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## CLINICAL SIGNIFICANCE OF VISFATIN AND HOMOCYSTEINE IN FORECASTING OF OSTEOARTHRITIS IN WOMEN OF PRE- AND POSTMENOPAUSAL AGE WITH TYPE 2 DIABETES MELLITUS

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Type 2 diabetes mellitus is a leading cause of death and has high prevalence. Patients with type 2 diabetes mellitus are often diagnosed with osteoarthritis, the vast majority of cases are found in pre- and postmenopausal women due to decreased estrogen levels, as well as their numerous hormonal and metabolic disorders. The study determined the prognostic significance of visfatin and homocysteine in the development of osteoarthritis in pre- and postmenopausal women with type 2 diabetes mellitus and built a prognostic model for the development of osteoarthritis. We studied 82 pre- and postmenopausal women: 20 women (1 group) with isolated type 2 diabetes mellitus and 62 women (group 2) with comorbid type 2 diabetes mellitus and osteoarthritis. The study found that reliable predictors of osteoarthritis in women with type 2 diabetes mellitus in pre- and postmenopausal women were waist circumference, levels of very-low-density lipoproteins, visfatin and homocysteine, which were included in a prognostic model with high levels of sensitivity and specificity: 96.8 % and 90.0 %, respectively. The value of the area under the curve was  $0.992 \pm 0.006$  [95.0 % CI 0.979–1.000],  $p < 0.001$ . The obtained prognostic model opens new ways of timely diagnosis of early osteoarthritis in pre- and postmenopausal women with type 2 diabetes mellitus.

**Key words:** comorbid course, predictors, premenopause, postmenopause, metabolic disorders, prognostic model.

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## КЛІНІЧНЕ ЗНАЧЕННЯ ВІСФАТИНУ ТА ГОМОЦИСТЕЇНУ У ПРОГНОЗІ ОСТЕОАРТРИТУ У ЖІНОК ПЕРЕД- І ПОСТМЕНОПАУЗНОГО ВІКУ ПРИ ЦУКРОВОМУ ДІАБЕТИ 2 ТИПУ

Цукровий діабет 2 типу є основною причиною смертності та має високу поширеність. У хворих на цукровий діабет 2 типу часто діагностують остеоартроз, переважна більшість випадків зустрічається у жінок в пре- і постменопаузі через зниження рівня естрогенів, а також їх численних гормональних і метаболічних порушень. У дослідженні було визначено прогностичне значення вісфатину та гомоцистеїну у розвитку остеоартрозу у жінок у пре- та постменопаузі з цукровим діабетом 2 типу та побудовано прогностичну модель розвитку остеоартрозу. Ми вивчали 82 жінки в пре- та постменопаузі: 20 жінок (1 група) із ізольованим цукровим діабетом 2 типу та 62 жінки (група 2) з коморбідним цукровим діабетом 2 типу та остеоартрозом. Дослідження показало, що надійними предикторами остеоартрити у жінок у пре- та постменопаузі з цукровим діабетом 2 типу були ІМТ, окружність талії, ЛПДНЩ, висфатин та гомоцистеїн, які були включені в прогностичну модель з високим рівнем чутливості та специфічності: 96,8 % і 90,0 % відповідно. АUC становила  $0,992 \pm 0,006$  [95,0% ДІ 0,979–1000],  $p < 0,001$ . Отримана прогностична модель відкриває нові шляхи своєчасної діагностики раннього остеоартрозу у жінок у пре- та постменопаузі з цукровим діабетом 2 типу.

**Ключові слова:** коморбідний перебіг, предиктори, пременопауза, постменопауза, метаболічні порушення, прогностична модель.

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2040 [14] and up to 700 million people by 2045 (almost twice as many for men and by 1.6 times for women [10]) due to high rates.

The WHO identifies diabetes mellitus (DM) as one of the leading chronic non-communicable diseases, ranking seventh among the world's leading causes of death. Diabetes worldwide has high prevalence rates of about 470 million patients and has a negative outlook for an increase to 642 million cases by 2040 [14] and to 700 million people by 2045 (almost twice as many in men and 1.6 in women) [10]) due to high rates of economic progress in many countries. More than 90.0 % of all cases of diabetes mellitus are diagnosed with type 2 diabetes mellitus [4], which is growing by 9.0 % annually and is increasingly detected in people under 40 years.

