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Dnepr, Ukraine**DIABETIC RETINOPATHY AND CLUSTERS OF METABOLIC SYNDROME IN PATIENTS WITH
TYPE 2 DIABETES MELLITUS****Ищенко В.А.**(1) — Днепропетровская медицинская академия МЗ Украины,
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г. Днепр, Украина**ДИАБЕТИЧЕСКАЯ РЕТИНОПАТИЯ И КЛАСТЕРЫ МЕТАБОЛИЧЕСКОГО СИНДРОМА У
ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА**

Resume. The purpose of the research is to study clusters of the metabolic syndrome (MS) in patients with type 2 diabetes mellitus (DM) at different stages of the diabetic retinopathy (DR). **Materials and methods.** The research was carried out on 83 patients (166 eyes), who were divided into two groups. **Results.** In the study of morphometric and biochemical clusters of MS in 59 patients with type 2 DR (average age — 58.20 ± 0.99 year, average length of DM — 9.19 ± 0.16 year) at different stages of DR with the help of the analysis of variance and binominal distribution law it has been shown that DR develops in patients with obesity — 83.4 % cases (with an increase in waist circumference), arterial hypertension (AH) — 71.4 % patients, hypercholesterolemia — 61.9 %, dyslipidemia — 47.6 % and hypertriglyceridemia — 52.3 %. Further DR progression associates statistically significantly with AH, dyslipidemia with android obesity, hypercholesterolemia and hypertriglyceridemia. **Conclusions.** Patients with type 2 DM at the proliferate stage of DR are in at a higher risk for development of vascular events including in the fundus, which should be considered in surgical, physiotherapeutic and medical treatment.

Резюме. Цель исследования: изучить кластеры метаболического синдрома (МС) при диабетической ретинопатии (ДР). Материалы и методы. Исследования проведены у 83 пациентов (166 глаз), разделенных на две группы. Результаты. При исследовании морфометрических и биохимических кластеров МС у 59 пациентов с СД 2-го типа (средний возраст — $58,20 \pm 0,99$ года, средняя длительность СД — $9,19 \pm 0,16$ года) на разных стадиях ДР с помощью дисперсионного анализа и закона биномиального распределения показано, что ДР формируется на фоне ожирения у 83,4 % больных (с увеличением окружности талии), артериальной гипертензии (АГ) — у 71,4 % больных, гиперхолестеринемии — у 61,9 %, дислипидемии — у 47,6 % больных и гипертриглицеридемии — у 52,3 %. Дальнейшее прогрессирование ДР статистически значимо ассоциируется с АГ, дислипидемией на фоне андроиного ожирения, гиперхолестеринемии и гипертриглицеридемии. Выводы. Пациенты с СД 2-го типа на пролиферативной стадии ДР находятся в группе повышенного риска возникновения сосудистых событий, в том числе и на глазном дне, что необходимо учитывать при хирургическом и медикаментозном лечении данной группы пациентов.

Keywords: *diabetic retinopathy; metabolic syndrome***Ключевые слова:** *диабетическая ретинопатия; метаболический синдром***Introduction**

Recently the interest in metabolic syndrome (MS) has started to move from cardiology [17] toward other medical fields, which can be observed in appearance of scientific publications dedicated to study of MS clusters in particular in ophthalmology, urology and naturally diabetology. Thus the influence of diabetes mellitus (DM) on the spread of diabetic retinopathy (DR) in patients with type 2 DM with MS [3], clinical functional and metabolic correlation between ischemic heart disease and DR in patients with type 2 DM [2], role of tissue renin-angiotensin-aldosterone system in development of MS, DM and vascular complications

[7], biometric and biochemical indicators of MS or risk of occurrence in patients with benign prostatic hyperplasia have been studied [5].

Purpose: to study MS clusters in patients with type 2 DM at different stages of DR.

Materials and methods

The research was conducted on 83 patients (166 eyes), who were divided into two groups. The first group (control) included patients with MS without type 2 DM (24 people of both genders, average age was 49.26 ± 2.14 years), the second group included 59 patients of both genders with type 2 DM, MS and DR (average age was 58.20 ± 0.99 years, average duration

of DM was 9.19 ± 0.16 years), which was divided into 3 study subgroups depending on the stage of DR.

