ORIGINAL ARTICLE

MELATONIN AND GRHELIN AS "EARLY" PROGNOSIS MARKERS OF PROGRESSION OF ARTERIAL HYPERTENSION AND OSTEOARTHRITIS IN THE CASE OF THEIR COMORBIDITY

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ABSTRACT

The aim: Of the study was to investigate the effect of melatonin on the serum levels of ghrelin in patients with hypertension combined with osteoarthritis in order to identify them as informative and reliable markers of early diagnosis of progression of these comorbid diseases.

Material and methods: To achieve the goals and objectives of this study, 60 patients with hypertension combined with osteoarthritis were involved and examined, in particular, serum ghrelin and melatonin levels were determined twice and divided into two groups.

Results: It was found that in patients of group I on the background of the four-week main course of treatment with the addition of melatonin (3 mg 1 time per day before bedtime), the average value of ghrelin increased by an average of ± 2.05 ng/ml ($p < 0,05$). In patients of group II, who, in addition to their usual treatment, did not receive additional melatonin, the dynamics of ghrelin growth was lower, on average increased by ± 0.54 ng/ml ($p < 0.05$). It was also found that the higher the BMI, the lower the serum ghrelin in the examined patients ($r = -0.56$, $p < 0.01$).

Conclusions: The data obtained show the correlation between ghrelin and melatonin concentrations ($r = +0.72$, $p < 0.001$) in patients with hypertension associated with OA. Therefore, indicators of their levels can be used as "early" reliable prognostic markers of development and progression of these mentioned comorbid pathologies.

KEY WORDS: hypertension, osteoarthritis, melatonin, ghrelin, body mass index

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INTRODUCTION

Today, the most important health problem of the population of Ukraine in terms of non-communicable diseases are diseases of the circulatory system (CS), among which arterial hypertension (AH) occupies a leading place. It is known that it is the "trigger" of almost all pathologies of the human heart and blood vessels, as well as a risk factor for serious illnesses or complications that lead to significant social and economic consequences.

Another major cause of disability and invalidity in the world, after cardiovascular disease, is joint disease, especially osteoarthritis (OA), the clinical manifestations of which are observed in almost 20% of the world's population. OA, along with coronary heart disease (CHD), alcoholism, diabetes, and depression, are among the 5 diseases that cause the long-lasted health problems [1].

Restriction of physical activity in patients with OA is known to be an important factor in increasing the risk of cardiovascular disease (CVD) and obesity. Chronic pain, causing a neuroendocrine response, is often the cause of complications in patients with CVD. This may be due not only to the common pathogenetic mechanisms of OA development, but also to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) used to treat it.

Osteoarthritis is often pathogenetically associated with components of the metabolic syndrome (MS) (insulin resistance, type II diabetes, obesity, hyperlipidemia, hypertension and coronary heart disease), which accelerates the progression of joint pathology. The combined course of these diseases is an important medical and social problem even in economically developed countries, in connection with which the study of clinical and pathogenetic features of the combination of OA with MS is particularly relevant [2].

In this regard, researchers are now paying considerable attention to the biochemical and molecular mechanisms underlying the development of the above pathologies. Their efforts are aimed at early detection of these diseases and the appointment of adequate comprehensive therapy.

Modern scientific sources have shown that low plasma ghrelin levels are associated with insulin resistance and hypertension and may affect blood pressure (BP). The inverse dependence of ghrelinemia and insulin resistance was also determined: the higher its level, the less pronounced insulin resistance [3]. Thus, low levels of ghrelin may be an indicator of the risk of type II diabetes and hypertension, which confirms the relevance of our study.

Despite the presence of a wide range of highly active drugs, which in accordance with clinical protocols and

recommendations are prescribed for the treatment of hypertension (ACE inhibitors, angiotensin II receptor blockers, calcium antagonists, diuretics, etc.), as well as the use of high-tech surgical advances (implants cardiac resynchronization therapy, etc.), the search for new effective and at the same time safe means of pharmacotherapy and highly informative and reliable biomarkers of the studied pathologies continues [4]. On the one hand, this is due to the prediction of an increase in the incidence of hypertension in the world, lesion due to this pathology of other organs and systems, combined with OA, and on the other – insufficient study of molecular targets and mechanisms of individual sensitivity to drugs of different composition.

In our opinion, one of the possible variants of the pathogenetic approach to the treatment of this combined pathology may be melatonin, which is known to act as a biological clock and cardioprotector, and also has antiischemic and antihypertensive effects [5], regulates blood pressure, heart rate (HR), coronary and cerebral circulation. In addition, it has been experimentally demonstrated that melatonin has a chondroprotective potential and may be involved in the pathogenesis of OA due to its effect on circadian rhythms of chondrocytes [6].