Diabetes mellitus (especially type 2) has a high comorbidity with cardiovascular diseases, diseases of the joints, gastrointestinal tract, kidneys and thyroid gland, lungs and others due to the same risk factors (obesity, dyslipidemia, endothelial dysfunction, etc.). According to studies by Priya Alva et al. [2] type 2 diabetes mellitus is closely associated with obesity and body mass index (BMI), especially in women due to hormonal changes in pre- and menopause: women with a BMI of  $25 < 30 \text{ kg/m}^2$  have a higher risk of developing 2 type diabetes mellitus. In the United States, about 90.0–95.0 % of type 2 diabetes mellitus is associated with obesity.

Among the comorbidities in patients with type 2 diabetes mellitus with obesity are often diagnosed with osteoarthritis (OA), the prevalence of which in obesity increases by 5 times [8] due to common risk

factors (primarily age and obesity) [11]. OA is more often diagnosed in women with estrogen loss during pre- and menopause, and the risks of developing OA are highest after menopause and are by 3.5 times higher than the corresponding risks for men at the age of 50–60.

OA has a fairly high global prevalence (more than 303 million cases in 2017) and has a high risk of disability. The study by Wu JH, et al. [15] probably ( $p < 0.05$ ) proved the relationship between type 2 diabetes mellitus and OA and greater risks for women due to hormonal changes in menopause: the prevalence of OA in type 2 diabetes was 32.65 % and was higher in women (38.05 %) than men (27.41 %). During hormonal changes, pre- and menopausal women develop a metabolic syndrome which is associated with obesity (especially visceral) and with insulin resistance and type 2 diabetes mellitus due to specific adipocytokines [7].

Many studies have linked obesity, type 2 diabetes mellitus and OA to increased visfatin (VF), insulin, and homocysteine (HC) [4]. According to studies, increased levels of VF correlate with diabetes mellitus, obesity, hypertension, renal and cardiovascular disease, as evidenced by the likely correlations of serum glucose, glycated hemoglobin and VF according to studies Buyukaydin B, et al. [3]. Other studies suggest an association between elevated VF levels and risk factors for OA (obesity, insulin resistance, and type 2 diabetes mellitus) [12] and the development of metabolic syndrome in pre- and menopausal women and obesity and OA.

HC, in turn, is also associated with systemic atherosclerosis, OA, type 2 diabetes mellitus, cardiovascular and other diseases. Hyperhomocysteinemia is associated with glucose intolerance, insulin resistance and disorders of the insulin signaling pathway and adversely affects nerve and endothelial cells, osteoclasts and osteoblasts, leading to decreased bone strength and the development of OA [9].

**The purpose** of the study was to determine the prognostic significance of visfatin and homocysteine in the development of osteoarthritis in pre- and postmenopausal women with type 2 diabetes mellitus and to build a prognostic model for the development of osteoarthritis.

**Materials and methods.** The study included 82 pre- and postmenopausal women, including 20 women (group 1) with isolated type 2 diabetes mellitus ( $58.6 \pm 7.1$  years) and 62 women (group 2) with comorbid type 2 diabetes mellitus and OA ( $59.7 \pm 4.0$  years).

Inclusion criteria were the presence of type 2 diabetes mellitus, the presence of OA, the pre- and postmenopausal period. Exclusion criteria were men, women with iatrogenic menopause (secondary) and those receiving hormone replacement therapy, acute and chronic inflammatory processes, cancer.

The diagnosis of type 2 diabetes mellitus was established in accordance with generally accepted criteria in clinical practice and the order of the Ministry of Health of Ukraine No. 1118 of 21.12.2012. 676 of October 12, 2006. The presence of menopause was confirmed by a gynecologist (according to the STRAW10 + classification).

