INTRODUCTION

Vitamin D is an important vitamin, required for the regulation of calcium and bone health [1]. Going far beyond its classical role in calcium and bone metabolism, the nonskeletal effects of the importance of vitamin D for various organs and systems have been confirmed, the relationship between its deficiency and various metabolic disorders, diseases of the cardiovascular, endocrine, immune, reproductive and other systems was revealed [2-3]. In Ukraine 81.8% of adults have an acute deficiency of vitamin D, 13.6% have an insufficient amount, and only 4.6% of Ukrainians have a sufficient level of vitamin D [4].

Vitamin D deficiency has been found to correlate with an increased incidence of autoimmune diseases, including type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis (MS), and Crohn’s disease [5-8]. However, it is unclear whether low vitamin D levels closely correlate with the development of autoimmune thyroid disease (AITD) [9].

Thyroid dysfunction is considered as a common endocrine disease and its prevalence has recently increased. This disease affects up to 1.5% of the population, predominantly females. The prevalence of hypothyroidism (HT) among adult females of different age groups ranges from 3-7.5% and is more frequent among elderly women [10]. Recent epidemiological studies indicate a relationship between thyroid autoimmunity and vitamin D deficiency [11-13]. Furthermore, the association of lower vitamin D levels with higher prevalence of AITD has been found to be significant in premenopausal, but not in postmenopausal women [14].

Menopausal transition is associated with an increased risk of metabolic syndrome and cardiovascular disease [15]. Metabolic syndrome (MetS) is a condition characterized by the contemporary presence of central obesity, arterial hypertension, altered lipidic and glycide metabolism. Previous reports indicated that increased thyroid-stimulating hormone (TSH) levels within the normal range were significantly correlated with metabolic syndrome parameters, insulin resistance and obesity [16].

Considering the multifactorial development, the high prevalence of hypothyroidism in Ukraine, and the lack of clear recommendations for effective prevention measures, there is a need for a more detailed study of risk factors in the occurrence of this pathology. Although the relationship between Vitamin D and HT has been established long ago, the interaction of thyroid hormone, vitamin D and its metabolites remains to be unexplored, which confirms the expediency of screening vitamin D level in patients with autoimmune thyroid disease.
THE AIM
To determine the level of vitamin 25 (OH) D3 in premeno-
pausal women with autoimmune pathology of the thyroid
gland. Establish a relationship between serum vitamin D
level with carbohydrate and lipid indexes in women with
autoimmune hypothyroid disease.

MATERIALS AND METHODS
146 women with autoimmune hypothyroid disease were
examined. The study included premenopausal women
between the ages of 40 and 54, the mean age was 46.6±0.8
years, menopause status was determined using a self-report
questionnaire about menstrual bleeding and its regularity.
Disease duration was 6.4 ± 1.7 (3 to 8) years. All partic-
ipants were on outpatient and inpatient treatment in the
department of endocrinology and endocrinological dis-
pensary at the Ternopil University Hospital. Patients with
concomitant chronic somatic diseases with severe or pro-
gressive course were excluded from the study. All patients
signed informed consent to participate in the study. The
research was conducted in compliance with all moral and
ethical principles according to World Medical Association
Declaration of Helsinki, after obtaining the conclusion of
the ethics committee at I. Horbachevsky Ternopil National
Medical University.

In order to establish or confirm the diagnosis, a general
clinical examination, laboratory and instrumental research
methods were performed. Anthropometric parameters
were measured in all patients and the body mass index
(BMI) was calculated according to the formula (mass (kg) / 
height$^2$ (m$^2$)).

To evaluate the functional status of thyroid gland, the
level of thyrotropic hormone (TSH), free thyroxine (fT4),
free triiodothyronine (fT3) in serum was determined using
the electrochemiluminescent method on an automatic an-
alyzer Roche «Cobas-411», via Rosche Diagnostics reagents
(Germany), Thyroid Peroxidase Antibody (TPOAb) was
determined via Orgentec GmbH kits (Germany).

The levels of total cholesterol (TC), high-density li-
oprotein cholesterol (HDLc) and triglycerides (TG) in
serum were determined to assess lipid metabolism using
automatic biochemical analyzer Roche «Cobas-501» via
Rosche Diagnostics reagents (Germany). According to lip-
oidogram indices were determined: low density lipoprotein
cholesterol (LDL cholesterol = TC – (TG / 2.2 + HDLc))
and atherogenic coefficient (AC = (TC – HDLc) / HDLc).

For the study of carbohydrate metabolism, basal glucose
level in serum was determined by glucose oxidase method
on the automatic biochemical analyzer Roche «Cobas-501»
and basal blood insulin level by electrochemiluminescent
method using Roche «Cobas-411» analyzer and Roche
Diagnostics test systems (Germany).

The HOMA-IR (Homeostasis Model Assessment for
Insulin Resistance) index was calculated by the formula: 
HOMA IR = (fasting glucose x basal insulin): 22.5.

