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# Pathogenetic aspects of diabetes-associated osteoarthritis

**V.L. Orlenko[1], K.Yu. Ivaskiva[1], M.H. Kravchuk[2]**

[1] State Institution «V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine»
[2]Bogomolets National Medical University

**Abstract.** Damage to the musculoskeletal system is one of the serious, but understudied complications of diabetes mellitus (DM). Inflammatory and/or degenerative structural changes in the joints against the background of long-term hyperglycemia in the initial stages cause limitation of joint mobility, and later lead to persistent contractures and disability of patients. Therefore, the studying formation mechanisms of joint lesions in patients with DM is extremely important and relevant. **The aim** of our study was to identify the levels of specific hormones and biochemical markers of connective tissue metabolism in patients with diabetic arthropathy and to establish their possible influence on the development of joint pathology in this category of patients. **Material and methods.** The presence and degree of severity of diabetic arthropathy was assessed according to the method of A. Rosenblum. Levels of insulin, leptin, and osteocalcin in blood serum were determined by enzyme-linked immunosorbent assay using Diaclone reagent kits (France) and a Stat fax 3200 tablet immunoenzymatic analyzer (USA). Collagenase activity was assessed according to the method developed by S. Lindy and J. Halme. Glycosaminoglycans were determined by the Orcin method described by S.A. Klyatsky and R.I. Lifshits. Hydroxyproline fractions were isolated from blood serum according to the method proposed by S. Frey. And hydroxyproline was identified using reagents produced by Merck (Germany). **Results.** As a result of the study, it was found that the development of arthropathy did not depend on the type of DM. The odds of developing arthropathy were the same in men and women with type 1 DM (T1DM). Women with type 2 DM (T2DM) were 6.4 times more likely to develop arthropathy than men. It was established that in both types of DM, an increase in insulin and leptin levels was observed along with the progression of arthropathy. Osteocalcin levels were 53.9% higher in patients with T1DM and arthropathy than in patients without arthropathy. Regardless of the type of DM, patients with arthropathy had an increased level of biochemical markers indicating catabolic processes in the connective tissue of collagenase and free hydroxyproline. **Conclusion.** Thus, the important role of the hormones insulin and leptin in the development of lesions of the articular system in patients with DM has been established. Determination of osteocalcin, collagenase and hydroxyproline levels was an important early marker of catabolic processes in patients with diabetic arthropathy.

**Keywords:** diabetes mellitus, diabetic arthropathy.

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Due to the progressive increase in the incidence and disability among patients of working age, DM remains one of the most significant medical and social challenges of our time. Damage to the musculoskeletal system is one of the serious but understudied complications of DM. Diabetes-related arthropathies are inflammatory and/or degenerative structural changes in the joints that initially cause limited joint mobility and then eventually result in contractures. According to various authors [1, 2], damage to the joints is frequently observed in patients with DM. Only some fragmentary studies, though, have provided a description of the progression, clinical presentation, and diagnosis of diabetic arthropathy.

There are many questions regarding the pathogenesis of diabetic arthropathy since the development of this condition is a complicated and multifaceted process [3]. The impact of metabolic factors and various hormones (insulin, leptin, osteocalcin, adiponectin, osteoprotegerin, etc.) on the occurrence of joint damage in diabetic patients has been conclusively demonstrated in the latest studies. Numerous recent randomized trials have shown the high comorbidity of both diseases [4, 5].

Insulin and leptin directly affect the structural components of the joints in diabetic patients. When chondrocytes are stimulated by leptin, they synthesize pro-inflammatory mediators that cause inflammation. These mediators then activate metalloproteases, including collagenase, which leads to joint damage. The direct effect of leptin on chondrocytes has been shown to synergize with interferon-γ and interleukin-1β by activating nitric oxide synthesis, which induces a wide range of pro-inflammatory cytokines and is a pro-inflammatory mediator in the cartilage, promoting metalloproteinase activation and chondrocyte apoptosis [6]. Leptin increases the production of pro-inflammatory cytokines through the activation of nuclear factor κB [7, 8]. These findings support the idea that leptin acts as a pro-inflammatory cytokine having a direct effect on immune-inflammatory responses and suggest that leptin emerges as a link between obesity and inflammation, which is associated with changes in cartilage homeostasis [9].

The only energy substrate for chondrocytes with an exclusively anaerobic metabolism is glucose. Insufficient glucose supply to chondrocytes impedes the synthetic processes and leads to primary degeneration of the cartilaginous tissue [10, 11].

