<0.01 |
| | DMFS index | 0.58 | p<0.01 |
| Sharp fluctuations in blood glucose level | DMFT index | 0.54 | p<0.05 |
| | DMFS index | 0.59 | p<0.05 |
| Frequent hypoglycemia | DMFT index | 0.53 | p<0.05 |
| | DMFS index | 0.56 | p<0.05 |
| Consumption of sweets | DMFT index | 0.52 | p<0.01 |
| | DMFS index | 0.55 | p<0.01 |
| Duration of DM | DMFT index | 0.48 | p<0.01 |
| | DMFS index | 0.57 | p<0.01 |
| Age | DMFT index | 0.36 | p<0.01 |
| | DMFS index | 0.54 | p<0.01 |
| Number of chronic diabetic complications | DMFT index | 0.43 | p<0.01 |
| | DMFS index | 0.41 | p<0.01 |
| Not balanced diet | DMFT index | 0.24 | p<0.01 |
| | DMFS index | 0.25 | p<0.01 |

of their adverse effects on the hard tissues of the teeth, namely, insufficiently effective oral hygiene, consumption of sweets and poor nutrition. Elimination of these factors is ensured by the efforts of both the patient and the dentist. Such cariogenic factors as xerostomia, sharp fluctuations in blood glucose level and frequent hypoglycemia are, in turn, partially controlled, therefore, individualized correction of these factors should be performed by patients and endocrinologist. At the same time, it is not always possible to achieve the target optimal indicators of glycemia and long-term compensation of type 1 diabetes in the medical and non-medical treatment of the disease. Risk factors such as the duration of diabetes, age and the presence of chronic diabetic complications are, of course, uncontrollable factors. At the same time, the frequency, rate of the onset and progression of diabetic complications depend on the degree of compensation, duration of diabetes and gender characteristics.

Thus, the identification of individually significant risk factors for caries onset, their complete elimination or partial correction in order to reduce the negative impact plays an important role in ensuring the success of caries prevention in patients with type 1 diabetes.

## DISCUSSION

Despite significant advances in modern dentistry, prevention of dental caries, especially in patients with diabetes, is one of the most urgent and unresolved problems, because the effectiveness of caries prevention measures in such patients is low and ranges from 22.4% to 48.5%, even with the use of therapeutic and prophylactic agents containing various fluorine compounds and their concentration [15, 16]. Taking this into account, the basis for the development of a scheme for the prevention of dental caries, according to the research results, should be the evaluation and individual consideration of all controlled as well as uncontrolled risk factors for the disease. Only then preventive measures can be successful, according to research conclusions of Sampaio N. et al. (2011), Coelho A., et al. (2018) [12, 17].

It should be noted that the study involved patients with type 1 diabetes with different duration and degree of compensation of the disease, while most current studies have examined the relationship between dental caries and type 2 diabetes. The analysis of the obtained data testifies to the high prevalence and intensity of dental caries in patients with type 1 diabetes. It is proved that the intensity of dental caries increases in patients with an increase in the duration of type 1 diabetes and age. The obtained results of the study in some way coincide with the data of Sampaio N. et al. (2011), Schmolinsky J. et al. (2019) [10, 17]. However, for the first time it was found that the intensity of carious lesions in patients increases with the increase in the number of chronic diabetic complications, it was highest in the presence of 4 or more complications. These three risk factors, by the way, are uncontrollable.

The onset and progression of chronic complications of diabetes depends on the control and correction of impaired metabolism, the quality of treatment of patients with diabetes, which is a controlled factor [2]. It is established that the patient's unsatisfactory self-monitoring of the blood glucose level, not following the diet with

frequent consumption of sweets, not taking into account the glycemic index of foods and inaccurate calculation of the required dose of insulin lead to unstable blood glucose level with significant fluctuations, making it impossible to achieve the compensated diabetes. And although Skiba OV (2016) believes that the influence of alimentary factor on the development of dental caries is minimized because patients with diabetes limit the use of easily digestible carbohydrates [15], the study shows that motivating patients to follow a balanced diet is an important factor both in prevention of caries lesions, and in achieving a stable blood glucose level.

## CONCLUSIONS

1. In patients with type 1 diabetes mellitus with the highest prevalence of dental caries, which was 100%, a high intensity of carious lesions was found, which according to the DMFT index was 14.1±0.43, and according to DMFS index – 30.7±1.53. The state of oral hygiene according to the OHI-S index was equal to 2.25±0.04, which corresponded to an unsatisfactory level.
2. The onset of dental caries in patients with diabetes is most affected by such factors as xerostomia, poor oral hygiene, sharp fluctuations in blood glucose level, frequent hypoglycemia and consumption of sweets. The presence of these factors should be taken into account when introducing caries prevention measures in patients with diabetes.
3. Among the identified risk factors for caries onset, poor oral hygiene and consumption of sweets are completely controllable, which further requires their elimination. Such caries factors as xerostomia, sharp fluctuations in blood glucose level and frequent hypoglycemia are partially controlled and need to be individually corrected in order to reduce the negative impact on the condition of the hard dental tissues.
4. Patients with type 1 diabetes should be informed about the importance of systematic self-monitoring of blood glucose level, limited consumption of sweets, effective hygienic oral care and visits to the dentist once every 3 months to prevent dental caries.

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ORIGINAL ARTICLE

# COST-EFFECTIVENESS OF LABORATORY TESTING IN AL ZAHRAA TEACHING HOSPITAL, AL NAJAF AL-ASHRAF, IRAQ

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## ABSTRACT

**The aim:** To develop a quantitative tool to identify the cost and benefits of the appropriate and inappropriate laboratory tests.

**Materials and methods:** This is a retrospective study, conducted in Al Zahraa teaching hospital for children's health and maternity in a period between March 2021 to March 2022. We study the total laboratory investigation done in three years; before the COVID-19 era (1-3-2018 to 1-3-2019) and two consecutive years (1-3-2020 to 1-3-2021 and 1-3-2021 to 1-3-2022) to exclude the effect of COVID-19 pandemic on the results. And try to divide these test numbers according to each hospital department and the position of the test ordering doctor (senior or junior). We compare the total number of laboratory investigations with the total patient seeking medical care in Al Zahraa hospital, out or inpatient, i.e., ORDERING INDEX. Also, we calculate the (AVERAGE ORDERING INDEX) by dividing the number of all ordered tests by one specific test.

**Results**: The total number of laboratory tests ordered in three (pre and peri COVID-19 pandemic) years show a significant increment in the last year (78249, 73600, and 1740249) respectively. Test ordering index, in the same way, shows significant increments over years (0.65, 0.64 Aand11.2) respectively. Biochemistry investigations constitute the largest proportion (50%) of all investigations that have been ordered last year. CBC is the most commonly ordered single test, in outpatient clinics, it is done 19510 times (Obstetrics and Gynecology 11850 *vs* Pediatric 7660). The positive (abnormal) results were only 4.8%.

**Conclusion**: For more and more years, laboratory investigations have been overused. A large number of normal results indicate that the test order was chosen at random. The most commonly overused test is the complete blood count.

**KEY WORDS:** laboratory investigations, cost, unnecessary tests, health expenditure

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## INTRODUCTION

A lab test is an investigation of one or more chemicals from a subject–in this case, a patient's specimen–in a site–lab dedicated to providing accurate and rapid findings; LTs are used for 1. Diagnosis (to rule in or rule out a diagnosis). 2. Observation (e.g., the effect of drug therapy). 3. Examining (e.g., for congenital hypothyroidism via neonatal thyroxine testing). 4. Do some research (to understand the pathophysiology of a particular disease process) [1].

Over the last few decades, physicians have become more reliant on laboratory services [2]. Factors affecting laboratories are to blame for the increased usage of laboratory services. Facilitated access, the introduction of auto analyzers, the development of new tests, and availability are all examples of this. Inexperience or lack of information about the proper use of tests, legal aspects, failure to examine past results, test ordering protocols that are difficult to change, or fear of mistakes of omission and lawsuits are all reasons that contribute to increased laboratory utilization. and from patients themselves, who are becoming more aware of their health concerns [3].

In certain cases, doctors order needless testing, which causes the patient unnecessary agony. These tests can raise the chance of false-positive results, which can lead to unnecessary action and physician referrals. Furthermore, laboratory utilization is a determinant element in the use of healthcare resources, accounting for 2-3 percent of overall healthcare spending in Europe [4]. Despite the inexpensive cost of an individual test, the high utilization of this technology leads to inefficient resource consumption. These funds could be redistributed to improve healthcare delivery. This is especially essential in low- and middle-income countries (LMICs), where public health care funding is limited and diagnostic tests must be paid for out of pocket [5]. The true cost of a laboratory test is difficult to determine since it may involve costs such as transporting and admitting the patient to the hospital for investigation, nursing care, and clinical staff who make the request and analyze the results [6].

In this audit, we try to assess the pattern of laboratory investigations requested in Al Zahraa hospital's main laboratory to point toward any abuse or overestimations of the laboratory tests (lab tests).

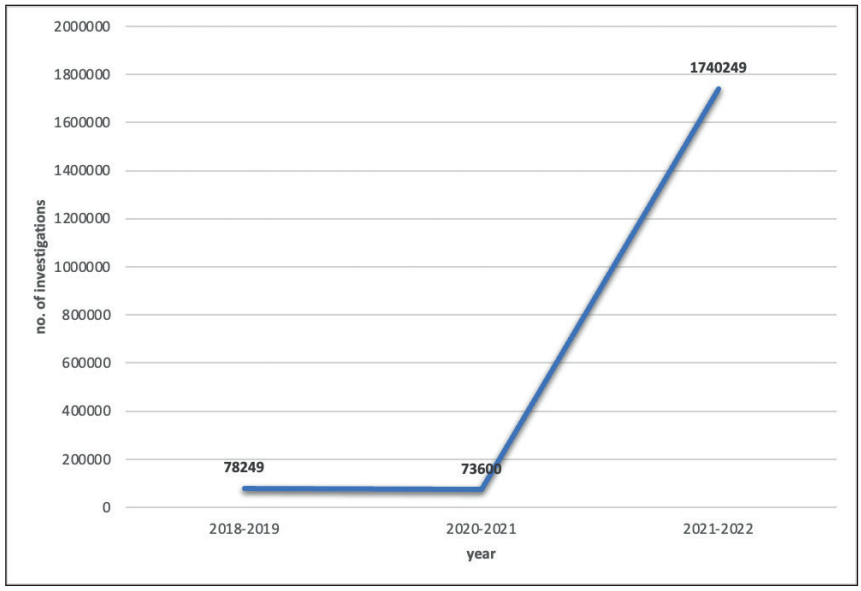



**Fig. 1.** The number of laboratory tests ordered in the last three years.

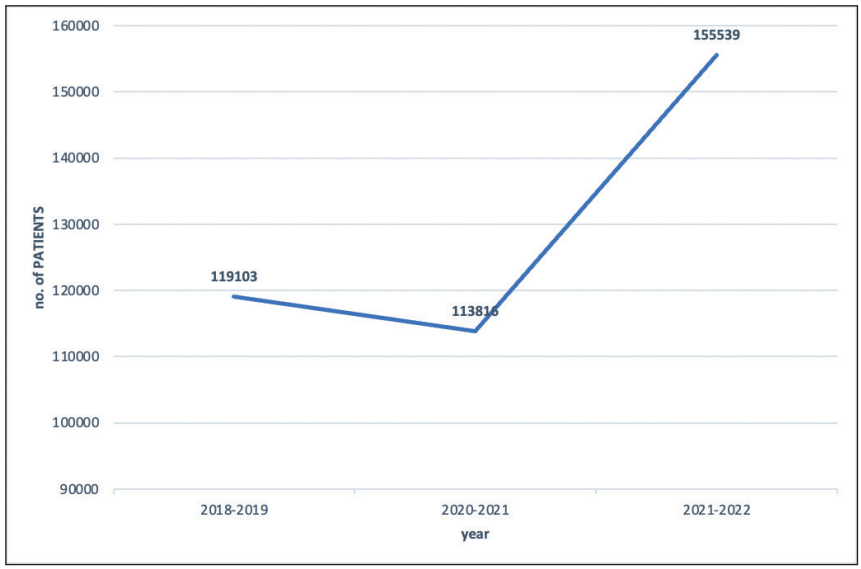



**Fig. 2.** The number of patients visiting Al Zahraa hospital in the last three years.

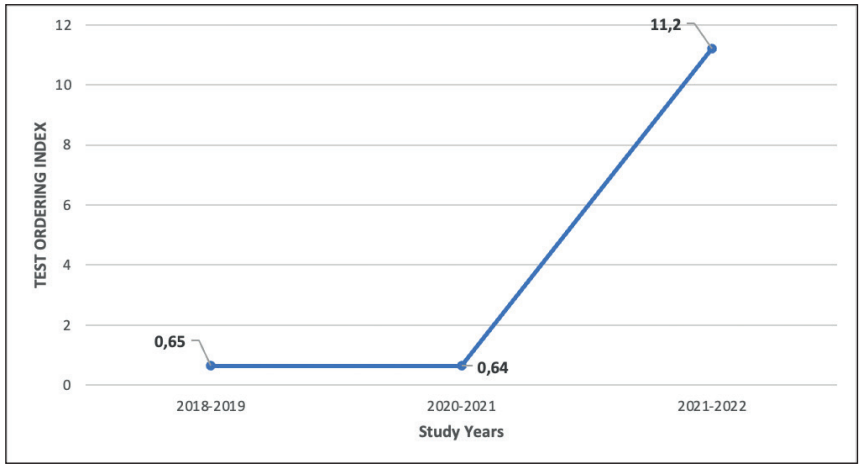



**Fig. 3.** Laboratory test ordering index in Al Zahraa hospital in the last three years.

## THE AIM

To develop a quantitative tool to identify the cost and benefits of the appropriate and inappropriate laboratory tests.

## MATERIALS AND METHODS

This is a retrospective study, conducted in Al Zahraa teaching hospital for children's health and maternity in a period between

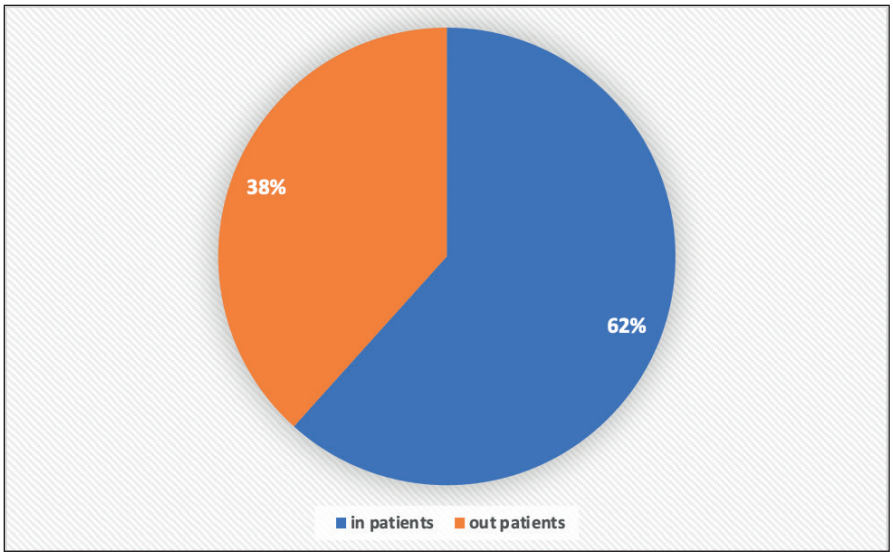



**Fig. 4.** Comparison between the inpatient and outpatient laboratory tests ordered in the 2021-2022 year.

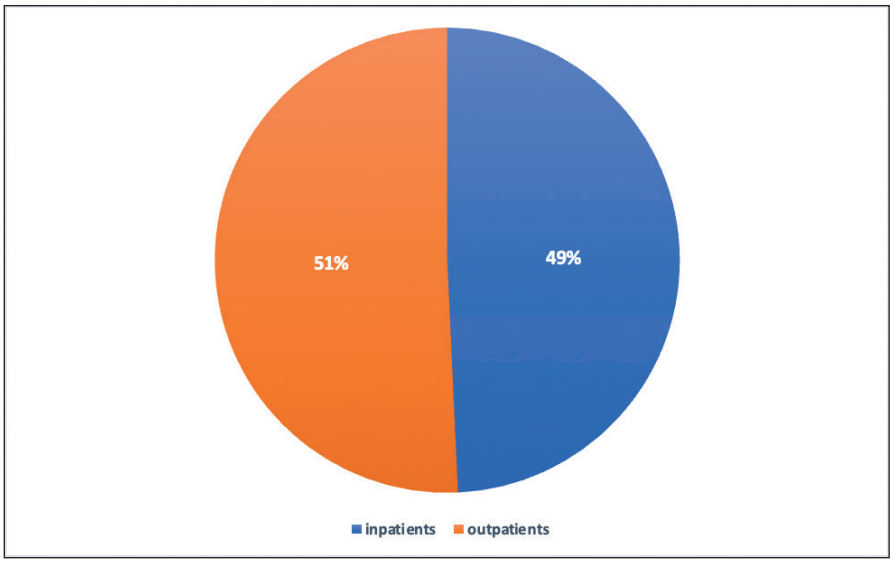
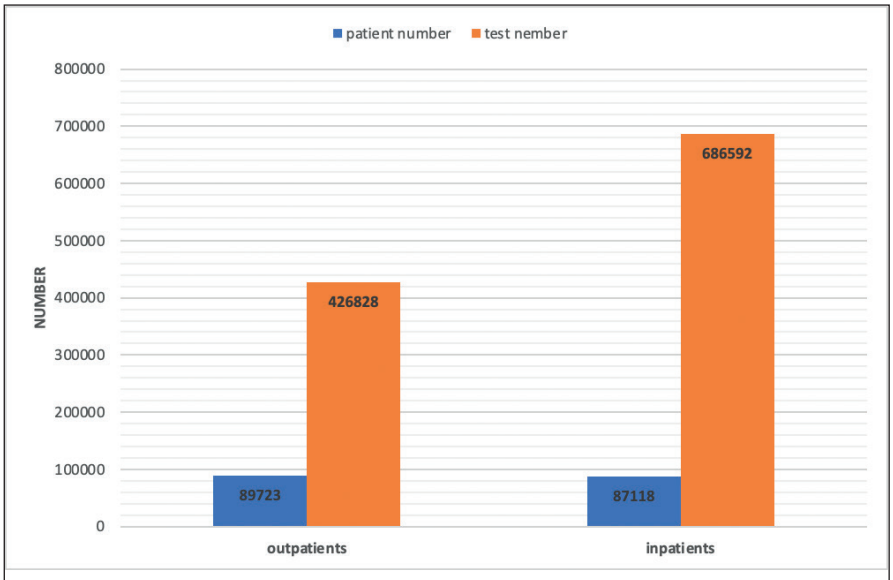



**Fig. 5.** Comparison between the numbers of patients seeking medical care in Al Zahraa hospital in outpatient clinics and inpatients ward during the 2021-2022 year.




| Test ordering index | outpatients | inpatients |
|---|---|---|
| | 4.75 | 7.88 |

**Fig. 6.** Comparison between the test ordering index in outpatient clinics and inpatients ward during the 2021-2022 year.

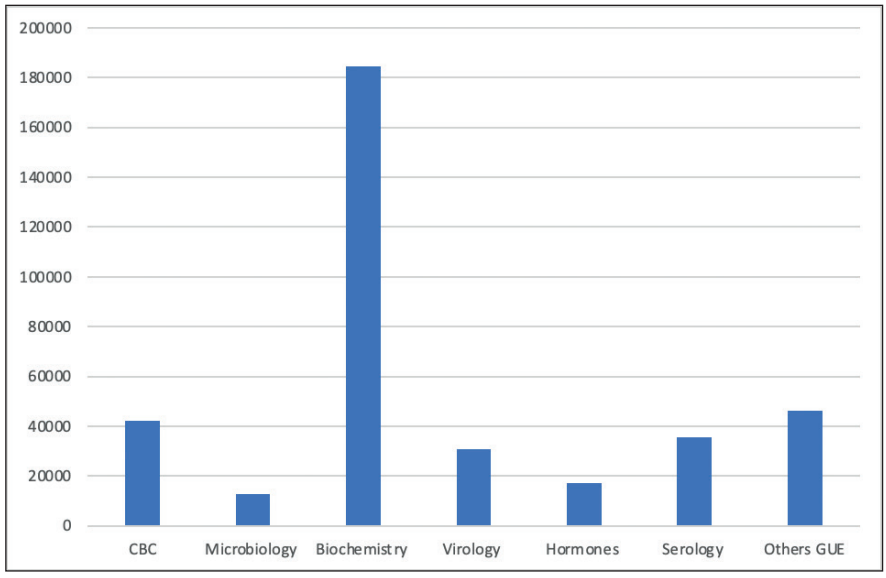



**Fig. 7.** Comparison among the types of laboratory tests ordered in the 2021-2022 year.

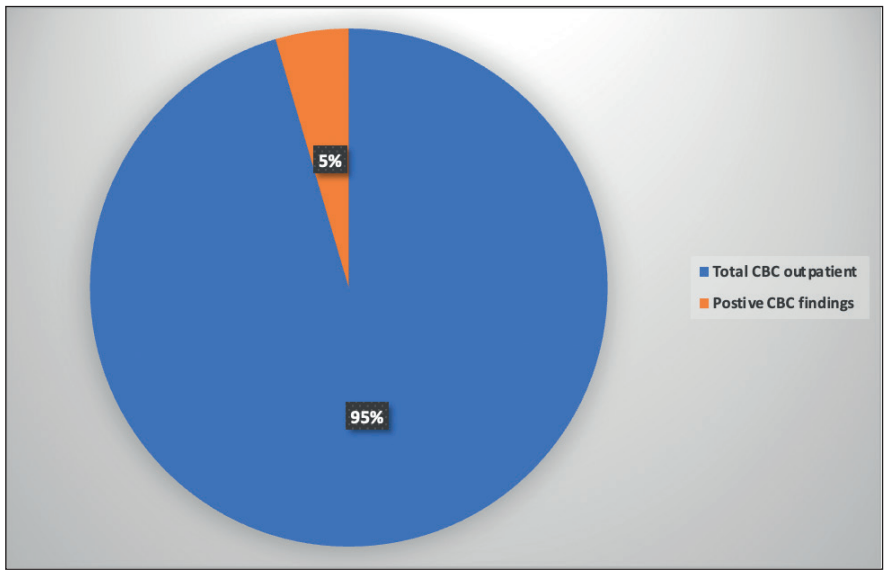



**Fig. 8.** Percentage of positive results of CBC tests that have been ordered in outpatient clinics in the study year 2021-2022.

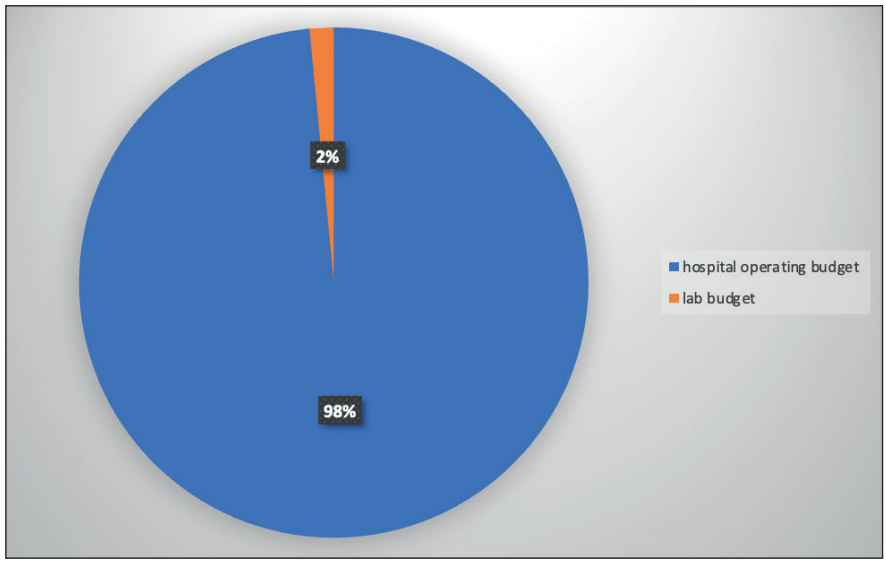



**Fig. 9.** Lab budget in proportion to total hospital budget in the study year 2021-2022.

March 2021 to March 2022. Al Zahraa teaching hospital is the main hospital for children and maternal health in Al Najaf governorate with a capacity of 350 beds, it is working as a tertiary center, and contains departments for pediatrics, obstetrics, gynecology, pediatric surgery, radiology, and anesthesia. It is containing an outpatient clinic with an average of 400 patients per day.

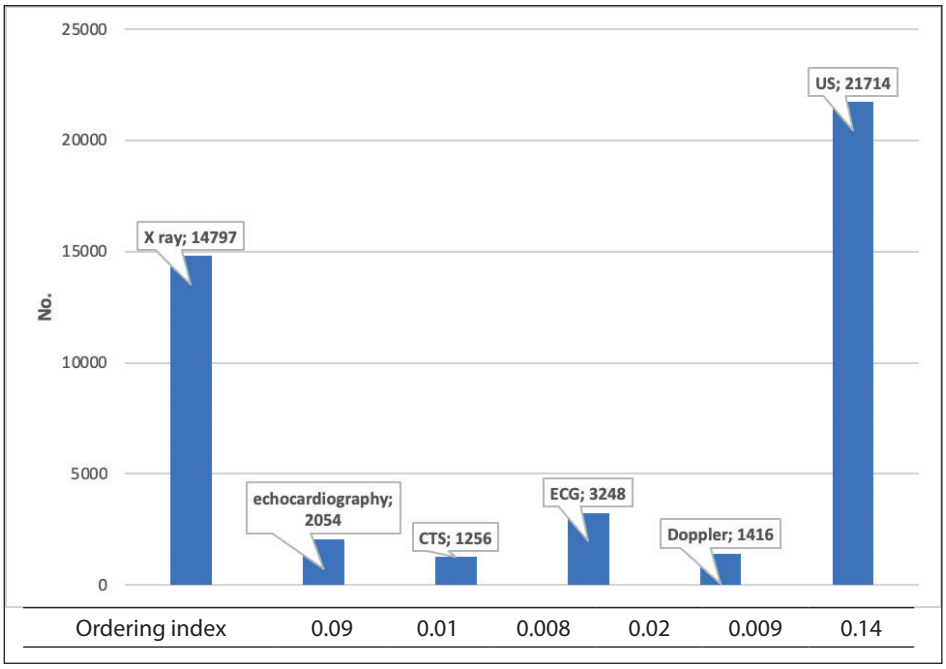



**Fig. 10.** Number of radiological tests that have been requested during the 2021-2022 study year with their corresponding ordering index.

We study the total laboratory investigation done in three years; before the COVID-19 era (1-3-2018 to 1-3-2019) and two consecutive years (1-3-2020 to 1-3-2021 and 1-3-2021 to 1-3-2022) to exclude the effect of COVID-19 pandemic on the results. And try to divide these test numbers according to each hospital department and the position of the test ordering doctor (senior or junior).

We compare the total number of laboratory investigations with the total patient seeking medical care in Al Zahraa hospital, out or inpatient, i.e., ORDERING INDEX. Also, we calculate the (AVERAGE ORDERING INDEX) by dividing the number of all ordered tests by one specific test.

We try to allocate the highest month of the year in the test ordering rate searching for explanations. We plan to measure the positive results tests over the total requested test in an attempt to point for inappropriate test orders. Also, to calculate the total cost of these laboratory tests to measure the cost of inappropriate tests.

## RESULTS

The total number of laboratory tests ordered in three (pre and peri COVID-19 pandemic) years show a significant increment in the last year as shown in figure 1.

The number of patients seeking medical care in different departments in A Zahraa hospital for the same above-mentioned years was as follows (Fig. 2)

From these above figures we can calculate the TEST ORDERING INDEX, as in figure 3.

In the 2021-2022 year, 62% of total laboratory investigations were done in inpatient wards, (Inpatient 686592 *vs* Outpatient 426828) (Fig. 4).

In the same year, 89723 patients have been seen in the outpatient clinic versus 87118 inward patients, which constitute 51% of total patients who visit the hospital (Fig. 5).

From the above two figures we can calculate the test ordering index in both in and outpatients as the following (Fig. 6).

Biochemistry investigations constitute the largest proportion (50%) of all investigations that have been ordered last year (Fig. 7).

CBC is the most commonly ordered single test, in outpatient clinics, it is done 19510 times (Obstetrics and Gynecology 11850 *vs* Pediatric 7660). The positive (abnormal) results were only 4.8% (Fig. 8).

The mean cost for the CBC test is 3.38$, so the yearly budget for only this test will equal 142048 $ (42026*3.38$). Taking into account that 95% have a negative result so the waste budget for unnecessary investigation will equal to 134945 $ per year.

The operating budget for Al Zahraa teaching hospital last year was equal to 24836972005 IQD, and the hospital lab budget during the same year was equal to 385711370 IQD (Fig. 9).

About the radiological investigations, the ultrasound is by far the most requested one (Fig. 10).

## DISCUSSION

In Iraq, health services are nearly free. With the rapid increment of the Iraqi population (2.39%), (7) these services will get exhausted. Iraq's health expenditure per capita climbed from 54 dollars in 2005 to 253 dollars in 2019, expanding at a 13.50 percent annual rate. Similarly, due to COVID-19, healthcare spending in the United States increased by 9.7% in 2020, reaching $4.1 trillion, or $12,530 per person [8].

Laboratory investigations constitute 2.3% of all health expenditure according to Rohr UP et al. [9]. In this study, 2% of all hospital budget goes to the lab. According to the European Diagnostic Manufacturers Association (EDMA), test prices in Europe account for only 0.8 percent of total health spending [10]. It is a potentially reducible expense, notwithstanding its minor contribution to total health expenditure. During the study year (1-3-2021 till 1-3-2022) a

total of 1122470 laboratory tests have been ordered, if it is compared with two other years (pre and peri COVID-19 pandemic) we found increments in 22.2 and 23.6 folds respectively. The trend of increment by utilization of laboratory tests observed by American practitioners was higher; 91% increment from 2000 till 2016 [11].

Taking into account the number of patients seeking medical a device in Al Zahraa teaching hospital in the study three years, the test ordering index is significantly rise from 0.65 in 2018-2019, to 0.64 in 2020-2021 to 11.2 in 2021-2022. Many reasons are likely to be at play in this study's increased usage of testing. The rise in utilization could be a direct result of the growing number of hospital doctors (46 *vs* 28 senior doctors before five years). Another possibility is that the tests are being utilized for "strategic, non-medical reasons," such as calming patients and wrapping up appointments. Furthermore, increased testing by general practitioners could reflect a shift in the patient-doctor relationship, such as a higher expectation from patients that they should be examined. Patients are becoming more aware and encouraged to explore healthcare options as shared decision-making becomes more common.

In the 2021-2022 year, 62% of total laboratory investigations were done in inpatient wards, (Inpatient 686592 vs Outpatient 426828). Additionally, the inpatient test ordering index is 7.88 vs 4.75 for outpatient which is logical if we take into account tan that the inpatient may have more serious diseases that required repeated tests to diagnose his condition and to follow up the treatment response.

Biochemistry investigations are by far the most frequently requested investigation in the hospital, it is ordered 184482 times. That account for more than 50% of all requested laboratory investigations in the study year 2021-2022. Compete blood count is the most single test that has been ordered last year, 42026 times. Khalifa M. [12] has found that 35% of total ordered tests were CBC, Renal Profiles, and Random Glucose levels. Horton S. et al. [13] have studied the top 25 tests in hospitals in five different countries (India; Kenya; Malaysia; Nigeria; United States). She found that CBC is the top requested investigation but, in a percentage, much lower than what we have found.

Despite this overutilization of CBC, the positive result is very low. In the outpatient clinics, only 4.8% of all requested CBC have critical results. The mean abnormal result rate (MARR) has lately gained popularity as a statistic for determining the appropriateness of laboratory tests [14]. The MARR is calculated by dividing the number of aberrant test results by the total number of tests ordered. According to the MARR, appropriate physician selectivity in test ordering gives aberrant results at a higher rate than random tests on healthy people. Brack AP. et al [14] have found that (MARR) is equal to 8.6% which is higher than our finding suggesting a lack of appropriate test selection in our doctors.

Regarding the radiological investigations, the ultrasound is the most frequently requested test (21714) followed by an X-ray (14797). The (Diagnostic Imaging Dataset Annual Statistical Release 2017/18) released by The National Health Service (NHS) in England found that X-ray is the most commonly ordered radiological test followed by ultrasound [15].

## LIMITATIONS

1. A lot of details that may make our audit more comprehensive can be gathered if we have well-organized computerized statistics about hospital works.
2. We cannot point to a group of doctors whether junior or senior that may be blamed for laboratory test overutilization.

# CONCLUSIONS

1. For more and more years, laboratory investigations have been overused.
2. A large number of normal results indicate that the test order was chosen at random.
3. The most commonly overused test is the complete blood count.
4. While doctors prefer to focus on reducing the number of so-called expensive tests, they pay little attention to low-cost tests that are conducted frequently. When you pay more attention to the indications for these tests, you can save a lot of money. Diagnostic costs are reduced significantly when recommendations and protocols are followed more closely.

## RECOMMENDATIONS

1. Interventions such as feedback, physician education, modifications to laboratory requisition forms, regulations governing laboratory test ordering, and financial incentives may be used to decrease this excessive waste of technician time and reagents.
2. Improving doctors' awareness of superfluous diagnostics and increasing junior doctors' supervision resulted in a considerable reduction in the number of needless tests conducted.
3. Hospital management should establish an action plan to reduce test waste, and then another similar study should be conducted to assess the improvement.

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**Conflict of interest**
*The Authors declare no conflict of interest*

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ORIGINAL ARTICLE

# PREVALENCE, CLINICAL AND FUNCTIONAL CHARACTERISTICS OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION COMPLICATED BY ACUTE HEART FAILURE

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## ABSTRACT

**The aim:** The study was designed to establish the prevalence of acute heart failure in patients with acute myocardial infarction, to determine the sex-age characteristics of acute myocardial infarction course in case of complications by acute heart failure of high classes (Killip III and Killip IV).

**Materials and methods:** We analyzed medical records of inpatients of the myocardial infarction department of the municipal non-profit enterprise Vinnytsia Regional Center for Cardiovascular Pathology in 2019. The survey covered 828 medical records of patients with acute myocardial infarction, average age (64.6 ± 0.38), including 569 (64.7%) males and 311 (35.3%) females.

**Results:** 129 (15.6%) patients with acute myocardial infarction were diagnosed high-class acute heart failure. Patients with high-class acute heart failure were statistically significantly elderly individuals of the average age (69.0 ± 1.3), ($p < 0.001$), including 53.7% of males, and 46.3% ($p < 0.001$) female patients. Patients with acute myocardial infarction complicated by acute heart failure were hospitalized within 2 hours of symptoms` onset with statistically significantly higher probability ($p = 0.004$). Patients with acute myocardial infarction complicated by acute high-class heart failure were statistically significantly more likely diagnosed with concomitant hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease than individuals with uncomplicated acute myocardial infarction. Acute myocardial infarction patients` mortality was 3.4%, while the one in patients with acute heart failure was 38% ($p < 0.001$).