THE AIM

The aim of our study examine the effect of melatonin on the serum levels of ghrelin in patients with arterial hypertension combined with OA, in order to identify them as informative and reliable markers of early diagnosis of the progression of these comorbid diseases.

MATERIALS AND METHODS

In accordance with the purpose and objectives of our dissertation research, a total of 130 patients of different ages and genders, patients with hypertension and OA were examined. Of these, 60 patients had arterial hypertension combined with OA, who were divided into two groups. Thus, group I consisted of 30 patients with arterial hypertension combined with OA, who took melatonin for a month, in addition to the main treatment. Group II included 30 patients who had comorbid conditions of arterial hypertension and OA and who were not given melatonin in their usual treatment. AH without concomitant OA was observed in 30 patients who made up group III. Group IV included 30 people with OA without concomitant arterial hypertension. The control group consisted of 10 healthy people.

The study described in this article involved 70 patients (n = 70 (100%)), of whom 60 were people of different ages (65.7 ± 1.3 years) and sex (47 women, 13 men) with AH, combined with OA, and the following average office blood pressure: systolic blood pressure (SAT) – 147.34 ± 3.24 mm Hg, diastolic blood pressure (DBP) – 88.18 ± 2.15 mm Hg, pulse (PBP) – 72.4 ± 1.35 beats/min. At the same time, the combination of diseases lasted for more than five years.

Criteria for inclusion of patients in the study were: verified diagnosis of hypertension stage II, 1 – 2 degrees in combination with a verified diagnosis of OA Ro-stage II, SFK I – II. The study did not include patients with concomitant autoimmune diseases, stage III hypertension, heart failure (FC III – IV), OA X-ray stage III – IV, as well as those who took corticosteroids or cyclosporine before the study or planned to take them during its holding. There were no smokers among the subjects. NSAIDs were not a criterion for exclusion from the study groups. The control group consisted of 10 healthy people.

Patients were examined according to the study program, in particular, serum ghrelin and melatonin levels were determined twice and divided into two groups. The first group consisted of 30 patients with arterial hypertension combined with OA, who agreed to take melatonin in addition to the main treatment for a month. The second group consisted of 30 people who had comorbid diseases with arterial hypertension and OA and who were not supplemented with melatonin in their usual treatment. The control group consisted of 10 healthy people. All patients voluntarily agreed to participate in the study.

Determination of ghrelin concentration in the serum of patients was performed using a set of reagents Human GHRL (grelin) ELISA Kit (Elabscience, USA) by enzyme-linked immunosorbent assay according to the instructions using a multichannel microspectrophotometer AutoPlex ELISA & CLIA Anayzer (92980) (Monobild, USA).

The concentration of melatonin in the serum of patients was determined using a set of reagents Melatonin ELISA (IBL International, Germany) enzyme-linked immunosorbent assay according to the instructions using a multi-channel microspectrophotometer AutoPlex ELISA & CLIA Anayzer (92980) (Monobild, USA).

In addition, all subjects were determined body mass index (BMI) by the method of Kettle: the ideal indicator – 18.5 – 24.9 kg / m^2, excess body weight – 25 – 29.9 kg / m^2, obesity I – 30.0 – 34.9 kg / m^2; obesity II degree – 35 – 40 kg / m^2, obesity III degree – more than 40 kg / m^2.

In addition, the relationship between BMI and serum ghrelin levels was determined.

All obtained data were processed by methods of variation statistics using the program Statistica 10.

RESULTS

According to the study plan, melatonin and ghrelin levels were first determined in 60 patients with combined pathology. Then, in addition to the main treatment, patients of group I were prescribed a monthly course of melatonin at a dose of 3 mg / day, and it was recommended not to drink alcohol, coffee and drugs that affect the melatonin-forming function of the pineal gland (corticosteroids, cyclosporine). All patients in this group were re-tested for serum melatonin and ghrelin levels after completion of melatonin therapy. Patients in group II also re-determined the following indicators.