There is increasing evidence that the subchondral bone (SCB) is the initiator and key player in the progression of osteoarthritis (OA). Recent studies prove the potential use of active metabolites of SCB in the diagnosis of early stages of OA [12-15]. It should be noted that in OA, the level of some markers of bone resorption increases long before the change in the concentration of markers of cartilage degradation, and this can be considered as a predictor of disease progression.

There are two types of cells in the SCB in OA: osteoblasts and osteoblast-like cells. The second type of cells, unlike normal osteoblasts, cannot form a complete bone matrix and is capable of producing large amounts of osteocalcin and bone isoenzyme alkaline phosphatase [16]. The demineralization of collagen fibrils and the activation of matrix metalloproteinases are thought to be the fundamental processes in the formation of the osteo-like matrix of SCB. These processes may be mediated by the influence of osteoblast-stimulating factor-1, which is actively expressed in the area of subchondral sclerosis by osteoblast-like cells and is involved in the suppression of type I, II, and X collagen synthesis [17].

The formation of an abnormal subpopulation of osteocytes in SCB is considered an important factor in the development of OA [18]. The processes occurring in this case lead to the activation of specific molecules that can serve as biological markers of remodeling. Osteocalcin has been shown to reflect the biological synthetic reserves of SCB osteoblasts. Therefore, it can be used to control the effectiveness of pharmacological action on bone and cartilaginous tissue [16].

Increased expression of osteocalcin, alkaline phosphatase, and type I collagen is associated with an excessive effect of leptin on osteoblasts in OA. Inhibition of leptin activity led to a decrease in the levels of osteocalcin and other markers of osteoblast differentiation [19]. These findings indicate the existence of feedback markers for the interaction of SCB with external factors in the OA pathogenesis. Osteocalcin is of interest for understanding the processes occurring in SCB during the early stages of remodeling, and it can be used as an independent marker of the effectiveness of pharmacological action. Low mineral activity of osteoblasts and high levels of osteocalcin may play an important role in the remodeling of SCB in OA.

The aim of our study was to identify the levels of specific hormones and biochemical markers of con-

nective tissue metabolism in patients with diabetic arthropathy and to establish their potential impact on the development of joint pathology in this category of patients.

## Material and methods

A total of 77 patients (28 men and 49 women) were included in the study. The patients were divided into two groups depending on the type of DM. 40 patients (17 men and 23 women) were diagnosed with T1DM, and 37 patients (11 men and 26 women) had T2DM. The mean age of patients with T1DM and their body mass index (BMI) were expected to be significantly lower than in the group of patients with T2DM ($p<0.001$). In this sample, patients with T2DM had a mean BMI 24.2% higher than those with T1DM ($t=10.5$; $p=0.001$). The groups did not differ statistically in the DM duration ($p>0.07$). No gender differences were found in the studied parameters ($p>0.2$). Arthropathy was diagnosed in 59 (76.6%) patients, and joint pathology was not detected in 18 (23.4%) patients. DM compensation was recorded at glycated hemoglobin levels up to 7%. The presence and severity of diabetic arthropathy were assessed using the A. Rosenbloom method. Insulin, leptin, and osteocalcin levels in blood serum were determined by enzyme-linked immunosorbent assay using reagent kits from Diaclone (France) and a plate enzyme immunoassay analyzer Stat fax 3200 (USA). Collagenase activity was assessed using the method developed by S. Lindy and J. Halme. Glycosaminoglycans were determined by the orcin method described by S.A. Klyatskin and R.I. Lifshitz. Hydroxyproline fractions were isolated from blood serum using the method proposed by S. Frey and hydroxyproline was identified with the help of reagents produced by Merck (Germany).

Statistical processing of the obtained data was carried out using the methods of variational statistics of the standard package for statistical calculations, Statistica 5.0 Microsoft Office Exel 2003.

## Results and discussion

Arthropathy was diagnosed in 75% of patients with T1DM and in 78% of patients with T2DM ($t=0.35$; $p>0.1$). **Table 1** shows the distribution of patients by type of DM, gender, and the presence of arthropathy. Analysis of variance (classic t-test was used for unrelated samples) revealed that women with T2DM were 6.4 times more likely to develop arthropathy than men (OR=6.39; CI=1.18-34.62, p=0.032). In T1DM, the chances of developing arthropathy in men and women were equal (OR=1.5; CI=0.36-6.32, p=0.581).