**Conclusions:** Patients with complicated myocardial infarction are characterized by statistically significantly higher comorbidity and increased lethality.

**KEY WORDS:** coronary heart disease, acute myocardial infarction, acute heart failure, lethality

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## INTRODUCTION

Cardiovascular diseases remain the leaders among pathologies of the internal organs. Acute myocardial infarction (AMI) is one of the diseases that exerts a strong influence over the quality of life, disability, mortality and inflicts significant material costs. The main reasons influencing the prognosis of AMI patients include the occurrence of complications, including acute heart failure (AHF). AHF is a symptom complex characterized by a rapid onset of symptoms of impaired cardiac function, namely reduced cardiac output, insufficient tissue perfusion, increased pressure in the pulmonary capillaries, and tissue stagnation [1]. Comorbid AHF in AMI patients is characterized by an unfavorable prognosis, both short-term and long-term one. Thus, according to the European registry, hospital mortality in patients with AMI complicated by AHF makes 5.5%, the year-round mortality - 26.7%, and readmission - 44.4% [2].

It is known that AHF in patients 65+is the main cause of hospitalization in the United States, Europe, and Australia with early hospital lethality ranging from 2 to 20% [3] characterized by a fairly high frequency of year-round readmission - up to 30% [4, 5].

According to EHFS II study, AHF symptoms are newly diagnosed in 42% of individuals with acute coronary syndrome (ACS) [1]. High-class AHF (Killip III and Killip IV) is characteristic of the highest lethality - about 50% [6].

It should be noted that the mortality rate in AHF patients remains quite high, namely 17% - 45% of individuals die within 1 year of the diagnosis [7-12].

Modern AMI treatment involves myocardial revascularization. This strategy has been adopted worldwide with a number of patients undergoing revascularization increasing every year. It should be noted that this approach has significantly reduced the hospital lethality [8]. Data from domestic scientists show that the frequency of AHF in AMI patients has reached 34% and 13% in males and females, respectively [9].

Thus, despite the introduction of clear diagnostic and treatment regimens, an extensive reperfusion network, the introduction of patient routing, AHF still remains among the main causes influencing the mortality of AMI patients [10]. The true prevalence of AHF and its types, AHF course depending on sex, age, anatomical and physiological features of coronary vessels, type and time of revascularization are still far from complete understanding.

**Table I.** Characteristics of patients surveyed

| Description | Estimate |
|---|---|
| Total, absolute | 828 |
| Average age, years | 64.6±0.38 |
| Males, absolute, % | 569 (64.7%) |
| Average age, years | 63.5±0.45 |
| Females, absolute, % | 311 (35.3%) |
| Average age, years | 69.2±0.52 |
| STEMI, absolute, % | 828 (94.1%) |
| nSTEMI, absolute, % | 52 (5.9%) |
| Reperfusion therapy, total, absolute, % | 473 (53.7%) |
| Reperfusion therapy, males, absolute, % | 288 (65.1%) |
| Reperfusion therapy, females, absolute, % | 154 (34.9%) |
| CVG without stenting, absolute, % | 484 (55%) |
| Thrombolysis, absolute, % | 24 (2.8%) |
| Discharged, absolute, % | 801 (91%) |
| Lethal cases, absolute, % | 79 (9%) |

Notes:
Quantitative indicators are presented as M ± m - mean ± mathematical error of the mean.

## THE AIM

The objective of our work was to establish AHF prevalence in AMI patients, to determine the sex and age characteristics of AMI course in the event of complications by high-class AHF (Killip III and Killip IV).

## MATERIALS AND METHODS

We conducted a retrospective survey of medical records of patients admitted to the myocardial infarction department of the Municipal Non-Commercial Enterprise Vinnytsia Regional Clinical Medical and Diagnostic Center for Cardiovascular Pathology in 2019. Total 828 medical records of AMI patients, average age (64.6±0.38) were surveyed (Table I).

Surveyed patients: males - 569 (64.7%), average age (63.5±0.45); females - 311 (35.3%), average age (69.2±0.52). The majority of patients had acute coronary syndrome with ST segment elevation (STEMI) - 828 (94.1%). 473 (53.7%) patients were subject to urgent invasive reperfusion, including 288 (65.1%) males and 154 (34.9%) females. 24 (2.8%) patients were subject to thrombolysis.

It is noteworthy that the vast majority of AMI patients were 50+ individuals (Fig. 1).

The 30-49-year-old group consisted of 74 patients (8.9%), including 66 (89.2%) males and 8 (10.8%) females (p<0.001). The 50-59-year-old group consisted of 201 (24.3%) patients, including 170 (84.6%) male and 31 (15.5%) female subjects, (p<0.001). The largest group was a 60-69-year-old one consisting of 290 (35%) patients, including 181 (62.4%) males and 109 (37.6%) females, (p<0.001). Throughout the study, there were 263 (31.8%) patients 70+, including 117 (44.5%) males and 146 (55.5%) female subjects. Thus, males statistically significantly dominated in the population under 60. In older age groups, this difference was less pronouncing, and at the age of 70+, females were more common than males (p=0.16) (Fig. 1).

Comparison of the sex-and-age structure shows that males statistically significantly dominated in the group 50-59 compared to the age group 60-69 (p<0,001). In turn, the group 60-69 had statistically significantly more males and fewer females than the group 70+ (p<0.001).

We analyzed the features of AMI clinical course in 2 groups of individuals. Group I consisted of 699 (84.4%) AMI patients without signs of high-class AHF. Group II consisted of 129 (15.6%) AMI patients with the signs of high-class AHF. It is noted that Group II patients were statistically significantly older than Group I patients -(69.0±1.3) and (63.4±0.9), respectively (p<0.001). Group I had statistically significantly more males than females, 469 (67.1%) and 119 (32.9%) patients, respectively (p<0.001). The same trend was seen in Group II: 65 (53.7%) males and 56 (46.3%) females (p<0.001).

The results were statistically processed on a personal computer using a software package for processing biological and medical information STATISTICA 6.1 version No. VHXR901E246022FA (StatsoftInc., USA) and Microsoft Excel.

Indicators showing the frequency of an indicator in a sample are presented in percent, quantitative indicators

**Table II.** Anamnestic data of patients with acute myocardial infarction

| Indicator | I group, n=699 | II group, n=129 | P |
|---|---|---|---|
| Primary MI | 588 (84.1%) | 121 (93.8%) | 0.004 |
| Recurrent MI | 111 (15.9%) | 8 (6.2%) | 0.004 |
| Admitted to hospital within 2 hours | 61 (8.7%) | 23 (17.8%) | 0.002 |
| Admitted to hospital within 6 hours | 286 (40.9%) | 51 (39.5%) | 0.77 |
| Admitted to hospital within 22 hours | 122 (17.4%) | 20 (15.6%) | 0.73 |
| Admitted to hospital within 24 hours | 112 (16.0%) | 9 (6.9%) | 0.008 |
| Admitted to hospital post- 24 hours | 118 (16.9%) | 26 (20.2%) | 0.37 |

Notes:
1. The percentage was compared between groups using the criterion $\chi 2$;
2. The difference was considered statistically significant with $p < 0.05$.

**Table III.** Comorbidities in different groups of patients with acute myocardial infarction

| Description | I group, n=699 | II group, n=129 | p |
|---|---|---|---|
| Stage 1 arterial hypertension | 7 (1.0%) | - | 0.25 |
| Stage 2 arterial hypertension | 21 (3.0%) | 16 (12.4%) | <0.001 |
| Stage 3 arterial hypertension | 429 (61.3%) | 85 (65.9%) | 0.33 |
| AH history up to 5 years | 88 (12.5%) | 15 (11.6%) | 0.76 |
| AH history 5-10 years | 74 (10.6%) | 19 (14.7%) | 0.29 |
| AH history over 10 years | 267 (38.2%) | 67 (51.9%) | 0.004 |
| Diabetes mellitus, newly diagnosed | 4 (0.6%) | 3 (2.3%) | 0.046 |
| Type 1 diabetes mellitus (DM) | 4 (0.6%) | - | 0.39 |
| Type 2 diabetes mellitus | 100 (14.3%) | 31 (24.0%) | 0.006 |
| DM history up to 5 years | 30 (4.3%) | 11 (8.5%) | 0.042 |
| DM history 5-10 years | 38 (5.4%) | 8 (6.2%) | 0.32 |
| DM history over 10 years | 35 (5.0%) | 9 (6.9%) | 0.25 |

Notes:
1. Quantitative indicators are presented as M ± m - mean ± mathematical error of the mean;
2. The indicators were compared between the groups using the χ2 criterion and Student's t-test;
3. The difference was considered statistically significant with p <0.05.

**Table IV.** Sex-age lethality characteristics

| Indicator | Total 828 | Group I, n=699 | Group II, n=129 | p between Groups I and II |
|---|---|---|---|---|
| | | | | |
| Discharged | 754 (91.1%) | 676 (96.7%) | 80 (62.0%) | <0.001 |
| Lethal cases | 72 (8.9%) | 23 (3.4%) | 49 (38.0%) | <0.001 |
| Average age | 68.4±0.8 | 67.9±0.8 | 71.8±1.1 | 0.39 |
| Lethal cases, males, absolute, % | 39 (54.2%) | 15 (65.2%)* | 24 (48.9%)** | <0.001 |
| Males, average age | 68.7±0.9 | 67.1±0.9 | 70.9±1.2 | 0.45 |
| Lethal cases, females, absolute, % | 33 (45.8%) | 8 (34.8%) | 25 (51.1%) | <0.001 |
| Females, average age | 69.5±1.0 | 68.4±0.7 | 72.1±1.3 | 0.38 |

Notes:
1. Quantitative indicators are presented as M ± m - mean ± mathematical error of the mean;
2. The indicators were compared between the groups using the Student's t-test;
3. The difference was considered statistically significant with p <0.05;
4. *- confidence difference of lethality in males and females of Group I: p=0.84;
5. **- confidence difference of lethality in males and females of Group II: p=0.80.

are given as "mean ± standard error of the mean (M ± m)," and the 25-75 interquartile range - in percentiles. The results were considered reliable with the error probability (p) <0.05.

For quantitative indicators, the normality of the distribution was previously determined using the Shapiro-Wilk and Kolmogorov-Smirnov criteria. In case of confirmation of the normal distribution of indicators, parametric methods were used for statistical analysis (Student's t-test for two independent variables. In case of abnormal distribution, nonparametric statistics (Mann-Whitney U-test for comparison of two independent variables) were used; a pairwise comparison of groups involving Mann-Whitney test was used. Feature frequencies between the groups were compared using the criterion χ2 [11].

## RESULTS

It was found that patients of both groups I and II had more common primary MI (Table II). It is noteworthy that AMI patients with AHF complications (Group II) had statistically significantly higher likelihood of admission within 2 hours of symptoms` onset (p=0.004). There is no statistically significant difference in the admission rate in a window between 6 and 12 hours. There was also no statistically significant difference in post-24-hour admission patients. So, according to our analysis, the time from onset of symptoms to hospital admission probably did not play a role in AHF development.

It was established that Group II AMI patients were statistically significantly more often diagnosed with concomitant arterial hypertension (AH) than Group I patients, 78.3% and 65.4%, respectively, p=0.005 (Fig. 2).

**Table V.** Sex-and-age characteristics of lethality in STEMI patients with acute heart failure of high classes

| Indicator | STEMI+AHF Killip III, n=50 | STEMI+AHF Killip IV, n=79 | p |
|---|---|---|---|
| Average age, years | 64.5±1.2 | 64.7±1.3 | 0.25 |
| Males, absolute, % | 26 (52%) | 39 (49.4%) | 0.71 |
| Average age, years | 63.7±1.4 | 64.6±1.2 | 0.34 |
| Females, absolute, % | 24 (48%) | 40 (50.6%) | 0.71 |
| Average age, years | 66.2±1.6 | 67.8±1.3 | 0.12 |
| Discharged, absolute, % | 45 (90%) | 35 (44.3%) | <0.001 |
| Lethal cases, absolute, % | 5 (10%) | 44 (55.7%) | <0.001 |

Notes:
1. Quantitative indicators are presented as M ± m - mean ± mathematical error of the mean;
2. The indicators were compared between the groups using the χ2 criterion and Student's t-test;
3. The difference was considered statistically significant with p <0.05.

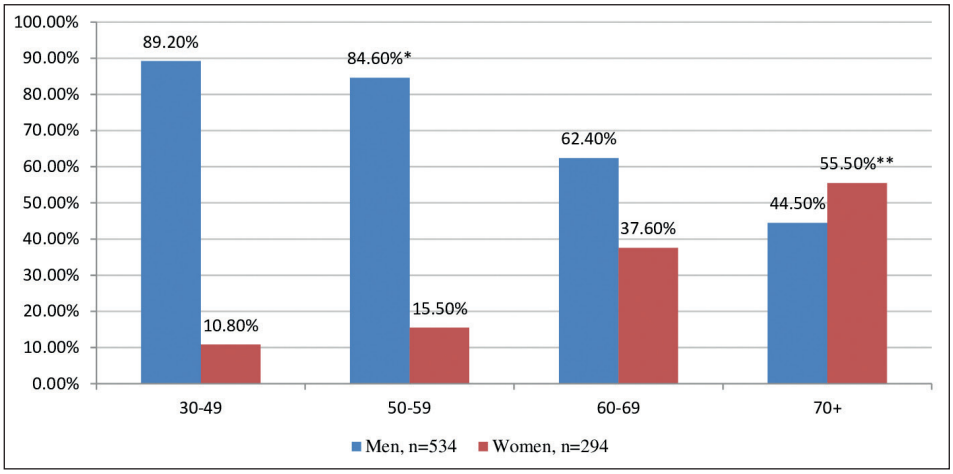


**Fig. 1.** Sex and age characteristics of all STEMI patients.
Notes:
1. * - statistically significantly more males in the group 50-69 than in the group70+
2. ** - statistically significantly more females in the group70+ than in the groups 50-59 and 60-69

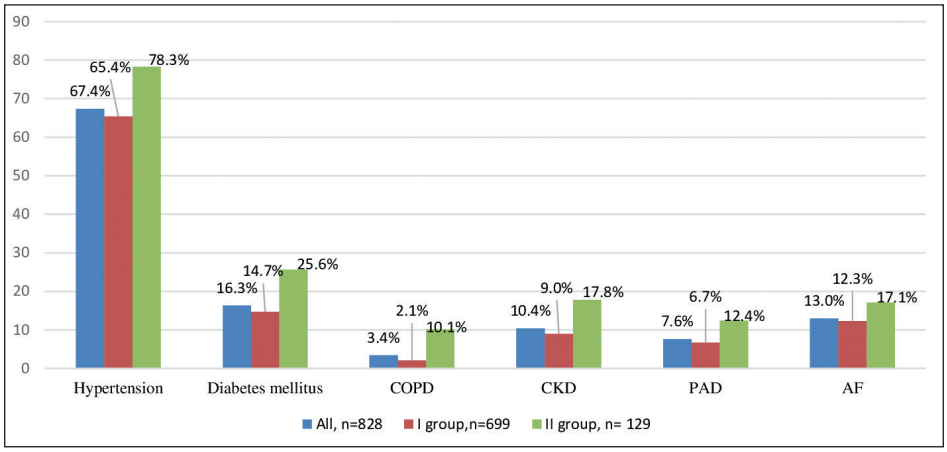


**Fig. 2.** Concomitant pathology in patients with acute myocardial infarction.
Notes:
1. Quantitative indicators are presented as M ± m - mean ± mathematical error of the mean;
2. The indicators were compared between the groups using the χ2 criterion and Student's t-test;
3. The difference was considered statistically significant with p <0.05.

There were 142 AMI patients (16.3%) with concomitant DM; 14.7% in Group I and 25.6% in Group II (p=0.006), respectively. Chronic obstructive pulmonary disease (COPD) in AMI patients was reported in 28 (3.4%) patients, statistically significantly more often in Group II patients; 2.1% and 10.1%, respectively (p<0.001). Chronic kidney disease (CKD) was diagnosed in 86 (10.4%) patients, including 9.0% of Group I subjects, and statistically significantly more often in Group II patients - 17.8% (p= 0.003). Concomitant peripheral artery disease (PAD) was anamnestic in 63 (7.6%) AMI patients, including 6.7% of Group I subjects, and statistically significantly more often (p=0.012) in Group II individuals - 12.4%. Atrial fibrillation (AF) - 108 patients (13.0%) - was also a frequent concomitant pathology with no statistically significant difference found in the frequency between Groups I and II (p=0.14).

While characterizing AH by blood pressure (BP), it was observed that Group II patients were statistically significantly more often diagnosed Stage 2 AH, 3.0% and 12.4%, respectively (p<0.001) (Table III).

Thus, AMI patients with high-class AHF complications were statistically significantly more often diagnosed with concomitant AH, DM, COPD, CKD than individuals with uncomplicated AMI.

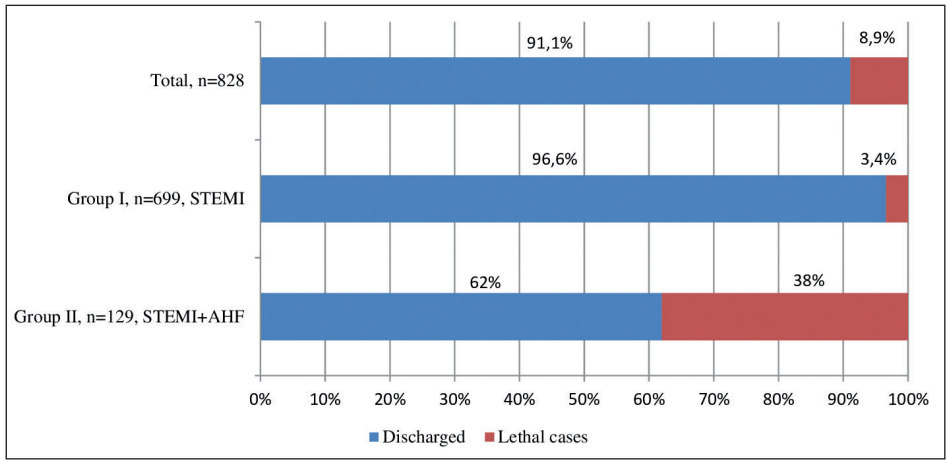


**Fig. 3.** Mortality in patients with acute myocardial infarction according to the retrospective analysis

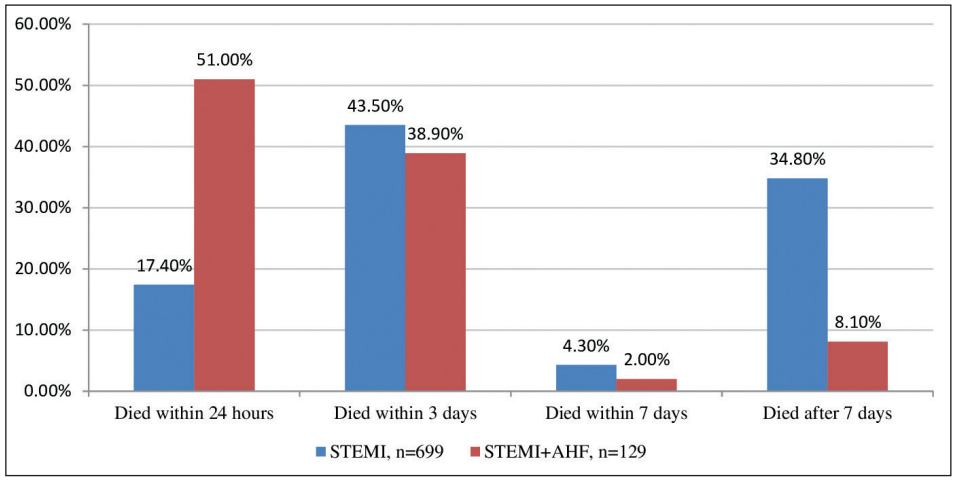


**Fig. 4.** Distribution of lethality depending on admission term

No difference was found for Stage 3 AH. At the same time, we found statistically significantly more individuals with AH history over 10 years in the Group II than on Group I, 38.2% and 51.9%, respectively (p=0.064). The DM course was also specific in patients with AMI complicated by AHF. In particular, in this group DM was newly diagnosed statistically significantly more often (p = 0.004) than in patients with type 2 DM (p=0.006). In particular, it should be noted that most DM patients had a history of the disease up to 5 years (p=0.042).

We revealed 72 lethal cases in 2019, which made 8.9% of the total, including 23 (3.4%) lethal cases in Group I, and 49 (38%) lethal cases in Group II (p <0.001) (Fig. 3).

Thus, hospital lethality was significantly higher in Group II. A detailed analysis of hospital lethality showed that AMI patients had 72 lethal cases (8.9%), including 39 in males (54.2%), average age (68.7±0.9), and 33 in females (45.8%), average age (69.5±1.0) (Table IV).

It was found that lethality in both males and females was significantly higher in Group II (p <0.001). All lethal cases in Group II patients included 25 females (51.1%), average age (72.1±1.3) and 24 men (48.9%), average age (70.9±1.2) (p=0.80). Group I patients also presented no significant sex differences - 15 (65.2%) in males, average age (67.1±0.9), and 8 (34.8%) in females, average age (68.4±0.7) (p=0.84).

The predominant number of lethal cases in AMI patients was observed within three days of hospital admission, n=58 (80.6%) (Fig. 4).

Lethality in Group II patients was significantly higher within the first 24 hours of admission - 51.0% vs. 17.4% (p<0.001), while the lethality in Group I statistically significantly prevailed 7 days following the admission – 34.8%, and 8.1% in AMI patients and AMI patients with high-class AHF complications, respectively (Table V).

## DISCUSSION

According to the results obtained in this study, the incidence of high-grade AHF Killip 3-4 is 15.6%, which is comparable to the results of previous studies, while according to our data, high-grade AHF occurred in 12.2% of men with AMI and in 32.0% of women with AMI, although both groups of patients are dominated by men, which differs from the results of other studies that show a high frequency of GOS and cardiogenic shock in men [1, 6, 9, 12].

We can explain these differences by the older age of women than men and, probably, the greater comorbidity in the older age groups, as well as the fact that we analyzed the presence of AHF of high gradations.

Interesting from our point of view is the fact that Killip III and Killip IV patients did not differ significantly by age and sex. Perhaps, Killip IV patients presented statistically significantly higher lethality, namely 44 lethal cases (55.7%) (p<0.001). These data are in harmony with the literature sources regarding the frequency of lethality in individuals with cardiogenic shock [12, 13].

An important aspect of the supervision of patients with AMI is the ability to predict the development of AHF. We found that patients with concomitant pathology were significantly more in the group of people with complicated AMI. The Jentzer J.C. et al. demonstrated that the predictors of mortality of patients with AMI are the AHF diagnosis, as well as age, late medical care, a history of myocardial infarction (MI), diabetes mellitus (DM), tissue hypoperfusion, renal and cardiovascular dysfunction [5], which confirms our results. In our opinion, further study of the predictors of the development of high-grade AHF and mortality of patients with AMI requires maximum attention for the possible prevention of such cardiovascular catastrophes.

## CONCLUSIONS

1. It was found that AMI patients included 129 (15.6%) individuals with AHF of higher classes (Killip III and Killip IV). Patients with high-class AHF were statistically significantly older than the midline, average age (69.0±1.3), ($p<0.001$), including 53.7% males and 46.3% females ($p<0.001$).
2. Patients with AMI complicated by high-class AHF were statistically significantly more often diagnosed with concomitant AH, DM, COPD, CKD than those with uncomplicated AMI.
3. It was noted that patients with complicated AMI included statistically significantly more patients with AH history over 10 years.
4. Hospital lethality was significantly higher in individuals with AMI complicated by high-class AHF: 38.0% in the group of AHF-complicated AMI patients, and 3.4% in the uncomplicated AMI group. The lethality in Killip IV patients reached 55.7%.

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ORIGINAL ARTICLE

# ASSESSMENT OF THE STATE OF IMMUNE SYSTEM IN PATIENTS WITH METASTATIC AND GLIAL BRAIN TUMORS AT THE PREPARATORY STAGE OF RADIOTHERAPY

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## ABSTRACT

**The aim:** To assess the state of the immune system in patients before radiation therapy and radiosurgery and compare the features of immunity in metastatic and glial brain tumors.
**Materials and methods:** Our study presents the results of immunograms of 41 patients. Of these: 18 patients with primary glial tumors and 23 patients with secondary metastatic tumors to the brain. The results of 20 conditionally healthy patients who did not have cancer are presented as a control group. The age of patients was 24-75 years. All patients have histological confirmation of the tumor diagnosis. Surgery was performed 1.0-3.0 years before the examination.
**Results:** When comparing the immune parameters of the number of T and B subpopulations of lymphocytes in patients with primary malignant brain tumors and secondary metastatic tumors, no statistically significant difference was found between these indicators. Glioblastomas show higher levels of IgG and IgA than other tumors, while the concentration of IgM is almost at the same level in all three groups of patients. There is a tendency to decrease the level of IgG and IgM in the blood of patients with metastatic tumors. In the study group of patients there is an inhibition of myeloperoxidase activity of neutrophils on the background of maintaining the function of NBT cell activity.
**Conclusions:** Both metastatic and primary malignant glial have partial changes in various parts of the immune system.

**KEY WORDS:** immune status, metastatic tumors, glial tumors, radiation therapy

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## INTRODUCTION

Cancer remains one of the leading causes of death worldwide and is expected to increase [1-3]. Primary and metastatic tumors are complex ecosystems consisting of neoplastic cells, extracellular matrix (ECM) and "additional" non-tumor cells, which include resident mesenchymal cells, endothelial cells and infiltrated inflammatory immune cells. Cross-dialogue between cancer cells and additional cells promotes tumor development and forms it. During tumor formation, the tissue structure is transformed into a highly specialized microenvironment characterized by damaged ECM and chronic inflammation [4].

Studies in recent decades have shown that immune cells are important participants in the cancer process and inflammation associated with cancer. Efforts have focused on understanding how immune cells affect tumor fate at different stages of the disease: early neoplastic transformation, clinically detected tumors, metastatic spread and in the surgical and radiotherapy phases. The study of the effects on the immune system of various methods of treating the tumor process, including radiation therapy (RT), has not yet been fully studied. Thus, in addition to the direct effect of radiation on cancer cells, RT can cause modifications in the local microenvironment and the immune system, which can affect tumor development [5-25]. Most tumor cells do not express major histocompatibility complex (MHC) class antigens and, as a result, they cannot directly activate specific tumor immunity mediated by CD4 + T cells, which is required for the development of antitumor immune responses. Tumor cells have quite complex mechanisms by which they can avoid immune surveillance [7,8,15].

These cells can produce immunosuppressive cytokines and involve inhibitory and regulatory cell types, reduce the expression of MHC class I molecules, cause anergy or deletion of T cells, and cause dendritic cell (DC) dysfunction [11,14,15,20-23]. The interaction of all these factors can promote not only the "invisibility" of cancer cells by the immune system, but also stimulate tumor growth, so it is important to determine the state of the immune system at all stages of combination treatment.

It has been shown that RT can help tumors become visible to the immune system [6,9-13,16-18,26]. After RT treatment, there is an increase in the pool of peptides for antigen presentation, which is reflected by MHC-I molecules. Through this mechanism, adaptive immune responses can promote the elimination of cells and tumor metastases that do not express MHC-II. CD4 + T cells can help kill tumor cells through several mechanisms. Despite the central role of CD4 + T cells in antitumor adaptive immunity, tumor antigens such as TAA can be presented to dendritic cells by CD8 + T cells and molecules in MHC-I

**Table I.** Cellular immunity. Absolute indicators

| Brain tumors | CD-3 | CD-4 | CD-8 | CD-19 | CD-16 |
|---|---|---|---|---|---|
| Metastases (n = 23) | 1,13±0,62 | 0,63±0,36 | 0,49±0,30 | 0,22±0,14 | 0,23±0,10 |
| Glioblastomas (n = 11) | 1,28±0,51 | 0,73±0,30 | 0,54±0,24 | 0,21±0,11 | 0,30±0,11 |
| Anaplastic astrocytomas (n = 10) | 1,15±0,54 | 0,68±0,31 | 0,48±0,26 | 0,20±0,12 | 0,21±0,09 |
| Control group (n=20) | 1,34±0,51 | 0,78±0,38 | 0,58±0,22 | 0,20±0,08 | 0,25±0,08 |

**Table II.** Cellular immunity. Relative indicators

| Brain tumors | CD-3 | CD-4 | CD-8 | CD-19 | CD-16 |
|---|---|---|---|---|---|
| Metastases (n = 23) | 70,22±7,47 | 39,94±8,40 | 30,52±6,97 | 14,86±5,92 | 15,36±3,60 |
| Glioblastomas (n = 11) | 69,60±14,06 | 39,62±9,44 | 29,68±8,08 | 12,06±5,29 | 17,60±5,49 |
| Anaplastic astrocytomas (n = 10) | 71,26±12,95 | 42,58±9,43 | 29,46±7,86 | 13,34±5,57 | 13,68±4,27 |
| Control group (n=20) | 73,25±5,43 | 41,28±10,47 | 31,7±8,13 | 11,09±3,29 | 14,82±5,42 |

class; this process can occur without the help of previous CD4 + T cells. The above data indicate the importance of determining the state of CD-4 and CD-8 cellular immunity at different stages of tumor treatment, especially before the onset of RT. At the same time, many issues related to the state of the immune system, the number of CD3, CD4, CD8 and other immune cells in the blood in tumors of different origin and location, including brain tumors need further study, which is necessary for successful treatment.

## THE AIM

Assess the state of the immune system in patients with brain tumors before radiation therapy and radiosurgery and compare the features of immunity in metastatic and glial brain tumors.

## MATERIALS AND METHODS

Our study presents the results of the immune status of 41 patients with brain tumors, of which 18 - with primary glial tumors (glioblastomas - 9, anaplastic astrocytomas - 2, anaplastic oligoastrocytomas - 2, anaplastic oligodendrogliomas -2, diffuse -3 astrocytes), with secondary metastatic tumors in the brain with localization of the primary focus in the breast - 9 patients, lungs - 5, skin (melanoma) - 3, intestine - 2, uterus - 1, pleura (mesothelioma) - 1, anonymous metastasis - 1. In The quality of the control group presents the results of 20 relatively healthy patients who did not have cancer. The age of patients was 24-75 years. Surgery was performed 1.0-3.0 years before the examination. All patients had histological confirmation of the diagnosis of the tumor, established according to modern histological classifications of tumors. Informed written consent for diagnostic tests by patients is given and stored in the medical history.

Assessment of the immune system in patients with brain tumors was performed taking into account the cellular, humoral and phagocytic immune system.

In determining cellular immunity, the relative and absolute number of major subpopulations of lymphocytes, such as CD-3 - total T lymphocytes, CD-4 - T lymphocytes - helpers, CD-8 - cytotoxic lymphocytes, CD-16 - natural killer lymphocytes, CD- 19 B lymphocytes. The concentration of these subpopulations was determined using the appropriate monoclonal antibodies from BectonDickinsomUSA, according to the recommended instructions and study protocols adapted to the determination of these cells in peripheral blood (Pinegin).

Determination of the level of serum immunoglobulins of the IgM, IgA class was performed using standard sets of monospecific sera from the company "Microgen" of the Ministry of Health in agar plates, according to the recommendations and instructions of the manufacturer. Phagocytic activity of leukocytes and neutrophils was determined using the NBT test by the colometric method Gordienko SN in the modification of Lisyany MI. Myeloperoxidase activity of neutrophils was performed by the colometric method on the activity of intracellular peroxidase in comparison with horseradish peroxidase by the method adaptive to ELISA analyzer-reader (Frimel).

Statistical processing of the obtained results was performed according to the program Statistica-8 with the determination of the peripheral mean (M) square deviation and Student's index. The level of significance $p < 0.05$ was chosen as a criterion for differences in indicators.

## RESULTS

The study of immune status in patients with brain tumors of primary and metastatic origin revealed changes in various parts of the immune system. Thus, when comparing the absolute number of individual subpopulations of lymphocytes revealed an imbalance in the composition of CD-3,4,8 T lymphocytes and 19 B lymphocytes, namely in comparison with a group of non-cancer patients. An increase in the indicated level of T lymphocyte subpopulations and a decrease in the level of CD-19 lymphocytes in the peripheral blood were found. When comparing immune parameters in patients with primary malignant brain tumors - glioblastomas and anaplastic astrocytomas, with secondary metastatic tumors, slight differences in the number of T

**Table III.** Humoral immunity

| Brain tumors | Ig A | Ig M | Ig G |
|---|---|---|---|
| Metastases (n = 23) | 1,60±0 | 0,92±0,070 | 9,48±0,070 |
| Glioblastomas (n = 11) | 1,81±0,32 | 1,05±0,36 | 11,47±2,84 |
| Anaplastic astrocytomas (n = 10) | 1,48±0,59 | 1,03±0,33 | 10,77±1,94 |
| Control group (n=20) | - | - | - |

**Table IV.** Phagocytic activity

| Brain tumors | Spontaneous NCT test | Induced (zymosan) | Myeloperoxidase activity |
|---|---|---|---|
| Metastases (n = 23) | 258,72±33,16 | 50,33±13,60 | 14,23±3,30 |
| Glioblastomas (n = 11) | 238,45±51,93 | 53,97±15,56 | 14,83±4,64 |
| Anaplastic astrocytomas (n = 10) | 249,8±49,43 | 57,55±15,51 | 17,50±4,59 |
| Control group (n=20) | 248,5±25,63 | 57,79±11,88 | 14,12±2,63 |

and B subpopulations of lymphocytes were found, namely, it was found that glioblastomas had the highest CD-3 and CD-4 levels. 8 lymphocytes, compared with other groups of tumors, although no statistically significant difference between these indicators was found (Table I).

The content of different subpopulations of lymphocytes in the blood of patients with metastatic tumors and anaplastic astrocytomas of III degree anaplasia was almost the same, which indicates the immunological similarity of the cancer process in the body regardless of tumor location, for example, in the brain or breast. Indicators of CD-16 content of natural killer cells are singled out. Thus, in metastatic tumors and anaplastic astrocytomas there was a decrease in the level of CD-16 cells in the blood, while in glioblastomas there was a 1.4-1.5-fold increase in the number of CD-16 lymphocytes compared with anaplastic astrocytomas (Table I). Similar changes in the readings of the immune system are found not only in determining the absolute number of certain subpopulations of lymphocytes, but also in the relative (percentage) level of lymphocytes, which also confirms the changes depending on the nature of the tumor process, namely primary or metastatic tumors. At the same time, when comparing the percentage and absolute content of certain subpopulations of lymphocytes, it can be noted that the determination of the absolute content of immune cells in the blood more clearly illustrates the state of the immune system than its percentage, but for completeness of the immune system and the percentage of certain subpopulations of lymphocytes in the peripheral blood (Table I, II).

When determining the indicators of humoral immunity, namely, the levels of different types of immunoglobulins in the peripheral blood, the dependence on the nature of the tumor process. Glioblastomas show higher levels of IgG and IgA than other tumors, while the concentration of IgM is almost at the same level in all three groups of patients (Table III). There is a tendency to reduce the level of IgG and IgM in the blood of patients with metastatic tumors (Table III). In contrast to cellular immunity, where there is an increased level of individual subpopulations of T lymphocytes compared with the control group, the levels of all immunoglobulins are white, which indicates a different effect of brain tumors on certain parts of the immune system.