Inclusion criterion was patient informed consent to participate in the study. Exclusion criteria were: presence of endocrine and somatic pathology leading to obesity (Cushing syndrome, hypothyroidism, postpubertal form of dyspituitarism, polycystic ovary syndrome, other endocrine pathologies, including hereditary, cerebral obesity), type 1 DM, acute infectious diseases, oncologic diseases (including a history), decompensation of comorbid pathology, psychological disorders, use of antipsychotics and antidepressants, presence of proteinuria, maculopathy, glaucoma and cataract.

The study was carried out in accordance with Helsinki Declaration of the World Medical Association (2008). The study and treatment of patient with type 2 DM was made by Unified Clinical Protocol on First and Secondary (Specialized) Medical Help "Type 2 Diabetes Mellitus" and Order of Ukrainian Ministry of Health # 1118 or as of 21 December, 2010 "On Approval and Implementation of Medical-Technological Documents for the Standardization of Medical Aid in Type 2 Diabetes Mellitus".

All patients who were included in the study and control group were examined: height, body weight, body mass index (BMI) was calculated, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were registered, concentration of total cholesterol (TCH) was determined, high density lipoprotein cholesterol (HDL CH), low density lipoprotein cholesterol (LDL CH) and triglycerides (TG). The presence of MS in the control group of patients was determined according to the accepted by the World Health Organization Work Criteria developed by experts from the National Institute of Health, USA (Adult Treatment Panel III, ATP III, 2001) and Consensus of the International Diabetes Federation (IDF) [11, 13].

Ophthalmologic examination was carried out according to the generally accepted methodology including visometry, tonometry, biomicroscopy, ophthalmoscopy, fluorescent angiography, if needed coherent retinal tomography. Diagnosis DR was

established according to the classification suggested by E. Kohner and M. Porta (1992), in which there are 3 main stages of diabetic retinopathy: non-proliferate, pre-proliferate and proliferate [15].

Comparison of independent data was made using analysis of variance. Initially distribution of the quantitative indicators was made in all samples in compliance with Gauss's law. Depending on the data distribution type Fisher's exact (parametric) test or non-parametric criterion of Kruskal-Wallis were used. Statistical characteristics were shown in the form of arithmetic mean (M) and standard error (m), as well as 95 % confidence interval (95% CI). To compare the results with the alternative variation of the trait (increase-decrease) to assess the significance of the difference the formula for defining Student's criterion t was used concerning related samples, what follows from the binomial distribution law (according to van der Warden formula) [12]. The level of statistical significance of differences was $p < 0.05$. Statistical analysis of data was carried out using software SPSS9.0.

Results

Average BMI in patients with type 2 DM corresponded to I degree of obesity, in the control group – II degree of obesity, though the confidence interval contained individual data, which indicated the presence of first and second degrees of obesity in all groups. At that relative frequency of obesity with different degree of manifestation in both groups of patients with DM was statistically more significant at the first stage of DR ($p < 0.001$) and statistically less significant at the second stage of DR ($p < 0.001$). Nevertheless on the whole relative obesity rate in all studied groups was statistically significantly lower than in the control group ($p < 0.001$). Increase in waist circumference (WS) over the recommended norm (more than 94 cm in men and 80 cm in women) was revealed in all studied groups and in the comparison group. Statistically significant differences ($p_1 = 0.01$) manifested in the biggest WS in women at the second stage of DR in comparison with the control group (Tab. 1).