**Table 1**. Distribution of patients by type of DM, gender and the presence of OA, % (n)

| Groups | Gender | Without OA | With OA |
|---|---|---|---|
| T1DM ($\chi^2$= 0.31; p=0.579) | males | 29 (5) | 71 (12) |
| | females | 22 (5) | 78 (18) |
| | both groups | 25 (10) | 75 (30) |
| T2DM ($\chi^2$= 5.25; p=0.022) | males | 45 (5) | 54.6 (6) |
| | females | 12 (3) | 89 (23) |
| | both groups | 22 (8) | 78 (29) |
| Both groups ($\chi^2$= 0.12; p=0.726) | males | 36 (10) | 64 (18) |
| | females | 16 (8) | 84 (41) |
| | both groups | 23 (18) | 77 (59) |

When analyzing the average levels of the studied hormones in patients with and without joint pathology, a significant increase in insulin and leptin was found in both types of the disease. The average levels of osteocalcin were significantly higher only in patients with arthropathy and T1DM **(Table 2)**.

A logit-regression analysis was carried out separately for patients with T1DM and T2DM to estimate the risk of developing arthropathy based on

**Table 2.** Mean hormone levels in diabetic patients without/with arthropathy, M±m (n)

| Hormones | T1DM | | | T2DM | | |
|---|---|---|---|---|---|---|
| | Without OA | With OA | p | Without OA | With OA | p |
| Insulin, mkU/mL | 5.5±0.7 (10) | 8.9±0.3 (30) | 0.001 | 6.4±0.3 (8) | 14.3±1.4 (29) | 0.001 |
| Leptin, ng/mL | 18.2±4.4 (10) | 32.3±3.8 (30) | 0.02 | 18.4±6.2 (8) | 39.8±3.9 (29) | 0.014 |
| Osteocalcin, ng/mL | 11.7±1.8 (10) | 25.5±3.2 (30) | 0.001 | 19.4±1.3 (8) | 19.4±1.4 (29) | 0.998 |

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the insulin level. The quasi-Newton method was used for analysis and model construction. For a group of patients with T1DM, the chances of developing arthropathy increase with increasing insulin levels (OR=3.80; CI 1.38-10.45). The model is statistically significant ($\chi^2$=19.7; p<0.001). The sensitivity of the model is 80.0% and its specificity is 86.4%.

The model constructed for a group of patients with T2DM also indicates a 2.6-fold increased risk of developing arthropathy with higher insulin levels (OR=2.62; CI 1.05-6.53). The model is statistically significant ($\chi^2$=18.4; p<0.001). The sensitivity of the model is 87.5% and its specificity is 88.9%.

There were statistically significant differences in the average insulin level depending on the stage of arthropathy and the type of DM (F=2.9; p=0.04). Thus, for the group of patients with T1DM, statistically significant differences were found only in patients with or without arthropathy (t=5.1; p<0.001) with corresponding levels of 5.5±0.7 and 8.9±0.3 mkU/mL. In the presence of arthropathy, there were no differences in the values of insulin levels at different stages of arthropathy (F=0.14; p=0.87).

In the group of patients with T2DM, insulin levels increased with the progression of the arthropathy stage (F=9.9; p<0.001). In patients with and without arthropathy and T2DM, the mean values of the «Insulin» indicator were 14.3±1.4 and 6.4±0.3, respectively (t=5.4; p<0.001). A more detailed analysis showed that there were no statistically significant differences in the average insulin level in the absence of arthropathy or its 1st stage (t=0.05; p=0.96). At the 2nd stage of arthropathy, the average insulin level was 1.7 times higher than at the 1st stage (t=2.9; p=0.015), and at the 3rd stage, it was 1.6 times higher than at the 2nd stage (t=2.5; p=0.022).

In 70.0% (T1DM) and 72.4% (T2DM) of patients with arthropathy, the presence of insulin resistance was revealed. A direct correlation was found between insulin resistance and the presence of arthropathy, both in T1DM (r=0.46; p<0.001) and in T2DM (r=0.68; p<0.001) (Spearman correlation). That is, for patients with T1DM, the greater the dose of exogenous insulin administered, the higher the chances of developing arthropathy. High doses of insulin are associated with severe complications of the underlying disease in patients with T1DM [1]. Our previous studies show that joint pathology frequently develops in the background of other late complications of DM, such as polyneuropathy, nephropathy, and angiopathy of the lower extremities. Additionally, it has been demonstrated that insulin resistance in patients with T2DM contributes to the pathogenesis of arthropathies by increasing the production of various cytokines and mediators, which in turn triggers nonspecific inflammation and the activation of metalloproteases, which destroy cartilage [12].