When determining the activity of the nonspecific phagocytic part of the immune system, it was found that in all groups of patients with metastatic and primary tumors, inhibition of myeloperoxidase levels in leukocytes, which was most significant in metastatic tumors. At the same time, the NBT activity of leukocytes, which is responsible for the phagocytic activity of neutrophils, was at the level of the comparison group in metastatic tumors and slightly reduced in the group of patients with glioblastomas (Table IV).

Therefore, in the study group of patients there is an inhibition of myeloperoxidase activity of neutrophils on the background of preservation of NBT function of cells, which indicates a selective violation of the phagocytic immune system, which is responsible for nonspecific immunity, and this may be due to the tumor effect on this tumor immunity.

## DISCUSSION

After analyzing the obtained data on the immune status of patients with brain tumors in preparation for radiotherapy, which will be directed to the tumor site, we can summarize them as follows. Thus, in patients before treatment, the function of the T cell of the immune system is preserved, except for a slight decrease in the level of B lymphocytes. Changes in the phagocytic activity of neutrophils are observed - on the one hand, inhibition of myeloperoxidase activity of cells against the background of preservation of their NBT activity, which is responsible for phagocytic activity.

Thus, in patients with brain tumors in preparation for radiation therapy there are no significant changes in the immune system, which would make it impossible to carry out such treatment and were one of the contraindications. Moreover, a certain activation of the immune system was detected, which is confirmed by an increase in the level of almost all subpopulations of T lymphocytes in the peripheral blood [6,12,18,21,29]. Changes in the humoral

and phagocytic links in these patients are insignificant and are also not a factor that limits this stage of treatment. The reasons, mechanisms of development and preservation of such imbalance in the composition and activity of immune cells in the body are known [30-32] and are associated with tumor factors first, and then with the nature of previous treatment, which has already been carried out these patients, especially with metastatic tumors.

The second feature of the obtained results is that no significant difference was found between primary malignant brain tumors and metastatic brain tumors, where the primary focus was more often in the breast. Immune parameters of patients with metastatic tumors were similar to those of patients with anaplastic astrocytomas, which belong to the III degree of anaplasia. The most malignant glial tumors - glioblastoma IV degree of anaplasia had a slightly increased level of subpopulations of T lymphocytes, which is difficult to explain, as it is known that these tumors have the most significant imbalance in immune cells and inhibition of specific antitumor immunity [11,19,24,28].

It is possible that further study of this issue and clarification of the features of treatment, will answer why in glioblastomas, tumors of IV degree of anaplasia, immune levels are higher than in anaplastic astrocytomas and metastases.

In patients with metastatic and primary brain tumors, certain changes in the cellular, humoral and phagocytic parts of the immune system are registered, which indicate different effects of the tumor process on the immune system and these changes are specific and depend on the histostructure of glial tumors [9,13,17,19,21,24,27,29].

## CONCLUSIONS

1. At metastatic and glial tumors of a brain changes in cellular, humoral and phagocytic departments of immune system are found.
2. The most significant changes in the level of cellular immunity are observed in glial tumors of IV degree of anaplasia, glioblastomas, which are characterized by an increase in the number of helper (CD-4) and cytotoxic (CD-8) cells compared with other patients and comparison groups.
3. Both metastatic and primary malignant glial have partial changes in various parts of the immune system. Thus, with reduced myeloperoxidase activity of neutrophils, decreased levels of IgM in the blood and B lymphocytes, indicating an imbalance in the functioning of the immune system, which must be diagnosed to prevent complications of an immune nature at each stage of combination treatment.
4. Detected immune imbalance in the composition and activity of immune cells is not a reason to cancel or not conduct radiation therapy, but on the contrary, determining the state of the immune system during radiation therapy can control the treatment process and prevent the development of immunological complications such as radiation immunodeficiency and thromocytopenia, etc.

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REVIEW ARTICLE

# CROSS-REACTIVITY TO ANTIBIOTICS: PROPOSITIONS FOR SELECTING ALTERNATIVES

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**ABSTRACT**

**The aim:** To analyze CR among antibacterials of different classes and to overcome some widespread misconceptions regarding CR between different classes of antibiotics.

**Materials and methods:** The narrative review represents an assessment of the most pertinent literary sources published in English language, which dealt with the issues of cross-reactivity between individual antibiotics and different classes of these ones.

**Conclusions:** With a high probability of type I AR in a patient in the past, it is better to plan the treatment of patients together with an allergist / immunologist. If this probability is estimated to be low, the choice of a particular antibiotic may be based to some extent on CR data.

**KEY WORDS:** allergic reaction, β-lactam antibiotics, fluoroquinolones, glycopeptides, macrolides

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## INTRODUCTION

Physicians usually prescribe, if necessary, an alternative aniticrobial in case of an allergic reaction (AR) to a particular antibiotic in a patient's past. In patients with allergies to penicillins restrictions mainly apply to other β-lactam antibiotics: cephalosporins, carbapenems, monobactams for preventing of cross-reactivity (CR). Certain circumstances should be considered for optimal treatment of patients with a history of AR to antibiotics. First, hypersensitivity to antibiotics subsides over time. Second, CR, even within a single class of antibiotics, is rare or may be absent. Third, the use of an alternative antibiotic is associated with increased treatment costs, prolonged hospital stays, and an increased risk of infection with resistant microorganisms such as vancomycin-resistant enterococci, *Clostridioides difficile* (previously *Clostridium difficile*) and methicillin-resistant *S. aureus* (MRSA) [1].

## THE AIM

The aim of this article is to analyze CR among antibacterials of different classes and to overcome some widespread misconceptions regarding CR between different classes of antibiotics insofar as presence of allergic reactions to antibiotics in patient's anamnesis influences the physician's choice of appropriate management of infections.

## MATERIALS AND METHODS

The narrative review represents an assessment of the most pertinent literary sources published in English language from 1990 to 2021, which dealt with the issues of cross-reactivity between individual antibiotics and different classes of these ones.

## REVIEW AND DISCUSSION

### CR BETWEEN β-LACTAM ANTIBIOTICS

*CR between penicillins* is most often due to the presence of an identical or similar R1 side chain and, very rarely, to a common β-lactam ring (Figure 1). Penicillin has neither a common nor an analogous R1-side chain with other penicillins, so the likelihood of cross-reactivity with other antibiotics of the same class is extremely low. In contrast, aminopenicillins (amoxicillin, ampicillin) and piperacillin have similar R1 side chains [2]. In patients with an allergic reaction to any of them (eg, ampicillin) usage of the other two (amoxicillin and piperacillin) will be dangerous without preliminary allergy testing.

Common misconception includes the statement that a patient with a history of penicillin allergy reactions should avoid all cephalosporins due to possible CR. In fact, CR *between penicillins and cephalosporins* is rare and occurs in cases of 1) structural similarity of R1-side chains, 2) similar 3-dimensional electronic and spatial properties, and 3) structural similarity of R2-side chains (only between cephalosporins). The β-lactam ring itself is not a significant antigenic determinant [2]. Patients with a history of AR to ampicillin, amoxicillin or piperacillin (before allergy testing) should avoid some 1st and 2nd generation cephalosporins for oral administration, i.e. cefadroxil (with identical R1-side chain with amoxicillin and similar one with ampicillin and piperacillin), cephalexin and cefaclor

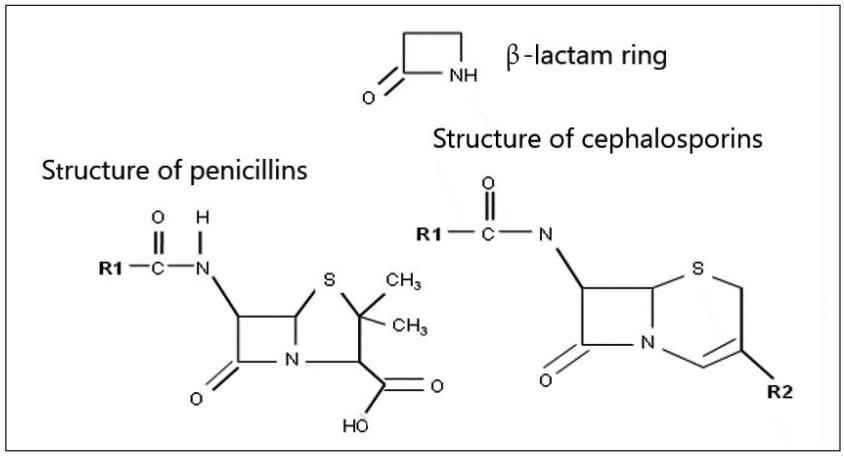


**Fig. 1.** Structural differences between *penicillins* and *cephalosporins*

**Table I.** Cross-reactivity between *cephalosporins*

| | Cefadroxil | Cephalexin | Cefazolin | Cefaclor | Cefuroxime | Cefixime | Cefdinir | Cefditoren | Cefpodoxime | Cefotaxime | Ceftriaxone | Cefoperazone | Ceftazidime | Cefepime |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cefadroxil | | | | | | | | | | | | | | |
| Cephalexin | | | | | | | | | | | | | | |
| Cefazolin | | | | | | | | | | | | | | |
| Cefaclor | | | | | | | | | | | | | | |
| Cefuroxime | | | | | | | | | | | | | | |
| Cefixime | | | | | | | | | | | | | | |
| Cefdinir | | | | | | | | | | | | | | |
| Cefditoren | | | | | | | | | | | | | | |
| Cefpodoxime | | | | | | | | | | | | | | |
| Cefotaxime | | | | | | | | | | | | | | |
| Ceftriaxone | | | | | | | | | | | | | | |
| Cefoperazone | | | | | | | | | | | | | | |
| Ceftazidime | | | | | | | | | | | | | | |
| Cefepime | | | | | | | | | | | | | | |

Note: cephalosporins with the same R1-side chains (red), with similar - light green. Empty cells - no similarity in R1-side chains.

(both of them have identical R1-side chain with ampicillin and similar one with amoxicillin and piperacillin). The incidence of CR between aminopenicillins (ampicillin, amoxicillin) and aminocephalosporins (cephalexin, cefadroxil, cefaclor) reaches 30-40% according to some European studies [3, 4]. On the other hand, if a patient with a history of AR to penicillins tolerates any of the listed cephalosporins with identical / similar side chain, there is no reason to avoid the use of other cephalosporins, even if the patient continues to avoid the use of penicillins [2].

The previous idea that in patients with AR to penicillins the prevalence of allergy to cephalosporins reaches 10% is not true. In fact, 90–99% of patients with a history of penicillin allergic reactions may actually tolerate that antibiotic due to a misinterpretation of past reactions to penicillin (such as nausea, vomiting, or diarrhea) as "allergic". Moreover, type I allergy to penicillins subsides over time [5]. Second, most reports of AR to cephalosporins in patients with a history of AR to penicillins related to the use of early generations of cephalosporins. The reasons for such reactions could be the similarity of R1-side chains in penicillins and cephalosporins of 1-2 generations [6], or contamination of early cephalosporins with penicillin due to features of manufacturing process until 1980s [7]. Finally, skin tests to confirm allergy to penicillins and cephalosporins were performed quite rarely [8]. Therefore, the real frequency of CR between penicillins and cephalosporins is probably less than 1% [9].

In some cases, CR is possible between penicillins and cephalosporins without identical or similar side chains.

Thus, CR between benzylpenicillin and cephalothin (a cephalosporin of 1st generation, which is absent on the pharmaceutical market of Ukraine) is associated with similar 3-dimensional electronic and spatial properties or with a common methylene group in the side chains of these antibiotics [10]. On the other hand, it is not possible to exclude contamination of cephalothin with penicillin during the manufacturing process as a cause of CR [11]. Another common misconception is that "a patient with a history of AR to any of the cephalosporins should avoid all cephalosporins because of possible CR." In fact, CR between cephalosporins occurs rarely and is due to the similarity of the R1 and R2 side chains of molecules [2]. The presence of identical or similar side chains in cephalosporins of 1st to 4th generations is presented in Table I. In patients with anamnestic indications for AR to cephalosporins, the lowest probability of AR will be in cases of usage of cefoperazone and cefdinir in the future. However, it is not reasonable to prescribe cefdinir to patients with AR to cefixime, because both of peroral 3rd generation cephalosporins have an identical R2-side chain [2].

Thus, hypersensitivity to a particular cephalosporin does not indicate hypersensitivity to the whole class of cephalosporins [12], and in the presence of allergy to cephalosporin of any generation CR to another drug of that or other generations will be absent if their molecules have side chains of different types [7, 13].

The low frequency of CR *between penicillins and carbapenems* (approximately 1%) was found in studies conducted in children and adults [14, 15]. In patients with a history of immediate-type penicillin AR and negative skin tests with penicillin, the use of carbapenems is safe. If a skin testing is not possible, a provocative test with carbapenem is recommended [16]. Although literature data on CR *between cephalosporins and carbapenems* are limited [13], it is likely to be quite rare (<1%) [17].

Aztreonam is the only representative of monobactams (another class of β-lactam antibiotics). CR between monobactams, on the one hand, and penicillins, cephalosporins and carbapenems, on the other, is extremely rare [13, 17]. The only exception to note is that aztreonam and ceftazidime have an identical R1 side chain [15, 16].

Finally, patients with a true AR to β-lactam antibiotic may develop an AR to various β-lactams as an independent hypersensitivity reaction, which is not related to CR [2]. It is also suggested the possibility of a simultaneous increase in sensitivity to different β-lactams in patients with previous contacts with these antibiotics [18].

## CR BETWEEN NON-B-LACTAM ANTIBIOTICS

Fluoroquinolones (FQ) rank second (after β-lactams) in the frequency of association with AR [19]. In patients with a history of AR to β-lactams, the risk of allergic reactions to FQ increases many times: adjusted odds ratio (OR) 23,654; 95% confidence interval (CI) 1,529–365,853 [20]. The increase in the incidence of AR to FQ over the last 10 years is associated with their widespread clinical use and / or with the introduction of moxifloxacin [20, 21]. Moxifloxacin is metabolized in the liver. Small portions of other FQ are also converted to reactive metabolites in the liver. It is believed that these partially metabolized intermediates may interact with proteins to form hapten-protein conjugates that trigger immune responses [20].

There are four generations of FQ: 1st (norfloxacin), 2nd (ciprofloxacin, ofloxacin), 3rd (levofloxacin) and 4th (moxifloxacin, gatifloxacin, hemifloxacin). Data on *CR between FQ* from reports in the literature are quite contradictory. CR takes place between FQ 1st and 2nd generations, to a lesser extent – between FQ 3rd and 4th generations. CR is low in patients with delayed-type AR to FQ [16]. Skin tests can predict hypersensitivity to the whole class of FQ, but are not useful for predicting the tolerance of some members of that class of antimicrobials [22].

In patients with AR of immediate type to FQ it is necessary to avoid all drugs of that class [16]. Levofloxacin is a relatively safe alternative in cases of hypersensitivity to FQ of 1st, 2nd and 4th generations [23].

Depending on the number of atoms in the macrocyclic lactone ring, there are 14-membered (erythromycin, clarithromycin, roxithromycin), 15-membered (azithromycin) and 16-membered (spiramycin, josamycin) macrolide antibiotics. Although *CR among macrolides* is insufficiently studied, it is believed that most patients with hypersensitivity to one of the macrolides will tolerate another macrolide with a different number of atoms in the lactone ring. [24]. CR between macrolide antibiotics and non-antibiotic macrolides is also absent. Examples are immunosuppressants tacrolimus, which has 23 atoms in the lactone ring, and sirolimus (29 atoms) [16]. However, there were described at least two cases of hypersensitivity to clarithromycin (14 atoms) and azithromycin (15 atoms) simultaneously [25].

A few of tetracycline antibiotics remain of clinical importance. Doxycycline and minocycline can serve as examples. Minocycline is used almost exclusively to treat acne. The frequency of *CR between tetracyclines* is not known for sure [16], and only one case of CR between doxycycline and minocycline has been described in the literature [26].

There are two structural classes among aminoglycoside antibiotics: streptidines (streptomycin) and deoxystreptamines (all other aminoglycosides: neomycin, kanamycin, gentamicin, amikacin, tobramycin, plasomycin). CR between them is absent [27]. However, neomycin contains diamino sugars (called neosamines), which are also present in kanamycin and tobramycin. That is why 65% of patients with neomycin allergy cross-react with tobramycin [28]. *CR among aminoglycosides* that contain a deoxystreptamine group (gentamicin, tobramycin, amikacin, neomycin, etc.) is at least 50% [29]. Therefore, all aminoglycosides containing this group are contraindicated in cases of known hypersensitivity to any aminoglycoside except streptomycin [27].

Vancomycin and teicoplanin are most commonly used glycopeptide antibiotics in clinical practice. *CR between glycopeptides* is not uncommon. AR to teicoplanin will take place in 10–58% of patients, who had a hypersensitivity reaction to vancomycin, with a high recurrence rate and new occurrence rate (up to 70%) for changes in the blood picture (neutropenia, leukopenia, thrombocytopenia) [30, 31]. Thus, teicoplanin should not be considered as an ideal alternative in the treatment of patients with hypersensitivity to vancomycin [16].

Co-trimoxazole represents a combined drug of trimethoprim and sulfamethoxazole. AR usually occur to the sulfonamide component, not to trimethoprim [16]. Patients with a history of sulfonamide AR may tolerate dapsone, an antileprosy drug, but data on CR are conflicting and it would be better not to use dapsone in patients with severe AR [32]. *CR between sulfonamide* antibacterial drugs and non-antibacterial sulfonamides is absent [33].

Several cases of *CR between metronidazole and tinidazole*, which belong to nitroimidazoles, were reported in the literature in 1990s [34, 35]. Studies using patch tests also indicate the presence of CR between metronidazole and other antifungal and antiparasitic imidazoles, i.e clotrimazole, ketoconazole, miconazole, albendazole. Thus, patients with proven hypersensitivity to metronidazole should avoid the use of the above listed drugs [16].

## CONCLUSIONS

Presence of AR to different classes of antibiotics directly influences the choice of drugs for the treatment of infections in those patients. If cases of a high probability of type I AR in a patient in the past, it is necessary to seek the help of an allergist / immunologist to develop recommendations and conduct the necessary investigations, including skin tests. If probability of type I AR is estimated to be low, the choice of a particular antibiotic may be based to some extent on CR data. The main points can be briefly summarized as follows:

- CR between β-lactams occurs rarely and is mainly due to the structural similarity of R1-side chains;
- levofloxacin is a relatively safe alternative in cases of hypersensitivity to fluoroquinolones of 1st, 2nd and 4th generations, but in cases of immediate-type AR to fluoroquinolones in a patient's past it is better to avoid the use of all members of this class;
- most patients with hypersensitivity to one of the macrolides will tolerate another macrolide with a different number of atoms in the lactone ring;
- in cases of AR to aminoglycosides (except for streptomycin) it is necessary to avoid the use of all antibiotics of that class (except for streptomycin);
- if there were AR to glycopeptides, it is safer (before carrying out skin tests) to use antibiotics of other classes, for example, oxazolidinones (linezolid);
- in patients with proven hypersensitivity to metronidazole should not be used other imidazoles (including antifungal and antiparasitic agents).

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*Research work 0117U000595 "Mucoactive and herbal medicines for the treatment of cough in acute infectious and inflammatory diseases of the lower respiratory tract.*

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REVIEW ARTICLE

# POTENTIAL THERAPEUTIC OPTIONS TARGETING THE GUT DYSBIOSIS IN CHRONIC KIDNEY DISEASE

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**ABSTRACT**

The gut microbiota plays an important physiological role in controlling not only the function of the gastrointestinal tract, but also in maintaining systemic homeostasis. Quantitative and /or qualitative disturbances of the gut microbiota (dysbiosis) are an important element in the complex pathogenesis of many diseases, including chronic kidney disease (CKD). In the disease, the mutual interactions between disturbed gut microbiota and the progression of CKD (pathophysiological "kidney-gut axis") have been demonstrated. The kidney failure causes water and nitrogen waste retention which leads to disturbances of motility, secretion and absorption in the gastrointestinal tract. These abnormalities contribute to the development of gut dysbiosis, accompanied by overproduction of toxic bacterial metabolites, with their translocation to the peripheral blood and development of endotoxemia. As a consequence, chronic kidney "low-grade" inflammation and oxidative stress develop, with further deterioration of kidney function in the mechanism of the "vicious cycle" of the kidney-gut axis. Considering the key role of gut dysbiosis and the kidney-gut axis, the attempts to restore the gut eubiosis seem to have an important role in the treatment of CKD and may be even regarded as a form of causal therapeutic intervention. The paper briefly discusses the basics of the pathophysiological kidney-gut axis in CKD and potential methods of modulating the abnormal gut microbiota in this disease, including the use of probiotic or prebiotic preparations, agents that absorb bacterial-derived toxins in the intestinal lumen, fecal microbiota transplantation and drugs used so far for other indications (acarbose, meclofenamate, lubiprostone).

**KEY WORDS:** treatment, chronic kidney disease, gut dysbiosis, kidney-gut axis

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## INTRODUCTION

Chronic kidney disease (CKD) is the final consequence of both primary kidney diseases of various etiologies and systemic clinical entities affecting kidneys (hypertension, diabetes and obesity). The mean global estimated prevalence of CKD is ca. 13.4% (it affects 8% to 16% of the population worldwide) and due to the long asymptomatic period, the disease is underrecognized by both patients and clinicians. CKD is an emerging, worldwide public health problem since it directly affects the global burden of morbidity and mortality and requires renal replacement therapy in its end-stage phase [1, 2]. In line with the fundamental, still valid definition provided by the Kidney Disease Improving Global Outcome (KDIGO), CKD is defined as abnormalities of kidney structure or function lasting for >3 months, with implications for health and CKD is classified based on cause, glomerular filtration rate (GFR) category (G1-G5) and albuminuria category (A1-A3) [3]. The definition of CKD formulated this way was sustained in the latest KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease [4]. The pathogenesis of CKD is complex and manifests itself in the progressive, irreversible structural pathological remodeling of the glomeruli and tubulointerstitial tissue, which leads to a gradual reduction in excretory functions (GFR decline), but also to an impairment of other endocrine and metabolic functions of the kidneys. The initial, favorable compensatory adaptive mechanisms (e.g. hyperfiltration of undamaged nephrons), acting in a "vicious circle" mechanism, finally intensify further disease progression [5]. In the current pathophysiological description of CKD, it is emphasized that the disease is characterized by the development of systemic, low-grade inflammation and increased oxidative stress [6]. One of the key elements of CKD pathophysiology is also the increase of the gut wall permeability ("leaky gut"). It results from the disturbances of the motor and secretory functions of the gastrointestinal tract which change the intestinal pH, sodium and water retention, changes in the blood supply to the intestinal wall and systemic functioning and locally released inflammatory mediators. The abovementioned factors lead to quantitative and qualitative changes in the gut microbiota, contributing to the increased synthesis of bacteria-derived uremic toxins. Translocation of these metabolites through a leaky gut in CKD maintains inflammation and, secondarily, exacerbates renal dysfunction. This relationship is known as the "kidney-gut axis" [7,8]. Thus, the development of gut dysbiosis and an abnormal mutual functional relationship between gut and kidneys ("kidney-intestine axis") are prospective points for potential therapeutic intervention in CKD.

The routine, conservative management in chronic kidney disease includes both changing the lifestyle and preventing cardiovascular diseases (smoking cessation, diet

modifications, avoiding the use of nephrotoxic drugs and individualizing the dosage of administered drugs according to the eGFR value) and pharmacological treatment. Pharmacotherapy of CKD is aimed at reducing proteinuria, treating arterial hypertension, dyslipidemia, controlling water, electrolyte and acid-base balance, treatment of calcium-phosphate disturbances and anemia. Moreover, taking into account the rich systemic clinical manifestation of CKD, it is also required to treat multiple disorders, such as: weakness, malaise, lethargy, somnolence, trouble sleeping, attention deficit, depression, inappetence, dry mouth, nausea, pruritus, dry skin, dyspnea, edema, cramps, and pain. In end-stage CKD, kidney replacement therapy is also necessary, including dialysis (hemodialysis or peritoneal dialysis) and kidney transplantation [9, 10].

Despite the important role of the gut dysbiosis in CKD pathogenesis and its progression, currently there are no established strategies to modulate the composition of the gut microbiota. Hence, it is certainly necessary to introduce agents that target gut dysbiosis and evaluate their therapeutic efficacy in common clinical practice.

## THE AIM

The aim of the article was to briefly discuss potential therapeutic interventions for the treatment of gut dysbiosis in chronic kidney disease. Gut dysbiosis is an important element of the comprehensive pathogenesis of CKD, and the restoration of eubiosis slows down the progression of CKD and the development of complications of this disease.

## MATERIALS AND METHODS

English-language papers were searched for in PubMed-NCBI and Google Scholar databases. The various applied search terms included: "kidney-gut axis", "kidney microbiota", "gut microbiota", "gut dysbiosis", "chronic kidney disease", "uremic toxins", "chronic kidney disease management". During the query, combinations of the above-mentioned search terms were used with the quantifier "AND". Articles published on or after 2000 were selected for the discussion below.

## REVIEW AND DISCUSSION

### NORMAL GUT MICROBIOTA

Gut microbiota is the biotic part of the microbial ecosystem that colonizes the gut. It is a collection including not just bacteria, but also other microorganisms (fungi, archaea, viruses and protozoans). However, the healthy gut microbiota is predominantly constituted by bacteria. They exhibit dynamic, temporal (age) and spatial (along the entire gastrointestinal tract) variation. The amount of microbiota increases as one travels from the esophagus distally to the rectum. Furthermore, the gut microbiota composition is affected by many environmental, physiological and pathophysiological factors, including the mode of delivery at birth, sex, ethnicity, diet, various diseases or administered drugs [11]. To sum up, the bacterial component of the gut microbiota consists mainly of 50 phyla, although four phyla are the most represented among the total as they account for up to 70-90% of total bacteria: *Firmicutes, Bacterioides, Actinobacteria* and *Proteobacteria*. Most of human gut microorganisms are strictly or relatively anaerobic and are symbionts, commensals or pathobionts coexisting in a stable balance in healthy individuals. The gastrointestinal tract is also inhabited by a number of fungi, especially from the genera *Candida, Saccharomyces, Aspergillus, Cryptococcus, Malassezia, Cladosporium, Galactomyces and Trichosporon* [12, 13]. The quantitative contribution to microbial communities of archaea, viruses or unicellular eukaryotes is minor. The composition of the physiological gut microbiota is presented in Table I.

The physiological role of gut microbiota is crucial in many ways for human health. Microorganisms inhabiting human gut protect against pathogens (colonization resistance) and synthetize various compounds necessary for maintenance of systemic homeostasis, affecting many cellular processes: vitamins, nutrients: amino acids and short-chain fatty acids – SCFA (acetate, propionate, butyrate), secondary bile acids (deoxycholic, ursedeoxycholic, lithocholic), neurotransmitters (gamma-aminobutyric acid; GABA, serotonin, dopamine, norepinephrine, acetylcholine, glutamate) and neuropeptides. Moreover, gut microbiota improves gut mucosal barrier integrity – it is involved in renewal of intestinal epithelial layer, recovery of intestinal epithelial injury, intestinal angiogenesis. It is also involved in maturation and education of the immune system and regulation of immunity processes (e.g. by activation of CD4+ T cells, Th17 cells and activation of Toll-like receptors). It has also been shown that physiological microbiota is involved in the development and maturation of the nervous system, regulation of appetite and behavior and that the gut microbiota is still in a mutual "cross-talk" with the brain ("the brain-gut axis"), which is the basis of the neuroendocrine regulation of the functioning of the gastrointestinal tract [7, 8, 11-13].

Taking into account the fundamental and pleiotropic role of gut microbiota in homeostasis of the human body, the qualitative and/or quantitative disturbances (dysbiosis) of bacterial element are implicated in not only gastroenterological diseases (e.g. functional dyspepsia, irritable bowel syndrome, inflammatory bowel diseases), but also in many other local and systemic diseases, such as: atherosclerosis, colorectal cancer, dental caries, depression, diabetes, multiple sclerosis, obesity, osteoporosis, Parkinson's disease and Alzheimer's disease [14, 15].

### GUT DYSBIOSIS AND EFFECTS OF BACTERIA-DERIVED UREMIC TOXINS ON KIDNEYS IN CKD

In CKD, the gut dysbiosis develops as a consequence of kidney water and nitrogen waste retention and gastrointestinal abnormalities (pH, motility, secretion) and this disorder contributes to the further deterioration of

CKD in the "vicious circle" mechanism – kidney-gut axis phenomenon [16, 17]. Overall, the quantitative and qualitative changes in the composition of the gut microbiota in CKD patients is associated with a systemic low-grade inflammatory state and results from disturbed intestinal transit, decreased protein absorption, decrease in dietary fiber (resistant starch) intake, treatment with oral iron, phosphorus binders and antibiotics and dynamic changes in fluid volume and pH changes as a result of renal replacement therapy. The changes in gut microbiota in the course of CKD are presented in Table I. To summarize, the gut microbial diversity in CKD patients is significantly reduced compared to the healthy control and the bacterial genera possessing urease, indole and p-cresol-forming enzymes (e.g. *Enterobacteriaceae*) as well as those ones producing lipopolysaccharide (*Haemophilus, Klebsiella*) are upregulated and predominate in the overall microbiological composition of the gastrointestinal tract [18].

The gut dysbiosis, disruption of the intestinal barrier structure and overproduced harmful bacterial metabolites with the cessation of beneficial bacterial derivatives (SCFA) contribute to the acceleration of chronic, low-grade inflammatory state in CKD. In physiological conditions and in the excess of carbohydrates, the saccharolytic fermentation prevails, leading to the SCFAs production, keeping of low intestinal pH and suppression of the proteolytic activity. CKD is demonstrated to be characterized by an abnormal intestinal motility and prolonged colon transit, decreased absorption of amino acids and reduced resistant starch intake. Furthermore, kidney dysfunction leads to increased blood levels of end products of purine metabolism (urea, uric acid, oxalates) that should be eliminated with urine. In CKD, colon is the main excretory organ for these waste metabolites accumulated in blood. Increased urea influx into the gut lumen occurs and urease-producing bacteria hydrolyze urea into bicarbonate and ammonia. Ammonia then undergoes a reaction with water to yield ammonium hydroxide that raises intestinal pH. It promotes mucosal irritation and alternation of intestinal permeability by affecting the tight junctions of the enterocytes. It results from the influx of leukocytes and increased local inflammatory mediators production leading to retraction and endocytosis of the transcellular tight junction proteins (claudins and occludins) [19]. The reduced metabolic changes of incompletely digested carbohydrates and the increased supply of amino acids in the colon lead to expansion of proteolytic microbial species and metabolization of aromatic amino acids into small molecule derivatives, such as p-cresol, p-cresyl sulfate (pCS), p-cresyl glucuronide (pCG), indoxyl sulfate (IS), indole-3-acetic acid (IAA), trimethylamine-N-oxide (TMAO), phenylacetylglutamine (PAG) and hippuric acid. In addition, sulfur-containing compounds are a source of hydrogen sulfide ($H_2S$). All these compounds cross the intestinal barrier, enter the peripheral blood and act as bacterial-derived uremic toxins, contributing to further decline in kidney functions [16, 19, 20]. In normal conditions, some of the uremic toxins bound to plasma proteins are eliminated from the body through tubular secretion (via organic anion and cation transporters located in the kidney tubular cells) and the unbound toxins are removed through glomerular filtration. In CKD both elimination processes are reduced which results in the accumulation in bacterial uremic toxins and the aggravation of kidney structure and functions [21]. The colon-origin uremic toxins exert detrimental effects on various kidney cell types, including glomerular, tubular, immunological or endothelial ones. Phenols (p-cresol, pCS and pCG) are the final metabolites of bacterial breakdown of tyrosine and phenylalanine. These derivatives have been demonstrated to activate intrarenal renin-angiotensin system and biochemical pathways associated with transforming growth factor (TGF), thus promoting the kidney interstitial fibrosis. Moreover, these toxins enhance the oxidative stress, reduce antioxidant capacity and elevate the pro-inflammatory cytokine levels in kidneys [21]. According to the European Uremic Toxins Work Group (EUTox), CKD patients are reported to have 21-fold higher blood concentration of PSC and this finding is associated with poor outcomes in both experimental and clinical studies [22]. Indole derivatives are generated from tryptophan and they have been also demonstrated to exacerbate the oxidative stress and inflammatory response in kidneys. IAA was found to induce glomerular sclerosis and interstitial fibrosis. Moreover, it activates the proinflammatory enzyme – cyclooxygenase-2. IS has been revealed to stimulate the NF-κB- and TGF-β-related pathways with overexpression of plasminogen activator inhibitor type 1 and these disturbances finally promote tubulointerstitial fibrosis [21]. In line with the EUTox, CKD patients were found to have a ca. 40-fold higher total IS level and patients subject to dialysis were characterized as possessing the highest blood IS concentration results since the compound is eliminated mostly by tubular secretion and the kidney replacement therapy does not replicate the kidney's high efficiency of tubular secretion [22]. PAG is derived during phenylalanine fermentation and TMAO is produced as a product of oxidation of trimethylamine, cleaved from choline, carnitine or betaine. These compounds are also regarded to increase tubulointerstitial fibrosis and collagen deposition and promote atherosclerosis by enhancing macrophage cholesterol accumulation and formation of foam cells [21]. Again, as with other uremic toxins, TMAO increases as kidney functions decline and EUTox reported that CKD hemodialyzed patients were demonstrated to have up to 40-fold higher TMAO concentration in blood before dialysis compared to healthy controls [22].

Moreover, the important consequence of endotoxemia in the course of CKD are also the immunological effects induced by lipopolysaccharide (LPS) that enters hepatic portal system and systemic circulation across the leaky intestinal wall. A part of LPS – lipid A serves as microbe-specific molecule that binds with the toll-like receptor-4 (TLR4), highly expressed in the monocytes/macrophages, endothelial cells, vascular smooth muscle cells and fibroblasts. The activation of TLR4 leads to the overproduction of pro-inflammatory cytokines (interleukin-1 and 6 and tumor necrosis factor α –

**Table I.** Composition of the normal gut microbiota and the gut microbiota in chronic kidney disease [16, 17].

| Normal gut microbiota | Gut microbiota changes in chronic kidney disease | |
|---|---|---|
| | Increase | Decrease |
| Small intestines (pH = 5-7):<br>Bacterioides, Clostridium, Streptococcus, Lactobacillus, Enterococcus, Actonobacteria, Corynobacteriaceae<br><br>Colon (pH = 5-5,7):<br>Bacterioides, Clostridium, Prevotella, Eubacterium, Ruminococcus, Streptococcus, Enterobacterium, Enterococcus, Lactobacillus, Bifidobacterium, Peptostreptococcus, Fusobacteria, Corynobacteria | Clostridium perfringens<br>Nesterenkonia<br>Brachybacterium<br>Enterococcus<br>Polyangiaceae<br>Thiothrix<br>Halomonadaceae<br>Pseudomonadaceae<br>Moraxellaceae<br>Escherichia coli<br>Klebsiella<br>Haemophilus | Lactobacillus<br>Bifidobacterium<br>Bacterioides |

**Table II.** Potential therapeutic interventions aimed at restoration of gut eubiosis and affecting the pathophysiological "kidney-gut" axis.

| Intervention | Examples |
|---|---|
| Diet modification | A diet low in protein and rich in non-digestible fiber |
| Modulation of gut microbiota composition in order to restore gut eubiosis | Administration of probiotics / prebiotics / symbiotics |
| | Fecal microbial transplantation (microbial replacement therapy) |
| Reducing the harmful effect of uremic toxins produced by the dysbiotic gut microbiota | Adsorption of gut-derived uremic toxins: oral adsorbents |
| | Colonic dialysis |
| Miscellaneous mechanisms | Acarbose |
| | Meclofenamate |
| | Lubiprostone |
| | Natural origin compounds: resveratrol, antioxidants from Lingonberry and omega-3 fatty acids |

TNF-α). These molecular signals promote the recruitment of local, residual, kidney immunocompetent cells, expression of adhesion molecules, overproduction of reactive oxygen and nitrogen species and intensification of pro-inflammatory pathways mediated through nuclear factor-κB (NF-κB). To summarize, the accumulating evidence points to gut dysbiosis and gastrointestinal dysfunction as a major source of chronic inflammation in CKD [23, 24].