In the course of the research it was found that in patients of group I on the background of the four-week main course of treatment with melatonin, the average value of ghrelin

Table I. Melatonin and ghrelin levels in the serum of patients with arterial hypertension combined with OA (M±m)

Indicator	Group I before treatment n = 30 (42.8%)	Group I after treatment n = 30 (42.8%)	Group II before treatment n = 30 (42.8%)	Group II after treatment n = 30 (42.8%)	Control n = 10 (14.3%)
Melatonin, pg/ml	38.88±5.16*	120.52±5.84 *,**	58.51±7.37*	72.77±9.10*,**	125.43±8.13
Ghrelin, ng/ml	2.31±0.08*	4.36±0.09 *,**	3.07±0.16*	3.64±0.10*,**	4.64±0.05

Note: * - the difference is significant compared to almost healthy individuals ($p < 0.05$). ** – the difference is significant compared to the rate in persons before treatment ($p < 0.05$).

Table II. Correlation between melatonin and ghrelin levels in the serum of patients with arterial hypertension combined with OA

Group	Correlation coefficient (r)	Significance level (p)
Group I	0,72	< 0,001
Group II	0,59	< 0,01

increased from 2.31±0.08 ng/ml to 4.36±0.09 ng/ml, i.e. an average of 2.05 ng/ml ($p < 0.05$). In patients of group II, who, in addition to their usual treatment, did not receive additional melatonin, the dynamics of ghrelin growth was lower: its rate increased from 3.08±0.16 ng/ml to 3.62±0.10 ng/ml (on 0.54 ng/ml) ($p < 0.05$).

The level of melatonin in patients of group I before treatment averaged 38.88±5.16 pg/ml, after – 120.52±5.84 pg/ml, and their difference was 81.64 pg/ml ($p < 0,05$). At patients of group II the indicator of level of melatonin at the beginning of research made 58.51±7.37 pg/ml, and after – 72.77±9.10 pg/ml (their difference – 14.26 pg/ml) ($p < 0,05$). The results of the study are given in Table I.

As you can see, the data in Table I and indicate a good effect of the proposed therapy, as the concentration of ghrelin in the serum of patients in group I increased by 57% and approached the control group. And in the serum of patients of group II, the concentration of ghrelin increased by only 15%, which confirms our hypothesis. The dynamics of ghrelin levels is shown in Fig. 1.

Table 2 shows the results of a study of the relationship between melatonin and ghrelin in the serum of patients with hypertension associated with OA, after the addition of melatonin to the main treatment (group I), and without the addition of melatonin to the main treatment (group II).

The dependence of the concentration of ghrelin on the level of melatonin in the serum of patients of group I is given in Fig. 2.

The image in Fig. 2 shows that the level of ghrelin is directly related to the level of melatonin, which, in our opinion, allows us to use them as "early" markers of development and progression of these comorbid pathologies.

The data in Table II show that the correlation coefficient (r) between the studied indicators for group I was +0.72 – a direct strong connection, which gives grounds to talk about the effectiveness of adding melatonin to the main treatment. It is assumed that in the case of cardiovascular pathology, the manifestations of cardioprotection of melatonin are associated with antioxidant, antistress, antidepressant properties, as well as immunomodulatory effects of the drug.

The average value of BMI in the subjects is 30.76±0.54 kg/m², which is much higher than normal (N = 18.5-24.9). Overweight was found in 43.3% of patients, grade I obesity in 41.7%, grade II obesity in 10%, grade III obesity in 3.3%. BMI was within the norm in only 1.7% of subjects. In the control group, the average BMI was 22.27±0.72 kg/m². The distribution of patients with hypertension combined with OA, according to BMI is shown in Fig. 3.

The study found that the higher the BMI, the lower the serum ghrelin in the examined patients ($r = –0.56$, $p < 0.01$). This also indicates that ghrelin plays an important role in the pathogenesis and clinical course of such comorbid pathologies as hypertension and OA.

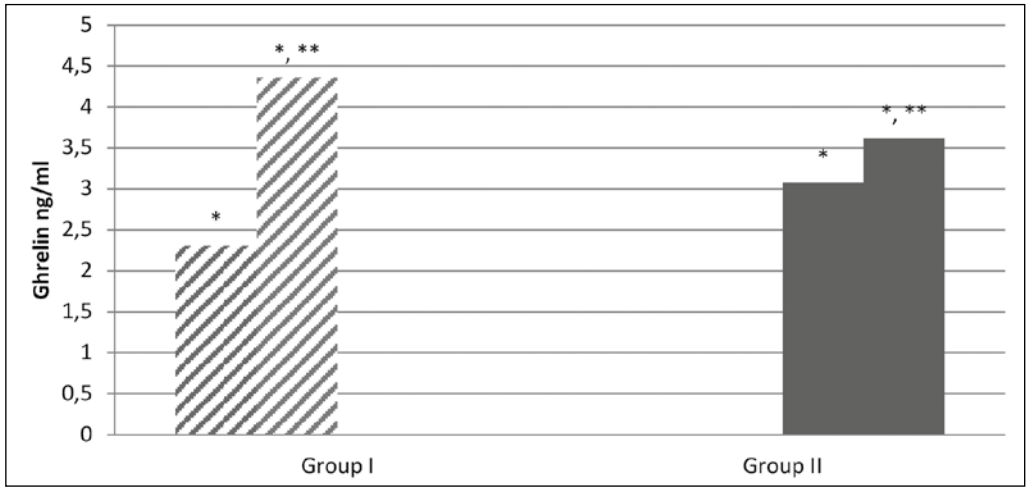

Fig. 1. Dynamics of ghrelin levels.