A logit-regression analysis showed an increased risk of developing arthropathy with an increase in leptin levels in patients with T1DM (OR=1.27; CI 1.03-1.57). The model is statistically significant ($\chi^2$=16.6; p<0.001). The sensitivity of the model is 71.4% and its specificity is 100.0%. For the group of patients with T2DM, a significant risk of developing arthropathy was also determined with an increase in leptin levels (OR=1.17; CI 1.02-1.35). The model is significant ($\chi^2$=15.1; p<0.001). The sensitivity of the model is 94.6% and its specificity is 61.5%.

An analysis of variance was used to determine differences in the average leptin levels according to «type of DM», «gender» and «stage of arthropathy». As a result, significant differences were noted in «gender» (F=3.3; p=0.02) and «stage of arthropathy» (F=6.7; p=0.01). There was insufficient evidence to conclusively prove the influence of all three factors (F=1.4; p=0.25).

An analysis of the distribution of mean leptin values in patients with T1DM revealed differences only in the presence or absence of arthropathy (t=2.4; p=0.02), while the mean leptin values at various stages of arthropathy did not differ statistically (F=0.25; p=0.78).

The average leptin levels increased in patients with T2DM as the arthropathy stage progressed, with a statistically significant difference between the groups of patients with the 1st and 2nd stages of arthropathy (t=2.6; p=0.03) and those with the 1st and 3rd stages of the disease (t=3.1; p=0.007). There were no statistically significant differences in the means of patients without arthropathy and the first stage of arthropathy (t=0.35; p=0.73), as well as those with the 2nd and 3rd stages of the disease (t=0.62; p=0.54).

A direct correlation was established between the levels of «leptin» and «insulin» in patients with T2DM (r=0.50; p=0.002). In patients without arthropathy, the correlation coefficient was 0.70

(p=0.050), and in patients with arthropathy, it was 0.41 (p=0.029). The values were divided into three categories: below the norm; above the norm; and the norm. It allowed us to carry out a correlation analysis with the determination of the Spearman coefficient. It was found that both types of DM had an increase in «insulin» and «leptin» levels along with the arthropathy progression (p<0.01).

A study of the risk of developing arthropathy depending on the level of osteocalcin did not confirm the hypothesis of an increased chance of developing arthropathy with an increase or decrease in the level of osteocalcin. The chances of patients are equal regardless of the type of diabetes and the level of osteocalcin. The constructed models are not reliable (p>0.1), have a specificity of 0.0% and a sensitivity of 100.0%. However, a logit model for patients with T1DM revealed a trend towards a higher probability of developing arthropathy with a rise in osteocalcin level.

An analysis of variance established the dependence of the «osteocalcin» level on the mutual action of such factors as «DM» and «arthropathy» (F=4.3; p=0.008), with a study power of 0.85 and a standard error of 0.05. Osteocalcin levels were often 53.9% higher in patients with T1DM and arthropathy than they were in patients without arthropathy (t=4.1; p=0.0003). No such differences were observed in patients with T2DM (p>0.5).

A more detailed analysis showed that the average osteocalcin level in patients with stage 1 arthropathy was significantly higher than in patients without arthropathy (t=4.9; p=0.0004) and in patients with stage 2 of arthropathy (t=2.2; p=0.042). Osteocalcin levels in patients with stages 2 and 3, as well as those with stages 1 and 3, did not differ statistically (p>0.1). The average osteocalcin levels in patients with T2DM and the 2nd stage of arthropathy were significantly higher than in those with the 1st stage (t=2.7; p=0.019). Other values did not differ statistically (p>0.2).

We also evaluated biomarkers that represent the synthetic and catabolic phases of collagen and glycosaminoglycan metabolism, which are the two building blocks of connective tissue. Deviation from the normal values of the concentration of the free fraction of hydroxyproline allows for evaluation of collagen catabolism, i.e., it is a biochemical marker of resorption of bone and cartilage tissues since the main protein of these tissues is collagen. Hydroxyproline is an amino acid that is a specific marker of collagen proteins. Remodeling, i.e., degradation or proteolysis, of collagen fibers of the intracellular matrix of cartilage and bone tissue is carried out by matrix metalloproteinases (MMPs) [16]. The activity of various MMPs (collagenases) has an extremely wide range of biological consequences since they degrade most components of the extracellular matrix [16-18].