To identify the clinical manifestations of climax, its severity, we used the calculation of the Kupperman menopausal index in the modification of EV Uvarova – modified menopausal index (MI) (0 points – no symptom, 1 point – mild, 2 points – moderate, 3 points – strongly expressed). A total score of 35–58 indicated a menopausal syndrome of moderate severity, 59 and above – a severe menopausal syndrome. BMI was determined by the formula: body weight (in kg) divided by the square of the patient's height (in m<sup>2</sup>). Waist and hip circumference were measured according to WHO recommendations with a centimeter tape. The ratio of waist and hips was determined by the formula: the length of the waist circumference is divided by the length of the hip circumference. Systolic (CAT) and diastolic blood pressure (DBP) were measured with a Microlife BP AG1-20 mechanical tonometer (Switzerland) on the brachial artery.

To determine the levels of blood VF and HC was used a variant of indirect non-competitive heterogeneous enzyme-linked immunosorbent assay with the “Labline-90” analyzer (Austria) using a commercial test system manufactured by “Elabscience” (China).

Fasting blood glucose (FBG) was determined to assess carbohydrate metabolism. The concentration of immunoreactive insulin (IPI) with an empty stomach was determined by enzyme-linked immunosorbent assay.

The state of lipid metabolism was assessed by the content of total cholesterol (TC), triglycerides (TG), cholesterol of low-density lipoproteins (LDL), cholesterol of very low-density lipoproteins (VLDL), and cholesterol (HDL). The atherogenic index (AI) was calculated mathematically.

Statistical processing.

Determining the associations of indices with the binomial dependent variable was performed using logistic regression analysis with the calculation of coefficients  $\beta$ , standardized coefficients  $\beta$  (odds ratio (OR) and their 95 % confidence intervals (CI)).

Regression analysis used the methods of simultaneous inclusion and inverse exclusion of Wald. The determination of the threshold value of the linear component of the model was estimated using ROC analysis with the calculation of the value of the area under the curve (AUC), its standard error and 95.0 % CI.

**Results of the study and their discussion.** Based on the results of the study and based on the study of the clinical significance of VF and HC, assessment of hormonal and metabolic status of pre- and postmenopausal women with type 2 diabetes mellitus, we determined the pathogenetic role of these indices as predictors of early OA. The obtained data can be used to expand knowledge about the combined course of type 2 diabetes mellitus and OA, to identify new pathogenetic links and patterns of comorbid pathology and progression of OA in this cohort of patients, improve diagnosis and develop a differentiated approach to choosing tactics of treating patients in this age group.

Clinical and anamnestic characteristics of the examined women are given in table 1.

Table 1

**Clinical-anamnestic, laboratory and biochemical characteristics and levels of HC and VF in women with type 2 diabetes mellitus and OA in pre- and menopause, M±SD**

Characteristics of the study group	Studied groups		
	1st (n = 20)	2nd (n = 62)	
<b>Clinical and anamnestic indices</b>			
Age, years	58.6±7.1	59.7±4.0	0.374
Duration of absence of menstruation, years	9.0±7.1	9.3±3.6	0.633
Menopausal index, points	25.0±13.1	21.7±13.0	0.268
Weight, kg	80.9±18.2	84.8±15.3	0.415
BMI, kg/m <sup>2</sup>	30.9±6.8	31.0±5.1	0.970
Waist circumference, cm	98.6±20.8	93.5±12.2	0.361
Thigh circumference, cm	113.7±18.2	109.0±11.6	0.596
Waist/thigh ratio	0.86±0.07	0.86±0.04	0.504
<b>Glucose metabolism</b>			
Fasting glucose, mmol/l	10.4±2.2	10.0±3.2	0.418
Hb <sub>1Ac</sub> , %	8.9±1.7	10.7±2.2	<0.001
<b>Lipid metabolism</b>			
TC, mmol/l	6.9±1.0	7.5±1.8	0.142
TG, mmol/l	2.9±1.4	2.9±1.1	0.783
HDL, mmol/l	1.4±0.4	1.3±0.3	0.623
LDL, mmol/l	3.5±0.7	3.8±0.9	0.177
VLDL, mmol/l	1.6±0.7	1.4±0.7	0.250
AI	3.4±1.4	3.1±1.7	0.200
<b>Biochemical markers</b>			
HC, ng/ml	15.0±3.4	23.6±6.1	<0.001
VF, nm/ml	3.9±1.2	5.5±1.0	<0.001

MI – menopausal index; Hb<sub>1Ac</sub> – glycosylated hemoglobin; TC – total cholesterol; TG – triglycerides; HDL – high density lipoproteins; LDL – low density lipoproteins; VLDL – very low density lipoproteins; AI – atherogenic index.