## TARGETED TREATMENTS FOCUSING ON GUT DYSBIOSIS IN CKD

The complex CKD therapy focuses on blood pressure control and targets risk factors and complications developing in CKD: diabetes, acute kidney injury, nephrolithiasis, metabolic acidosis, metabolic bone disease, anemia. Taking into account the important pathophysiological role of "the kidney-gut axis", additional therapeutic interventions aimed at modulating the composition of the intestinal microbiota, restoring eubiosis, eliminating the harmful effects of uremic toxins synthesized in the gut and reducing endotoxemia-induced inflammation seem to be rationale. Some options on the aberrant axis of gut microbiota in CKD are listed in Table II. The restoration of gut eubiosis is generally considered to be effective and beneficial and may be at least an adjuvant for general treatment in CKD [23, 24].

### *DIET MODIFICATION*

The easiest method to restore intestinal eubiosis seems to be an increase of the amount of resistant starch (e.g. high amylose maize-resistant starch; found in corn, potatoes, banana) in the diet of CKD patients, which are the source of energy for beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*. However, despite the potential nephroprotective role of this kind of alimentotherapy, such management is also associated with some concerns due to the increased risk of intake of potassium and phosphorus [23].

### *MODULATION OF GUT MICROBIOTA*

The supplemental use of probiotics, prebiotics or synbiotics is currently the most widely used method of directly or indirectly modulating the composition of the gut microbiota and restoring eubiosis. Probiotics are defined as natural or genetically modified live microorganisms that confer a health benefit on the host when administered in adequate amounts. The alternative definition of probiotics indicates specific bacterial strains that effectively promote the health of humans. Traditionally, probiotic preparations mostly comprise *Lactobacillus* species (e.g. *L. rhamnosus, L. plantarum, L. sporogens, L. casei, L. bulgaricus, L. acidophilus*) and *Bifidobacterium* species (*B. bifidum, B. bifidus, B. lactis, B. longum, B, breve, B. infantis*). Addition-

ally, commercially available probiotics also often include: *Streptococcus thermophilus, Streptococcus acidophilus, Lactococcus lactis*, *Enterococcus* SF68 and *Escherichia coli* Nissle 1917 [23-25]. The prebiotics are non-digestible (for host) food ingredients (e.g. inulin, fructo-oligosaccharides, galacto-saccharides, soya-oligosaccharides, xylo-oligosaccharides and pyrodextrins) that promote the overgrowth and/or activity of *Bifidobacteria* and *Lactobacilli* species, while suppressing harmful groups of bacteria, such as *Bacterioides, Clostridia, Enterobacteria* in the colon. The normal diet also contains prebiotic compounds in the form of dietary fibers composed of carbohydrates: resistant starch and non-starch polysaccharides (celluloses, hemicelluloses, pectins, gums and mucilages). Of note, there is also evidence that consumption of resveratrol – a natural polyphenol that occurs in grapes, berries and in other fruits is also associated with the overgrowth of beneficial bacteria, thus the compound is also a good candidate as prebiotic. Synbiotics are dietary supplements that are a combination regimen of both probiotics and prebiotics [23-25]. There are many systematic reviews and meta-analyzes confirming the health-promoting effects of supplementation with preparations modulating the composition of the intestinal microbiota, including alleviation of inflammation and reduction of CKD progression [23,26-28]. Their detailed description is beyond the scope of this review. However, it should also be emphasized that there are also reports that oppose the above-mentioned conclusions [29] and it seems that due to significant methodological differences in clinical trials aimed at evaluating clinical efficacy of probiotics/prebiotics/synbiotics in CKD, further studies are required to clearly confirm the positive aspects of using such preparations in patients with CKD. In particular, the use of various probiotic strains alone or in combination with a prebiotic additive in individual studies is noteworthy, which makes it difficult to conclude unambiguously on the basis of individual reports [19].

The adjuvant therapy with probiotics/prebiotics and synbiotics is based on the restoration of the gut microbial balance and disruption of the pathologic "kidney-gut axis" and, ultimately, reducing the production of uremic toxins of intestinal origin. The potential underlying mechanisms of beneficial, ameliorative effects induced after probiotics and prebiotics administration in CKD patients involve: maintaining intestinal homeostasis, improving the integrity of the intestinal barrier and increase of enterocyte regeneration (thus, reducing the "leaky gut" phenomenon), competitive exclusion of many pathobionts colonization, increased production of compounds with beneficial biological effects (e.g. SCFAs, vitamins), regulation of gastrointestinal motility, improvement of digestion (due to synthesis of secondary bile salts) and neutralization of carcinogens or xenobiotics [25]. The increased synthesis of SCFAs is of key importance in the beneficial effects of gut microbiota-modulating preparations. Unlike uremic toxins, SCFAs exert protection against the progression of kidney disease. SCFA are built from 3-7 carbon units. The most common produced SCFAs are acetate (C2), propionate (C3) and butyrate (C4) and other less abundant SCFAs include isobutyrate (C4), valerate (C5) or 2-methylbutanoate (C5). These compounds are produced through anaerobic fermentation of dietary fibers and/or through metabolism of amino acids, such as: leucine, arginine, glycine and lysine. At the molecular level, SCFAs act through specific G-coupled membrane receptors: GRP41 (located in peripheral blood mononuclear cells, kidneys, adipose tissue, spleen, lymph nodes), GRP43 (expressed on the surface of colonic-ileal region, kidneys, monocytes) and GRP109a (found mostly in adipose tissue, colon and kidneys) [7,30,31]. SCFAs may also influence the intracellular signaling by binding to $H^+$/monocarboxylate transporters (MCTs) or the $Na^+$/monocarboxylate transporters (SMCTs) found in the intestines (mostly in distal colon). Both MCTs and SMCTs also control the transport of SCFAs from the lumen of the colon to the intestinal epithelial cells. SCFAs are potent modulators of the activity of immune cells and these compounds are considered to contribute to the alleviation of the persistent inflammatory state in CKD due to enhancement of anti-inflammatory mechanisms and improvement of kidney functions. In macrophages, SCFAs shift metabolism into oxidative phosphorylation and lipid metabolism that change their phenotype into the anti-inflammatory M2 profile. In CD4 T cells, SCFAs induce interleukin-10 synthesis by inhibiting histone deacetylases and activating the mammalian target of rapamycin pathway (mTOR). The SCFA-induced increased mitochondrial bioenergetics, oxidative phosphorylation and β-oxidation in CD8 T cells are important in their differentiation into memory cells. SCFAs also contribute to enhanced antibody production in B cells. Moreover, SCFAs may be converted into acetyl-CoA in the cytoplasm of immune cells and boost the activity of the tricarboxylic acid cycle that induces the anti-inflammatory and memory profile in immune cells. To summarize, increased production of SCFAs induced by probiotic/prebiotic/synbiotic supplementation results in an anti-inflammatory, immunomodulatory effect, which is beneficial for reducing the progression of CKD. Noteworthily, SCFAs exert also some direct renoprotective effects. GRP41 and GRP43 receptors were also found in distal and collective tubules and their SCFA-induced activation was demonstrated to reduce the TNF-α-stimulated synthesis of chemoattractant proteins (e.g. monocyte chemoattractant protein-1) and diminished infiltration of kidney interstitial by pro-inflammatory cells. GRP109a receptor is also expressed in podocytes and experimental studies revealed that SCFAs ameliorated glomerular damage and fibrosis [31]. To summarize, SCFAs exert beneficial effects since these compounds contribute to the resolution of the chronic inflammation and reduction of inflammatory-induced pathological damage of the kidneys. Therefore, there are rationales to assume that supplementation with probiotic/prebiotic /synbiotic preparations brings benefits, in line with the basic assumption that these preparations increase the intestinal SCFA production.

### *ADSORPTION OF UREMIC TOXINS*

Another possibility of breaking the pathophysiological "kidney-gut axis" is reduction of the blood level of gut-derived uremic toxins by using absorbents that can bind these toxins in the lumen of the gastrointestinal tract. As mentioned above, most gut-derived uremic toxins after entering blood are protein-bound compounds, making it difficult to eliminate them by renal replacement therapy. On the other hand, spontaneous elimination of these toxins with urine in CKD is also impaired due to reduction of GFR and loss of tubular secretion mechanisms. Hence the concept of reducing the amount of bacterial toxins absorbed into the blood by absorbing them into the lumen of the gastrointestinal tract and excreting them in the feces developed. In practice, such an absorption therapy is used in Asian countries (Japan, Korea, Taiwan). So far, the most used inert binding compound acting as an intestinal adsorbent compound is AST-120 (Kremezin®, Kureha Chemical Industry Co., Ltd., Tokyo, Japan). The drug is built from fine spherical particles (about 0.3 mm in diameter) composed of porous microcrystalline carbon and it is characterized by a large surface area and adsorbing capacity for various uremic toxins, mostly indoles [32, 33]. The administration of oral absorbents attenuates systemic accumulation of bacterial-derived uremic toxins and it contributes to the control of inflammation in CKD. Selected clinical trials (Evaluating Prevention of Progression in CKD; EPPIC) demonstrated that patients with moderate to severe CKD treated with AST-120 were demonstrated to delay the GFR further decline, but, on the other hand, AST-120 administration was unable to suppress the initiation of dialysis, transplantation and doubling of serum creatinine level. The meta-analysis of eight clinical studies confirmed that AST-120 is an effective agent in lowering of blood indoles level, but it is controversial in terms of slowing CKD progression and mortality [34]. Moreover, therapy with AST-120 is difficult for many patients to accept due to its very unpleasant texture and taste and since it is difficult to take the exact prescribed dose because of granule retention in the oral cavity. Thus, these limitations could reduce the patient's adherence during the treatment and, in turn, it could reduce drug efficacy. Recently, a new orally administered carbon adsorbent capsule was developed – DW-7202 (Renamezin®, Daewon Pharm; Seul, Korea). It is based on the furan resin as the raw material, unlike the phenol-based formula, made from petroleum pitch, used in AST-120. A recent clinical study showed that patients preferred DW-7202 over AST-120 and changes in GFR and serum creatinine, cystatin C and IS level were comparable for both oral adsorbents [35].

On a margin, the so-called "colonic dialysis" should also be mentioned. It seems that this method also enables the elimination of bacterial toxins, however, not by their adsorption in the lumen of the gastrointestinal tract, but by using the colon mucosa as a filtering membrane.

During colonic dialysis, osmotically balanced solution is injected into the colon (up to the descending colon) to flush out gut-derived toxins and persistent stool. In this procedure, colonic mucosa acts as a semipermeable membrane, separating the infused dialysate in the colon lumen and the colon mucosa capillary blood. The osmotic pressure gradient difference, through the principle of diffusion and permeation removes toxins and necessary supplement material. This technique is used in some medical centers in China and several case studies suggest that it may improve renal function in patients with CKD and even delay progression of the disease. However, the actual effectiveness and safety of colon dialysis remains unclear and therefore further research is required [36, 37].

### *FECAL MICROBIOTA TRANSPLANTATION*

The fecal microbiota transplantation; FMT (also known as microbial replacement therapy; MRT) is the process of transferring properly prepared gut microbiota from a healthy donor to the recipient harboring a gut dysbiosis. Similar to supplementation of the gut microbiota-modulating preparations, the procedure is aimed at restoration of gut eubiosis. FMT seems to be an even potentially superior alternative to probiotics since probiotics did not provide such broad diversity of administered microbes compared to FMT [38]. However, due to the concern regarding the real clinical efficacy and the still ongoing debate on the ethical issues and safety of FMT, the procedure in the common clinical practice has not expanded beyond the original, well-established indication in the treatment of recurrent *Clostridium difficile* infection [7,39]. FMT has also had variable success for inflammatory bowel disease treatment and is gradually studied as a novel treatment modality for some diseases characterized by an alternation in their gut microbiota, including CKD, functional gastrointestinal disorders (functional dyspepsia, irritable bowel syndrome), non-alcohol fatty liver disease, obesity or even neuropsychiatric illnesses [38]. The results of clinical trials evaluating the role of FMT in CKD are also promising. In one study, Barba et al. [40] showed that mice with the experimental CKD model, subjected to the FMT procedure after 4 weeks of kidney failure inducement, were characterized by a decreased p-cresyl sulfate accumulation in blood along with a noticeable improvement of gut microbiota disturbance. FMT may be performed via several routes, including oral, nasogastric, colon enema or during colonoscopy. The disadvantage of FMT is that the process is not standardized and heterogeneous at each stage. The response to the FMT depends on the immune system and genetic predisposition of the recipient as well as the donor and, thus, immune screening of both participants in FMT prior the procedure is critical since the success of FMT depends on the precise matching of the recipient and donor. The diversity of the gut microbiota of a healthy donor is also debated since every individual's microbiota is unique, so it is challenging to define a set of standard "healthy" microbiota. There is an obvious assumption that high diversity of gut microbiota is associated with a healthy gut, but donors have to be tested for potential transmissible pathogens [39]. Overall, FMT is regarded to be a safe

therapy. The typical, FMT-associated effects are mild and involve gastrointestinal ailments like abdominal discomfort, nausea/vomiting, flatulence or bloating. However, the data on long-term outcomes related to safety profile and changes in the microbiome is lacking, thus, further studies with long-term follow-up are still necessary [38]. These reservations cause that FMT for indications other than treatment of recurrent *Clostridium difficile* infection (including its application in CKD) should be performed only in experimental settings.

### *MISCELLANEOUS*

There are medicines used for specific indications, such as acarbose for diabetes or meclofenamate - a non-steroidal anti-inflammatory and analgesic drug used to relieve mild to moderate inflammation and pain. It was found that these drugs can also be effective in reducing the blood levels of gut derived-uremic toxins. Acarbose is an intestinal alpha-glucosidase inhibitor that increases the number of undigested carbohydrates reaching the colon. This drug reduces the colon pH value, thereby inhibiting bacterial metabolism of amino acids and their deamination. In experimental studies, meclofenamate was demonstrated to reduce the hepatic conjugation and synthesis of IS, which was associated with improved kidney function and reduced blood urea nitrogen and serum creatinine levels. Moreover, a meclofenamate-induced increase of tubular secretion of uremic toxins via OAT transporters in proximal tubules was observed. Another drug whose effect may be promising in terms of its use in alleviating the consequences of gut dysbiosis in CKD is lubiprostone. It is an activator of chloride ClC2 channel located on the apical membrane of intestinal epithelium. The increase of water secretion into intestinal lumen induced by lubiprostone enhances intestinal transit and may shorten the time of uremic toxins absorption into the portal circulation. It seems that further research, in addition to the existing, well-established use of the above-mentioned drugs, may provide additional indications for their use [33].

There are also some compounds of natural origin, such as resveratrol, antioxidant complex from Lingonberry (*Vaccinium vitis-idaea* L.) and omega-3 fatty acids with the attributed positive effect on the intestinal microbiota. In experimental studies, these compounds were revealed to modulate the composition of the gut microbiota and exert some activity in reduction of the synthesis of intestinal bacterial toxins. However, the exact mechanism of action of these compounds remains unknown and these studies are still in the phase of pre-clinical experimental trials [33].

## CONCLUSIONS

The gut dysbiosis is a significant disorder found in patients with chronic kidney disease and it is a part of the pathophysiological "kidney-gut axis". Gut dysbiosis causes intestinal metabolic disarrangements and contributes to overproduction in the gut lumen and accumulation in the blood of bacterial uremic toxins, accompanied by development and maintenance of chronic inflammation. These disturbances lead to the gradual kidney failure in CKD. Modulating the composition and metabolic activity of the disturbed gut microbiota is therefore a promising, therapeutic option aimed at reduction of the progression of CKD and such therapy may become an element of comprehensive treatment of this disease.

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REVIEW ARTICLE

# USE OF COMPUTER NAVIGATION IN TOTAL HIP ARTHROPLASTY (LITERATURE REVIEW)

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## ABSTRACT

**The aim:** Analyze the accuracy and ease of use of various computer navigations in total hip arthroplasty.

**Materials and methods:** Data from about 50 literature sources for the last two decades have been analysed.

**Conclusions:** Analyzing the accuracy and ease of use of various computer navigations in total hip arthroplasty, we offer two the most promising for further study and improvement systems: a semi-active navigation system and augmented reality system in total hip arthroplasty.

**KEY WORDS:** hip arthroplasty, computer navigation, computer assisted orthopedic surgery

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## INTRODUCTION

Modern traumatology and orthopaedics are significantly concerned with developing and introducing effective surgery methods for the patients with diseases and traumas of the hip joint. According to the WHO, by 2050 twenty-five percent of population will be diagnosed with the bone and joint disorders [1]. Many authors suppose that the best, and sometimes the only treatment choice on late disorder stage is hip arthroplasty [2]. This surgical intervention restores the joint function, improves life quality and, regarding the working-age population, aids in their ability to work [3]. The operation is made for almost all age groups, from teenagers to the elderly and senile patients [4]. Nowadays about 1.5mln operations of hip arthroplasty are carried out annually [5]. The number of hip replacement interventions is still increasing, as about 572000 operations a year are predicted in the USA in the nearest time[6].

A successful total hip arthroplasty (THA) depends on such factors as the correct implant choice, optimum access, appropriate rehabilitation and postoperative management, with the endoprosthesis components correct position [7].

Throughout the endoprosthetics development surgeons and engineers have paid great considerable attention to the endoprosthesis design, ways of attachments and the materials as well as the surgical access. The late trend is represented with developing various methods of the correct and most "anatomical" implants alignment [8]. Berend K.R. et al. think that the correct alignment of the cup during hip arthroplasty is the most important factor for the desired operation success [9]. Correct implant alignment is a difficult task both with the primary endoprosthetics (in simple and complicated cases) and the revision interventions.

The hardest is location of endoprosthesis components in bone tumour operations or interventions related to previous surgical errors, with significant bone defects or absence of bone reference points [10]. Incorrect implant position may in short-term perspective result in the endoprosthesis head dislocation, and in the long-term perspective it affects wearing out of the inlay and implant functional capacity. Correct cup alignment helps to avoid early aseptic instability and dislocation of endoprosthesis.

In 1978 G.E. Lewinnek wrote about the so-called "safe zone", aligning the acetabular component within the region, the dislocation risk is minimised: 40 ± 10 °, inclination, 15 ± 10 ° anteversion [11].

Various authors suggested different cup position with the THA, particularly: vertical inclination angle 35 °-45 °[12]; 45 ° ± 5 °; 20° -30° in males and 45° in females [13]; 25 °-45 °[14]; 25°-50° [15]. The anteversion angle was suggested equal to 0 -10 °[13]; 15 ° ± 5 ° [16]; 10 ° -20 ° [17]. Some authors state that the so-called combined anteversion is a more important parameter than only anteversion of the endoprosthesis acetabular component [18].

The acetabular component is affected by the pelvic tilt, i.e., an angle between the anterior pelvic plane and frontal of the patient [16,19], depending on the patient's posture. The safe zone (Lewinnek) doesn't consider sagittal pelvic mobility. So, the authors use a new term "functional acetabular component alignment" [20]. The functional alignment of the acetabular component is represented with its alignment regarding the sacral-pelvic balance. According to Lembeck and authors, pelvic tilt of 1 ° will lead to functional cup anteversion by 0.7° [21]. The studies of Dorr et al. have

**Table I.** Computer navigation

| | CASPAR® | ROBODOC® | Acrobot® | MAKOplasty® | Intellijoint HIP® | VR-HIP | Hip Sextant ™ |
|---|---|---|---|---|---|---|---|
| Navigation system type | CT-based navigation | CT-based navigation | CT-based navigation | CT-based navigation | Navigation without images | CT-based navigation | Mechanical navigation system, |
| Navigation kind | Active robot-engineered system | Active robot-engineered system | Semi-active robot-engineered system | Semi-active robot-engineered system | Passive | Passive | Passive |

shown that each new increase of the anterior pelvic tilt by 1 ° will cause decrease in the acetabulum anteversion by 0.7 °– 0.8° [15]. The authors, having studied pelvic motion, concluded that the pelvic tilt should be regarded during the acetabular component implantation, with no permanency of anteversion angle. The anteversion and inclination angle, measured on the post-operative roentgenograms, depend on the position of the patient: recumbent and upright [22]. Here it becomes obvious that after the hip bone alignment, the pelvic tilt changes are comparable to its initial ones [23].

All this proves relevance of studying the computer navigation for alignment and precise implant alignment during the THA by confirming its position basing on intra-operational and quantitative assessment in real time. The computer-assisted orthopaedic surgery is a direction of orthopaedic surgery, used for correct positioning of surgical instruments during the operative intervention.

## THE AIM

Analyze the accuracy and ease of use of various computer navigations in total hip arthroplasty.

## MATERIALS AND METHODS

Analysis of 49 literature sources contains information about the main errors in the identification of components of the endoprosthesis, which may be related to the human factor, pelvic tilt and other reasons, and proves relevance of using computer navigation in different countries. The literature review contains the analysis of original articles and sources in four main scientometric databases: PubMed, Scopus, Web of Science.

## REVIEW

The CAOS(Computer Assisted Orthopedic Surgery) systems are divided into passive, active, and semi-active systems, according to the used surgical facilities and way of their functioning (Table I.). Passive systems, such as navigation, help operator in pre-operative planning as well as in informing about implant position during the operation, without his active participation in surgery. Active systems include surgical robots, which autonomously perform different surgery stages, scheduled by the operator. Semi-active systems use the implant computer alignment, which was planned before the operation. Navigation system, based on augmented reality, is also widely used.

The following navigation systems are used in orthopaedics: navigation without images, CT-based navigation, X-ray-based navigation. The image-based systems usually use pre-operation tomography in order to increase intra-operation registration. The other authors also describe methods of visualization, including fluoroscopy and ultrasonography [24].

### PASSIVE CAOS SYSTEMS

With these systems used, pins are inserted into the pelvis and hip bone, where the marker spheres are attached. Information from the marker spheres on three-dimensional bone parameters is transmitted to the personal computer using infrared rays[39]. The screen shows a virtual model of the pelvic bones, hip bone, instruments and the information required for aligning the implants. To define position of the pelvic and hip bones one should attach a special indicator to appropriate protruding bone points.

In order to provide for the correct endoprosthesis alignment, the surgeon should use various anatomical reference points, transverse ligament of hip socket, posterior edge of the hip socket, etc. [26]. The use of transverse ligament helps to define cup position in dysplastic coxarthrosis [27]. Here it is of extreme importance to detect variability of the ligament position according to the gender [28]. Another reference point may be represented with the posterior edge of the hip bone socket, if no expressed bone spurs are observed around it. Some authors suggest using inguinal fold as a reference point to align the cup. During operation the guide for aligning the acetabulum is directed perpendicular to the inguinal fold, which provides for correct inclination setting. The above-mentioned methods are often used for the hip arthroplasty, but they help to define just certain parameters, required to implant alignment, e.g., cup position [29].

### ACTIVE CAOS SYSTEMS

The robot-technical CAOS is gaining popularity in the world. First medical research of the hip arthroplasty dates back to the 90ies of previous century. Later, the robots Robodoc and CASPAR® (Orto Maquet, Rastatt, Germany), were created, as well as their modifications, which are being

constantly improved and modernised. The most widely used robot-engineered systems for hip arthroplasty are the haptic systems, where surgeons physically direct a robot-engineered hand through the control desk.

## SEMI-ACTIVE CAOS SYSTEMS

In the semi-active system a robot-engineered hand follows the operator hand, holding surgical instruments, it doesn't move outside the milling trajectory. The systems Acrobot® (Acrobot Company Ltd., London, theUK),system MAKOplasty® (Stryker, Orlando, Florida, the USA), Intellijoint HIP® (Intellijoint Surgical, Inc., Kitchener, Ontario, Canada) and others are represented in the market. Using Acrobot® system, operator directs the system manually by the burr on the robotic lever tip within the milling path, defined according to pre-operational 3D-based planning

## THE AUGMENTED REALITY FACILITIES

Another modern technology deals with the augmented technology facilities used during aligning hip arthroplasty components. The Augmented reality (AR) — is projecting any digital information ( image, video, text, graphic image, etc.) over the screen of any facilities. As a result, reality is augmented with artificial elements and new information. The method may be realized using applications to smartphones and tablets, augmented reality glasses, stationary screens, projection facilities and other technologies. There are several other definitions of the augmented reality. In particular, Ronald Azuma in 1997 defined it as a system which: 1) combines virtual and realissues; 2) interacts in real time;3) works with 3D [30].

When using active or semi-active CAOS system, the main interface for the feedback information reflection is within the working field. This means that the surgeon must distribute his attention between the operation field and the screen. The augmented reality technology helps the surgeon to concentrate on the patient, directly providing the viewable feedback information. The surgeon can assess the information feedback, relying on the visual assistance, necessary for precise course of operation. The first steps in this technology use belong to Rodriguez F. (2018) [31] The AR technology can improve accuracy while restoring natural anatomy as well as provide for the better quality control after the final component implantation. Soon the technology would join all the information necessary for a surgeon, the information may be used at all operative stages – from directing the operative access till the implant final position.

# DISCUSSION

In patients with well-expressed subcutaneous adipose tissue, registering such points may be complicated and variable, which leads to decrease in accuracy of the passive navigation system [32]. Faulty detection of any bone point by 1 cm leads to faulty detection by the navigation system of anteversion by 6 ° and inclination - by 2.5 ° [33]. Ultrasound indicators are then used to enhance the accuracy of optical navigation systems [34]. This enhances the implant alignment accuracy, but significantly prolongs surgical intervention ( due to the time spent for attaching the pins and ultrasound study of bone reference points) [35]. As information between the passive navigation system components (marker spheres on the patient, the PC) is transmitted via infrared rays, practice reveals that the surgeons have often been the obstruction, so they often should come far from the operation table in order to provide for correct navigation system functioning, which has rather complicated its use. Contact of the marker spheres with blood or other liquids destroys the navigation system function [36].

The accuracy of implants alignment using active navigation systems makes up about 1 degree or 1 mm [37]. The initial robot-engineered results show improved alignment of acetabular components and decreased occurrence of endoprosthesis head dislocation in early postoperative period. A retrospective study of 2017 which analyzed 300 cases of hip arthroplasty, including 100 robot-engineered procedures, showed 0% dislocation speed in robot-engineered group and 3.0-5.0 % dislocation in ordinary group [38]. As the robot-engineered hip arthroplasty is a relatively new operative intervention method, there are few studies of long-term functional results. The study of 2018, which compared the effectiveness of robot-engineered computer navigation system to ordinary hip arthroplasty with average study period of 14 years has shown insignificant improvement in the robot-engineered group [39].A prospective cohort study of 2019 reports improved accuracy of the robot-engineered system in safe Lewinnek zones compared to the ordinary hip arthroplasty group (96 % against 68 % respectively; $p = 0.02$). Besides, the study revealed that the use of robot-engineered navigation system was associated with improved restoration of the hip joint center ($p < .001$) and combined displacement ($p < .001$)[40]. Evidences prove that the use of robot-engineered computer navigation system may lead to the decrease in speed of early acetabulum component dislocation.

Robotic systems, as well as optical navigation systems, have numerous disadvantages. Their use enhances the implant alignment accuracy, but prolongs the operation duration [41]. Medical robots are huge, which causes certain technical difficulties related to their positioning in the operation room ( they obstruct mobility in operating room) [42]. One should mention their high cost, which is another obstacle for their wide use in medical institutions where hip arthroplasty procedure is carried out [43]. The use of the system requires computed tomography examination, which provides for considerable patient exposure to radiation.

In the corpse study Nawabi D.H. et al. [44] have stated that the use of semi-active system MAKOplasty® has shown more accurate cup alignment than manual implantation. Domb B.G. et al. [45] claim that the use of MAKOplasty®

system was associated with improved cup alignment in safe Lewinnek zone in 100% cases, compared to 80% in the group where the "free hand" method was used. The advantage of MAKOplasty® system is confirmed by more precise endoprosthesis acetabular component alignment. The disadvantages, mentioned by the authors, are continuous ray exposure of the patient during the CT scanning and high cost of the facilities.

According to literature data, surgeons master the semi-active robot-engineered system faster and easier that the active robot-engineered system. Though, confirmation of compatibility, safety and effectiveness of the method requires for more factual material [46].

The effectiveness of the augmented reality facilities has been assessed in several scientific papers. So, for surgical hip arthroplasty Fotouhi et al. [47] used joined data of real time computer navigation to provide for the cup alignment accuracy, thus reaching low level of error, respectively 1.9 mm, and 0.53 °. Liu H et al. [48] used the data obtained by robot-engineered equipment for drilling the hip guide holes. They compared position and orientation of the drilled holes to pre-operative plan, and the mean inaccuracies were about 2 mm and 2 °. The studies of Hiranaka T. et al. [48] showed that the use of augmented reality facilities during hip arthroplasty provides for increased accuracy as well as prolonged patient radiation exposure and operative intervention duration. Previous results show that the augmented reality may help the surgeon to improve the effectiveness and safety of hip arthroplasty, particularly regarding implants correct alignment [49].

## CONCLUSIONS

The views of specialists on optimum position of the hip joint endoprosthesis acetabular component have diverged recently. The most optimum position of the acetabular component is the 45° abduction and 10 -15°anteversion. With posterior access, anteversion should be increased to 20-25 °.

The literature review has shown that computer navigation provide for more accurate cup alignment compared to the traditional method. The surgeons master semi-active robot-engineered system faster and easier than the active robot-engineered one. The authors have confirmed decreased incidence of dislocations and aseptic instability of endoprosthesis components associated with computer navigation used for the hip joint arthroplasty.

Analyzing the use of various computer navigations in total hip arthroplasty, we consider active systems to be the most accurate ones, and semi-active and augmented reality systems for their ease of use.

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REVIEW ARTICLE

# HEATED TOBACCO PRODUCTS: WE STILL NEED TO KNOW A BIT MORE

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## ABSTRACT

**The aim:** This research aims to analyze the challenges we came across due to the rapid spread among the population (including young people) of tobacco heating devices.
**Materials and methods:** Analysis of 20 literature sources containing information about tobacco heating systems was performed. The search for literary sources was carried out in two main scientific databases: Scopus and PubMed. The review included original articles, research, and official recommendations from medical associations.
**Conclusions:** Tobacco heaters reduce harmful substances in the inhaled air compared to conventional tobacco cigarettes, but these new devices provide effective nicotine absorption, which prolongs a person's nicotine dependence and prevents smoking cessation. The main problem we face due to the rapid spreading of these devices - potentially tobacco heating systems can pose health risks and further research on such risks, especially long - term, are needed. Tobacco heating devices, regardless of their manufacturer and design, should be subject to restrictions similar to traditional cigarettes.

**KEY WORDS:** Heated tobacco products, health risks, electronic nicotine delivery systems

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## INTODUCTION

All forms of tobacco consumption, including smoking cigarettes, cigars, pipes, chewing or sniffing tobacco, as well as the impact of its combustion products on non-smokers (passive or forced smoking), significantly increase morbidity and premature mortality caused by more than twenty different diseases.

Most studies have shown that the risk of disease depends on both the number of cigarettes burned and the duration of smoking. World Health Organization (WHO) experts estimate that 4 million people worldwide die from smoking-related diseases each year. If the smoking situation does not change, in 2025 the annual loss will be 10 million people. In Ukraine, smoking is the indirect cause of one in five deaths of people over the age of 35.

Under the Framework Convention on Tobacco Control (FCTC), the WHO has launched a comprehensive tobacco control strategy [1]. The WHO Framework Convention on Tobacco Control (WHO FCTC) is the first treaty negotiated under the auspices of the World Health Organization. The WHO FCTC is an evidence-based treaty that reaffirms the right of all people to the highest standard of health. The WHO FCTC represents a paradigm shift in developing a regulatory strategy to address addictive substances; in contrast to previous drug control treaties, the WHO FCTC asserts the importance of demand reduction strategies as well as supply issues. Articles 9 and 10 of the FCTC include specific policies to curb tobacco use by regulating ingredients and emissions of tobacco products. The overall goal is to reduce toxicity, dependence and consumer attractiveness. The parties to this convention have committed themselves to limiting the supply and demand of tobacco products through a wide range of policies and measures. Although the FCTC has been successfully applied to traditional tobacco products, questions remain about how to cover new products.

## THE AIM

This research aims to analyze the challenges we came across due to the rapid spread among the population (including young people) of tobacco heating devices.

## MATERIALS AND METHODS

Analysis of 20 literature sources containing information about tobacco heating systems was performed. The search for literary sources was carried out in two main scientific databases: Scopus and PubMed. The review included original articles, research, and official recommendations from medical associations.

## REVIEW AND DISCUSSION

To help countries implement the FCTC, WHO has introduced the MPOWER technical package [2]. MPOWER

are a set of six cost-effective and high impact measures that help countries reduce demand for tobacco. These measures include:

- Monitoring tobacco use and prevention policies.
- Protecting people from tobacco smoke.
- Offering help to quit tobacco use.
- Warning about the dangers of tobacco.
- Enforcing bans on tobacco advertising, promotion and sponsorship.
- Raising taxes on tobacco.

Some 5.3 billion people are now covered by at least one of these measures - more than four times the 1 billion who were covered in 2007 [3]. Some 5.3 billion people are now covered by at least one of these measures - more than four times the 1 billion who were covered in 2007.

More than half of all countries and half the world's population are now covered by at least two MPOWER measures at the highest level of achievement. This reflects an increase of 14 countries and almost one billion more people since the last report in 2019.

More than half of the world's population are exposed to tobacco products with graphic health warnings. However, progress has not been even across all MPOWER measures. Some measures like raising tobacco taxes have been slow to move and 49 countries remain without any MPOWER measures adopted.

However, new nicotine, nicotine - free and tobacco products operated by electronic systems have also been sold aggressively in many countries around the world. These include:

1) *Electronic nicotine delivery systems* (ENDS) and electronic non-nicotine delivery systems (ENNDS), commonly referred to as electronic cigarettes, are devices that heat a liquid to create an aerosol that is inhaled by the user. Aerosols for e-cigarettes typically contain nicotine and toxic substances that are harmful to both users and non-consumers exposed to passive aerosols [4 - 7]. People who use these products in combination with smoking of regular cigarettes, which is the most common form of e-cigarette use, are exposed to toxic chemicals from two or more products [8].