Table 1

Some morphometric clusters of the metabolic syndrome at different stages of DR (M $\pm$ m)

Indicator	Statistic indicator	Obesity (control)	Diabetic Retinopathy		
			I stage	II stage	III stage
		1	2	3	4
Body Mass Index, kg/m ²	N	23	42	9	8
	M $\pm$ m	35.2 $\pm$ 1.1	32.8 $\pm$ 0.8	33.7 $\pm$ 1.7	33.7 $\pm$ 1.8
	95% CI	33.6-36.7	31.7-34.1	31.3-36.3	31.1-36.3
Relative Frequency BMI > 30 kg/m ²	N	22	35	6	6
	M $\pm$ m	95.70 $\pm$ 4.23	83.40 $\pm$ 5.74 $P_1 < 0.001$	66.70 $\pm$ 15.71 $P_{1-2} < 0.001$	75.00 $\pm$ 15.31 $P_1 < 0.001$ $P_2 < 0.05$ $P_3 < 0.1$
Waist Circumference (M), cm	N	13	20	4	4
	M $\pm$ m	114.3 $\pm$ 3.8	114.4 $\pm$ 2.7	106.7 $\pm$ 6.1	108.0 $\pm$ 6.1
	85% CI	109.4-119.1	110.5-118.3	98.0-115.4	99.2-116.7

Waist Circumference (F), cm	N M±m 95% CI	10 101.80±4.24 95.7-107.8	22 107.50±2.86 103.4-111.6	5 120.2±6.0 111.6-128.7 P ₁ =0.01	4 107.5±6.70 97.8-117.1
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Note: N – number of the studied patients; P – level of statistical significance of differences; M – males; F – females.

Increase in SBP over the upper acceptable limit of the norm was typical for both patients with DM and for the patients in the control group. Among patients with type 2 DM maximal SBP was determined at the third stage of DR whereas the minimal one was observed at the second stage of DR. At that the relative rate of the arterial hypertension (AH) (by SBP) was *была* statistically more significant at the first and third stages of DR in comparison with the control ($p < 0.001$) and had the highest value at the third stage of DR. Statistically significant ($p < 0.001$) decrease in relative frequency of AH (by SBP) was revealed at the second

stage of DR in comparison with other stages. Increase in the normal level of DBP was revealed at the first, third stages of DR and in the control group, whereas at the second stage of DR DBP was statistically less significant ($p = 0.05$) in comparison with other stages of DR. Relative frequency of AH by DBP was statistically more significant ($p < 0.02$) at the first and third stages of DR in comparison with the control group and statistically less significant ($p < 0.001$) – at the second stage of DR in comparison with the other stages and the control group (Tab. 2).

Table 2

Functional clusters of the metabolic syndromes at different stages of DR (M±m)

Indicator	Statistic indicator	Obesity (control)	Diabetic Retinopathy		
			I stage	II stage	III stage
		1	2	3	4
SBP, mm Hg	N	21	42	9	8
	M±m	140.8±5.25	149.20±3.72	140.20±8.02	152.30±8.51
	95%	133.4-48.3	143.9-154.4	128.9-151.5	140.3-164.3
Relative Frequency SBP > 139 mm Hg, %	N	11	30	4	6
	M±m	52.4±10.9	71.4±6.9	44.4±16.5	75.0±15.3
			P ₁ <0.001	P ₂ <0.001	P _{1,3} <0.001
DBP, mm Hg	N	21	42	9	8
	M±m	87.00±2.78	88.30±1.97	80.00±4.25	89.70±4.51
	95% CI	83.1-90.9	85.5-91.1	74.0-85.9 P ₂ =0.05	83.3-96.1
Relative Frequency DBP > 89 mm Hg, %	N	10	25	2	5
	M±m	47.6±10.8	59.50±7.57	22.20±13.80	62.5±17.1
			P ₁ <0.02	P _{1,2} <0.001	P ₁ <0.02 P ₃ <0.001

Note: N – number of the studied patients; P – level of statistical significance of differences.

Study of the biochemical (laboratory) parameters of MS revealed that patients with obesity and patients with type 2 DM average concentration of GCH exceeded the upper limit of the norm. At that in the group of the diabetic patients the content of GCH in blood plasma was lower than that in the control group, which was confirmed when comparing the relative frequency of hypercholesterolemia. Thus it was revealed its statistically significant decrease at all stages of DR ($p < 0.001$, $p < 0.02$, $p < 0.01$ respectively) without statistically significant intergroup differences between them. The concentration of total HDL CH was

within normal values both in the studied groups and in the control group with statistically significant ($p = 0.04$) increase in its content in the group of patients with the second stage of DR in comparison with the first stage. Relative frequency of the decrease concentration of CH HDL turned out statistically less significant in all the studied groups in comparison with the control group ($p < 0.01$, $p < 0.001$, $p < 0.001$ respectively). Nevertheless it has been determined that among the patients with DM statistically significant highest relative frequency of the decreased CH HDL concentration was typical for the first stage of DR (Tab. 3).