The mean age of the examined women was 58.6±7.1 in group 1 and 59.7±4.0 in group 2. The duration of the absence of menstruation was somewhat predominant in the group of comorbid combinations of type 2 diabetes mellitus and OA compared to the group of isolated type 2 diabetes mellitus. According to the questionnaire, the mean levels of menopausal index were recorded in the study groups. The weight of sick women and BMI of the body prevailed in the group of comorbid pathology, compared to the group of isolated type 2 diabetes mellitus (84.8±15.3 and 31.0±5.1, respectively, compared to 80.9±18.2 and 30.9±6.8). Next, we analyzed the predictors associated with the presence of OA in women with type 2 diabetes mellitus. The obtained data are given in table 2.

Multivariate logistic regression analysis showed that among the reliable independent predictors are the following: duration of absence of menstruation (OR=0.652 [95.0 % CI 0.452–0.939], p=0.022), diabetic microangiopathy (OR=28.322 [95.0 % CI 1.075–746.233], p=0.045), BMI (OR=2.146 [95.0 % CI 1.338–3.440], p=0.002) and waist circumference (OR=0.754 [95.0 % CI 0.671–0.921], p=0.006). Other factors included in the analysis did not show a significant association with the presence of OA in the examined women. Subsequent analysis identified a significant association with the presence of OA in women with type 2 diabetes mellitus: BMI (OR=1.875 [95.0 % CI 1.266–2.778], p=0.002) and waist circumference (OR=0.791 [95.0 % CI 0.690–0.905], p=0.001). Thus, an increase in BMI by 1 kg/m<sup>2</sup> is significantly associated with almost a twofold increase in the chance of OA in type 2 diabetes mellitus. At the same time, an increase in waist circumference by 1 cm was significantly associated with a decrease in the chance of OA in type 2 diabetes mellitus by 21.9 %.

Clinical and anamnestic predictors associated with osteoarthritis in women with type 2 diabetes mellitus

Predictors	method of simultaneous inclusion				Wald method of inverse exclusion			
	OR	95,0 % CI		p	OR	95,0 % CI		p
		low	upper			low	upper	
Age, years	\	0.919	1.896	0.132	–	–	–	–
Duration of 2 type diabetes mellitus, years	0.980	0.864	1.111	0.748	–	–	–	–
Duration of the absence of menstruation, years	0.652	0.452	0.939	0.022	0.958	0.840	1.094	0.529
MI	0.942	0.876	1.012	0.103	–	–	–	–
BMI, kg/m <sup>2</sup>	2.146	1.338	3.440	0.002	1.875	1.266	2.778	0.002
Waist, cm	0.754	0.617	0.921	0.006	0.791	0.690	0.905	0.001
Fasting glucose, mmol/l	0.615	0.425	0.890	0.010	0.623	0.458	0.847	0.003
Hb <sub>1Ac</sub> , %	2.423	1.359	4.318	0.003	2.514	1.519	4.162	<0.001
TC, mmol/l	0.975	0.581	1.636	0.923	–	–	–	–
TG, mmol/l	0.741	0.312	1.760	0.497	–	–	–	–
HDL, mmol/l	3.772	0.163	87.135	0.407	–	–	–	–
LDL mmol/l	0.718	0.170	3.028	0.652	–	–	–	–
AI	2.818	1.092	7.274	0.032	1.797	1.045	3.092	0.034

Note: OR – odds ratio; CI – confidence interval

Thus, the reliable association with the presence of OA was determined by the levels of glucose (OR=0.615 [95.0 % CI 0.425–0.890], p=0.010) and glycosylated hemoglobin (OR=2.423 [95.0 % CI 1.359–4.318], p=0.003); the value of the spacecraft (OR=2.818 [95.0 % CI 1.092–7.274], p=0.032). At the limit of the established level of reliability, the association of hemoglobin with the presence of OA was obtained: OR=1.060 [95.0 % CI 0.994–1.130], p=0.076. Using Wald's inverse exclusion method, a significant effect of fasting glucose and glycosylated hemoglobin levels was determined: OR=0.623 [95.0 % CI 0.458–0.847], respectively (p=0.003) and OR=2.514 [95.0 % CI 1.519–4.162], respectively. (p<0.001). The influence of the level of VLDL was found on the limit of reliability: OR=0.383 [95.0 % CI 0.111–1.117], p=0.079. A reliable association was preserved with respect to the spacecraft: VS=1.797 [95.0 % CI 1.045–3.092], p=0.034.