A few years ago, we investigated ENDS and, as a conclusion, noted that they has proven to be effective in removing of tobacco-related complaints, but so far, the ENDS cannot be available as safe and effective method to completely abandon smoking [9]. Existing production regulations do not standardize either the ENDS itself or the liquid for them, because of which the composition (including the content of harmful to health substances) is not actually regulated. In addition, there are no data about the long-term effects of ENDS usage, which is a priority area for further research.

In recent years, there is growing evidence that the use of ENDS is associated with lung injury, with some evidence of acute lung injury, lipoid pneumonia, eosinophilic pneumonia, liquid pneumonia and obliterative bronchiolitis [10]. In addition, additional data suggest that ENDS may have an impact on other aspects of lung health [11]. E-cigarettes can also pose a serious threat to lung health, especially in unregulated conditions. For example, in the second half of 2019, the United States investigated an outbreak of lung injuries related to the use of e-cigarettes or vaporizing products, which has claimed about 70 lives to date. These injuries, known as EVALI (lung injuries associated with the use of e-cigarettes or vaporized products), have since been reported to have a strong link, and research is underway into whether there are other chemicals of concern that could have contributed to these injuries [12].

Lung damage associated with an e-cigarette or evaporation product is determined by the presence of pulmonary infiltrates in the imaging; use of electronic nicotine delivery systems during the previous 90 days; and the absence of other possible causes, such as infection, heart, tumor or rheumatic causes. A significant proportion of patients hospitalized for lung injury associated with e-cigarettes or vapor products required hospitalization in the intensive care unit, and up to a third of patients required mechanical ventilation.

2) *Heated tobacco products* (HTP) are tobacco products that produce aerosols containing nicotine and toxic chemicals when heating tobacco or activating a device containing tobacco. These aerosols are inhaled by users during the process of sucking or smoking with the device. They contain the highly addictive nicotine, as well as tobacco-free additives and often have a flavoring. Tobacco can be in the form of specially designed cigarettes (for example, "thermopiles" and "neo sticks"), pods or corks.

In October 2018, the Conference of the Parties (COP) 8 directly proposed to extend the scope of relevant legislation to HTP. Previous WHO minimization strategies focused exclusively on traditional cigarettes, not on new technical advances, often referred to as modified or reduced exposure / risk. From a toxicology perspective, on the one hand, it makes sense to combine minimization approaches with new technologies. On the other hand, there are concerns that tobacco heaters may create the deceptive impression of almost harmless tobacco consumption and, in addition to residual pollutant emissions, will also have a high potential for addiction.

In Ukraine, the first model came on the market in 2016, which in the literature is called the THS 2.2 (tobacco heating system 2.2). The manufacturer has conducted large-scale studies to reduce harmful and potentially harmful substances in emissions. Subsequent studies have shown that lower exposure also reduces health risks if you completely switch from a regular tobacco cigarette to a tobacco heater. The company then applied to the Food and Drug Administration for the use of modified-risk tobacco products for the sale of its own tobacco heating device with risk reduction claims in 2016, but it was rejected. In 2020, U.S. Food and Drug Administration authorized the marketing of THS 2.2 [13]. This marks the first tobacco products to receive "exposure modification" orders, which permits the marketing of a product as containing a reduced level of or presenting a reduced exposure to a substance or as being free of a substance when the issuance of the order is

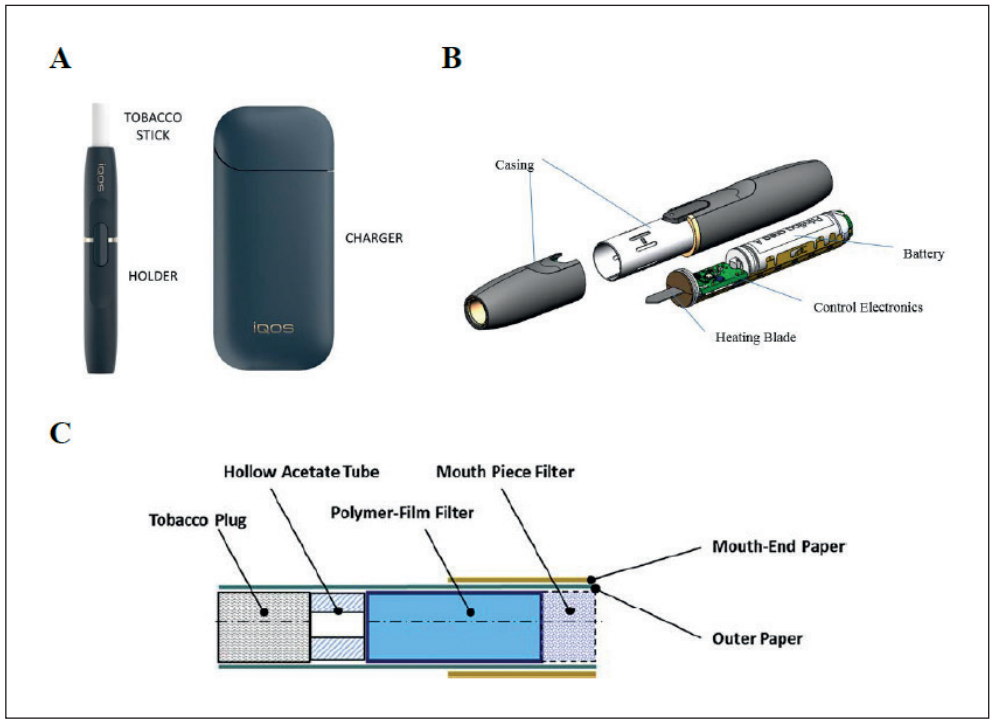


**Fig. 1.** THS 2.2 components (A), a schematic exploded view drawing of the Holder (B), and a schematic cross-sectional view of the Tobacco Stick (C) (adopted from fda.gov)

expected to benefit the health of the population. Importantly, the authorization for these products requires the company to conduct postmarket surveillance and studies to determine whether the MRTP orders continues to be appropriate, including assessing the potential for increased use among youth. However, this device is now sold in more than fifty countries.

The tobacco heater, available in Ukraine, consists of 3 components with different functions (Fig. 1). This includes a tobacco stick with treated tobacco, a heater (holder) similar to a handle into which a tobacco stick is inserted, which is then heated by an electric heating rod, and a charger (charger) that recharges the heater after use. The tobacco heater automatically stops the heating process after 6 minutes or 14 puffs, so that the products of pyrolysis and the release of contaminants are limited both in time and in the maximum number of puffs per stick. The tobacco stick contains a compressed tobacco stick and several filter elements. The tobacco stick consists of a dried tobacco suspension, which becomes thin for paper with brown tobacco foil. This is about 70% tobacco, as well as humidifiers, binders and flavors. Water and glycerin are used as humectants to prevent drying and support the formation of aerosols when heated. The filter elements consist of 2 independent systems: a polymer film filter that cools the aerosol, and then a mouthpiece filter made of soft cellulose acetate, which mimics the sensory aspects of a regular cigarette.

Conventional tobacco cigarettes are very well researched and standardized products. Cigarette smoke is an aerosol consisting of approximately 4,800 compounds, 89 of which were classified as hazardous to health [14]. With each puff in the glow zone, a temperature of about 900 °C is reached, which causes the tobacco to burn. In the absence of oxygen in the adjacent tobacco rod, endothermic reactions occur, which thermally decompose organic and inorganic material. The gaseous reaction products reach the distillation zone, where the temperature drops to 600–200 °C, depending on the distance from the glow zone. Most of the substances harmful to health are produced here. The aerosol is formed by evaporation of volatile components and distillation. Low-boiling substances enter directly into the smoke. Behind the distillation zone is the condensation zone, where part of the smoke condenses again. Therefore, the inhaled main smoke consists of solid particles and a gaseous phase.

The nicotine value of a tobacco heater is comparable to that of regular cigarettes. The value of the total mass of the particles is sometimes higher. However, the total particle weight of the tobacco heater has a different composition, as the proportion of water and humidifiers is much higher. If we compare the content of carbonyl compounds of formaldehyde, acetaldehyde, acrolein and crotonaldehyde, the emissions of tobacco heater are 80-96% compared to conventional tobacco cigarettes. The content of volatile and semi-volatile compounds in emissions is 97–99% lower in a tobacco heater compared to conventional cigarettes.

Thus, C. Haziza et al. showed that a few days after switching to a tobacco heater, a significant decrease in 16 biomarkers associated with smoking was observed in the blood or urine [15]. Measurement of biomarkers for 1,3-butadiene (monohydroxybutenylmercapturic acid, MHBMA), acrolein (3-hydroxypropylmercaptonic acid, 3-HPMA), benzene (S.-phenylmercapturic acid, S -PMA) and acrylonitrile, respectively, 92 %, 59 %, 94 % and 87 % according to a study conducted in Poland. Compared to the reduced emissions, the impact on the relevant biomarkers was less clear. The other two studies were three-month and

were conducted in Japan and the United States [16, 17]. They also began with a 5-day inpatient phase, followed by 90 days of outpatient care. However, quantitative information on the compliance of study participants is missing in outpatient studies. In a study conducted in Japan, compliance is described as "particularly high." A study in the United States reported a "good" fit for the tobacco heating group, but a "poor" fit for the tobacco withdrawal group, which increased variability and thus made it impossible to interpret the results. In addition, former employees of the manufacturer pointed to violations in the conduct of clinical trials. This emphasizes the need for independent evaluation of the source data.

The study by Schlage et al. (2018) showed that heated tobacco products can reduce the risk of lung cancer [18]. Prolonged exposure to total solids from IQOS had less biological effect on human bronchial epithelial cell line compared to total solids from cigarette smoke. The aerosol ejected from IQOS has been shown to damage human bronchial epithelial cells; however, the cytotoxicity of IQOS was lower than that of flammable cigarettes, but showed higher toxicity than the e-cigarette, which was consistent with data from the tobacco industry. Evidence suggests that the use of IQOS products may increase the risk of respiratory disorders, and this risk is likely to be greater than the risk associated with e-cigarettes [19].

In a study by Walczak et al. (2020) investigated the morphology and dynamics of the mitochondrial network in human bronchial epithelial cells (BEAS-2B) exposed to total solids (TPMs) formed by an aerosol from a tobacco heating system (THS 2.2) [20]. Comparison of the effects of TPM with 3R4F and THS 2.2 showed that a similar range of changes in mitochondrial dynamics and biogenesis was observed at 7.5 μg / ml 3R4F TPM and 150 μg / ml THS 2.2 TPM. The seven-day exposure to the test components of cigarette smoke causes mitochondrial stress, while the 12-week exposure showed signs of cellular adaptation to the stressor.

Quitting smoking significantly reduces the risk of developing serious chronic diseases. Tobacco sponsors now suggest and support that nicotine addicts should switch from regular smoking to alternative products that will at least reduce the overall harm from smoking, although there are not enough longitudinal studies to support this idea. However, there are less invasive and highly effective treatments (drugs or behavioral interventions). On the other hand, heated tobacco products are another alternative that has appeared on the market alongside e-cigarettes.

## CONCLUSIONS

Tobacco heaters reduce harmful substances in the inhaled air compared to conventional tobacco cigarettes, but these new devices provide effective nicotine absorption, which prolongs a person's nicotine dependence and prevents smoking cessation. The main problem we face due to the rapid spreading of these devices - potentially tobacco heating systems can pose health risks and further research on such risks, especially long - term, are needed. Tobacco heating devices, regardless of their manufacturer and design, should be subject to restrictions similar to traditional cigarettes.

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REVIEW ARTICLE

# GENETIC INFLUENCES ON PAIN MECHANISMS

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## ABSTRACT

**The aim:** To review the available results for genetic influences on pain syndrome development.

**Materials and methods:** In the period from 2009 to 2020, a total of 45 research papers describing the key points of genetic influences on pain mechanisms in both adults and children were published in Ukrainian and English and they are now included in the PubMed, EMBASE, Cochrane, and Google Scholar research databases.

**Conclusions:** Pain is a comprehensive characteristic of a person; therefore, it is inevitable that several genes with little individual effect interact with each other and environmental factors, influencing pain susceptibility and chronic pain syndrome manifestation. This requires searching for biomarkers for diagnosing and predicting the development of acute and chronic pain syndromes, especially in pediatric practice.

**KEY WORDS:** pain, pain genes, chronic pain

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## INTRODUCTION

Pain is the main motivating factor forcing people to seek medical care and pain responses are characterized by significant interindividual differences. Over the past decade, there has been a significant breakthrough in the study of genetic aspects of nociception and pain management. Although genetic factors play an important role in the interindividual variability in nociception, there are other factors that influence the pain experience itself: mood, behavior, expectations, prior pain experience, gender, psychosocial and environmental factors. Understanding the role of the genetics is the first and most important step to explaining the discrepancy between pain threshold, pain tolerance and susceptibility to chronic pain.

Nociception, the process of perception of intense thermal, mechanical, or chemical stimuli by a subpopulation of peripheral nerve endings – nociceptor, is the ability of organism to detect damaged tissues. Nociception involves the four processes of transduction, transmission, modulation, and perception [1]. Nociceptive pain is generated by pin prick, touching hot objects, or exposure to any other chemical, thermal, or mechanical stimuli. Lack of the ability to experience nociceptive pain is catastrophic: damaged tips of fingers and toes, lips and tongues, reduced life expectancy, as witnessed in individuals with congenital insensitivity to pain due to rare recessive gene mutations resulting in either loss of the nociceptors or their functional disruption [2].

There are several levels of blocking the nociceptive signal: at the site of generation (transduction) with topical agents, local anesthetics, anti-inflammatory drugs, or by eliminating pain generator (amputation or organ removal, e.g., cholecystectomy); at the level of the paraaortic ganglia (the abdominal ganglion) with local anesthetics; at the site along the pathway of nociceptive pain transmission with regional anesthesia, nerve ablation (radiofrequency ablation), neuromodulation (invasive or non-invasive peripheral nerve stimulation); at the level of the spinal cord (transmission or modulation) with the subarachnoid block and intrathecal drug delivery systems, neuromodulation; at the level of the central nervous system with opioids, general anesthetics.

Nociception involves the following components: the nociceptors, mediators of inflammation; the nociceptive, antinociceptive and pain-modulating neuronal pathways and neurotransmitters; the neuronal ion channels; the neurotransmitter receptors and other messenger systems. They help in transmitting, conducting, and modulating noxious stimuli. Pain is a subjective emotional experience that results from a complex processing of noxious stimulus in the pain matrix. Functional genomics of pain is the study of genetic basis of pain, including the genetics of nociception, hereditary pain conditions (erythromelalgia, congenital insensitivity to pain), chronic pain conditions, genetic background of psychological factors that determine pain experience.

## THE AIM

A large number of recent studies on pain require clear structuring. Genetic factors are important components that influence the occurrence and intensity of pain; therefore, the aim and objectives were to review the available results for the influence of genetic factors on the formation of pain processes.

## MATERIALS AND METHODS

In the period from 2009 to 2020, a total of 45 research papers describing the key points of genetic influences on pain mechanisms in both adults and children were published in Ukrainian and English and they are now included in the PubMed, EMBASE, Cochrane, and Google Scholar research databases. Evidence review Following an extensive search of electronic databases, we included observational research, a systematic review and meta-analysis, randomized controlled trials, a prevalence study using a nationwide database, analysis of a family-based cohort and twin study covering genetic influences on the formation and perception of pain of varying intensity in patients with identical pathology or disease severity.

A pain gene has been described as 'a gene for which there are one or more polymorphisms that affect the expression or functioning of its protein product in a way that affects pain response.' Although some genetic studies have focused on pain in specific body sites and suggested possible genetic variants associated with pain phenotypes, the overall understanding of pain genetics remains unclear [3].

Current limitations in our knowledge include: the extent to which pain as a phenotype is determined by the additive genetic components, mainly presented by single nucleotide polymorphisms – SNPs); whether the genetic mechanisms of pain are different or similar in various body sites or in different disorders; whether the genetic relations between pain phenotypes and other common comorbidities are different or similar. Many pain phenotypes have been shown to be associated with depression and neuroticism in epidemiological studies. Understanding the genetic correlations between pain, depression and neuroticism may help elucidate the degree of their shared genetic architecture and become the basis for future causal inferences [4].

Catecholamines such as adrenaline, norepinephrine, and dopamine play a key role in the transmission and modulation of pain. Catechol-O-methyltransferase (COMT) is an enzyme that is involved in the breakdown of catecholamines and is a key regulator of pain perception, cognitive functions, and emotional state. Low COMT activity results in elevated catecholamine levels and, therefore, increased pain sensitivity [5, 6]. High dopamine levels result in the depletion of enkephalins, thereby leading to upregulation of opioid receptors and increased pain sensitivity. Three common haplotypes of the human COMT gene, which are divergent in two synonymous and one nonsynonymous position, code for differences in COMT enzymatic activity and are associated with pain sensitivity. They include the low pain sensitivity (LPS) haplotype, the average pain sensitivity (APS) haplotype, and the high pain sensitivity (HPS) haplotype which have been described based on four common single-nucleotide polymorphism genes encoding COMT [7]. COMT polymorphism has been found to affect RNA stability and protein translation [8]. The LPS phenotype demonstrated the greatest COMT activity, while the HPS phenotype exhibited the lowest. Even a single LPS haplotype has been found to decrease the risk of postoperative pain; it also affects the consumption of opioids [9]. In a study of postoperative pain and opioid consumption in children who underwent adenotonsillectomy, the carriers of the minor alleles were found to require more analgesic intervention as compared to heterozygous carriers of the major alleles [10, 11].

Rare conditions associated with pain have been identified by genetic mapping of family-based diseases caused by mutations in a single gene (the Mendelian gene.). Recognized hereditary syndromes associated with reduced pain sensitivity include channelopathy-associated congenital insensitivity to pain; loss-of-function mutations accompanied by the inability of the affected individual to feel pain [12]; hereditary sensory and autonomic neuropathy (HSAN) type I-V which is associated with a number of genetic anomalies and results in various patterns of sensory and autonomic dysfunctions, peripheral neuropathy [13]. These syndromes involve the loss of pain sensitivity or reduced pain sensitivity followed by other autonomic disorders and sensory deficit. Type IV is known as congenital insensitivity to pain with anhidrosis. Recognized hereditary conditions associated with pain intensification [14] include erythromelalgia and paroxysmal extreme pain disorder, familial hemiplegic migraine, hereditary neuralgic amyotrophy, hereditary pancreatitis. In addition to these rare Mendelian disorders, pain sensitivity is considered to change in approximately 50% of the general population due to genetic differences. A lot of genetic variants are associated with pain sensitivity [15].

The most common genes of pain are μ-opioid receptor (OPRM1), COMT, guanosine triphosphate cyclohydrolase-1 (GTPCH-1), transient receptor potential vanilloid type 1 (TRPV1), melanocortin-1 receptor (MC1R). Other genetic variants associated with changes in acute pain sensitivity include ADRB2, HTR2A, IL1RN, KCNJ6, MAOA, MAOB [16], P2RX7 [17]. Wide variability in gene expression and genetic polymorphism can explain some individual variations of acute pain and the efficacy of analgesia in this group of patients [18].

Effective perioperative pain control in children is often challenging; up to 50% of pediatric patients receive inadequate pain management and experience serious opioid side effects [19]. The choice of anesthesia administered to surgical patients includes regional anesthetic techniques and systemic analgesia, their combinations; it depends on the intensity of pain, the route of drug administration and planning the patient's rehabilitation period. Moreover, combinations of anesthetic agents may have various effects in different categories of patients (cancer patients, gynecological patients, trauma patients, neurosurgical patients, etc.) The algorithms for assessing pain and choosing the type of anesthesia administered to surgical patients, including pediatric patients, are not standardized as well.

Postoperative pain in children is still a serious problem as it often cannot be managed for a number of reasons. Prolonged postoperative pain leads to prolonging hospital stay, increasing treatment costs, extending the rehabilitation period. The intensity of acute postoperative pain, especially within the first 6 hours after surgery, is an important predictor of chronic

pain. *Severe acute pain occurring within the first postoperative month may develop into chronic pain [20].* Among patients with chronic pain, 22.5% of individuals note the association of pain with the surgical site. There is less evidence of postoperative chronic pain in children; however, a year after surgery, an estimated 20% of children experience pain in the spine and joints that is most likely due to an inadequate analgesia. A significant proportion of patients with postoperative chronic pain develop sensory anomalies that indicates a neuropathic component of pain development [21].

The best perioperative anesthesia is regional analgesia as it allows for quality pain management with minimal side effects. Local anesthetics act by blocking sodium channels and the mutations in the gene SCN9A encoding sodium channels demonstrate the resistance to lidocaine. Genetic variability is associated with the risk of local anesthetic toxicity as well. A κ-agonist such as buprenorphine can be substituted for a μ-agonist such as morphine in patients with an inactive OPRMI allele. This gene encodes one of at least three opioid receptors in humans; μ-opioid receptor (MOR). The MOR is the main target of endogenous opioid peptides and opioid analgesics such as beta-endorphin and enkephalins. The MOR plays an important role in addiction to other opioid drugs such as nicotine, cocaine, and alcohol through the modulation of the dopamine system. Several transcript variants encoding different isoforms have been found for this gene [22].

Abdominal wall surgeries account for 88% of all pediatric surgeries. To provide analgesia and protect from surgical aggression, due to psychological characteristics of children, general anesthesia is used; however, the main reason for using this type of anesthesia is that pediatric anesthesiologists have insufficient knowledge of the technique and methods of regional anesthesia due to the prevalence of the myth about excessive invasiveness of regional analgesia [23]. Analgesic efficacy of different types of regional anesthetic blocks has not been studied sufficiently. Peripheral nerve blocks can have advantages over central nerve blocks due to their safety and analgesia duration [24]. As the perioperative period may involve long-term and persistent opioid use, the application of regional anesthesia, as a part of multimodal pain management regimen results in reducing opioid use after surgery, thereby providing adequate postoperative analgesia as compared to opioids [25, 26]. According to the recently published data, peripheral nerve blocks were used only in 25.5% out of 12 million surgeries; regional anesthesia techniques were used in 3.3% of these cases only [27]. For success of regional anesthesia, it should be indicated correctly, block the target nerve, and use the appropriate technique and equipment [28]. In addition, regional anesthesia is, or should be, an integral part of any Enhanced Recovery After Surgery (ERAS) program, while opioids should be avoided, if possible, due to their unfavorable side effects [29].

## REVIEW AND DISCUSSION

There are a wide range of responses to the administration of agents for postoperative pain management, depending on the patient's age, gender, race, anxiety level, surgery type, prior pain experience, and genetic factors. Two-thirds of the variability in the response to morphine and side effects are currently considered to result from genetic changes in both adults and children. Pain from the internal organs, muscles and bones is described as diffuse, often poorly localized as compared to well-localized pain signals coming from the skin. Visceral pain is rated as more unpleasant than somatic pain and is accompanied by a greater fear [30]. Consequently, it is becoming clear that bone pain and ischemic pain are accompanied by visceral pain. Ischemic pain and bone pain are believed to be transmitted through the afferent nerve fibers which, like visceral pain, are associated with the sympathetic afferent fibers, distributing themselves along the blood vessels [31]. *Transduction, modulation, and perception of visceral and somatic pain are very similar, with a few exceptions. Visceral and somatic pain, however, significantly differ in the transmission [32].* When assessing the impact of visceral pain on the patient's postoperative recovery, one should consider the interindividual variability in visceral pain intensity. Depending on the procedure performed, visceral or somatic pain may predominate. For example, after laparoscopic inguinal hernia repair, the most intense pain is diagnosed on the day of surgery, with visceral pain significantly dominating over superficial pain. As primary somatic pain subsides within the first few postoperative days, visceral pain increases, probably, due to the irritation and inflammation of the parietal peritoneum [33]. In uncontrolled acute perioperative visceral pain, it may progress into chronic pain. Prolonged aggressive stimulation of the internal organs and peripheral sensitization of the visceral nociceptors can result in central sensitization. So far studies on chronic pain have not differentiated acute visceral and somatic pain as a risk factor for developing chronic postoperative pain [34]. A high incidence of chronic pain syndrome is observed in minor and minimally invasive (laparoscopic) surgeries. Probably, physicians consider these surgeries as less painful and, therefore, patients receive inadequate pain management [6]. Chronic pain is pain that occurs on at least 50% of the days for 6 months or pain that persists for longer than 3 months [35].

Low awareness of pain mechanisms is accompanied by little or no treatment for underlying biochemical aberrations including nutritional deficiencies (5.2%), oxidative stress (0.7%), or metabolic abnormalities (0.1%). This is surprising considering the rapidly growing number of high-quality randomized controlled trial data that provide conclusive evidence that treatment with vitamin B, acetyl-L-carnitine, alpha-lipoic acid, coenzyme Q10 (CoQ10), N-acetylcysteine mitigates severe and persistent pain while improving body functions [36, 37, 38]. Some experts assert that chronic pain syndrome occurs in the presence of the three following factors: micronutrient deficiency, metabolic abnormalities, and oxidative stress. The studies have found that elevated homocysteine level causes inflammation by increasing the level of arachidonic acid and the proinflammatory production of prostaglandin E2 [39]. Elevated homocysteine level indicates a correlation between inflammation and chronic pain.

The search for pain biomarkers is now a top priority in pain medicine; however, it is very difficult to identify the objective biomarkers for such a subjective condition as pain [40, 41].

Pain is always subjective; it is an invisible and internal experience, while the neural circuits and biochemistry of the nociceptive pathways can be explored [42]. Today there is no perspective therapy for neuropathic pain management. Modern therapeutic regimens include tricyclic antidepressants, ion channel modulators (gabapentin, pregabalin, carbamazepine, lidocaine) and some anticonvulsants. However, this arsenal of drugs does not provide the expected efficacy and causes side effects. Opioids and other analgesics are considered as less effective in neuropathic pain management [43]. Peripheral nerve injury, traumatic brain injury, toxic neuronal death result in the release of endogenous toll-like receptor (TLR) agonists (fibronectin, gangliosides, mRNA, hyaluronic acid) in the spinal cord. These agonists activate astrocytes, Schwann cells, microglia, and macrophages via TLRs, which can result in the increased expression of proinflammatory mediators. In addition, TLRs located on the other cell surfaces may be involved in the development of pain hypersensitivity [44].

## CONCLUSIONS

Today, there are limited clinical and experimental studies on the genetic and immune mechanisms of pain syndrome development. A thorough understanding of the genetic influence on pain response will allow for improving the diagnosis and management of pain. Currently, there are no clear biomarkers for diagnosing and predicting the development of acute and chronic pain syndromes, especially in pediatric practice. Lack of specific pain biomarkers makes impossible to determine the efficacy of pain management and predict disease progression. Further development of genomics and pharmacogenetics of pain will, probably, allow for formulating clear algorithms for diagnosis, management, and prevention of acute pain, as well as the mechanisms of chronic pain syndrome development.

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REVIEW ARTICLE

# THE SYSTEM OF PROMOTING A HEALTHY LIFESTYLE IN THE UKRAINIAN REGIONAL PRINT MEDIA

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## ABSTRACT

**The aim:** To analyze the peculiarities of media reform in the system of promoting a healthy lifestyle of Ukraine, to disclose the foreign experience of denationalization of print media.

**Materials and methods:** The theoretical and methodological basis and materials of the research consist of the scientific works of leading scientists on the issues of promoting a healthy lifestyle of Ukrainian print media and the possibilities of promotingthis process in social media in accordance with international practice, information from open registers, and interviews with editorial staff.

**Conclusions**: Having investigated the process of reforming the media, which is designed to promote a healthy lifestyle, we can draw the following conclusions that a significant part of modern Ukrainian media in one way or another reveals the problems of forming the basic principles of a healthy lifestyle for children and youth. The print media not only ensure freedom of speech, the development of democracy, the formation of perfect information society, but also contribute to the promotion of a healthy lifestyle, the ideology of changing the attitude of the individual and society to personal health. According to the results of the survey, 85 % of the media of the Ternopil region were successfully reformed. Taking into account the statistics, we note that the district editions of the Ternopil region, which expressed a desire to reform, were ready to go through all the procedures provided by the legislation of Ukraine.

**KEY WORDS:** Healthy lifestyle, media, medical system, denationalization, perspectives

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## INTRODUCTION

The system of standards in the field of health care consists of state social regulations and industry standards. State social standards in the field of health care are established in accordance with the Law of Ukraine "On State Social Standards and State Social Guarantees".Various tools in certain areas are designed to ensure a certain range of standards. One of the goals of the medical direction is to promote a healthy lifestyle. In the modern world, a healthy lifestyle and its components are aimed at improving and strengthening the human body as a whole, as well as prevention of various types of diseases.Today, when the state of health and standard of living is at a low level, this topic acquires a global character of society. Everyone wants to be healthy, but most people do nothing for it. However, the formation of a self-concept should begin precisely with the correct thinking over.The main role of mass media in a welfare state is to provide positive information that will be demanded by the population. In order to form value orientations and motivations as well as support and strengthen one's own health, it is necessary that positive medical information be broadcast regularly taking into account the characteristics of the audience (interests, age, gender). The effectiveness of the mass media depends on how accessible the information is and how competently and professionally methods of keeping health are offered.

In the context of European integration processes and globalization challenges, there was an urgent need for a reform of the media in Ukraine aimed to financial, content and editorial independence from state and local self-government authorities. In this regard, the withdrawal of public and communal enterprises from among the founders of the media should have made it impossible for the authorities of different levels to influence the editorial policies of the media. The process of denationalization would contribute to changing the media functioning vector and, in particular, the effective development of professional journalism, media pluralism, raising the level of trust in mass media with high-quality content, and raising the paying audience. It was given three years, from 2016 to 2018 to denationalizate print media. Since this process was multi-staged, not all editorial offices were able to complete it by the specified date. This has caused a number of problems such asfinancial and legal, the main of which was the possibility of losing the certificate of state registration, the status of the official printed publication in the context of the Law on Reform [1].

The process of print media denationalization was the subject of study by media researchers, lawyers and

sociologists. In particular, various aspects of it were disclosed in the writings of M. Bilousenko [2], D. Kuzin [3], L. Prysiazhna [4], A. Safarov [5]. A significant contribution to the solution of these problems was made by such Ukrainian scientists as L. Honiukova [6], M. Lohunova [7], M. Piren[8], V. Kniazev [9], A. Kolodiy [10], S. Kurpil [11], I. Lubkovych [12], V. Lugovyi [9], S. Chukut [13], V. Shpak [14], G. Khlystun [15].

## THE AIM

The purpose of the research is to analyze the process of denationalization of regional print media on the example of district newspapers of Ternopil region. The purpose of the study involves the following tasks:

1) to study the peculiarities of media reform in Ukraine;
2) to disclose the foreign experience of denationalization of print media;
3) to focus attention on the main problems of reforming Ukrainian media;
4) to analyze the process of denationalization of regional, printed mass media from 2016 to 2018.

## MATERIALS AND METHODS

The theoretical and methodological basis and materials of the research consist of the scientific works of leading scientists on the issues of promoting a healthy lifestyle of Ukrainian print media and the possibilities of promotingthis process in social media in accordance with international practice, information from open registers, and interviews with editorial staff.

In the process of scientific research methods of comparison and generalization were applied. The method of comparison allowed to compare and contrast the peculiarities of the phased reformation of the state and communal printed mass media from 2016 to 2018. The application of the generalization method made it possible to bring together the leading moments inherent not only in the declared research, but also in all work in general. This method was useful in systematizing individual facts, which were obtained in the course of working out the appropriate source base, as well as in the result of empirical research. The survey (mail questionnaire) identified difficulties in the process of reforming, possible innovations in district media, features of funding and mechanisms for the functioning of denationalized newspapers. On the basis of the questionnaire, the received data were analyzed.

The use of the analysis method proved to be appropriate, since it allowed to clearly separate various components of the investigated phenomenon, to find out what situation prevails in the field of scientific knowledge of the given topic, to focus on the dynamics of the reform of state and communal media in Ternopil region. The synthesis method was useful when systematizing the data obtained through analysis.

The inductive method provided an opportunity for the individual elements of the investigated issue to compose the general picture inherent in the current state of promoting a healthy lifestyle, to demonstrate the interdependence of existing legislative documents with the results of empirical research. Using deductive method, conclusions were made, specific data were derived from the general data set and the prospects and risks associated with the privatization of print media were formulated.

## REVEIW AND DISCUSSION

In 2014, the Government of Ukraine launched a large-scale local government reform, which, in particular, provides the transfer of more powers of regional significance from the central government to local governments, expanding their resource base and finance, etc. During the first phase of the reform (2015-2018) 876 joint territorial communities were created whose budgets have increased by an average of 5-7 times. The local budget's revenues increased by UAH 165.4 billion. (from UAH 68.6 billion in 2014 to UAH 234 billion in 2018). It should be considered that state support for the development of regions and communities has increased 39 times (from UAH 0.5 billion in 2014 to UAH 19.37 billion in 2018). The question about the financing of the state and municipal press in Ukraine is arising. The liquidation of districts creates specific problems for journalists, as it requires both legal re-registration and restructuring of editorial work to cover the life of communities in the new territorial boundaries.

The formation of a healthy lifestyle should be the main direction of social policy in the field of health care. Comprehensive health promotion and prevention programs should not be reduced to separate measures for the organization of medical care, it is necessary that they include measures of hygienic education, combating alcoholism, drug addiction, smoking and other risk factors, activation of physical culture, measures to formation of a healthy lifestyle.

Among the printed publications preferred by modern people, periodicals turned out to be quite common (70% of respondents said that they often read them). Entertainment and informational magazines (38%) and newspapers (36%) take first place here, while 16% said they read newspapers daily, 33% - two or three times a week, 20% - once a week, 24% - only by chance. And only 6% practically do not read at all. Reading newspapers and magazines turned out to be one of the most favorite forms of spending free time, as indicated by 48% of all respondents.

Among the sports and health topics in the printed media, such sections as "Family Space", "Body Builders", "Healthy Look" and "TheSport", etc. can be distinguished.

In most cases, the current purpose of mass publications and TV channels is not to promote the improvement of working, recreation, and living conditions, but to lead a healthy lifestyle, keep and strengthen health.

It can be seen from this table I. that a considerable percentage of the population in Ukraine trusts mass media. Meanwhile, the press is the leader in the level of trust amongthe means of mass communication as 71%

**Table I.** The level of trust of the population of Ukraine in printed media (% of the total number of respondents)

| Mass media | I trust completely | I'd rather trust than not | More likely I don't trust it | I don't trust it completely | Difficult to answer |
|---|---|---|---|---|---|
| Press | 25 | 46 | 15 | 8 | 6 |
| TV | 10 | 32 | 40 | 10 | 8 |
| Internet | 8 | 35 | 31 | 12 | 14 |

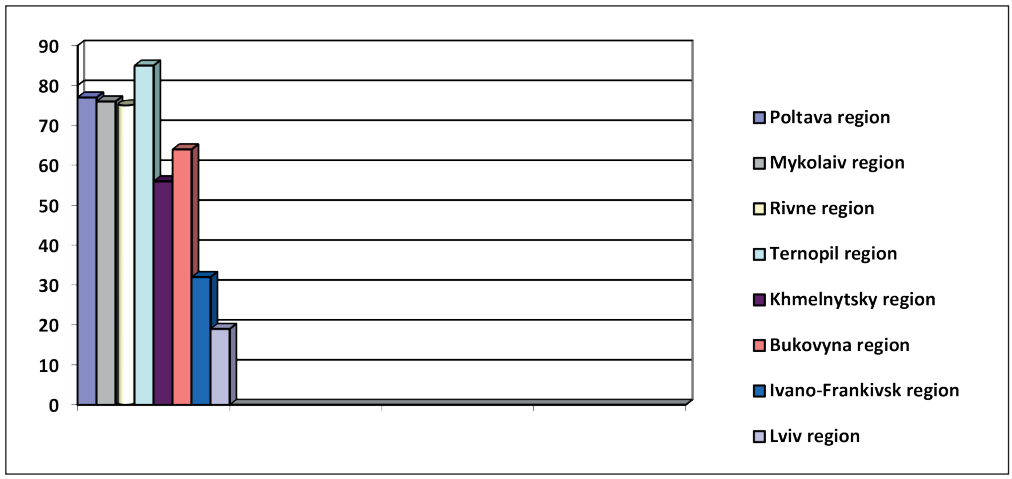


**Fig.1.** The dynamics of reforming the press

of respondents trust it. The second place is taken by the Internet - 43%; 42% of the respondents trust television. As you can see, the press is trusted more than other means of mass communication.