Table 3

Biochemical clusters of the metabolic syndromes at different stages of DR (M±m)

Indicator	Statistic indicator	Obesity (control)	Diabetic Retinopathy		
			I stage	II stage	III stage
		1	2	3	4
Total cholesterol, mM/l	N M±m 95%	20 6.19±0.28 5.80-6.59	42 5.59±0.19 5.32-5.86	9 5.49±0.41 4.90-6.08	8 6.01±0.44 5.38-6.63
Relative Frequency of Hypercholesterolemia, %	N M±m	16 80.00±8.94	26 61.90±7.49 P ₁ <0.001	6 66.70±15.71 P ₁ <0.02	5 62.50±17.12 P ₁ <0.01
HDL CH, mM/l	N M±m 95% CI	20 1.15±0.07 1.04-1.35	42 1.14±0.05 1.06-1.21	9 1.37±0.11 1.22-1.53 P ₂ =0.04	8 1.18±0.11 1.02-1.35
Relative Frequency HDL CH < 1.03 mM/l, %	N M±m	12 60.0±10.9	20 47.60±7.71 P ₁ <0.01	2 22.2±13.8 P ₁₋₂ <0.001	2 25.0±15.3 P<0.001

Note: N – number of the studied patients; P – level of statistical significance of differences.

Content of LDL CH unlike HDL CH exceeded the upper limit of norm both in the control group and in the patients with type 2 DM with statistically significant ($p = 0.02$) decrease at the first stage of DR in comparison with the control group. It was revealed that the relative frequency of dyslipidemia (by LDL CH) was statistically more significant at all stages of DR in comparison with the control group ($p < 0.01$, $p < 0.001$, $p < 0.05$ respectively). At that the statistically significant ($p < 0.01$) increase in the relative frequency of dyslipidemia (by LDL CH) takes place in patients at the second stage of DR compared with the first stage, as well as statistically significant decrease in the relative frequency of the sought dyslipidemia in the group with the third stage of DR in comparison with the

second stage ($p < 0.02$) (Tab. 4). It is typical that the value of the relative dyslipidemia at the third stage of DR (37.5 ± 17.1) (%) in fact reached the value typical for the first stage (40.50 ± 7.57) (%). Concentration of TG in all the studied groups and in the control group was above the upper limit of normal reaching the level of the control group of the patients at the first stage of DR and decreased in patients with the second and third stages of DR. At that it has been revealed that statistically significant decrease in the relative frequency hypertriglyceridemia was typical for patients with the second and third stages of DR in comparison with the first ($p < 0.01$) and control groups ($p < 0.01$) (Tab. 4).

Table 4

Laboratory clusters of the metabolic syndromes at different stages of DR (M±m)

Indicator	Statistic indicator	Obesity (control)	Diabetic Retinopathy		
			I stage	II stage	III stage
		1	2	3	4
HDL CH, mM/l	N M±m 95%	20 3.82±0.20 3.53-4.10	42 3.31±0.13 3.11-3.50 P ₁ =0.02	9 3.62±0.30 3.19-4.04	8 3.78±0.31 3.33-4.24
Relative Frequency HDL CH > 3.3 mM/l	N M±m	5 25.00±9.68	17 40.50±7.57 P ₁ <0.01	5 55.6±16.5 P ₁ <0.001 P ₂ <0.01	3 37.5±17.1 P ₁ <0.05 P ₃ <0.02
TG, mM/l	N M±m 95% CI	20 2.46±0.36 1.94-2.98	41 2.45±0.25 2.10-2.81	9 1.59±0.55 0.81-2.36	8 1.99±0.58 1.16-2.81
Relative Frequency TG > 1.68 (F) and 1.78 (M), %	N M±m	20 55.0±11.1	42 52.30±7.71	9 33.4±15.7 P ₁ <0.01 P ₂ <0.01	8 37.5±17.1 P ₁ <0.01 P ₂ <0.01

Note: N – number of the studied patients; P – level of statistical significance of differences; M – males; F – females.