We also assessed the effect of phosphorus and calcium levels, as well as systolic and diastolic blood pressure levels, the degree of neurovegetative and psychoemotional symptoms according to the questionnaire, as well as the presence of diabetic microangio- and neuropathies, but these indices did not reveal the impact on possible development of OA and were not further included in our analysis.

To improve the accuracy of the prognostic model, it was decided to assess and add serum markers that may be associated with the presence of OA in women with type 2 diabetes mellitus (VF, HC and insulin).

In the simultaneous analysis of all studied markers, the reliable predictors were the levels of HF and HC: respectively, OR=4.046 [95.0 % CI 1.498–10.923] (p=0.006) and OR=2.406 [95.0 % CI 1.390–4.166] [p=0.002]. These two markers are highly associated with the presence of OA in the examined women.

Also, reliable predictors of the presence of OA in pre- and postmenopausal women with type 2 diabetes can be BMI (OR=8.315 [95.0 CI 1.421–48.652], p=0.019), waist circumference (OR=0.455 [95.0 % CI 0.236–0.877], p=0.019), VLDL (OR=0.025 [95.0 % CI 0.001–0.887], p=0.043); the level of VF (OR=32.293 [95.0 % CI 1.801–579.066], p=0.018) and the level of HC (95.0 % CI 3.620 [95.0 % CI 1.332–9.822], p=0.012).

$$Y = -22.244 + [\text{BMI, kg/m}^2 \times 2.118] - [\text{waist circumference, cm} \times 0.788] - \\ - [\text{VLDL, mmol/l} \times 3.683] + [\text{Visfatin, ng/ml} \times 3.475] + \\ + [\text{Homocysteine, mmol/l} \times 1.286]$$

Statistical parameters for assessing the efficacy of the developed prognostic complex were assessed as sensitive (96.8 %), accurate (95.1 %) and specific (90.0 %).

The limit value of this model can be chosen 0.7900, while the indices of prognostic efficacy change slightly: sensitivity – 95.2 %, specificity – 95.0 %, accuracy – 98.3 %.

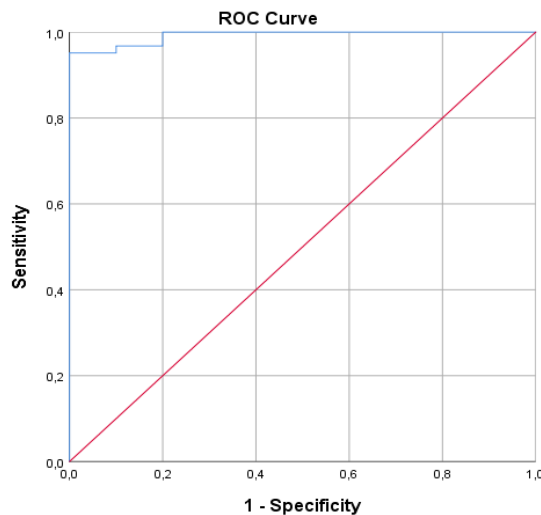


Fig. 1. ROC curve of the prognostic capability of the developed model's linear component (AUC=0.992±0.006 [95.0 % CI 0.979–1.000],  $p<0.001$ )

levels, respectively. Tsiklauri L, et al. [13] also showed a significant increase in OA levels of VF ( $2.25\pm 0.36$ ;  $p=0.002$ ) and HC ( $18.04\pm 8.44$ ;  $p<0.05$ ).

### Conclusions

1. Among the most significant predictors of the presence of OA in pre- and postmenopausal women with type 2 diabetes mellitus were identified BMI (OR=1.875 [95.0 % CI 1.266–2.778]); waist circumference (OR=0.791 [95.0 % CI 0.690–0.905]); fasting glucose (OR=0.623 [95.0 % CI 0.458–0.847]) and glycosylated hemoglobin (OR=2.514 [95.0 % CI 1.519–4.162]); VLDL (OR=0.383 [95.0 % CI 0.111–1.117]); AI: (OR=1.797 [95.0 % CI 1.045–3.092]) and phosphorus (OR=0.059 [95.0 % CI 0.003–1.159]).