The independence of the press from public institutions is the basis for functioning of democracy and high-quality informing of society.

State support for the media is always an intervention in the market, so it must be coherent and justified by a worthy goal. According to Robert Picard, a media business economist, when it comes to newspapers, we are dealing with two markets simultaneously: the market of ideas and information on the one hand, and the market of things (advertising, paper, delivery, etc.) on the other. R. Picard argues that tax benefits or financial assistance of the same size for all publications distorts competition and does not create incentives for publications to optimize the publishing process. At the same time, selective assistance to individual publications, for example, with more of their content, stimulates competition and, as a result, quality in both markets. The scientist emphasizes that state intervention in the functioning of these markets should be minimal and not cause negative effects on any of them [15].

On January 1, 2016, the Law of Ukraine «On the Reform of State and Communal Printed Media» came into force. The reason for the adoption of the Law was to release Ukrainian media from the influence of state or local authorities, which would promote the creation of independent media, which will become an instrument for the establishment of democratic values and a component of civil society. On November 23, 2016, the Cabinet of Ministers of Ukraine approved the resolution No. 848 «On approval of the list of printed mass media and editors reformed in the first stage». The approval of the list of state and municipal print media and editorial offices was a prerequisite for the start of the first phase of denationalization , stipulated by the above mentioned Law of Ukraine.

The first reading of the Law was characterized by significant gaps in the current legislation, for the overcoming of which were developed 3 bills: draft law No. 6560 dated 06/08/2017. During September 2017 additional problems were identified that could not be resolved within the framework of the current legislation on reform: there was no procedure for the transformation of state and communal media into official publications (Article 10 of the current Law); the status of the labour collective as a participant in legal relations related to the establishment of mass media and legal entities is not defined; there is a conflict between the requirements of Articles 5 and 9 of the Law on preservating the title of the print media and legislation on decommunization, etc.

Analyzing the current Law on Press Reform, we emphasize the following destructive issues: there is no clear definition of the jurisdiction of reform cases, there is no procedure for drafting editorial boards, the possibility of creating official print media, the lack of effective tools to protect the rights of the staff and to influence the inaction of the founders.

According to the Law, the reform of print media should take place in two stages: the first in 2016 and the second in 2017–2018. The first stage involves the implementation of certain legal procedures: the submission by the labour collective of a proposal for denationalization and the decision to reform the founder, its order (stage I or II) and its method. On the basis of these decisions, the State Committee for Television and Radio Broadcasting creates two lists - a consolidated one, which includes information on all state and municipal media to be reformed, as well as a separate

list of print media that are undergoing reform at the first pilot stage. This list, with a half-year delay, was approved by the Cabinet of Ministers of Ukraine. At the second stage (by the end of 2018), print mass media and editorial boards that have not undergone denationalization on the first are to be reformed (part 5 of Article 2 of the Law).

The law provides four ways of reforming the print media, whose founders are state authorities and local self-government:

- «the withdrawal of state authorities, other state bodies and local self-government bodies from the founders (co-founders) of the printed media and editorial staff;
- the withdrawal of state authorities, other state bodies and local self-government bodies from the founders (co-founders) of the printed mass media and editorial staff with transformation into a reforming economic entity;
- the output of state authorities, other state bodies and local governments from the founders (co-founders) of the printed mass media and editors with the subsequent privatization of property of the editorial staff;
- transformation of the publication into the official printed publication».

Covering the processes of denationalization of print media in Ukraine, it is advisable to analyze the experience of European countries in which media privatization has come to an end. It should be noted that in most states there is a proper regulatory framework for reforming the press. Novelties of the legislation are aimed at protecting the media from attempts to concentrate and nationalize property by establishing a requirement to scatter property. The current legislation regulates the plurality and diversity of the media, protects the media markets from monopolization by limiting the share of foreign investments in one company by at most 33 percent, so that no investor is allowed to own more than one third of any company.

Media reform took place over a long period of time. For example, in Moldova, it began in the early 1990's and lasted until 2005, in Estonia, until 1996, although a small proportion of specialized and children's publications were under state control even till1997.

The process of denationalization of the Estonian press was characterized by the commercialization of activities (the creation of its own commercial departments) and increased political pressure, which resulted in a number of newspapers being privatized by editors or journalists. In general, in the process of reforming the media in Estonia, two main schemes were used: 1) the transfer of the print media to the media workforce («Postimees», «Paevaleht»); 2) competitive privatization. Under the first scheme only one edition was privatized, all other Estonian media were planned to be suspended on the terms of the competition.

The denationalization of the press in Latvia took place in two main stages: through the so-called «spontaneous privatization» by mass media teams («Lauku Avize», «Cina») and privatization in general, in accordance with the privatization law («Diena»). The first stage of denationalization was rather rapid and took place under conditions of legislative uncertainty. The second stage of the privatization of the media began in 1992 after the adoption of the Law on privatization of state property. As of the end of 1992, almost all state publications were privately owned. Over the next few years, privatization of adjacent segments of the market such as the publishing industry and distribution network took place.

In contrast to Latvia, in Lithuania, the process of denationalization of print media from the very beginning was within the legal framework. Members of the editorial board set up a business society, which, under competitive conditions, redeemed the property of the state media, after which each founder of the company could freely dispose of its share in the authorized capital. As a result of the privatization of 1991– 1992, virtually all state and communal press was transferred to the ownership of labour collectives in the above-mentioned scheme, but in the mid-1990s, most founders of new business partners sold their shares to foreign and most powerful national companies, which subsequently led to a significant concentration of media ownership on print media – today the entire market of print advertising is actually divided between five publishers of newspapers and magazines.

In Hungary, deregulation took place under a scheme similar to that of the Latvian, the labour collective of the mass media created business associations, entered into negotiations with foreign investors, founded printed publications with names similar to those which were issued in previous years and re-profiled media to investors' needs and market economy.

In Poland, the process of media reform took place in two stages. The first was the denationalization of the publishing and printing association Press-Book-Movement, which included news agencies, periodicals and distribution companies, and the second, publishing houses and the distribution network were privatized. In 1990, the Sejm adopted the Law "On the Elimination of the Workers' Publishing Cooperative 'Press-Book-Movement'". A special liquidation commission was created, whose mandate was to resolve such issues as: the free transfer of property of print media to labour collectives, sale of printed media to private owners, ensuring the accounting of balances of non-privatized property and its transfer to the control of the state treasury. Only the property of those newspapers that had sufficient circulation and, in the opinion of the commission, could survive in market conditions, were transferred to the labour collectives. The rest of the media that did not meet the criteria were sold to all those who offered the highest price. The privatization of the media by the labour collective was carried out under the following conditions: 1) "the liquidation commission made a decision on the possibility of transferring the property of the media to the labour collective; 2) not less than 50% of the members of the labour collective of the mass media should have formed a limited liability company and to contribute to its authorized capital share in the amount not less than three minimum wages; 3) the commission had to decide on the transfer of all media assets to the balance of the newly formed economic partnership" [16].

In Slovakia, the denationalization of the media was carried out through their sale on competitive terms. Some media outlets were redeemed by foreign investors (newspaper "Novyi Vremya"), while others were economic partnerships, founded by members of media labour collectives (newspaper "Pravda").

Unlike a number of other European countries, in Slovenia, privatization took place on the basis of a special law passed in the early 1990's. For Slovenia, the following model of privatization was typical: «The share of state property in the media was transferred to the management of three social public funds – the Pension (10% of the state share in the authorized capital of each media), the Compensation Fund (10%) and the Development Fund (20%). Subsequently, these shares were transferred to authorized investment agencies that carried out their free sale. After the completion of this phase of the privatization process, the second was a shares buyout in the authorized capital by the members of the staff of the media. The buyout was permitted if the decision was supported by at least one-third of the members of the labour collective. When buying shares, members of the labour collective were given a discount – they could buy a property with a 25% discount from its real value. The buyout itself, according to the law, could have been carried out during four years, each year the labour collective had to buy at least 1/4 of the shares that could be transferred to the labour collective; during this 4-year period, the enterprise whose founders were members of the labour collective did not have the right to receive loans and issue bonds» [15].

Having described the process of denationalizing print media in European countries, we will highlight the main issues of reforming process in the Ukrainian media.

According to the statistical data, on the initial stage of the reform 244 out of all-Ukrainian print media were prepared for change, which was 33.3% of the total number of editorial offices. It should be noted that by the end of 2016 no print media had completed its reform process. This is due to the delayed decision of the Cabinet of Ministers of Ukraine No. 848, the complicated procedure of the reform algorithm, and the imperfection of the original Law.

According to the studies by the Center for Democracy and Rule of Law, «as of June 30, 2017 only 62 print media were re-registered, which is approximately 25%.» It is worth mentioning that, as of December 1, 2018, 759 publications were subject to privatization.

As a result of the monitoring of Dezhkomteleradio, as of December 18, 2018, 53% of the total number of editorial boards that are actually functioning has been reformed in Ukraine.

A recent survey among Ukrainian newsrooms (196 surveyed newsrooms) carried out by the Ukrainian Media Business Association in December 2017 has identified the following obstacles:

- 45 % (87 editions) indicate the absence of problems during the reform;
- 18 % (37 editions) have not yet experienced difficulties, as they have only just begun to reform;
- 16 % (31 editions) stated difficulties while concluding a contract on coverage of government activities and 16% have problems with the preparation of documents. However, 52% of editors have already stated that they have concluded agreements with state bodies;
- 13 % (25 editions) complain about obstacles on the part of the founders in carrying out privatization, ie., the absence of decisions or delay in adopting the decision;
- 11 % (22 editions) claim a violation of the right to preferential rent of property, which is guaranteed by the law. Only 50% of the respondents received it;
- 5 % (10 editions) declare the pressure of the founders on the team or the same conflict situations in the team;
- 4 % (8 editions) indicate the impossibility to implement the reform following the law.

According to the experts of the State Committee for Television and Broadcasting, an important prerequisite for a low level of reform is the irresponsibility of the authorities and labour collectives (of print media from major cities of Ukraine) to the process. The reason is the constant postponement of the registration process of the object until the re-registration.

The leader in the process of denationalization is Ternopil region. As Angela Cardinal, co-chairman of the coalition of public organizations "Ternopil Center for Reforms", said that 85 percent of it was from Ternopil region, and this was the largest among all regions. For comparison, in Poltava region this number is 75.

Mykolayiv region – 76, and Rivne region – 75 percent. With other neighboring regions, the gap in favour of Ternopil region is much larger. Thus, in Khmelnytskyi region 56 percent of communal newspapers were reformed, 64 in Bukovyna, 32 in Ivano-Frankivsk region, and only 19 in Lviv region (Fig.1.).

As a whole, the reform indicator of communal newspapers in the Ternopil region was completely obstructed by the fact that, according to information of the department of state registration of printed mass media and public formations of the Main Territorial Department of Justice in the Ternopil region, editorial boards of two editions – «Halytskyi Visnyk» (Borschiv) and «Rada» (Regional Municipal Enterprise "Publishing House Rada") did not apply at all. And the editors of another two – «Chortkiv Visnyk» and the regional newspaper «Svoboda» did not have time to complete the reform process.

The «Ternopil Press Club» (that enters the Coalition of Civic Organizations "Ternopil Center for Reforms") provided essential assistance to the editorial boards during the process of denationalization and at the beginning of their independent activity during all stages of the reform. Within the framework of the project «Comprehensive support for communal media in their preparations for denationalization», with the assistance of the Ukrainian Media Project (U-Media), implemented by Internews in Ukraine and funded by the United States Agency for International Development (USAID), the Ternopil Press Club provided Complete basic information about the process of denationalization.For this purpose, the best specialists of Ukraine were attracted to familiarize themselves with the

basics of media business, with the experience of successful media companies, options for monetization of content, new opportunities for newspapers after reforming. 30 training and experience exchange seminars were conducted, more than 500 telephone and written legal consultations were provided, three practical manuals were issued, 10 TV and video workshops were organized between the regions, a model of the new Charter for the editorial boards, that became limited liability companies, was developed. And about 300 publications were published coveragingthe print mediareform. The permanent and professional legal support of the project helped the directors and labour collectives of the regional newspapers ofTernopil region to correctly pass the initial stage of denationalization and be prepared for the following stage, to protect themselves from errors and unnecessary risks, and also helped to resolve the problems that arose. Significant help to reformed editorial offices was provided by the regional organization of the National Union of Journalists of Ukraine.

These included educational and training events, legal counseling, and personal involvement of the manager and lawyer of the organization in solving local conflicts and problems. Joint efforts, undoubtedly, have become a decisive precondition for the leadership of Ternopil region in implementing one of the most important social reforms [17].

The financial support of municipal district newspapers in the process of privatization by the authorities, according to the Ternopil Regional State Administration, was provided in the following way. The sum of UAH 200,000 was allocated to *Zborivska Dzvinytsia* in accordance with the district media support program. Funding for the Chortkiv *Voice of the People* is UAH 50,000 for six months. The Ternopil District Council allocated UAH 500,000 in support of *Podilske Slovo*, and the Shumskyi District Council allocated UAH 50,000 to the *Shumshchyna News*.

In order to study the media reform in the Ternopil region, a poll was conducted – a mail questionnaire. The object of the survey was the editorial staff. Of the 20 regional newspapers in Ternopil region, every third editorial office of all communal newspapers subjected to reform provided information for this study.

According to the poll in 2017 nine district newspapers were reformed, the rest were reformed in 2018. The first one to go through all the necessary procedures was the newspaper «Ternopil Vechirniy», the last one was «Zborivska dzvinutsia». All reformed editions (except for «Ternopil Vechirniy», which chose the status of a private enterprise) became limited liability companies.

According to the results of our survey among the representatives of the editorial offices of the district newspapers "Novyny Shymshchyny", "Zborivska dzvinytsia", "Novyi Den'","Podil'ske slovo","Visnyk Nadzbruchchya","Holos Narody", we received the following results:

1. 100% of the publications are printed newspapers, of which 80% are in the form of online newspapers.
2. 99% have a local distribution.
3. The average circulation of editions that have been reformed is 3000 copies ("Visnyk Nadzbruchchya" – 2830, "Novyny Shymshchyny" –3980, "Zborivska dzvinytsia" – 3000, "Novyi Den'" – 3200, "Podil'ske slovo" – 2000, "Holos Narody" – 2500).
4. Frequency of publications: once a week – 100%.
5. In 20% of the editions there were changes in the number of employees, in 80% of the media changes in staffing did not take place. For example, in "Visnyk Nadzbruchchya" out of 8 employees that worked before the reform process only 3 left in the reorganized newspaper, the staff of "Zborivska dzvinytsia "decreased by 1 person.
6. The process of privatization in regional newspapers of Ternopil region was held according the following model: meeting of the labour collective – determination the way of privatization – decision to withdraw public authorities and local governments as the go-founders – public announcement of the decision through the media – a property inventory – transfer documents to derzhkomteleradio – inclusion to a consolidated list of reforming entrepreneurs – state registration – meeting of labour collective – choosing the form of management – reform of the editorial board – approval of the charter – the transfer of documents to state registrator and to the department of justice – receiving a certificate of state registration – informing social institutions about the changes in functioning the print media – petition to the state committee to be included in the register of publishers – concluding agreements with former contributors on englighting their activities in the media.
7. The main obstacles in the reform process (2016–2018). 40 % state that there are no significant obstacles, 18 % of editorial boards had problems with signing a contract to cover the activity of public authorities, 20 % of editorial boards complained about the difficulties involved in preparing documents for reformation process, 15 % of editorial boards stated that co-founders prevented them from carrying out reforms, in particular, they failed to take a decision or delayed with its approval, 5 % of editorial boards indicate the pressure from the founders on the members of the labour collective or the conflict within the staff itself, 2 % of the editors stated the impossibility to be formed in accordance with the current Law.
8. The main financial costs are on printing the newspaper – 35, salaries and taxes – 45 %, room maintenance– 10 %, promotions related to the publication advertising – 5 %, computer hardware and stationery – 5 %.
9. The lion's share of financing independent newspapers depends on advertisers, that place their adverticements of commercial, political and social character.
10. 87 % of editorial boards state that they check the compliance of advertising with the requirements of the Law "On Advertising". Only 65% distinguish ads and private ads. Fewer editorial boards duly fulfill the requirements for marking advertisements – their number is about 60 %.
11. 92 % of editorial boards declare that they are checking defamation risks when placing materials.
12. For the purpose of obtaining information, 85 % of editors use the Law of Ukraine "On access to public information", 82 % – the Law on Citizens' Appeal.

13. Innovation related to reform: the creation of converged media, that place materials on various information platforms, which contributes to increasing the audience, and hence potential subscribers.
14. Risks: the liquidation of the media, which did not begin the reform in time; financial crisis; unpreparedness of subscribers to subscribe to newspapers; complicated relations with state authorities that can offer biased reports; conflict of interests of certain groups in which the media will act as a mediocre arbitrator; unsystematic investment.
15. The prospects of denationalization will be in effective development of professional journalism, media pluralism, raising the level of trust to the media with high-quality content, the growth of paying audiences, community-building based on the cultural and historical features of the region, and integration into the local cultural environment.

According to the analysis of risk factors for health, the active growth of all bad habits occurs during the adolescence period.

Actually, in the period of adolescence the interest of schoolchildren in the events of collective life is especially noticeable, the exchange of opinions between them on various issues increases, and relations between people become the object of attention.

As a result of the formation of a collective opinion in the class, relatively independent from the opinion of adults, as it happens in the younger classes in relation to the teacher, teenagers begin to realize the advantages and disadvantages of the situation in the family. Thanks to the communication of teenagers, one family influences another family, the relationships within it.

This problem is covered more often and to some extent more thoroughly in the press and in periodicals. Analysis of periodicals for the last quarter of 2020 showed that nowadays there are very few Ukrainian publications which could be interesting for young people. Russian magazines were the most popular among them.

In the course of the analysis, Ternopil printed mass media became the object of attention. The printed material can be thematically divided into the following blocks:

- explanation of the harmfulness of smoking, alcohol and drug use - in "Halytsky Visnik", "Pidgayetska Zemlia", "Medical Academy";
- description of physical exercises - in "Chortkivsky Visnyk", "Svoboda", "Medical Academy", "University Hospital";
- advice from psychologists, medical specialists - in "Nova Ternopilska Gazeta", "Free Life", "Medical Academy", "University Hospital";
- folk medicine prescriptions - in "Svoboda", "Medical Academy", "University Hospital";
- problems of sex education - in "Nova Ternopilska Gazeta", "Free Life", "Medical Academy", "University Hospital".

Thus, the analysis of the content of the listed magazines shows that in most of them the topic of a healthy lifestyle is covered irregularly and rather superficially. Among the newspapers, the "Medical Academy" and "University Hospital" newspapers can be positively noted where the promotion of a healthy lifestyle among the residents of Ternopil is the dominant topic of a significant number of publications. The newspaperalso introduced special sections "Young people - about a healthy lifestyle" and "Be fit from your youth", which contain quite meaningful recommendations for young people.In their articles, newspaper correspondents consider such topics as children's health, healthy nutrition, suicide, alcohol and drug use, etc.

## CONCLUSIONS

Having investigated the process of reforming the media, we can draw the following conclusions:

1. From the above-mentioned material, it can be concluded that a significant part of modern Ukrainian media in one way or another reveals the problems of forming the basic principles of a healthy lifestyle for children and youth.
2. The denationalization of print media is a significant step in ensuring freedom of speech, the development of democracy, the formation of a perfect information society.
3. Analyzing the experience of media privatization in European countries, we note that the free transfer of publications to members of labour collectives as the ownerns in practice did not lead to the expected consequences – the "socialization" of the media ended with the alienation of members of the labour collective of their share in the authorized capital in favour of third parties; in most countries, media privatization was concluded on a competitive basis; the process of denationalization of print media was not accompanied by the budget support in the first stages after the completion of privatization; a great number of the reformed media has been absorbed by multinational companies or have ceased to exist.
4. Denationalization of the press was uneven in different regions of Ukraine. In fact, at the first stage no editorial staff completed the reform due to the imperfection of the current legislation, the lack of legal awareness of editors, the problem of document legalization and the systemic obstacles of local authorities that did not understand the importance of the process created various barriers to denationalization. However, despite significant difficulties, 53 % of state and communal media have been reformed.
5. The most common way of denationalization is the exit of state authorities, other state bodies and local governments from the founders (co-founders) of the print mass media with the transformation of the editorial staff into a business entity preserving the name, purpose, language and thematic focus of the print media.
6. According to the results of the survey, 85 % of the media of the Ternopil region were successfully reformed. Taking into account the statistics, we note that the district editions of the Ternopil region, which expressed a desire

to reform, were ready to go through all the procedures provided by the legislation of Ukraine.

7. Despite the difficulties associated with the reform process (problems with concluding an agreement on the coverage of public authorities, document preparation, obstruction of local authorities to implement the reform, pressure from founders on the members of the labour collective), in the long run, one can hope for high-quality journalism, that will be expressed in information transparency, and, consequently, increase of the audience's confidence in media content. This will increase the number of paying readership.

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CASE STUDY

# PERSISTENT FEVER IN A PATIENT WITH CONGENITAL HEART DISEASE AND A HIGH-VELOCITY SHUNT: A CASE REPORT

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**ABSTRACT**

In patients with congenital heart disease (CHD), presence of intracardiac shunt can be a substrate for infective endocarditis (IE). Our aim was to highlight that this diagnosis should always be suspected when CHD patients present with persistent fever.

In this case report, we describe the case of a 33-year-old female patient with a history of perimembranous ventricular septal defect (VSD) who presented to the hospital with persistent fever. Six months ago, the patient had undergone a tooth extraction under antibiotic prophylaxis. The transthoracic echocardiogram revealed a mobile mass, consistent with vegetation in the tricuspid valve. The blood cultures grew Streptococcus mitis. Antimicrobial treatment was initiated for IE. Symptoms and inflammation markers improved, but the patient relapsed in the 4th week of treatment. Transesophageal echocardiogram revealed a new mobile vegetation attached to the right ventricular outflow tract and the patient was referred for surgery. Her postoperative course was uneventful.

**KEY WORDS:** congenital heart disease, infective endocarditis, ventricular septal defect, antibiotic prophylaxis

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## INTRODUCTION

The population of adults with congenital heart disease (CHD) is expanding, and is considered to be the major substrate for infective endocarditis (IE) occurrence in younger patients. The reported incidence of IE (1.1-1.6 per 1,000 patient-years) in patients with CHD is significantly higher than the corresponding one in the general population (5-15 per 100,000 patient-years) and more frequently affects the right heart [1]. The diagnosis should be considered in all CHD patients with ongoing infection or fever. Ventricular septal defect (VSD) is one of the most common CHD in childhood, and there is an increasing prevalence of VSD in the adult population [2]. The endocardial injury related to a small unoperated VSD in adults carries a substantially increased risk of IE (1.7-2.7 per 1,000 patient-years), but also increases the risk of vegetation reseeding. [3]. Surgical repair of CHD often decreases the risk of IE, on condition that there is no residual lesion. In this case report, we describe a young female with VSD who was diagnosed with IE after a dental procedure and, despite adequate antimicrobial therapy, needed a surgical treatment.

## CASE REPORT

A 33-year-old female with perimembranous VSD was presented in a tertiary hospital with a high-grade persistent fever. She reported a low-grade fever of unknown origin lasting 6 months, without any localizing signs and symptoms. The fever began following a tooth extraction, for which she had been prescribed antibiotic prophylaxis. Initially the patient was managed as lower lobe pneumonia with empiric antibiotic therapy, based on a computed tomography (CT) scan, showing a dense area in the left lower pulmonary lobe. The patient continued having fever recurrences for weeks, and was not improved after different antibiotic trials on an outpatient basis.

On admission to our hospital, she had high fever (39.5°C), tachycardia (100 beats/minute), a blood pressure of 100/70 mmHg, a respiratory rate of 18 breaths/ min, and oxygen saturation 98% in room air. Her physical examination revealed a systolic cardiac murmur at the left sternal border. Her lungs were clear to auscultation, and her abdomen was soft, non-distended, and non-tender without hepatosplenomegaly.

Laboratory studies were significant for leukocytosis (11.5 x103 /mm3) with neutrophilia, anemia (hemoglobin 9.2 g/dL), and elevated C-reactive protein (CRP) at 12.2 mg/dL. Liver function tests, blood urea nitrogen and serum creatinine were within normal limits. Chest X-ray, serial ECG and cardiac enzyme levels were also normal. Due to the high suspicion of IE, repeat blood cultures were drawn, and a transthoracic echocardiogram (TTE) was performed. The latter revealed a mobile vegetation in the atrial aspect of the tricuspid valve's septal leaflet with mild tricuspid regurgitation (figures 1A, 1B). Blood cultures were positive for Streptococcus mitis.

A baseline transesophageal echocardiogram (TOE) was conducted confirming the TTE findings (figure 2A). TOE also showed a small perimembranous VSD (2mm) with a left to right shunt (figure 2B) and a peak pressure gradient of 65mmHg (figure 2C). A definite diagnosis of IE was set, since the patient met 2 major modified Duke criteria (imaging and

**Fig. 1.** ( 1A, 1B) . Transthoracic echocardiogram (TTE)
The red arrows point towards the tricuspid valve vegetation

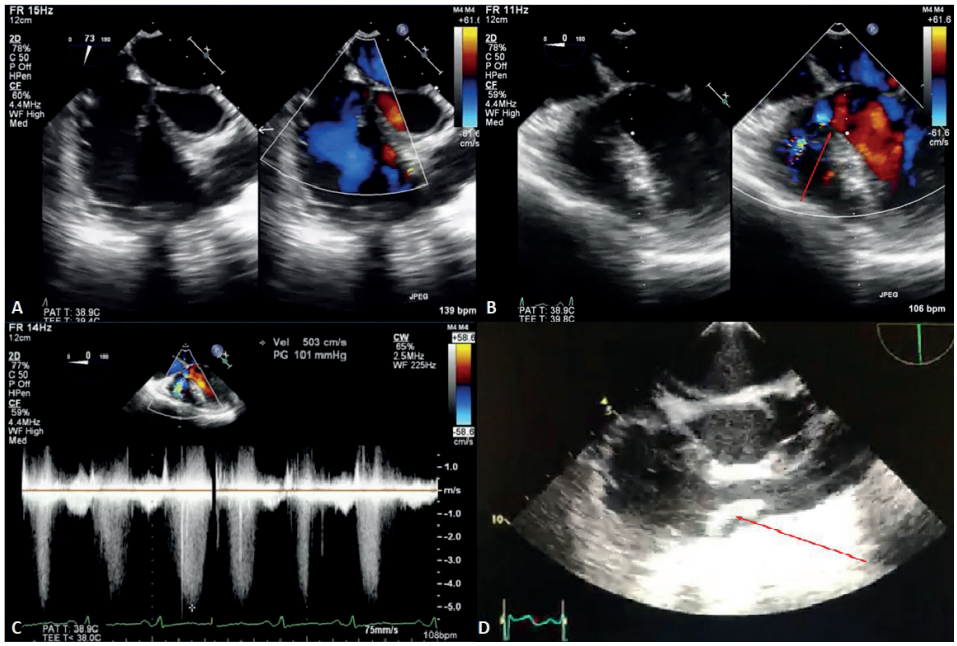

**Fig. 2.** ( 2A, 2B, 2C, 2D) Transesophageal echocardiogram (TOE)
Panel A shows a vegetation in the atrial aspect of the septal leaflet of the tricuspid valve and resultant mild tricuspid valve regurgitation.
In panel B the red arrow points towards the perimembranous ventricular septal defect (2mm), which causes a left to right shunt
Panel C shows peak pressure gradient of 65mmHg
Panel D shows the vegetation attached to the right ventricular outflow tract (RVOT) at the impinging area of the high velocity jet

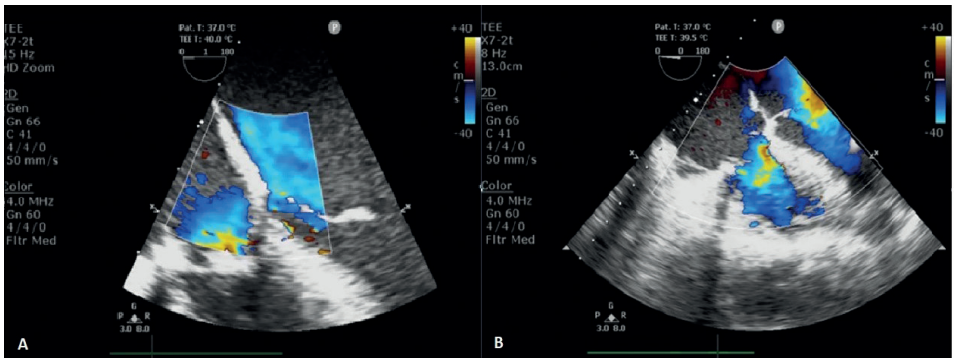

**Fig. 3.** (3A, 3B) Transthoracic echocardiogram (TTE) following vegetation removal, triscupid valve repair and VSD closure
The valve shows minimal TR and absence of vegetation

blood culture positive for IE) [2]. Empirical treatment with gentamycin, ciprofloxacin and vancomycin was initiated, which was rearranged as linezolid/ceftriaxone based on the antibiogram of the blood cultures.

During the fourth week of the patient's treatment, her fever recurred, along with chest pain and dyspnea. New sets of blood cultures were drawn and a new TOE was performed. The latter revealed a mobile vegetation attached to the right ventricular outflow tract (RVOT) at the high-velocity VSD jet's impinging area and worsening of the tricuspid regurgitation (figure 2D). Fever persisted even after antibiotic therapy was climaxed to linezolid and ceftaroline, and inflammation markers rose. Due to the persistent infection, despite adequate antimicrobial therapy, the patient was referred for surgical treatment of the lesions. She underwent surgical excision of the vegetations from the RVOT and tricuspid valve, tricuspid valve leaflet repair, annuloplasty and surgical VSD closure (figures 3A, 3B). Her postoperative course was uneventful.

Diagnostic inertia and a low index of clinical suspicion is usually the reason an IE is missed in patients with ongoing fever. Patients with CHD and intracardiac high-velocity shunts may be more prone to IE, following spontaneous bacteremia. As described in this case, the high-velocity jet through the unrepaired VSD might have caused endocardial injury, forming a nidus for IE. The lesions may be encountered throughout the course of the impinging jet, either on the tricuspid valve,

or the right ventricular endocardium. Left-to-right shunt in restrictive VSD explains why, IE affects the right heart more frequently in these patients than in acquired cardiac disease. Despite, contemporary guidelines do not suggest antibiotic prophylaxis before high-risk procedures for this subset of patients. Emphasis is placed on good oral, dental and skin hygiene [3].

In the setting of persistent infection, surgical management is prompted. Several risk score models are available to guide the decision-making in terms of which patients will benefit from further surgical treatment. Patients with worse outcomes are (mostly older patients with multiple comorbidities including diabetes and renal disease) [1, 4]. Both European and US guidelines recommend that surgical treatment of right-sided IE should be thoroughly considered in the following situations: i. microorganisms difficult to eradicate (e.g. persistent fungi) or bacteraemia for >7 days ii. persistent tricuspid valve vegetations >20 mm after recurrent pulmonary emboli with or without concomitant right heart failure or iii. right HF secondary to severe tricuspid regurgitation with poor response to diuretic therapy [1, 3].

Importantly, the correction of the predisposing congenital defect has been described as a secondary preventive measure. Elimination of the defect resolves the issue of chronic localized endocardial inflammation caused by the high velocity impinging jet. It may also minimize the chances of vegetation reseeding following initial treatment of IE. Even if logical, these assumptions lack, backup from systematic studies. Available observational data suggest that surgical closure decreases the risk of endocarditis by at least 50% [1, 5]. However, there is no sufficient evidence to designate the risk of future bacterial endocarditis as an adequate reason for surgical closure of the defect, due to the lack of relative randomized controlled trials.

## LEARNING POINTS:

- In patients with CHD, presence of intracardiac shunt can be a substrate for infective endocarditis (IE). This diagnosis should always be suspected when CHD patients present with persistent fever.
- The endocardial injury related to the high-velocity ventricular septal defect left-to-right shunt can cause IE via endocardial damage, but also increases the risk of vegetation reseeding.
- Correction of the predisposing lesion might prevent the recurrence of endocarditis.

## CONCLUSIONS

Our case highlights that IE should be highly suspected in patients with CHD and persistent fever, especially in the setting of high-risk procedures for bacteriemia. The endocardial injury related to a high-velocity left-to-right jet may be causally and increase the risk of vegetation reseeding following an initially successful trial of IE treatment. The correction of the predisposing lesion might treat the root of the problem and prevent the recurrent IE episodes.

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CASE STUDY

# ACUTE CORONARY SYNDROME IN A PATIENT WITH MULTIPLY CORONARY ARTERY ECTASIA AND ASCENDING AORTIC ANEURYSM

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**ABSTRACT**

This report describes a case of multiply CAE presenting as a ST-elevation myocardial infarction in an adult patient with bicuspid aortic valve (BAV) and ascending aortic aneurysm. Coronary angiography revealed multiply ectasia in left anterior descending artery and right coronary artery. A computer tomographic aortogram confirmed the presence BAV with signs of calcification and an enlarged ascending aorta.

The patient underwent coronary artery bypass grafting of left descending and circumflex coronary arteries and tube graft replacement of ascending aorta in 1 month after ACS in experienced centre. In patients with ACS due to CAE culprit, the emphasis is to restore flow. Medical treatment as well as lifestyle changes and risk factors control, and serial imaging assessment of aortic aneurysm constitute the second part of the management of these patients. We need prospective studies and registries to improve patient care and outcome.

**KEY WORDS:** Coronary artery ectasia, ascending aorta aneurysm, acute coronary syndrome, bicuspid aortic valve

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## INTRODUCTION

Most of the patients with an acute coronary syndrome (ACS) have evidence of a coronary stenosis and thrombus. Nevertheless, in 1-14 % there are no signs of obstructive coronary artery disease [1]. The identification of underlying cause should lead to individual management strategies. This report describes a case of multiply coronary artery ectasia (CAE) presenting as a ST-elevation myocardial infarction (STEMI) in an adult patient with bicuspid aortic valve and ascending aortic aneurysm.