Discussions

The results of the carried out research on studying morphometric, functional and biochemical clusters of MS in patients with type 2 DM at different stages of DR

revealed that all patients with DR have phenotypic and clinical-biochemical signs of the metabolic syndrome in particular obesity according to BMI ($31.7-36.3 \text{ kg/m}^2$), increase in WS regardless of gender (up to

118.3 cm in males and up to 128.7 cm in females), arterial hypertension (SBP up to 164 mm Hg and DBP up to 96 mm Hg), dyslipidemia (increase in LDL CH to 4.24 mM/l) on the background (to 6.63 mM/l) and hypertrygliceridemia (up to 2.81 mM/l). The data similar to urs but without arranging the patients by stages of the diabetic retinopathy, were obtained by R. Huseynova and V. Mirzezade (2010) [3]. The results of the examination of 115 patients with type 2 DM with MS and 45 patients with type 2 DM without MS have been analyzed in our study. The authors in their research demonstrated increase in BMI, SBP, DBP, triglycerides, total cholesterol and LDL CH along with normal values of HDL CH in patients with type 2 DM with MS, however with the unexplained absence of significant difference of these values with the patients with type 2 DM without MS.

According to the results of the work it can be seen that DR starts on the background of obesity in 83.4 % patients (with increase in WS), AH — in 71.4 % patients, hypercholesterolemia — in 61.9 %, dyslipidemia — in 47.6 % patients and hypertrygliceridemia — in 52.3 %. Development of DP is accompanied by such unfavorable statistically significant changes in values of MS as increase in relative frequency (specific gravity of patients) AH (by SBP and DBP), increase in relative frequency of dyslipidemia on the background of obesity, hypercholesterolemia and hypertrygliceridemia.

Further development of DR is associated with the increase in weight circumference in women (at the second stage), certain decrease in specific gravity of patients with obesity (at the second and third stages), increase in specific gravity of patients with dyslipidemia (by LDL CH) (at the second stage) along with retaining high specific gravity of patients with AH by SBP and DBP (at the third stage), hypercholesterolemia, stable values of HDL CH and decrease (but not up to the norm) of TG concentration in blood (at the second and third stages).

Increase in relative frequency of AH indicates that the patients at the third stage of DR are in the greater risk group for occurrence of vascular events including in the fundus since the level of control over the arterial pressure does not correspond to the accepted international and Ukrainian protocols and clinical recommendations. Thus, scientific evidence analysis, carried out by Y.M. Sirenko (2012) [6], show that the optimal levels of the arterial pressure for preventing development of cardio-vascular complications in patients with type 2 DM are the following values: SBP — 130–135 mm Hg and DBP — < 80 mm Hg, but not < 140/80 mm Hg as it is stated in European recommendations on prevention of cardio-vascular diseases released in 2012 [10]. Considering the presence of national clinical recommendations “Arterial Hypertension” and “Unified Clinical Protocol approved by the Order of Ukrainian Health Ministry # 384 as of 24 May 2012 [1], according to Ukrainian cardiologists, the target level of AP for patients with type 2 DM stated in them, should not be changed and should remain 130/< 80 mm Hg. In our study patients with DR do not reach the optimal level of control over the blood pressure.

The role of AH as second (after compensation of carbohydrate metabolism) significant risk factor for development and progression of DR was determined as it is shown in the literature review and clinical studies by M.L. Kyrylyk (2012) [4], M.A. Testa et al. [16] as early as 1985, who revealed that even the slightest increase in BP within ranges from 130/80 to 140/90 mm Hg expedites the progression of DR.

Research WESDR [14] shows that in case of DM high DBP is a powerful risk factor as well as unsatisfactory compensation of DM. Presence of AH in the beginning of the disease was accompanied by the increase in the risk for the development of the proliferate stage of DR by 91 %. The lowest risk of DR is observed at DBP < 75 mm Hg. The other authors also revealed that the development and progression of DR to a greater extent correlates with the level of diastolic BP [9].