Our observations support the hypothesis that osteoarthritis pathogenesis is mediated by increased MMP activity **(Table 3-4)**.

**Table 3.** Biochemical markers of connective tissue metabolism in the blood serum of patients with T1DM, M±m

| Markers | Without OA (n=24) | With OA (n=16) | p |
|---|---|---|---|
| Collagenase, mmol/L | 4.94±0.21 | 3.94±0.12 | 0.001 |
| Free hydroxyproline mmol/L | 7,80±0,16 | 7.15±0.17 | 0.008 |
| Protein-bound hydroxyproline, mmol/L | 12.83±0.13 | 12.51±0,23 | 0.242 |
| GAGs, g/L | 0.061±0.003 | 0.056±0.003 | 0.150 |
| Hyaluronidase, mmol/L | 228.83±1.31 | 226.81±2.12 | 0.426 |

**Table 4.** Biochemical markers of connective tissue metabolism in the blood serum of patients with T2DM, M±m

| Markers | Without OA (n=25) | With OA (n=12) | p |
|---|---|---|---|
| Collagenase, mmol/L | 4.47±0.16 | 3.88±0.24 | 0.046 |
| Free hydroxyproline mmol/L | 7,83±0,17 | 7.04±0.27 | 0.014 |
| Protein-bound hydroxyproline, mmol/L | 12.67±0.15 | 12.35±0,27 | 0.269 |
| GAGs, g/L | 0.057±0.003 | 0.055±0.003 | 0.597 |
| Hyaluronidase, mmol/L | 225.96±1.36 | 223.83±2.75 | 0.441 |

An analysis of variance showed that the mean collagenase levels varied depending on the stage of arthropathy (F=6.7; p<0.001) but did not differ according to the type of DM (p=0.23). The mean collagenase levels were different in patients with T1DM and T2DM, and with or without arthropathy. Thus, patients with T1DM and arthropathy had collagenase levels that were 16.6% higher (t=3.1; p=0.004) than those with T1DM and without arthropathy. The same indicator for T2DM was

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17.1% (t=2.6; p=0.025). In T1DM, a linear increase in the mean collagenase levels was found with the progression of arthropathy (R2=0.95), with statistically significant differences in collagenase levels between stage 1 and 3 of arthropathy (t=2.8; p=0.016). No other statistically significant differences were established.

The correlation analysis revealed a direct relationship between the level of osteocalcin and collagenase in the general study group (r=0.32; p=0.006), in the group of patients with T1DM (r=0.37; p=0.023) and in the group of women (r=0.37; p=0.012).

A more detailed analysis showed that a direct correlation between osteocalcin and collagenase parameters was determined only in women with T1DM (t=0.48; p=0.026). No correlations were noted between the levels of other metabolic enzymes and calcium.

## Conclusions

1. The study found that the development of arthropathy does not depend on the type of DM. The chances of developing arthropathy in men and women with T1DM were equal. Women with T2DM were more likely to develop arthropathy than men.
2. The chances of detecting arthropathy are higher with insulin and leptin levels in T1DM and T2DM. A direct correlation was found between insulin resistance and the presence of arthropathy in T2DM. In women with T2DM, the average leptin level was 1.8 times higher than in men.
3. A direct correlation was established between the levels of «Leptin» and «Insulin» in patients with T2DM and arthropathy. It was found that both types of DM had an increase in «Insulin» and «Leptin» levels along with the arthropathy progression.
4. Osteocalcin levels were 53.9% higher in patients with T1DM and arthropathy than they were in patients without arthropathy.
5. Regardless of the type of DM, patients with arthropathy had elevated levels of biochemical markers that indicate catabolic processes in the connective tissue (collagenase and free hydroxyproline).
6. A direct correlation between osteocalcin and collagenase levels in women with T1DM was determined. Patients with T1DM and arthropathy had collagenase levels that were 16.6% higher than those with T1DM and without arthropathy. The same indicator for T2DM was 17.1%.