Note: * – the difference is significant compared to almost healthy individuals ($p < 0,05$). ** – the difference is significant compared to the rate in persons before treatment ($p < 0.05$).

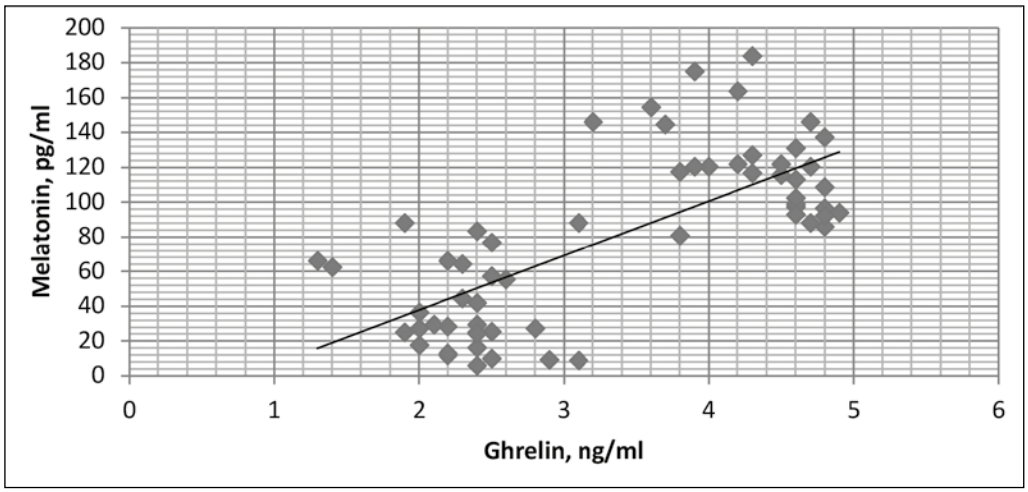

Fig. 2. Dependence of ghrelin concentration on the level of melatonin in the serum of patients of group I.

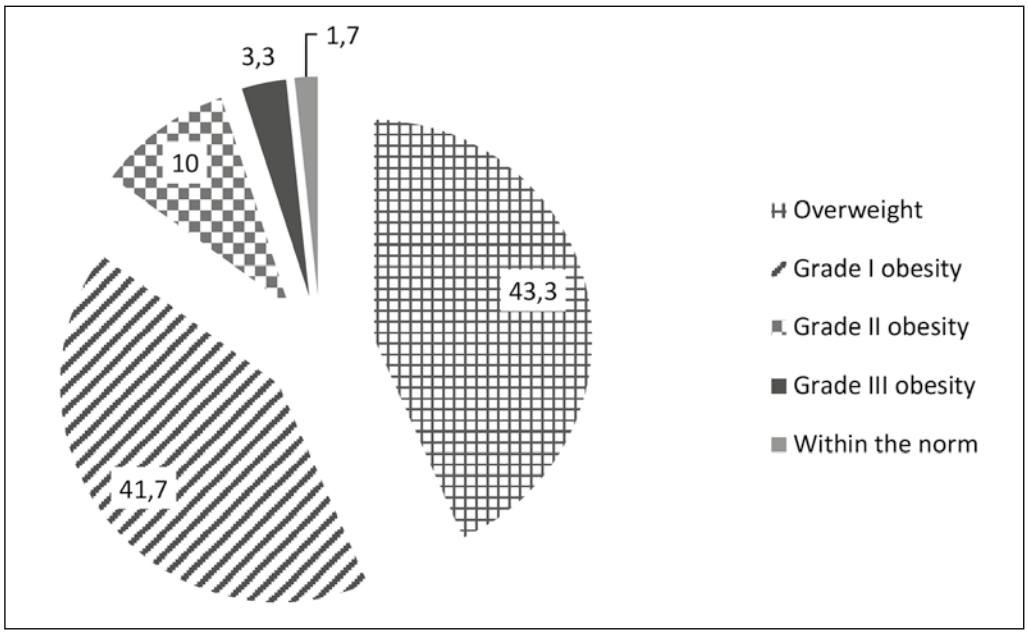

Fig. 3. Distribution of patients with hypertension combined with OA, according to BMI.