2. Direct reliable association was also obtained with respect to the studied markers: VF and HC (respectively: OR=4.046 [95.0 % CI 1.498–10.923] and OR=2.406 [95.0 % CI 1.390–4.166]).

3. The model for predicting the development of OA in women with type 2 diabetes mellitus included the most significant predictors, including BMI, waist circumference, VLDL, VF and HC, which according to regression analysis identified a reliable association with OA in pre- and postmenopausal women. with type 2 diabetes mellitus.

4. The efficacy of the model showed high levels of sensitivity and specificity: 96.8 % and 90.0 %, respectively. The AUC was  $0.992\pm 0.006$  [95.0 % CI 0.979–1.000].

5. According to the ROC-analysis, the optimal limit value of the coefficient of the developed model was determined at the level of 0.7900, at which the efficacy indices of the model were: sensitivity – 95.2 %; specificity – 95.0 %.

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## ROLE OF TRIGGER FACTORS AND EFFECT OF DIAMINE OXIDASE DEFICIENCY ON CLINICAL MANIFESTATIONS OF ATOPIC DERMATITIS

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When examining 87 patients with moderate and severe forms of atopic dermatitis aged 16 to 49 years, trigger factors in various clinical forms of atopic dermatitis were analysed. It was revealed that diamine oxidase deficiency and trigger factors aggravate the course of atopic dermatitis. Diamine oxidase deficiency in atopic dermatitis was combined with insignificant dynamics in relation to IgE and slow regression of the SCORAD index. It was revealed that the degree of influence of diamine oxidase on the course of atopic dermatitis (especially at SCORAD $\geq$ 25) makes it possible to identify a group of patients who need additional regulation of tissue histamine conversion and active blocking of exogenous histamine liberators. A low level of diamine oxidase activity correlated with a slow regression of clinical symptoms of dermatosis, including more persistent pruritus, deterioration of the general condition, insomnia, irritability, and psycho-emotional asthenia.

**Key words:** aetiology of atopic dermatitis, diamine oxidase, clinical forms of atopic dermatitis, SCORAD index

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## РОЛЬ ТРИГЕРНИХ ФАКТОРІВ ТА ВПЛИВ НЕДОСТАТНОСТІ ДІАМІНОКСИДАЗИ НА КЛІНІЧНІ ПРОЯВИ АТОПІЧНОГО ДЕРМАТИТУ

При обстеженні 87 пацієнтів з середніми та важкими формами atopічного дерматиту віком від 16 до 49 років проаналізовані провокуючі фактори при різних клінічних формах atopічного дерматиту. Виявлено, що дефіцит діаміноксидази та тригерні фактори посилюють перебіг atopічного дерматиту. Дефіцит діаміноксидази при atopічному дерматиті поєднувався з незначною динамікою по відношенню до IgE та повільним регресом індексу SCORAD. Виявлено, що ступінь впливу діаміноксидази на перебіг atopічного дерматиту (особливо при SCORAD $\geq$ 25) дозволяє виділити групу пацієнтів, яким необхідна додаткова регуляція конверсії тканинного гістаміну й активне блокування гістамінолібераторів, що надходять екзогенно. Низький рівень активності діаміноксидази корелював з повільним регресом клінічних симптомів дерматозу, включаючи більш стійкий свербіж, погіршення загального стану, безсоння, дратівливість та психоемоційну астенізацію.

**Ключові слова:** етіологія atopічного дерматиту, діаміноксидаза, клінічні форми atopічного дерматиту, індекс SCORAD

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Atopic dermatitis (AD) is a chronic allergic disease characterized by genetic determinism, hyperimmunoglobulinemia E, a recurrent course, and age-related skin manifestations.

In the last decade, there has been an increase in the incidence of atopic dermatitis and associated processes, which include bronchial asthma, allergic rhinitis, and allergic conjunctivitis. According to official statistics, about 20 % of the population of Ukraine suffer from atopic diseases that significantly affect the patient's quality of life [3].