CAE is a rare incidental coronary anomaly. Regardless of its severity and extent, an etiology, prognosis, morbidity, and mortality related to this abnormality are still a matter of debate. However, several investigations have suggested that congenital, inflammatory, and connective tissue disorders are possible etiologies and that the atherosclerotic process is the main cause in the majority of the cases [2,3,4]. In addition, the prognosis differs significantly between studies with the annual mortality rate having been reported between 2% to 15% [5] .

## CASE REPORT

A 45-year-old overweight hypertensive male presented to an emergency department with crushing chest pain at rest and palpitation 1 hour after onset of symptoms. There was no family history of aortic, collagen vascular, or congenital heart disease. A Marfanoid habitus was not present on physical exam. His respiratory rate was 20/min, heart rate – 100/min, blood pressure – 160/90 mm of Hg, oxygen saturation – 94 % on room air, temp. – 36.6°C, BMI – 28 kg/m2. Chest auscultation did not reveal any obvious abnormal heart murmurs.

Electrocardiography (ECG) demonstrated ST segment elevation in I, AVL, V2-V6 leads (Fig.1A). Bedside transthoracic echocardiography showed hypokinesia of anterior - lateral segments of left ventricle and normally functioning bicuspid aortic valve (BAV) with a dilated ascending aorta (diameter 5 cm).

In light of on-going severe chest pain and elevated high-sensitive troponin T-level at 585.0 ng/ml (normal range 12.7-24.9 ng/ml), the patient was transferred for emergency coronary angiography. Multiply ectasia in left coronary artery, in particular a small sac-like aneurysm in 11 segment and a spindle-shaped aneurysm in 13 segment; a large-sized fusiform aneurysm with contrast stasis in the 6-7 segments of left anterior descending artery; ectasia in 1 segment of right coronary artery were revealed (Fig.1. B, C, D).

A computer tomographic aortogram confirmed the presence BAV with signs of calcification and an enlarged ascending aorta measuring 50 mm in the sinuses of Valsalva, 44 mm in sinotubular junction and 55 mm in tubular aortic segment (Fig. 1.E, F). No aortic root or descending aortic aneurysm or dissection was evident.

The patient was recommended surgical revascularization and ascending aorta replacement. He underwent coronary artery bypass grafting of left descending and

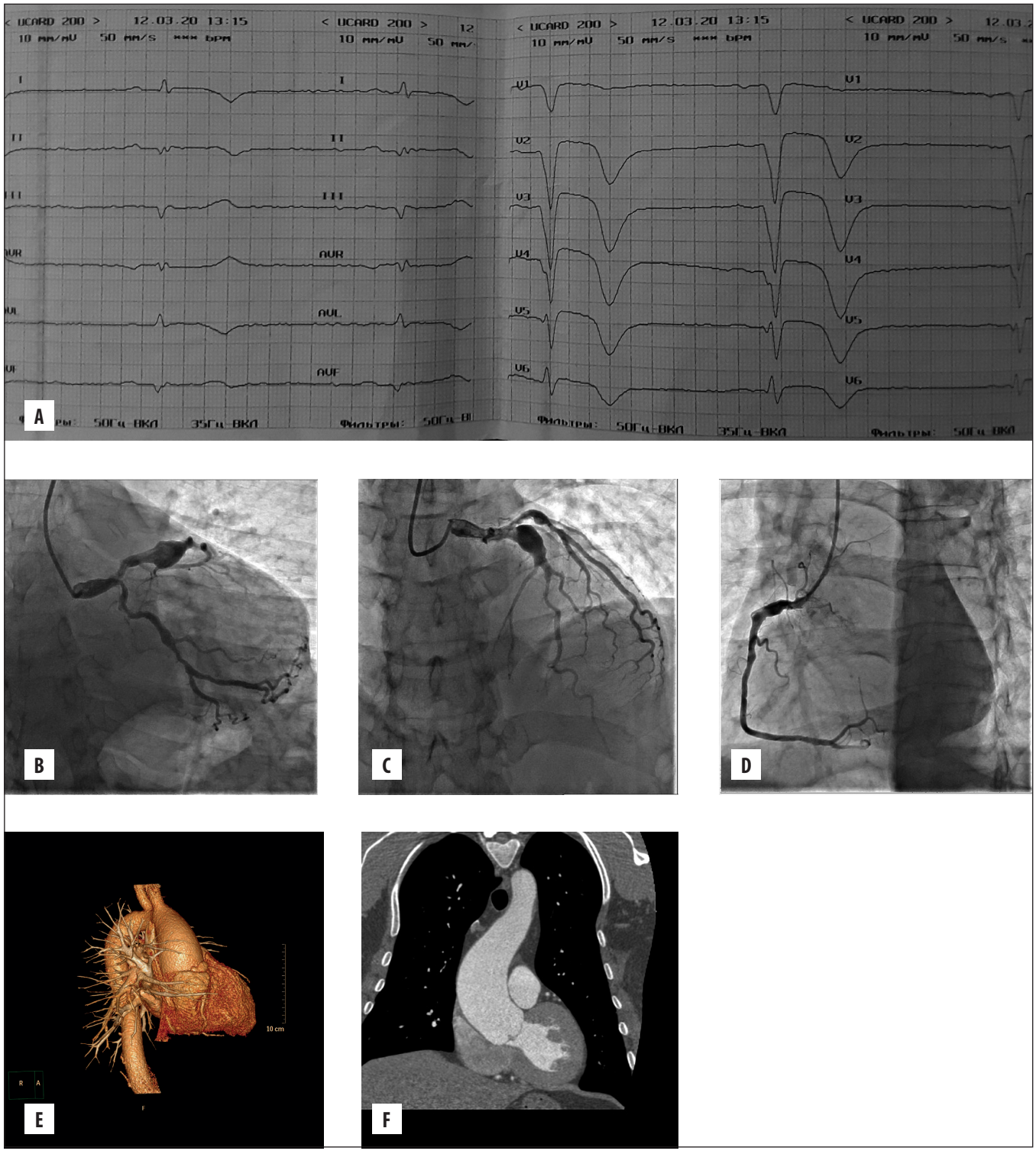


**Fig.1.** A: ECG: Initial electrocardiogram demonstrated normal sinus rhythm with 1.0 mm ST-segment elevation and negative T wave in leads I, AVL, V2-V6
B.C.D: Coronarography: Aneurysmically enlarged left coronary artery, a small sac-like aneurysm in 11 segment and a spindle-shaped aneurysm in 13 segment; a large-sized fusiform aneurysm with contrast stasis in the 6-7 segments of LAD; in the right coronary artery - ectasia in 1 segment
E.F: CT scan demonstaring bicuspid aortic valve with signs of calcification and an enlarged ascending aorta in tubular segment.

circumflex coronary arteries and tube graft replacement of ascending aorta in 1 month after ACS in experienced centre. Follow up in 1 year was unremarkable. The patient was adherent to healthy lifestyle and pharmacological treatment.

Our case describes the case of multiply CAE presenting as STEMI in adult men with predisposing atherosclerotic risk factors, but without significant coronary stenosis ≥ 50 %. The dilatation of the ascending aorta and BAV was an incidental finding on transthoracic echocardiography, confirmed on CT scan.

CAE is the aneurysmal dilatation of coronary artery defined as a dilatation with a diameter of 1.5 times the adjacent normal coronary artery based on CASS registry [6, 7, 8]. Its frequency in general population is ranging from 1.5% to 5%, in subjects with a strong positive family history of MI with male predominance [9, 10].

Up to 50% to 70% of patients with BAV have evidence of aortic dilatation, which typically involves the aortic root and ascending aorta, but not the descending aorta. CAE occurred with and without dilatation of the ascending aorta, is another frequent appearance of BAV disease [11, 12]. It had been speculated that CAE and aortic aneurysm share a similar histology and pathogenic process, which is generalised impairment of the wall of the entire arterial system [13]. The matrix metalloproteinases, a group of enzymes that degrade various components of the extracellular matrix in the arterial wall, have been found to be elevated both in patients with CAE and those with aortic aneurysm [4]. By retrospective review of coronary angiograms, CAE was found more than twice as frequently in CMR-confirmed BAV compared with TAV disease. Most studies showed an underlying congenital anomaly in the aortic media associated with BAV that predisposes these patients to develop dilatation with an aggravation induced by the valve dysfunction [7].

Likewise, no consensus exists about the natural history, the clinical management, and optimal treatment of this condition, despite CAE represents not only an anatomic variant but also a clinical constellation of CAD, that has been associated with an increased risk for ACS [9, 11]. In patients with ACS due to CAE culprit, the emphasis is to restore flow. Percutaneous coronary intervention of an aneurysmal/ectatic culprit vessel had lower procedural success and a higher incidence of no-reflow and distal embolization [4]. For CAE involving the left main coronary artery, multiple or giant (>20 mm, or > 4× reference vessel diameter) aneurysms, surgical resection is considered the first-line therapy [5,14]. Elective surgical repair remains the mainstay for the management of symptomatic or asymptomatic aortic aneurysm of which the diameter > 55 mm or ≥ 50 mm when additional risk factors are present [15,16]. Medical treatment as well as lifestyle changes and risk factors control, and serial imaging assessment of aortic aneurysm constitute the second part of the management of these patients [7].

## CONCLUSIONS

Clinical presentation of aneurysmal dilatation of coronary arteries and ascending aorta with BAV range from random findings on cardiac imaging to ACS, and their management is still challenging. Knowledge of the possible clinical presentation, accurate imaging assessment, and interventional or surgical treatment of these diseases are essential to achieve optimal results. We need prospective studies and registries to improve patient care and outcome.

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CASE STUDY

# MANAGEMENT OF RECURRENT CSF LEAK AFTER OCCIPITAL TUMOR SURGERY: A CASE REPORT

DOI: 10.36740/WLek202207134

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**ABSTRACT**

We present the case of a 10-year-old male with recurrent CSF leakage after surgery for an occipital tumor. Initial management of the CSF leak, including debridement, re-exploration, and lumbar drain insertion, failed to address the problem. The last resort was the insertion of the EVD, which managed to stop the leak.

Cerebrospinal fluid leakage remains one of the most common complications in neurosurgery. CSF leakage can prolong hospitalization, require further surgery, and cause tension pneumocephalus, CSF infection, and wound dehiscence. Management of postoperative cerebrospinal fluid leakage includes suturing the surgical wound and applying pressure dressings or through surgical means such as cerebrospinal fluid diversion and re-exploration.

**KEY WORDS:** CSF leak, brain tumor, disease

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## INTRODUCTION

Cerebrospinal fluid (CSF) leakage is a common postoperative problem after intracranial surgery[1, 2]. Cerebrospinal fluid leakage poses a significant risk of morbidity and a potentially life-threatening condition due to the risk of meningitis [1, 3]. Infratentorial procedures are six times more likely to occur than supratentorial procedures. [4]. In posterior fossa surgery, the rate of complications might be as high as 17%.[5]. CSF leaking is associated with a high risk of morbidity and is possibly fatal due to the danger of meningitis. [5–7]. Furthermore, the costs related to treating patients affected by this complication have been estimated to be 141% greater than that of patients without a CSF leak.1The incidence of CSF leakage occurs in 32% of posterior fossa surgery cases [8, 9]922 subjects who underwent resection of vestibular schwannomas from 1970 to 2010. Intervention: Surgical resection of vestibular schwannoma. Main Outcome Measures Patient demographics, surgical approach used, CSF leak incidence, meningitis, treatment, and success in the management of CSF leaks. Results: Postoperative CSF leaks were observed in 12.9% of our patients. There was no significant difference between the type of approach and the presence of CSF leak with translabyrinthine, suboccipital and middle fossa CSF leak rates of 12%, 12%, and 13%, respectively (p = 0.07.

Treatment of postoperative CSF leak after brain tumor surgery includes initial conservative management with pressure dressings and suturing of the wound. CT therapy choices include starting with conservative methods such as re-suturing the wound and then deciding on CSF lumbar drainage if the CSF leakage does not stop. [8, 10], or, as a first strategy, to use CSF lumbar draining in conjunction with conservative therapy [9]. In the event that these procedures fail, surgical repair is performed [11].If conservative management fails, lumbar spinal drainage may be considered. Surgical re-exploration is recommended as a last resort [1, 12]

## CASE REPORT

A 10-year-old male came to our hospital with chief complaints of headache and blurred vision in the last three years, which had worsened since three days before admission. The patient was diagnosed with Wilm's Tumor in 2014, during which he had a left nephrotomy and subsequent chemotherapy and radiotherapy.q Contrast brain MRI revealed a solid extra-axial mass with a cystic component in the left occipital region (Figure 1). The patient then underwent surgical removal of the tumor. The bone was found to be infiltrated by the tumor and thus not reinserted after surgery. Duraplasty is performed using periosteal grafts and water-thigh sutures. The postoperative period went smoothly. Histopathological examination revealed a small round cell tumor.

On the 10th postoperative day, the patient showed wound dehiscence at the surgical site along with a yellowish-green discharge (Figure 2). We decided to perform debridement and dural exploration with primary sutures. CSF was found to leak through the suture site of the dura mater, and thus, fibrin glue was applied to the dura mater. Granulation tissue and fluid collections were found beneath the galea. In a microbial culture, both granulation tissue and liquid showed the growth of Escherichia fergusoni, which was sensitive to Meropenem.

On day 14, post debridement, the patient showed recurrent wound dehiscence at the same site. Re-debridement and dural repair were performed concurrently with the placement of a lumbar drain. The defect was found at the edge of the dural suture. We have re-sewn the dural defect with a periosteal graft.

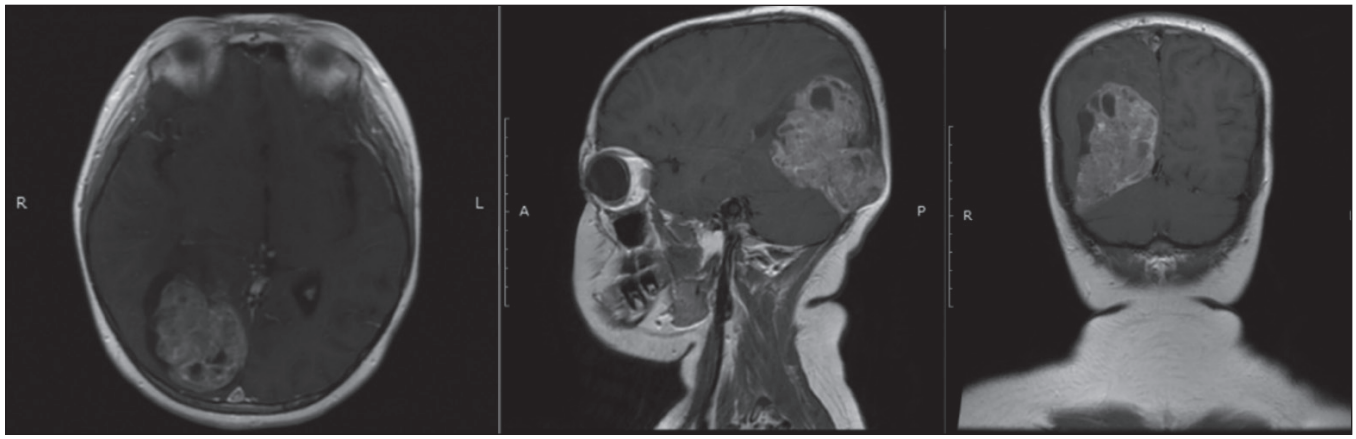


**Fig. 1.** Contrasted brain MRI demonstrated solid mass with cystic component on the cortical and subcortical region of the occipital lobe with perilesional edema. After contrast administration, it showed rim contrast enhancement and bone destruction on the right occipital, suggesting a metastatic process

**Fig. 2.** Surgical wound ten days after surgery. Blue arrow demonstrating wound dehiscence

**Fig. 3.** Bulging scalp on craniectomy site three days after Lumbar drain removal

CSF samples were collected and sent for microbial culture, revealing different results (Stenotrophomonas maltophilia sensitive to Ceftazidime) from previous microbial cultures from subgaleal fluid collection. The patient was then given Ceftazidime injection with routine wound care.

At seven post debridement, the wound was dry, and there was no discharge. The lumbar drain produces 20cc of CSF and is then removed. However, three days after removing the lumbar drainage, the patient was febrile, and we found a prominent scalp at the craniectomy site (Fig. 3), with no evidence of wound dehiscence or wound discharge. A contrast brain CT scan revealed a subgaleal effusion. The tumor bed was seen to be filled with CSF and connected to the ventricular system (Figure 4). We decided to perform extra ventricular drainage (EVD) on the Right Kocher point, and we found clear cerebrospinal fluid with an initial pressure of 14 cm H2O. CSF microbial culture revealed the same bacterial growth as the previous one (Stenotrophomonas maltophilia is sensitive to Ceftazidime). We successfully continued Ceftazidime injection along with routine wound care and pressure bandages. The EVD produces a daily average of 250cc CSF.

The wound healed on day 17 after EVD. There was no palpable subgaleal effusion, and two repeated CSF cultures showed clear fluid with no evidence of bacterial growth. We managed to challenge the EVD (Dependent Test) by clamping it for two days. During observation, the patient had no signs of intracranial hypertension; the craniectomy site was flat without a palpable subgaleal effusion (Fig. 5). The EVD was then removed, and the patient was discharged three days later.

Cerebrospinal fluid (CSF) leakage from surgical wounds remains one of the most common complications in neurosurgery. The reported incidence of CSF leakage depends on the site

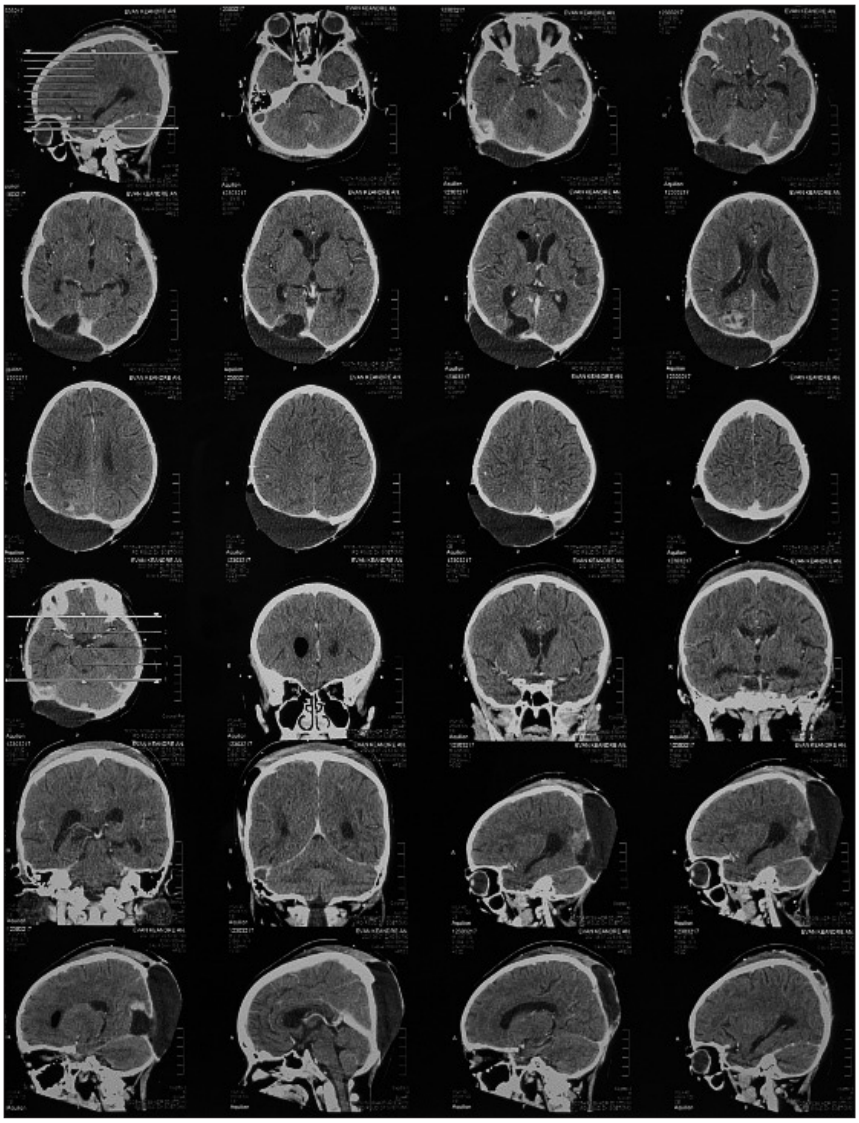

**Fig. 4.** Head CT-scan with contrast demonstrating subgalea effusion and connection between the tumor bed and the ventricular system
**Fig. 5.** After removal of EVD before patient discharged. The wound was healing and dry

of surgery, with posterior fossa surgery being the most likely [1, 13–15]randomized, double-blinded single-center trial in patients undergoing elective craniotomy with dural opening. They compared their standard dural closure by running suture alone (with the use of a dural patch if needed. Craniectomy is associated with postoperative CSF leakage [16–18]PubMed, and Cochrane database were searched for studies reporting CSF leakage after intradural cranial surgery in patients up to 18 years old. Meta-analysis of incidences was performed using a generalized linear mixed model. RESULTS: Twenty-six articles were included in this systematic review. Data were retrieved of 2929 patients who underwent a total of 3034 intradural cranial surgeries. Surprisingly, only four of the included articles reported their definition of CSF leakage. The overall CSF leakage rate was 4.4% (95% CI 2.6 to 7.3%. In the postoperative phase, the dura may periodically protrude due to CSF buildup or increased pressure, for example, when the patient coughs or strains [17]we analyzed the impact of different factors in CSF leak development after a retrosigmoid approach. Identifying risk factors related to a specific approach may help the surgeon to tailor the perioperative management and to appropriately counsel patients regarding their risk profile. METHODS: We retrospectively reviewed the clinical, surgical, and outcome data of 103 consecutive patients (M/F, 47/56; mean follow-up 35.6 ± 23.9 months. In patients who have had a craniectomy, the dural sutures may tear when the dura protrudes during this episode. As a result, minor defects in dural closure may enlarge, and cerebrospinal fluid is more likely to leak and collect in the muscle and subcutaneous planes, causing pseudomeningocele and CSF leakage from the wound [18, 19]access to the posterior fossa involved a suboccipital craniectomy. More recently, posterior fossa craniotomies have been described, although the long-term benefits of this procedure are not clear. The authors compared the postoperative complications of craniectomies and craniotomies in children with posterior fossa tumors. Methods. From a total of 110 children undergoing surgery for posterior fossa tumors, 56 underwent craniectomy and 54 had a craniotomy. The mean duration of the hospital stay was longer in the craniectomy group (17.5 compared with 14 days. In this case report, however, the site of surgery did not predispose to CSF leak. Complete resection of the tumor until it penetrated into the ventricle resulted in CSF leakage, shown on postoperative CT scan (Figure 6).

The potential morbidities brought about by CSF leakage are prolonged hospitalization, additional surgery, tension pneumo-

cephalus, CSF infection, and wound dehiscence [1, 13, 20–23]. Mechanical pressure on the dural or fascial wound edges exerted by CSF is thought to impair proper apposition of the wound margins and therefore prevent healing [24]. Interestingly, it has been observed that surgical tissue exposed to CSF does not bleed, shows smooth edges, and has no evidence of granulation tissue formation [20]. In our patient, all CSF leak morbidities, except pneumocephalus, were obtained. According to sensitivity, wound dehiscence and CSF were eventually healed by combining additional surgery, routine wound care, and definitive antibiotics. The total length of stay in the hospital was 83 days.

Management of patients with postoperative cerebrospinal fluid leakage includes non-operative management, including suturing of the wound and pressure dressings, cerebrospinal fluid diversion, and re-exploration [1, 12, 19, 22, 25–27]. In this case report, the initial management was debridement, application of dural sealant, and primary suture. However, the patient experienced recurrent wound dehiscence at the same site. Kushel et al. [14].Revealed no statistically significant difference in the frequency of CSF leaks and pseudomeningoceles between patients who received dural sealants and those who did not. Cerebrospinal fluid leakage and pseudomeningocele have more to do with circulating cerebrospinal fluid than with dural sealing. Therefore, it is not surprising that we did not find any additional benefit after using the sealant.

We repaired the dura after repeated CSF leaks, re-stitched the wound, and inserted continuous lumbar drainage (CLD). CLD has shown a high success rate of 98% in patients with CSF leak [28]yet well-recognized complication of skull base fractures, skull base surgeries, and variety of spinal procedures. Continuous lumbar drainage (CLD. However, in our case, CSF accumulation was still present at the craniectomy site. This is due to the ineffective drainage of CSF from CLD as indicated by CSF production of 20cc/day. So, we decided to perform an EVD to allow faster CSF clearance and thus ensure natural wound closure[14].

In this case, the EVD was removed seventeen days after insertion, and CSF cultures were sterile on two occasions. As the clinical and neurological condition remained stable, the wound healed well, and there was no evidence of subgaleal effusion; the patient was discharged on day three post-EVD. The patient did well in the outpatient unit at one month of follow-up.

## CONCLUSIONS

Cerebrospinal fluid leakage in surgical wounds carries a significant risk of morbidity. Postoperative management of CSF leaks includes simple re-suture and pressure dressing, CSF diversion (continue lumbar drain, external ventricle drain), and re-exploration.

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CASE STUDY

# DUNBAR SYNDROME: CLINICAL MANIFESTATION IN ADULTS, DIAGNOSTIC PROBLEMS (CASE REPORT)

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**ABSTRACT**

In this case we used CBC and biochemical tests, ECG, ultrasound of the abdominal cavity and heart, CT scan with and without IV contrast. Women with complains on recurrent severe abdominal pain in epigastric region and right part of the abdomen radiating to the back, nausea, vomiting. Making laboratory and instrumental tests for confirmation of the diagnosis. Surgical treatment of DS was performed and after one year of the follow up there were no complications. DS may mimic other medical conditions such as gallbladder diseases, gastritis/peptic ulcer, appendicitis, colorectal malignancy, hepatitis, atherosclerotic diseases etc. That is why DS is a diagnosis of exclusion. This case illustrates pathway to find correct diagnosis and improve management tactic.

**KEY WORDS:** Dunbar syndrome, median arcuate ligament, case report

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## INTRODUCTION

The compression syndrome of the celiac artery is a complex of symptoms, accompanying the outcast compression of the celiac artery by anatomical elements (sickle bunch and / or medial legs of the diaphragm, solar plexus, tumors, etc.) and due to narrowing disruption (stenosis) His lumen with the formation of chronic mesenteric syndrome ischemia. Typically, the ligament runs across the largest blood vessel in the body (aorta) and sits above the celiac artery without causing problems. But sometimes the ligament or artery may be out of place, causing syndrome. The ligament may also put pressure on the network of nerves surrounding the celiac artery (celiac plexus) [1].

This syndrome also known as MALS (Median Arcuate Ligament Syndrome), CACS (celiac artery compression syndrome), Dunbar syndrome (DS), Harjola-Marable syndrome.

DS is different than median arcuate ligament compression. Median arcuate ligament compression occurs in about 10% to 25% of the population and doesn't cause any symptoms. Chronic abdominal pain is a very common condition that can have significant negative, long-term psychosocial consequences, including increased risk for anxiety, school and work absences, poor functional capacity, and a poor quality of life [2].

The cause is not fully understood; however, it is suspected that there could be a combination of vascular (blood supply) and neurogenic (neurological) components involved [3].

The abdominal pain after eating is the most common symptom, found to be present in approximately 80% of individuals, while weight loss was found in approximately 48% and abdominal bruit was appreciated in approximately 35% [4].

Other symptoms include: weight loss (usually >20 pounds), and abdominal bruit (abnormal sound of a blood vessel when blocked or narrowed), nausea, diarrhea, vomiting, and delayed gastric emptying [3, 5].

Diagnostic methods include different variants of imaging, such as CT scan, MRI, ultrasound, and arteriography. But in clinical practice sometimes it is hard to say when it is necessary to use this methods, especially looking on rareness of DS.

## CASE REPORT

Women M., 37 yo was admitted to the City Clinical Hospital (Vinnitsa) with complains on severe abdominal pain in epigastric region and right part of the abdomen radiating to the back, nausea, vomiting. History: these complains appeared rapidly day ago; used NSAIDs to relief pain without any effect. She noticed epigastric abdominal pain sometimes, but NSAID usually helped.

CBC: Hb – 140 g/L, RBC – 4,3 T/L, platelets – 299 G/L, WBC – 7,5 G/L, stabs – 6%, segmental – 52 %, eosinophils – 1%, lymphocytes – 38%, monocytes – 3%, ESR – 10 mm/h.

Glucose level 3,7 mmol/l

General protein 63g/L, ALT 0,15 U/L, bilirubin: general 13,1 μmol/l, conjugated 4,5 μmol/l, unconjugated 8,6 μmol/l.

Prothrombin index 84 %, serum fibrin 2,0 g/L

Serum C-reactive protein 30 mg/L (Normal range 4-10 mg/L).

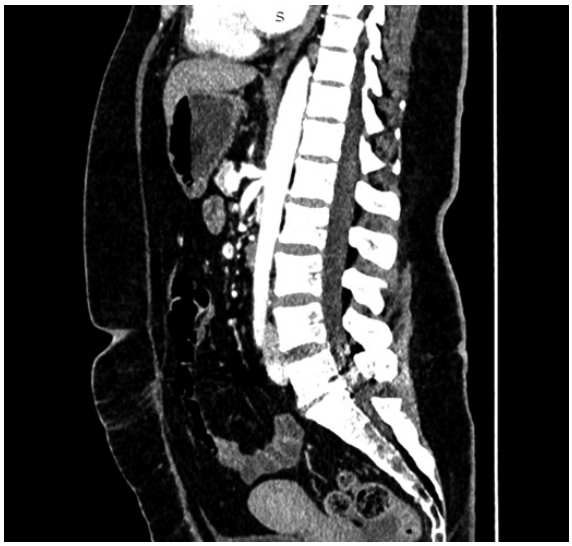

**Fig. 1.** CT of the abdomen, sagittal view

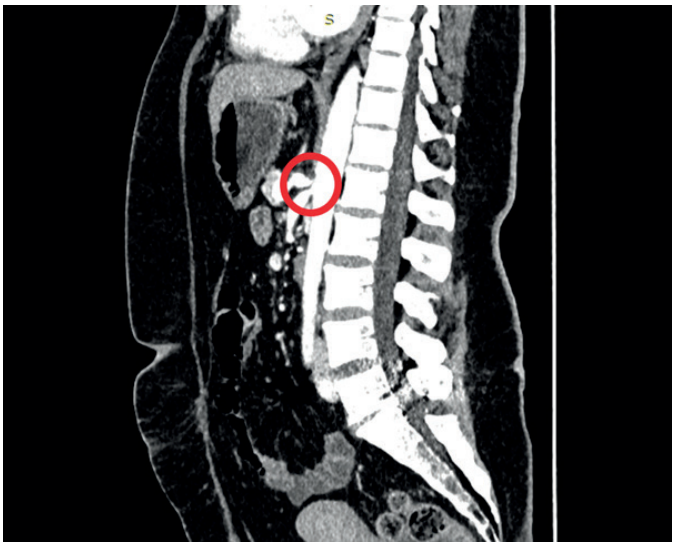

**Fig. 2.** CT of the abdomen, sagittal view

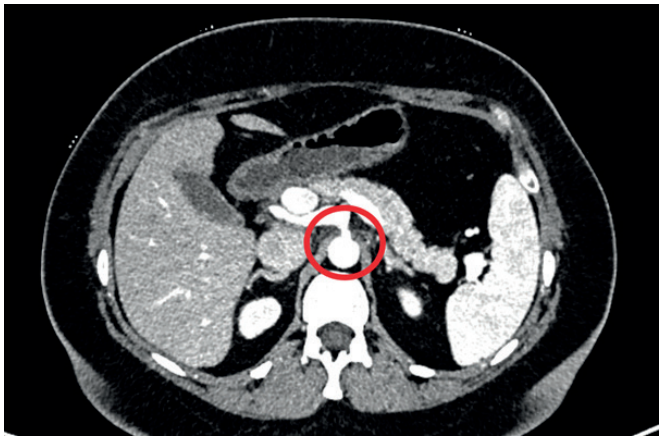

**Fig. 3.** CT of the abdomen, axial view

Serum lipase 165 U/L (Normal range 10-140 U/L), L-amilase 220 U/L

Procalcitonin 1,8 ng/mL (Normal range 0.15 and 2.0 ng/mL)

Ultrasound of the abdominal cavity: changes in the pancreas, no signs of biliary tract disoders.

EchoCG: left ventricle diastolic dysfunction, EF 68%, dilatation of left atrium and ventricle.

Chest X-ray: normal

Diagnosis: Acute pancreatitis, mild severity

She was treated with rehydration therapy and pain control for a week. A regular diet was recommended on admission.

She was admitted to the hospital one more time after 3 weeks with the same complains.

CBC: Hb – 145 g/L, RBC – 4,2 T/L, platelets – 305 G/L, WBC – 7,2 G/L, stabs – 1%, segmental – 60 %, eosinophils – 1%, lymphocytes – 33%, monocytes – 5%, ESR – 10 mm/h.

Glucose level 4,3 mmol/l

Prothrombin index 87 %, serum fibrin 2,2 g/L

L-amilase 328 U/L

To differentiate the diagnosis CT scan of abdominal cavity (without IV contrast) was performed: diffuse changes of the pancreas; concernments in both kidneys. As a result, therapy of acute pancreatitis was repeat with IV fluids and pain control used epidural analgesia.

Third episode of the postprandial abdominal pain occurred after 4 weeks she was discharged from the surgical department.

CBC: Hb – 149 g/L, RBC – 4,5 T/L, platelets – 262 G/L, WBC – 7,55 G/L, stabs – 8%, segmental – 54 %, eosinophils – 1%, lymphocytes – 30%, monocytes – 7%, ESR – 15 mm/h.

Glucose level 3,5 mmol/l

General protein 71 g/L, urea 5,8 mmol/L, creatinine 105 μmol/l, bilirubin: general 9,1 μmol/l, conjugated 2,8 μmol/l, unconjugated 6,3 μmol/l.

Prothrombin index 81 %, serum fibrin 2,9 g/L

Heart ultrasound: left ventricle diastolic dysfunction, EF 68%, dilatation of left atrium and ventricle, aortic insufficiency I degree.

Ultrasound of the abdominal cavity: diffuse changes of the liver and pancreas.

FEGDS: catarrhal esophagitis, catarrhal gastroduodenitis, signs of pancreatic-biliary disorders.

CT scan with IV contrasting: mediastinum lipomatosis. Compression of the celiac trunk by the diaphragmatic crurae, collateral circulation between gastroduodenal artery and superior *mesenteric* artery (fig. 1, 2, 3). Ascites. Concernments in both kidneys. Transpedicular fixing system.

Diagnosis: Median arcuate ligament syndrome (MARS). Chronic rheumatic heart disease, non-active stage, combined mitral heart defect: mitral insufficiency II degree and mitral stenosis I degree, heart failure 0 degree.

Treatment. Endovascular celiac artery stenting with release of the median arcuate ligament were performed. One year follow up didn't find any complications or recurrence of the symptoms.