Analysis of own biochemical data shows that the concentration of HDL CH in the blood of patients with obesity and in patients with DR does not correspond to the clinical recommendations developed by the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) in 2016 [8], according to which the concentration of LDL CH in blood of patients with MS and type 2 DM (these two pathologies are not considered separately nowadays) should not exceed 2.6 mM/l and tryglyceridemia on an empty stomach and after eating should be less than 1.8 mM/l. The fact of a decrease in relative frequency of hypertrygliceridemia at the second-third stages of DR probably indicates that it plays an important role at early stages of DR being one of the pathogenetic triggers.

Assuming the obtained results of analysis of forming and manifestation in clusters of MS in patients with type 2 DM in ophthalmological patients it is reasonable to state that the patients with DR are the patients with the forming android obesity, AH, hypercholesterolemia, dyslipidemia, hypertrygliceridemia, that is with classical clusters of MS.

Some features can be noted: patients with type 2 DM and DR have the lower value of relative obesity frequency, hypercholesterolemia, hypertrygliceridemia and have the higher value of the relative AH frequency.

Conclusions

1. The occurrence of the non-proliferate stage of DR is characterized by the statistically significant negative dynamics of MS clusters such as increase in specific gravity of patients with AH and dyslipidemia on the background of obesity in comparison with the control group.

2. Transition to the pre-proliferate stage of DR is characterized by statistically significant further increase in the relative frequency of dyslipidemia in comparison with the first stage and formation of the abdominal obesity (increase in WS) in women.

3. Development of the proliferate stage of DR is associated with the statistically significant increase in the relative frequency of AH in comparison with the second stage against the background of obesity, dyslipidemia and hypertrygliceridemia.

4. Patients with type 2 DM at the third stage of DR are in the high-risk group for occurrence of vascular events including in the fundus which should be considered in surgical, physiotherapeutic and medical treatment.

Conflict of interest. Authors claim that there is no conflict of interest in this paper.

List of references

1. Arterialna hipertenzija. Onovlena ta adaptovana klinichna nastanova, zasnovana na dokazakh. Dodatok do Nakazu MOZ Ukrainy № 384 vid 24.05.2012 "Pro zatverdzhennya ta vprovadzhennya medyko-tehnolohichnykh dokumentiv zi standartyzatsiyi medychnoyi dopomohy pry arterialniy hipertenzii" [Arterial Hypertension. Updated and Adapted Evidence-Based Clinical Recommendation. Supplement to the Order of the Ministry of Health of Ukraine # 384 as of May 24, 2012 "On Approval and Implementation of Medical and Technological Documents on Standardization of Medical Assistance for Hypertension"] — www.moz.gov.ua/ua/portal/dn_20120524_384.html.
2. Bodanova A.A., Mkrtumyan A.M., Davydov A.L. et al. Struktura pozdnikh sosudistikh oslozhneniy pri vpervye vyyavlennom sakharnom diabete 2 tipa // Sakharnyy diabet. — 2006. — T. 9, № 4. — S. 35-37. [Bodanova A.A., Mkrtumyan A.M., Davydov A.L. et al. The structure of late vascular complications in firstly diagnosed type 2 diabetes mellitus // Diabetes mellitus. - 2006. - V. 9, # 4. - P. 35-37.] — DOI: <http://dx.doi.org/10.14341/2072-0351-6187>.
3. Guseynova R.R., Mirzazade V.A. Vliyaniye dlitelnosti sakharnogo diabeta na rasprostranennost diabeticheskoy retinopatii u bolnykh sakharnym diabetom 2 tipa s metabolicheskim sindromom // Sakharnyy diabet. — 2010. — T. 13, № 2. — S. 94-96. [Huseynova R.R., Mirzazade V.A. The influence of the duration of diabetes on the development of diabetic retinopathy in patients with type 2 diabetes mellitus with metabolic syndrome // Diabetes mellitus. - 2010. - V. 13, # 2. - P. 94-96.] — DOI: <http://dx.doi.org/10.14341/2072-0351-5682>.
4. Kirilyuk M.L. Medikamentoznoye lecheniye i profilaktika diabeticheskoy retinopatii pri sakharnom diabete 1 tipa // Mizhnarodnyy yendokrinologichnyy zhurnal. — 2012. — № 5(45). — S. 70-75. [Kirilyuk M.L. Drug treatment and prevention of diabetic retinopathy in type 1 diabetes mellitus // International Endocrinology Journal. - 2012. - # 5 (45). - P. 70-75.
5. Kyrylyuk M.L., Kostyev F.I., Pidayev A.V., et al. Biometrychni ta biokhimichni pokaznyky metabolichnoho syndromu abo ryzyku yoho vynyknennya u khvorykh iz dobroyakisnoyu hiperplaziyeyu peredmikhurovoyi zalozy // Klinichna endokrynolohiya i endokrynnna khirurhiya. — 2012. — № 3(40). — S. 53-58. [Kirilyuk M.L., Kostiev F.I., Pidaev A.V., Shatalyuk S.S. Biometric and biochemical indicators of metabolic syndrome or risk of its occurrence in patients with benign prostatic hyperplasia // Clinical endocrinology and endocrine surgery. - 2012. - # 3 (40). - P. 53-58].
6. Sirenko Y.M. Tsilovyy riven AT pry tsukrovomu diabete 2-ho typu: otsinka naukovykh