Determination of level 25 (OH) D in serum was per-
formed in autumn-winter period, by electrochemilumi-
nescent method on Elecsys 2010 (Roche Diagnostics,
Germany), using the 25-OH Vitamin D ELISA kit (EU-
ROIMMUN, Germany). Vitamin D status was evaluated
according to the recommendations of the International
Society of Endocrinologists, according to which vitamin
D deficiency is set at a level of 25 (OH) D below 20 ng/
ml (50 nmol/l), insufficiency of 25 (OH) D in the range of
20–30 ng/ml (50-75 nmol/l) and sufficiency of 25 (OH) D
above 30 ng/ml (75 nmol/l).

Statistical processing of the results and visualization
of the obtained data were performed using the statistical
analysis package STATISTICA 12. The values of the in-
vestigated parameters are given in the form of arithmetic
mean values and their mean error (M ± m). The probability
of difference between the groups was evaluated using the
t-test (Student). Correlation analysis and the Pearson linear
correlation coefficient were calculated to assess the degree
of correlation. The correlation of quantitative indicators
was considered as strong at correlation coefficient values
from 0.70 to 1.00, mean strength from 0.30 to 0.69 and
weak to 0.29. The difference between values was considered
significant at p <0.05.

RESULTS
The diagnosis of hypothyroidism was based on characteristic
clinical symptoms and hormonal study results. The average
level of TSH was – 4.40 ± 0.21 mIU/L; fT3– 1.97 ± 0.09
pmol/L; fT4– 12.96 ± 0.37 pmol/L; TPOAb –112.87 ± 5.61
IU/ml, p <0.05. To compensate for hypothyroidism, patients
received levothyroxine sodium in replacement doses ranging
from 50 to 150 μg. According to TSH levels, compensated
hypothyroidism was diagnosed in 94 women (64.4%) and sub-
compensated in 52 (35.6%). Body mass index (BMI) averaged
29.4 ± 0.29 in 49.3% of the surveyed, which corresponds to
overweight; in 44.5% of women was observed obesity.

The average glucose level reached 5.3 ± 1.2 mmol /L,
which corresponds to the reference values. Basal insulin
levels exceeded the control value in 68.2% of patients,
HOMA-IR averaged 3.31 ± 0.08 (p <0.05).

Hypercholesterolemia more than 5.2 mmol/L was found
in 54 (26.8%) of women, HDL cholesterol <1.15 mmol/L
in 69 (48.3%), LDL cholesterol > 2.6 mmol/L in 76 (75.6 %),
AC >3 was observed in 64% (Table I).

The mean level of 25 (OH) D in women with autoim-
mune hypothyroid disease was 16.42 ± 0.57 ng / ml, which
corresponds to vitamin D deficiency (<20 ng / ml). (Fig. 1).

Comparative analysis of carbohydrate and lipid metab-
olism in the study groups showed a significant increase
of their levels in vitamin D insufficiency and deficiency
patients. In the group of women with vitamin D deficien-
cy were higher BMI, insulin resistance index HOMA and
AC in comparison to women who had sufficient level of
vitamin D. In the third group, in comparison with the first
group, the level of LDLc was twice higher, and the AC was
three times higher. Mean LDL cholesterol values were
higher by 24.4%, BMI by 42.5%, HOMA insulin resistance
index by 52.6%.
Therefore, in women with autoimmune hypothyroidism and vitamin D deficiency were observed significant adverse disorders of carbohydrate and lipid metabolism which determines the degree of metabolic and cardiovascular risk.

Pearson correlation analysis was performed in the study groups to determine the relationship between vitamin D levels and anthropometric parameters, hormonal status, lipid and carbohydrate metabolism in premenopausal women with autoimmune hypothyroidism (Table II).

No correlation was found between level of 25 (OH) D and age, ($p>0.05$). A strong negative correlation was found between 25 (OH) D and the level of TPOAb ($r=-0.77$) and with TSH ($r=-0.72$). Positive correlations of mean strength were found with T3 ($r=0.43$) and T4 ($r=0.44$), $p<0.05$. Our results indicate that vitamin D deficiency is correlated with a decrease in thyroid function and the presence of TPOAb.

In the analysis of the relationship of metabolic parameters was established a strong negative correlation between serum 25 (OH) D concentration and BMI ($r=-0.74$), and TC level ($r=-0.72$); negative mean correlation was with AC ($r=-0.65$), LDLc ($r=-0.58$), HOMA-IR ($r=-0.57$) and TG ($r=-0.46$), $p<0.05$. The results of correlation analysis show that in premenopausal women with autoimmune hypothyroidism vitamin D level has linear relationships with anthropometric parameters and components of metabolic disorders which increases the risk of cardiometabolic complications.

**Fig. 1.** Distribution of premenopausal women with autoimmune hypothyroidism according to the level of serum vitamin D.