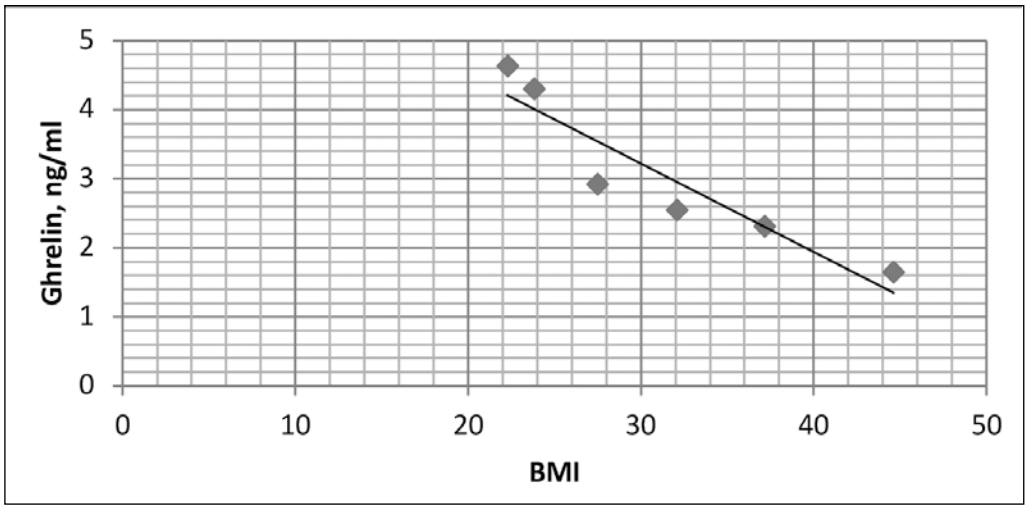

Fig. 4. Relationship between BMI and serum ghrelin levels.

The dependence of ghrelin levels in the serum of the studied patients (n = 70 (100%)) on BMI is shown in Fig. 4.

Consequently, ghrelin levels are inversely related to BMI in patients.

DISCUSSION

It is known that ghrelin regulates energy metabolism and human eating behavior. It, as a gastrointestinal hormone, has various biological properties and effects: it stimulates

the release of growth hormone, improves appetite, causes anabolic effects, affects carbohydrate metabolism and the work of the cardiovascular system [7]. It is this set of functional properties and led to our interest in this hormone.

We would like to note that according to scientific sources, and the results of our research, ghrelin levels are inversely correlated with body mass index (BMI), body fat index, obesity, leptin, obestatin and insulin levels, adipocyte count [8]. It is known that ghrelin increases in response to weight loss due to low-calorie diets, lifestyle modifications, cancer cachexia, neuropsychiatric anorexia, chronic insufficiency – heart, kidney, liver. Ghrelin levels are thought to increase during fasting and have an antidepressant effect. The vasodilatory effect of ghrelin and its participation in the regulation of systemic hemodynamics and blood pressure have also been established. The hormone reduces the manifestations of endothelial dysfunction in patients with metabolic syndrome by increasing the bioavailability of nitric oxide [4]. In case of weight gain, the level of ghrelin in the blood decreases.

Given all the above, we decided that it would be appropriate before this study for all patients to determine BMI to establish the relationship between BMI and serum ghrelin levels.

CONCLUSIONS

1. The obtained data indicate the correlation between concentrations of ghrelin and melatonin ($r = +0.72$, $p < 0.001$) in patients with hypertension associated with OA.
2. The role of ghrelin in the pathogenesis of hypertension combined with OA is important and obvious.
3. Indicators of ghrelin and melatonin levels can be used as "early" reliable prognostic markers of development and progression of the mentioned comorbid pathologies.
4. Melatonin (3 mg 1 time a day before bedtime), as a component of complex therapy of arterial hypertension combined with OA, facilitates the course of these diseases due to its cardioprotective, antihypertensive and chondroprotective effects.
5. Ghrelin level correlates with BMI in patients with arterial hypertension combined with OA ($r = –0.56$, $p < 0.05$).

Further studies of the effect of ghrelin and melatonin on the course of arterial hypertension and OA in the case of their comorbidity will help to improve treatment tactics and thus positively affect the quality of life of patients, reduce the number of cases of disability.

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The Authors declare no conflict of interest.

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