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## List of abbreviations:

**DM** – diabetes mellitus
**GAG** – glycosaminoglycans
**OA** – osteoarthropathy
**SCB** – subchondral bone
**T1DM** – type 1 diabetes mellitus
**T2DM** – type 2 diabetes mellitus

# Патогенетичні аспекти діабетичного остеоартриту

**В.Л. Орленко, К.Ю. Іваськіва, М.Г. Кравчук**
ДУ «Інститут ендокринології та обміну речовин ім. В.П. Комісаренка НАМН України»
Національний медичний університет ім. О.О. Богомольця

**Резюме.** Ураження опорно-рухового апарата є одним із серйозних, але маловивчених ускладнень цукрового діабету (ЦД). Запальні та/або дегенеративні структурні зміни в суглобах на тлі тривалої гіперглікемії на початкових етапах спричиняють обмеження рухливості суглобів, а згодом призводять до стійких контрактур і інвалідизації хворих. Тому вивчення механізмів формування ураження суглобів у хворих на ЦД є надзвичайно важливим і актуальним. **Метою** нашого дослідження було виявити рівні специфічних гормонів і біохімічних маркерів метаболізму сполучної тканини у хворих на діабетичну артропатію та встановити їх можливий вплив на розвиток патології суглобів у цієї категорії хворих. **Матеріал і методи.** Всього в дослідження було включено 77 пацієнтів. Наявність та ступінь тяжкості діабетичної артропатії оцінювали за методом А. Розенблума. Рівні інсуліну, лептину та остеокальцину в сироватці крові визначали методом імуноферментного аналізу з використанням наборів реактивів фірми Diaclone (Франція) та планшетного імуноферментного аналізатора Stat fax 3200 (США). Колагеназну активність оцінювали за методикою, розробленою S. Lindy і J. Halme. Глікозаміноглікани визначали орциновим методом, описаним С.А. Кляцкіним та Р.І. Ліфшицем. Фракції гідроксипроліну виділяли із сироватки крові за методом, запропонованим С. Фреєм. А гідроксипролін ідентифікували за допомогою реактивів фірми Merck (Німеччина). **Результати.** У результаті дослідження виявлено, що розвиток артропатії не залежить від типу цукрового діабету. Шанси розвитку артропатії в чоловіків і жінок із ЦД 1-го типу були однаковими. Жінки з ЦД 2-го типу мали в 6,4 раза більше шансів на розвиток артропатії, ніж чоловіки. Встановлено, що при обох типах ЦД разом із прогресуванням артропатії спостерігалося підвищення рівнів інсуліну та лептину. Рівні остеокальцину були на 53,9% вищими в пацієнтів із ЦД 1-го типу та артропатією, ніж у пацієнтів без артропатії. Незалежно від типу ЦД у хворих на артропатію спостерігався підвищений рівень біохімічних маркерів, що вказують на катаболічні процеси в сполучній тканині колагенази та вільного гідроксипроліну. **Висновок**. Таким чином, встановлена важлива роль гормонів інсуліну та лептину в розвитку уражень суглобової системи в пацієнтів із ЦД. Визначення рівнів остеокальцину, колагенази та гідроксипроліну є важливими ранніми маркерами катаболічних процесів у пацієнтів із діабетичною артропатією.

**Ключові слова:** цукровий діабет, діабетична артропатія.

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**Correspondence address**: Orlenko Valeriya Leonidivna, orleva@ukr.net; State Institution «V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine», Vyshgorodska Str., 69, Kyiv 04114, Ukraine.
**Information about the authors**: Orlenko Valeriya Leonidivna, Dr. Sci. (Medicine), Head of Department of Scientific and Advisory Preventive Care for Patients with Endocrine Disorders, ORCID: 0000-0002-8400-576X; Ivaskiva Kateryna Yuriyivna, Ph (Medicine), Senior Researcher fellow of Department of Scientific and Advisory Preventive Care for Patients with Endocrine Disorders, ORCID: 0000-0003-1680-4663; Kravchuk Mariya Hryhorivna, Ph (Medicine), Sciences, Associate Professor, Associate Professor of the Department of Biology ORCID ID 0000-0002-0175-5750.
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**Адреса для листування:** Орленко Валерія Леонідівна, orleva@ukr.net; ДУ «Інститут ендокринології та обміну речовин ім. В.П. Комісаренка НАМН України», вул. Вишгородська, 69, Київ 04114, Україна.
**Відомості про авторів:** Орленко Валерія Леонідівна, д-рка мед. наук, старш. наук. співроб., завідувачка науково-консультативного відділу амбулаторно-профілактичної допомоги хворим з ендокринною патологією, ORCID: 0000-0002-8400-576X; Іваськіва Катерина Юріївна, канд. мед. наук, старша наукова співробітниця науково-консультативного відділу амбулаторно-поліклінічної допомоги хворим з ендокринною патологією ORCID: 0000-0003-1680-4663; Кравчук Марія Григорівна, канд. мед. наук, доцентка, доцентка кафедри біології ORCID ID 0000-0002-0175-5750.
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