dokaziv // Mizhnarodnyy endokrynologichnyy zhurnal. — 2012. — № 6(46). — S. 10-14. [Sirenko Y.M. Targeted blood pressure level in type 2 diabetes mellitus: evaluation of scientific evidence // International Endocrinology Journal. - 2012. - # 6 (46). - P. 10-14].

7. Shestakova M.V. Rol tkanevoy renin-angiotenzin-aldosteronovoy sistemy v razvitii metabolicheskogo sindroma, sakharnogo diabeta i yego sosudistikh oslozhneniy // Sakharnyy diabet. — 2010. — T. 13, № 3. — S. 14-19. [Shestakova M.V. The role of tissue renin-angiotensin-aldosterone system in the development of metabolic syndrome, diabetes mellitus and its vascular complications // Diabetes mellitus. - 2010. - V. 13, # 3. - P. 14-19.] — DOI: <http://dx.doi.org/10.14341/2072-0351-5481>.

8. Catapano A.L., Graham I., de Backer G. et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias // European Heart Journal. — 2016. — Vol. 37, Issue 39. — P. 2999-3058. — doi:10.1093/eurheartj/ehw272.

9. Chase H.P., Garg S.K., Jackson W.E. et al. Blood pressure and retinopathy in type 1 diabetes // Ophthalmology. — 1990. — № 97. — P. 155-159.

10. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice // Eur. Heart J. — 2012. — Vol. 33(13). — P. 1635-1701.

11. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) // JAMA. — 2001. — Vol. 285. — P. 2486-2497.

12. Glantz S.A. Primer of biostatistics. 4th Edition. — McGraw-Hill, New York, St. Louis, San-Francisco, Madrid, Milan, Sydney, Tokyo, Toronto; 1994.

13. Grundy S.M., Cleeman J.I., Daniels S.R. et al. Diagnosis and Management of the Metabolic Syndrome // Circulation. — 2005. — Vol. 112. — P. 2735-2752. — <http://dx.doi.org/10.1161/CIRCULATIONAHA.105.169404>.

14. Klein R., Klein B.E.K., Moss S.E. et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes // Ophthalmology. — 1998. — Vol. 105. — P. 1801-1805.

15. Kohner E.M., Porta M. Screening for diabetic retinopathy in Europe: A field handbook. — Boehringer Mannheim, Italy, 1992.

16. Testa M.A., Puklin J.E., Sherwin R.S. et al. Clinical predictors of retinopathy and its progression in patients with type 1 diabetes during CSII and conventional insulin treatment // Diabetes. — 1985. — Vol. 34(Suppl. 3). — P. 61-68.

17. The metabolic syndrome and cardiovascular disease mortality in middle-aged men / H.-M. Lakka, D.E. Laaksonen, T.A. Lakka [et al.] // JAMA. — 2002. — Vol. 283. — P. 2909-2916.