DS occurs most frequently in females aged 40 to 60 with duration of symptoms ranging from 3 months to 10 years

[6, 7]. There are several debates in the diagnosis and treatment of DS as this is rare clinical situation. Postprandial abdominal pain, vomiting, and weight loss are the typical clinical symptoms for this syndrome. However, these patients are frequently diagnosed and treated as gastritis, peptic ulcer or acute (chronic) pancreatitis before the correct diagnosis is confirmed [8].

The etiology of DS remains unknown but a case report of monozygotic twins suggests a congenital origin [9]. Whether the pathophysiology is primarily vascular or neuropathic origin remains undetermined [10]. Isolated vascular compression of the celiac artery as the sole etiologic factor seems unlikely. DS can cause asymptomatic compression in 10%–24% of the population. Collateral circulation by the superior mesenteric artery provides adequate blood supply; therefore, postprandial abdominal pain should not be expected with celiac artery compression alone [11].

The compression of the celiac artery by the median arcuate ligament is believed to cause intermittent mesenteric ischemia. However, this explanation alone may not completely explain the condition as there is usually a rich collateral network of mesenteric vessels between the celiac artery and the superior mesenteric artery. Therefore, there may be a role for underlying celiac nerve plexus dysfunction as well when considering the etiology of this condition. Nerve dysfunction may lead to abnormal splanchnic vasoconstriction, leading to ischemia [6].

The etiology of DS is likely multifactorial, including compressive effects on the celiac artery and surrounding neurogenic structures. In celiac artery compression, it has been noted that either the celiac artery is located slightly higher or the median arcuate ligament located lower than expected.

Nowadays, surgery is the only treatment option for DS. Several management strategies are instituted for the treatment of DS including interventional angioplasty or stenting and surgical procedures such as releasing of the median arcuate ligament compressing the celiac artery or bypass surgeries [12, 13]. The releasing of the ligament may be done by open, laparoscopic or robotic surgery [14, 15]. Minimally invasive techniques have gained popularity in the surgical management of this condition limiting open surgery to more complicated celiac by-pass procedures. Some patients may require prolonged use of analgesics while some others may necessitate para-spinal celiac ganglion blockage as an additional measure to completely alleviate the symptoms [8].

In a large series, significantly higher symptomatic relief was achieved through combined release of the MAL and revascularization. If celiac artery compression alone is corrected, evidence suggests up to 53% will be asymptomatic on long-term follow up. Combined release and revascularization however increase the long-term success to 79% [16]. Therefore, some patients may require additional revascularization procedures such as mesenteric artery stenting or bypass to provide long-term symptomatic relief as in a presenting case.

Since delay of revascularization is unlikely to adversely affect outcome, most choose ligament release first, followed by revascularization via stenting or bypass if symptoms persist. Endovascular celiac artery stenting alone without release of the ligament is discouraged because of clinical failure and recurrent stenosis [17].

About 60% to 70% of the patients report symptom relief after surgical treatment. Symptom relief has been reported to be immediate in some instances. In others, it may take up to a few months for the resolution of the pain [18]. The presence of postexertional pain has been shown to be correlated with symptomatic improvement after surgery while the presence of emesis and unprovoked pain preoperatively has been shown to be associated with suboptimal surgical outcomes postoperatively. Patients who have a good response to a diagnostic celiac plexus block preoperatively also seem to report better symptom relief following surgical intervention. The presence of atherosclerotic risk factors may predict poorer outcomes postoperatively [19].

## CONCLUSIONS

DS may mimic other medical conditions such as gallbladder diseases, gastritis/peptic ulcer, appendicitis, colorectal malignancy, hepatitis, atherosclerotic diseases etc. That is why DS is a diagnosis of exclusion. This case illustrates pathway to find correct diagnosis and improve management tactic.

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CASE STUDY

# CLINICAL CASES OF LIFE-THREATENING ARRHYTHMIAS: LONG AND SHORT QT SYNDROMES

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## ABSTRACT

**The aim:** To present clinical cases of sudden cardiac death in patients with prolonged and shortened QT interval.

**Materials and methods:** The study includes description of two different clinical cases with prolonged and shortened QT interval after sudden cardiac death. Verification of the diagnosis was performed using the criteria recommended by the European Society of Cardiology (ESC) and European Heart Rhythm Association (EHRA).

**Clinical case:** Two clinical cases of syncope with life-threatening arrhythmias, confirmed by electrocardiographic and clinical diagnostic criteria, indicating a change in the dispersion of the QT interval, are presented. The first case represents a patient with intermittent syncope. The patient had previously had attacks of sudden palpitations with fainting. The patient came after another episode of syncope. Further follow-up revealed clinical and electrocardiographic signs of ventricular tachycardia paroxysm. Than the prolongation of the QT interval is set. In this clinical case, verification of QT prolongation syndrome was established in the elderly. Another clinical case is associated with QT syndrome, which remains difficult to diagnose. Such cases have been described relatively recently. The clinical picture of the syndrome of short QT interval in the presented clinical case was characterized by the appearance of syncopal states. The patient showed changes in the adjusted QT interval <320 ms. The causes of syncope in a patient with a short QT interval were paroxysms of atrial fibrillation (AF) or ventricular arrhythmias. At the same time the anatomical structure of a myocardium remains normal and unchanged. The hereditary nature of the disease in the patient has been proven.

**Conclusions:** Timely diagnosis of prolongation (LQTS) or shortening (SQTS) of the QT interval after ECG and Holter monitoring allows you to identify a group of patients with an increased risk of developing ventricular arrhythmias, syncope and sudden cardiac death. Implantation of a cardioverter-defibrillator is an effective and safe method of preventing sudden cardiac death in patients with long and short QT syndromes.

**KEY WORDS:** sudden cardiac death, long and short QT syndromes, life-threatening arrhythmias

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## INTRODUCTION

Every year, sudden cardiac death (SCD) causes the death of 400 thousand people, and in 10-20% of cases, death is due to the presence of hereditary pathology [1, 2]. Identification of hereditary pathology in families with a high risk of developing SCD allows the doctor to timely decide on the implantation of cardioverter-defibrillators (ICD) [3].

Long QT syndrome (LQTS) is a genetically determined disease with a high risk of sudden cardiac death (SCD), characterized by permanent or transient prolongation of the QT interval on the electrocardiogram (ECG), episodes of loss of consciousness against the background of life-threatening ventricular polymorphic tachycardia or ventricular fibrillation [4]. LQTS may be deal with over than 600 mutations in 16 different genes [5], encoding proteins of transmembrane ion-selective channels (mainly potassium or sodium), which leads to disruption of the functioning of the latter, resulting in an increase in the duration of the action potential in cardiomyocytes, initiating the appearance of polymorphic ventricular tachycardia and "torsade de pointes" tachycardia [5]. The incidence of LQTS is 1 in 2500 people [5]. The average age of clinical manifestation of the syndrome is 14 years [6]. Factors contributing to the electrical instability of the myocardium with the subsequent development of life-threatening arrhythmias are physical activity, emotional states, swimming, loud, sharp beeps (for example, an alarm clock), the postpartum period, less often arrhythmias occur during sleep or at rest [6]. The first manifestation of the syndrome may be SCD. Patients who survived an episode of cardiac arrest have a high risk of a recurrent episode, even on the background of therapy with beta-blockers - 14% over 5 years [7].

At the same time, short QT syndrome (SQTS) is rarely diagnosed, since it was described relatively recently in 2005 by Gussak I, et al. [8], and therefore virtually unknown. In 2005, the results of the observation of 15 patients with a short QT interval [8] were published. The work convincingly demonstrated that shortening of the QT interval is an inherited trait and is associated with a high risk of developing life-threatening arrhythmias. Long-term follow-up of the families of these patients led to the conclusion that shortening of the QT interval is also one of the unfavorable risk factors (RF) for the development of SCD [8]. The prevalence of short QT syndrome in the population is unknown, but available publications indicate its widespread prevalence [9]. The electrocardiographic characteristics of

short QT syndrome are represented by a decrease in QTc time < 320 ms, a decrease or sometimes complete absence of the ST segment, and tall, narrow, symmetrical T waves in the chest leads [9]. The QT interval should be measured at rest, at a normal heart rate (HR) [10]. Short QT syndrome is the most common cause of death in children and adolescents. The disease can debut from the moment the patient is born, much less often in adulthood [11].

## THE AIM

The aim of the work - to present clinical cases of sudden cardiac death in patients with prolonged and shortened QT interval.

## MATERIALS AND METHODS

The study includes description of two different clinical cases with prolonged and shortened QT interval after sudden cardiac death.

Verification of the diagnosis was performed using the criteria recommended by the European Society of Cardiology (ESC) and European Heart Rhythm Association (EHRA) [12].

## CLINICAL CASES

### T INTERVAL, FIRST DIAGNOSED IN OLD AGE

Patient (women) K., 66 years old, was admitted to the Kyiv Heart Center with complaints of interruptions in the work of the heart, periodic increase in blood pressure (BP) up to 180/100 mm Hg. accompanied by headache, dizziness.

From the anamnesis it is known that the patient has been suffering from arterial hypertension (AH) for about 5 years. Over the past 3 years, interruptions in the work of the heart have been disturbing, for which the patient was examined in 2018 and 2020, and during daily ECG monitoring, frequent single atrial extrasystoles were recorded in the amount of more than 7000, with a predominance during the wakefulness period. Ventricular arrhythmias were not detected. Over the past few months, she has been taking bisoprolol 5 mg/day, amlodipine 5 mg/day, acetylsalicylic acid 75 mg/day, trimetazidine 35 mg/day, atorvastatin 10 mg/day. Due to the increase in interruptions in the work of the heart over the past 2-3 months, the patient underwent 24-hour ECG monitoring, where in the early morning hours ventricular flutter was recorded with a frequency of 300, lasting about 6 seconds, which developed against the background of a prolongation of the QT interval of more than 500 ms (Figure 1).

The patient does not exclude that this arrhythmia could develop during the loud ringing of the mobile phone alarm clock, while, after waking up, she does not notice any changes in the general condition, syncope, presyncope.

During a detailed survey, the patient indicated repeated syncope at a young age, mainly against the background of high body temperature with tonsillitis. At the age of approximately 40 years, there was an episode of clinical death on the background of hyperthermia with an infectious disease of the upper respiratory tract. This condition occurred at home in front of the spouse, was characterized by a sudden loss of consciousness within a few minutes, lack of cardiac activity and respiration, and was accompanied by a change in the color of the skin to gray-cyanotic and an act of spontaneous urination. As a result of first aid by her husband, the patient regained consciousness. In occasion of the given episode to doctors did not address and was not surveyed.

An objective examination of the general condition is satisfactory. On examination: the skin is clean. On palpation: the thyroid gland is normal, the pulse is the same on both hands, 72 per minute, there are no peripheral edema. Auscultation: vesicular breathing in the lungs, clear, non-rhythmic heart sounds, frequent extrasystoles. Stool, diuresis is not disturbed.

Results of instrumental and laboratory research methods. ECG dated January 2, 21 (Figure 2): sinus rhythm, irregular, heart rate (HR) 70 beats/min. Frequent atrial extrasystole, with episodes of bigeminy. P=0.1 s, P-Q=0.18 s, QRS=0.08 s, Q-T=0.46 s, Q-Tc (corrected)=0.50 s. Dispersion Q-T 01/05/2015. Q-Td=51 ms, Q-Tcd=448 ms, Q-Tcdn=129 c.u.

High resolution ECG 01/06/2021. Late potentials of the ventricles are not recorded. The total power of the neurohumoral modulation spectrum is within the conventional norm. The state of neurohumoral regulation is characterized by a moderate level of sympathetic, low level of vagal and humoral-metabolic influences. The balance of the divisions of the autonomic nervous system is characterized by a mixed (balanced) type of autonomic modulation of the heart rate.

Daily ECG monitoring 01/30/2021. Duration of observation is 22 hours 52 minutes. Heart rate during the day: average - 86 beats / min, minimum - 65, maximum - 133; Heart rate at night: average - 70 bpm, minimum - 63, maximum - 86. Circadian index - 1.23. Against the background of sinus rhythm with heart rate from 37 to 136 (average - 82), single supraventricular extrasystoles were registered - 7640, during the day - 6288, at night - 1352, an episode of ventricular flutter with a frequency of 300 per minute, lasting 6 seconds. Ischemic ECG changes were not registered. Load tolerance is average.

BP profile 01/03/2021. 125/70, 140/80, 110/65, 125/75, 135/75mmHg Art.

Echocardiography 02.01.2021. Left atrium - 34 mm (41*50 mm in 4-chamber position). Right atrium - 28*32 mm (in 4-chamber position). The end-systolic size of the left ventricle (LV) is 32 mm, the end-diastolic size of the LV is 52 mm. The thickness of the interventricular septum is 11/14 mm, the thickness of the posterior LV wall is 11/14 mm, the LV ejection fraction is 69% (M-mode), 71% (B-mode). Right ventricle - 17 mm. Systolic pressure in the pulmonary artery 29 mm Hg. Aortic valve - leaflets are sealed, regurgitation 1 st. Mitral valve - leaflets are not changed, regurgitation 2 st. Tricuspid valve - leaflets are not changed, regurgitation 2 st. LV myocardial contractility -

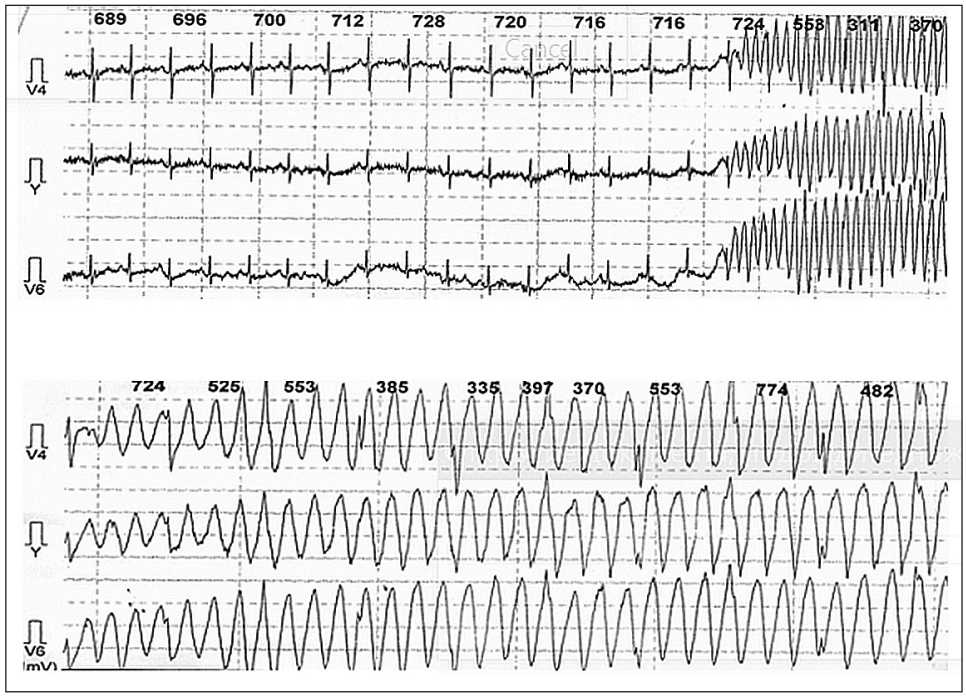


**Fig. 1.** ECG in 24-hour ECG monitoring

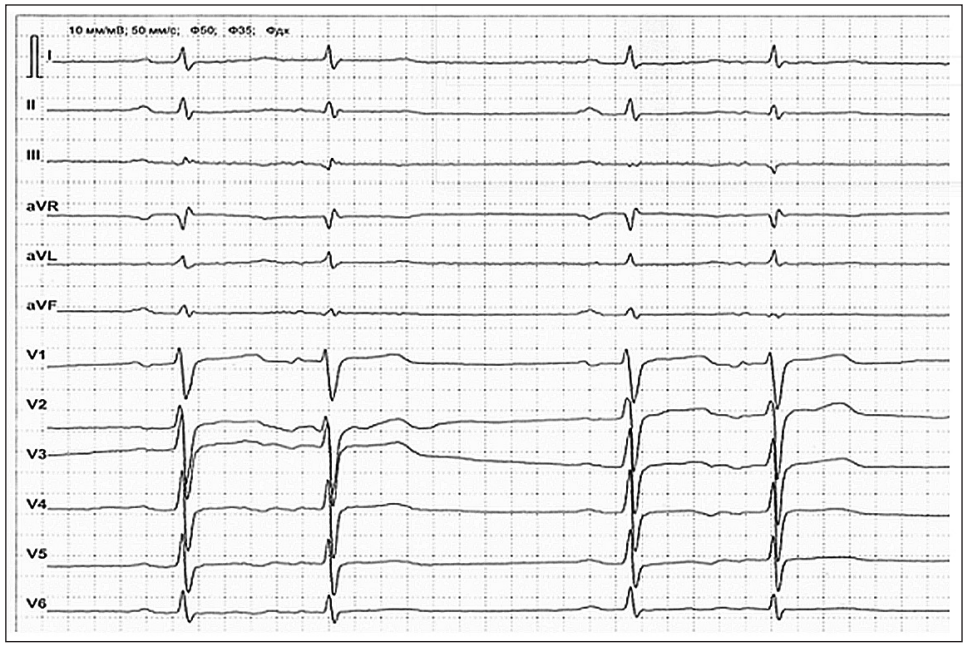


**Fig. 2.** ECG in admission

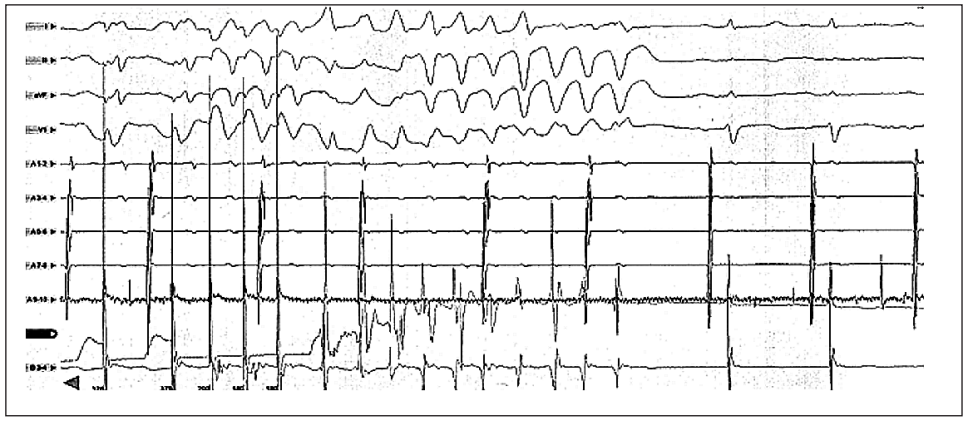

**Fig. 3.** Induction of paroxysm of non-sustained polymorphic ventricular tachycardia during endocardial pacing

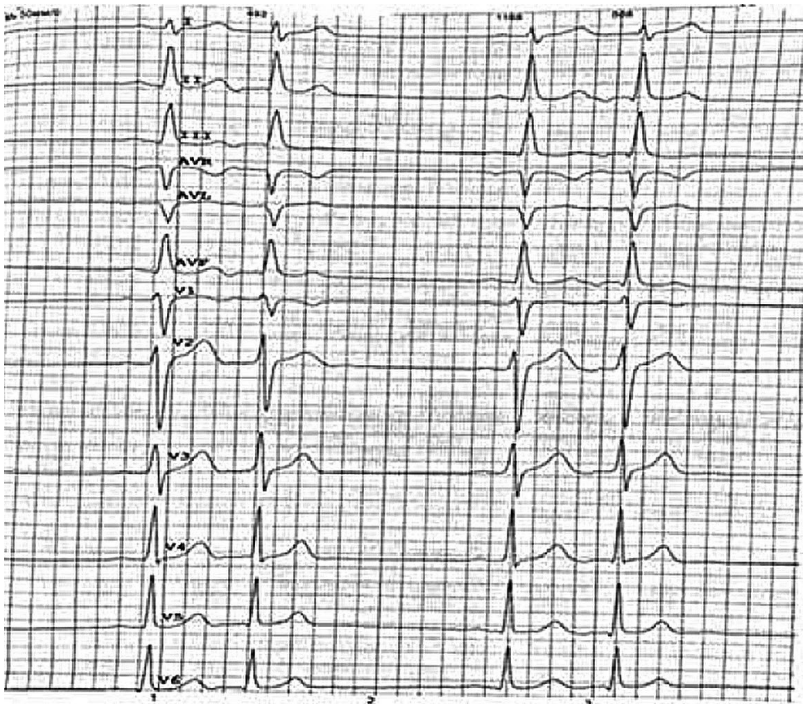


**Fig. 4.** Patient's ECG dated March 10, 2021. Velocity 50 mm/sec


**Fig. 5.** Patient's ECG dated March 14, 2021

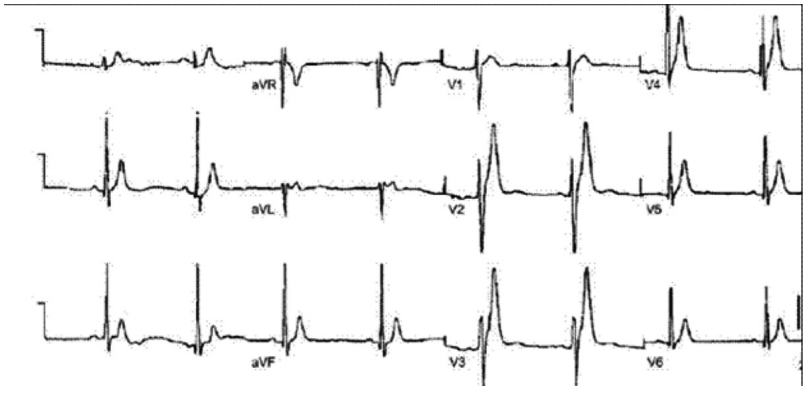


**Fig. 6.** ECG of the patient's older brother dated March 16, 2021

normokinesis. Conclusion: Signs of atherosclerotic lesions of the aorta and aortic valve. Aortic valve insufficiency 1 st. Regurgitation 2 st. on the mitral valve.

Coronary angiography. 01/09/2021. Left coronary artery: trunk - short, bifurcation, without stenosis. Anterior interventricular artery - the contours are uneven, clear, 20% stenosis at the border of the 1st and 2nd segments. The circumflex artery - without visible hemodynamically significant changes. The right coronary artery is hypoplastic, without visible hemodynamically significant changes. The type of blood supply to the heart is left.

Endocardial electrophysiological study of the heart. 01/09/2021. During programmed endocardial pacing, 2 paroxysms of non-sustained polymorphic ventricular tachycardia were induced (Figure 3).

A drug test with adrenaline: a paradoxical response - prolongation of the QT interval by more than 10% of the baseline.

Based on the results of the examination, a diagnosis was set: Transient long QT syndrome. Paroxysmal polymorphic ventricular tachycardia. Ventricular flutter. An episode of sudden cardiac arrest in history. Syncope. Ischemic heart disease: cardiosclerosis. Frequent atrial extrasystole. Atherosclerosis of the aorta and aortic valve. Aortic valve insufficiency 1 degree. Relative insufficiency of the mitral valve of the 2nd degree. Arterial hypertension of the 2nd degree. Risk 4. H 1.

Treatment was prescribed: beta-blockers (metoprolol - 50 mg 2 times a day), perindopril - 4 mg per day, acetylsalicylic acid - 75 mg per day, atorvastatin - 20 mg per day. Due to the high risk of SCD, in accordance with the recommendations of the European Society of Cardiology, implantation of a cardioverter-defibrillator was recommended, which she temporarily abstained from.

24-hour ECG monitoring on 06/12/2021 during treatment. The average daily heart rate is 77 beats/min, the average during the day is 84 beats/min, the average at night is 68 beats/min, the minimum heart rate is 45 beats/min. Circadian index - 1.23. On the background of sinus rhythm with a heart rate of 45 to 118, single supraventricular extrasystoles were registered - 6179, single ventricular extrasystoles - only 5 per day. Ischemic ECG changes were not registered. ECG during treatment: sinus rhythm, regular, heart rate 64 beats/min. Semi-horizontal position of the electrical axis of the heart.

P=0.1 s, P-Q=0.18 s, QRS=0.08 s, Q-T=0.40 s, Q-Tc=0.41 s.

## A CASE OF SUDDEN CARDIAC DEATH IN A PATIENT WITH A SHORTENED PQ INTERVAL

Patient (man) V., 22 years old, was admitted on March 9, 2021 to the Regional Cardiology Center in Chernivtsi due to an episode of loss of consciousness with successful resuscitation by the emergency medical team.

Recently, he has noted the appearance of rhythm disturbances in the form of frequent extrasystoles. Previously active complaints did not present.

There were no operations. Candidate Master of Sports in field hockey. He always endured physical activity without restrictions.

The general condition is satisfactory, consciousness is clear. Height - 183 cm. Weight - 75 kg, BMI - 22 kg/m$^2$. Skin and visible mucous membranes is in physiological color, no rashes. Peripheral lymph nodes are not enlarged. There is no peripheral edema. Musculoskeletal system: the joints are externally unchanged; there is no pain on palpation of muscles, joints and bones.

Auscultation: in the lungs vesicular breathing, rales are not heard. Heart sounds: arrhythmic, clear, no murmurs. Heart rate: 84 per minute, frequent extrasystoles per minute (more than 15 per minute), pulse is normal, blood pressure on the right and left hand is 120/70 mm Hg. The pulsation on the peripheral vessels is preserved, there are no noises on them.

ECG dated 03/10/21. Sinus bradycardia with a heart rate of 50 per minute. Electrical axis =90$^o$. Supraventricular extrasystole according to the type of bigeminy (polyfocal).

The diagnosis was set: arrhythmia according to the type of frequent supraventricular extrasystole, allorhythmia according to the type of bi-, and trigeminy. The corrected QT interval is 0.33 s.

ECG from 03/14/21. sinus arrhythmia. Heart rate 59-66-71bpm. Compared to the ECG dated 03/10/21, bradycardia and supraventricular extrasystoles are not recorded.

Echo-CG from 10.02.21. The aorta is condensed; size 2.7 cm (N to 3.7 cm). The amplitude of the opening of the AV is 1.8 cm (N 1.5-2.6 cm). Aortic valve: the leaflets are not sealed; the maximum pressure gradient is 4.9 mm Hg. Left atrium long axis - 2.5 (N 2.3-3.7). LA Volume 45 (N 4158 ml). Left ventricle: EDD - 4.0 (N 3.7-5.6 cm), ESD - 2.9 (N 2.3-3.6 cm), EDV 101 ml (N 60-120 ml). EF according to Simpson - 58%. Interventricular septum thickness - 0.8 cm (N 0.61-1 cm). The thickness of the posterior wall of the left ventricle is 0.8 cm (N 0.61-1 cm). Mitral valve: MDH 1.6 mmHg. Deflection of the front leaf by 4.8 mm. Right ventricle: anteroposterior size 1.8 cm (N 2.5-3.0 cm). Signs of insufficiency of valves: mitral I st., tricuspid 1 st.

On the ECG of previous years, similar changes, in the form of a shortening of the QT interval, were noted in 2018, Figure 5.

Velocity 50 mm/sec. As can be seen from this figure, the corrected QT interval is 0.34 s. QT is shortened.

Diagnosis. Rhythm disturbance according to the type of frequent supraventricular extrasystole, allorhythmia with type of bi-, trigeminy (syndrome of a shortened Q-T interval). Moderate prolapse of the anterior leaflet of the mitral valve with moderate mitral regurgitation.

Treatment. Bisoprolol 5 mg 1 time per day, acetylsalicylic acid 75 mg 1 time per day. At discharge, the condition is satisfactory.

Consultation with an arrhythmologist at the Kiev Heart Center. According to the ECG study of close relatives. A shortening of the QT interval was revealed in the older brother and father. They don't complain either. The physical exertions are tolerated satisfactorily. On the ECG (from 03/16/21) of the patient's older brother, a shortening of the corrected QT interval to 0.32 sec is noted.

Leads I, II, III. Speed - 50 mm/sec. There is a shortening of the QT interval to 0.28 sec. Corrected QT 0.32 s.

The patient and his relatives refused to undergo genetic analysis. In the future, observation with implantation of a cardioverter-defibrillator is recommended.

## DISCUSSION

The first presented clinical case of late diagnosis of long QT syndrome in a 66-year-old patient with clinical manifestation at a young age deserves attention, since repeated syncope is likely in such patients. The patient had an episode of sudden cardiac arrest. The history and results of the examination of the patient, as well as the absence of external causes contributing to the prolongation of the QT interval, may indicate the presence of a congenital long QT interval syndrome caused by a mutation in one of the responsible genes, which can be verified using molecular genetic research methods [13].

According to the recommendations of the European Society of Cardiology 2021 [14], the criteria for long QT syndrome are: QTc ≥480 ms on repeated 12-lead ECGs (Recommendation Class I) or the presence of > 3 risk factors for LQTS (Recommendation class I); in the presence of QTc ≥460 ms on repeated 12-lead ECGs, in the presence of unexplained syncope, and in the absence of secondary reasons for prolongation of the QT interval, an ECG diagnosis of LQTS should be assumed (Class 2A). The use of beta-blockers is recommended for patients with a clinical diagnosis of LQTS - Class I (B). Absolute indications for implantation of a cardioverter-defibrillator in patients with LQTS: implantation of a cardioverter-defibrillator in combination with the use of beta-blockers in patients who survived an episode of sudden cardiac arrest with a clinical diagnosis of LQTS, including those resuscitated after sudden cardiac arrest. Relative indications for implantation of a cardioverter-defibrillator in patients with LQTS: implantation of a cardioverter-defibrillator in addition to beta-blockers in patients with LQTS, in the presence of syncope and / or ventricular tachycardia against the background of adequate doses of beta-blockers [14].

Short QT syndrome (SQTS) is a rare disease whose prevalence in the population is unknown.

At the same time, little is known about the predictive value of a shortened QT interval. According to the authors, short QT syndrome is the most common cause of death in children and adolescents. Gussak (2005) first described the association of a short QT interval with paroxysms of atrial fibrillation (AF) and ventricular fibrillation. The main clinical manifestations of the disease are syncopal conditions caused by paroxysms of AF and ventricular tachycardia, which is accompanied by an increased risk of sudden cardiovascular death, cases that have been described in patients of all age groups [15].

At the same time, episodes of ventricular arrhythmias in this syndrome may be the only arrhythmia or be combined with AF. The presence of polymorphism of arrhythmias in this syndrome significantly distinguishes it from most others. Most often, ventricular arrhythmias appear after 40 years [15].

Researchers believe that there is a relationship between the frequency of arrhythmia attacks and the length of the QT interval. Shortening of the QT interval in children with a burdened family history correlates with the severity of clinical manifestations. The shorter the corrected QT interval, the more often paroxysms of arrhythmias occur and the higher the risk of sudden cardiovascular death [16].

Other clinical situations associated with secondary QT interval shortening include Brugada syndrome, chronic fatigue syndrome, hyperthermia, early ventricular repolarization syndrome, acidosis, digitalis preparations use, atropine prescription, and catecholamines increase. Secondary shortening of the QT interval increases the risk of arrhythmogenic events [17].

It is assumed that with the SQT1 mutation, the provoking factor for cardiac arrhythmias is usually physical activity and loud sounds, with SQT3 - sudden nocturnal awakening.

The main problem in practical medicine for long and short QT syndromes is the lack of multicenter randomized controlled trials.

The only effective treatment for patients with long and short QT syndromes is currently implantation of a cardioverter-defibrillator.

Implantation is recommended for all patients for secondary prevention of sudden cardiac death, unless there are absolute contraindications or patient refusal. At the same time, the use of implantable cardioverter-defibrillators for the primary prevention of sudden death has not been reliably proven.

## CONCLUSIONS

Accurate diagnosis of prolongation or shortening of the QT interval during ECG and Holter monitoring will make it possible to identify a group of patients with an increased risk of developing ventricular arrhythmias, syncope, and sudden death. Beta-blockers are effective agents for the prevention and treatment of ventricular arrhythmias in patients with congenital and acquired forms of long and short QT interval syndrome. Implantation of a cardioverter-defibrillator is an effective and safe method of preventing sudden cardiac death in patients with both long and short QT syndromes.

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**Conflict of interest:**
*The Authors declare no conflict of interest.*

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Pallas Kliniken

Kliniki Pallas specjalizują się w okulistyce i medycynie estetycznej. Zatrudniamy ponad 350 pracowników w 18 lokalizacjach i jesteśmy jednym z wiodących świadczeniodawców w Szwajcarii. Poprzez innowacje stale rozwijamy naszą ofertę usług w tych dziedzinach. Czy to poprzez nowe metody leczenia, sprzęt, dodatkowe lokalizacje i współpracę, a może poprzez współpracę z Państwem w najbliższej przyszłości?

W celu uzupełnienia istniejącego zespołu w naszej grupie w lokalizacjach **Olten, Aarau i Solothurn** poszukujemy osoby z inicjatywą i niezależną osobowością na stanowisko

# specjalista oftalmologii (k/m/i) 60–100%

## Główne obowiązki

Specjalista oftalmologii w naszych placówkach w Olten, Aarau lub Solothurn zapewnia profesjonalną obsługę medycznych konsultacji zachowawczych. Osoba ta będzie kompetentnie wykorzystywać swoje umiejętności we współpracy z obecnymi lekarzami specjalistami. Do jej obowiązków będzie należało zapewnienie naszym pacjentom optymalnej opieki. Wraz ze zgranym zespołem będzie świadczyć usługi medyczne na najwyższym poziomie. Będzie korzystać z szerokiej sieci wybitnych lekarzy, ciągłych szkoleń wewnętrznych i zewnętrznych oraz nowoczesnego środowiska pracy.

## Profil kandydata

- Specjalizacja w dziedzinie oftalmologii
- Kilkuletnie doświadczenie w dziedzinie oftalmologii
- Przedsiębiorcze myślenie i działanie zorientowane na sukces i cel, z wysokim zrozumieniem jakości i obsługi
- Wysoka inteligencja emocjonalna i odporność w kontaktach z pacjentami, pracownikami oraz innymi partnerami wewnętrznymi i zewnętrznymi
- Umiejętność szybkiego rozpoznawania problemów i samodzielnego opracowywania rozwiązań
- Wybitne kompetencje doradcze w języku niemieckim, wyrażane w mowie i piśmie w sposób zrozumiały i adekwatny do adresata

## Nasza oferta

W ramach udzielania konsultacji udostępniamy nowoczesną infrastrukturę, w której można profesjonalnie leczyć pacjentów, zarówno ambulatoryjnie, jak i stacjonarnie. Zapewniamy optymalne i jak najlepsze wsparcie podczas pracy. Oprócz uregulowanych godzin pracy (brak dyżurów nocnych i niedzielnych), które pozwalają na spędzanie czasu z rodziną i czas wolny, oferujemy także możliwości szkoleń wewnętrznych i zewnętrznych. Chętnie udzielimy dodatkowego wsparcia podczas stawiania pierwszych kroków w Szwajcarii.

Wykorzystując swoje wieloletnie doświadczenie, innowacyjność, a przede wszystkim umiejętność aktywnego słuchania, mogą Państwo naszym pacjentom pozwolić odczuć wyraźną różnicę.

Szukają Państwo wszechstronnej i ciekawej pracy w rodzinnej grupie przedsiębiorstw? Prosimy o przesłanie swojej aplikacji.

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