**Table I.** Indicators of metabolic and hormonal disorders in premenopausal women with autoimmune hypothyroidism depending on the serum level of 25 (OH) (M ± m).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>$p_{1,2}$</th>
<th>$p_{1,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44,83±1,70</td>
<td>46,16±0,69</td>
<td>48,92±0,39</td>
<td>0,043</td>
<td>0,014</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>21,28±1,10</td>
<td>26,79±0,49</td>
<td>30,33±0,273</td>
<td>0,010</td>
<td>0,005</td>
</tr>
<tr>
<td>25(OH)D, (ng/ml)</td>
<td>39,02±2,09</td>
<td>23,02±0,46</td>
<td>13,84±0,38</td>
<td>0,009</td>
<td>0,007</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>2,41±0,53</td>
<td>2,58±0,36</td>
<td>4,94±0,23</td>
<td>0,007</td>
<td>0,005</td>
</tr>
<tr>
<td>fT3 (pmol/L)</td>
<td>2,94±0,32</td>
<td>2,60±0,19</td>
<td>1,75±0,09</td>
<td>0,004</td>
<td>0,002</td>
</tr>
<tr>
<td>fT4 (pmol/L)</td>
<td>17,60±1,89</td>
<td>15,21±0,73</td>
<td>12,16±0,41</td>
<td>0,015</td>
<td>0,008</td>
</tr>
<tr>
<td>TPOAb, (IU/ml)</td>
<td>36,07±6,68</td>
<td>46,93±1,67</td>
<td>189,35±2,19</td>
<td>0,022</td>
<td>0,043</td>
</tr>
<tr>
<td>FBG, mmol/L</td>
<td>2,34±0,31</td>
<td>2,37±0,11</td>
<td>3,57±0,08</td>
<td>0,008</td>
<td>0,002</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>3,19±0,17</td>
<td>4,43±0,21</td>
<td>6,61±0,11</td>
<td>0,005</td>
<td>0,002</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2,46±0,36</td>
<td>2,66±0,14</td>
<td>4,03±0,10</td>
<td>0,003</td>
<td>0,002</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>1,66±0,09</td>
<td>1,52±0,05</td>
<td>1,32±0,02</td>
<td>0,001</td>
<td>0,001</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>2,66±0,29</td>
<td>2,79±0,15</td>
<td>3,97±0,06</td>
<td>0,003</td>
<td>0,001</td>
</tr>
<tr>
<td>HDL mmol/L</td>
<td>0,94±0,09</td>
<td>2,03±0,21</td>
<td>4,19±0,12</td>
<td>0,004</td>
<td>0,002</td>
</tr>
<tr>
<td>LDL mmol/L</td>
<td>44,83±1,70</td>
<td>46,16±0,69</td>
<td>48,92±0,39</td>
<td>0,043</td>
<td>0,014</td>
</tr>
<tr>
<td>AC</td>
<td>21,28±1,10</td>
<td>26,79±0,49</td>
<td>30,33±0,273</td>
<td>0,010</td>
<td>0,005</td>
</tr>
</tbody>
</table>

**Notes:** $p_1$ - the probability of difference in a group with sufficient vitamin D; $p_2$ - the probability of difference with the indicator in the group with vitamin D insufficiency; $p_3$ - the probability of difference with the indicator in the group with vitamin D deficiency.

BMI: Body mass index; TSH: Thyroid-stimulating hormone; fT3: Free triiodothyronine; fT4: Free thyroxine; TPOAb: Thyroid peroxidase antibodies; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; AC: Atherogenic coefficient.
ASSOCIATION BETWEEN VITAMIN D STATUS AND METABOLIC DISORDERS IN PREMENOPAUSAL WOMEN...

Several studies have shown that subjects with cardiovascular disease, which is associated with vitamin D deficiency [20]. In addition, it is believed that vitamin D has an important role in the pathogenesis of cardiovascular diseases. Clinical studies have evaluated the mediate effect of vitamin D directly on cardiovascular function through regulation of lipid metabolism by cholecalciferol [19]. In addition, it is believed that the development of atherosclerosis begins at an early age, and its accelerated development underlies the increased risk of cardiovascular disease, which is associated with vitamin D deficiency [20]. Several studies have shown that subjects with an adequate serum concentration of 25 (OH) D and high vitamin D intake have a more favorable lipid profile than those who have a vitamin D deficiency [21-23].

Our results indicate that vitamin D deficiency is correlated with a decrease in thyroid function and the presence of TPOAb. Similar results were obtained by the researchers Viktoria F. Koehler et al, who found an increase in the incidence of vitamin D deficiency in patients with autoimmune thyroid disease, especially with autoimmune thyroiditis [24]. The relationship between thyroid hormones, vitamin D and its metabolites remains unexplored. The available literature suggests that the relationship of 25 (OH) D and thyroid hormones is complex and should be considered not only as a mechanism for regulating phosphorus-calcium homeostasis, but as a mechanism for cardiovascular pathology in patients with hypothyroidism and vitamin D deficiency. The need for additional administration and adequate doses of vitamin D to prevent cardiovascular disease in patients with autoimmune hypothyroidism remains insufficiently studied. Vitamin D deficiency screening is recommended for all patients with autoimmune thyroid disease, especially in premenopausal women.

**REFERENCES**


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

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Received: 2020-05-13
Accepted: 2021-06-01