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ONCOSTATIN M, INTERLEUKIN-6, GLUCOMETABOLIC PARAMETERS AND LIPID PROFILE IN HYPERTENSIVE PATIENTS WITH PREDIABETES AND TYPE 2 DIABETES MELLITUS

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Abstract

Background and aims: *Essential hypertension and type 2 diabetes mellitus possess some common pathogenetic components, in particular, activation of immune inflammatory response, the intercellular mediators of which are cytokines. In our study, hypertensive patients were examined, depending on presence of concomitant prediabetes or type 2 diabetes mellitus, for the level of pro-inflammatory cytokines oncostatin M, interleukin-6 in conjunction with glucometabolic parameters and lipid metabolism parameters.* ***Material and methods:*** *A total of 94 hypertensive patients were examined. Oncostatin M and Interleukin-6 plasma level detected using ELISA (BSM).* ***Results and conclusions:*** *The 1st group consisted of hypertensive patients. The 2nd group included hypertensive patients with prediabetes. The 3rd group were hypertensive patients with type 2 diabetes mellitus. We have revealed the increased circulating level of oncostatin M and interleukin-6 in patients 1st group, which confirms the pathogenetic value of hypertension as a stimulus for hyperproduction of these cytokines. In 2nd group the level of oncostatin M and interleukin-6 decreased, which could probably be explained, on the one hand, by dual effects of the family of interleukin-6 the representatives of which either contribute to the development of insulin resistance or, vice versa, enhance the insulin sensitivity of tissues.*

key words: *oncostatin M, interleukin-6, prediabetes, diabetes, essential hypertension.*

Background and aims

Essential hypertension (EH) is a global medical and social problem in the whole world. The epidemiological situation in Ukraine raises concerns. Thus, according to official statistics of the Ministry of Public Health, in 2015 the number of adults with EH was 10,450,502 persons, of which 4,612,465 persons were employable [1].

Presence of comorbidities, in particular, that of type 2 diabetes mellitus (DM) substantially aggravates the course and prognosis of EH. According to the data of a string of large-scale studies, the prevalence of type 2 DM among

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hypertensive patients is 2-2.5 times higher than in normotensive persons. Coexistence of these two diseases doubles the risk of a stroke, nephropathy, diabetic retinopathy [2,3].

Reduction of cardiovascular diseases rate takes on great importance for the field of practical healthcare, and early detection of such risk factors such as EH, carbohydrate metabolism disorders, type 2 DM, dyslipidemia, overweight and obesity are likely to become leading means of its answer [3].

In case of concurrent course of EH and type 2 DM, alongside with carbohydrate metabolism disorder, lipid metabolism disorders are characteristic for most patients. Basic characteristics of dyslipidemia, which is typical of EH and type 2 DM, is increased plasma level of triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C), decreased level of high-density lipoprotein cholesterol (HDL-C) and prominent increase and long-lasting preservation of postprandial hyperlipidemia as compared to normotensive patients [4].

According to the data of different authors, EH and type 2 DM possess some common pathogenetic components, in particular, activation of immune inflammatory response, the intercellular mediators of which are cytokines [5]. Over recent years the possibility of involvement of pro-inflammatory cytokines in pathogenesis of glucometabolic disorders and dyslipidemia, including in EH and type 2 DM patients was appeared.

Oncostatin M is a representative of the IL-6 cytokine family. Physiological and pathophysiological role of this cytokine is not entirely explored yet.. In general, members of the IL-6 family are deemed pro-inflammatory cytokines. However, over recent years an increasing number of communications are appearing as to anti-inflammatory properties of representatives of this interleukin family [6].

IL-6 is produced mainly by immunocompetent cells and is an active participant of immune processes. Alongside with pro-inflammatory action it exerts a multifarious influence over the metabolic processes. In particular, over recent years the scientific attention is fixed upon the role of IL-6 in metabolic diseases: obesity, metabolic syndrome, type 2 DM. Based upon the conducted research an assumption has arisen that it may be IL-6 that is one of the factors contributing to the formation of insulin resistance (IR) [7]. At the modern level of scholarly knowledge, it is possible to assume that one of the major factors determining various effects of insulin in human organism is IL-6.

The aim of the current research was to evaluate the level of pro-inflammatory cytokines oncostatin M and interleukin-6 (IL-6) in conjunction with glucometabolic parameters and lipid metabolism parameters in patients with EH depending on the presence of concomitant prediabetes or type 2 diabetes mellitus.

Materials and methods

A total of 94 patients with EH were examined. The diagnosis of EH was carried out based on the recommendations of the European Society of Hypertension for arterial hypertension management [8]. The diagnosis of type 2 DM and prediabetes that included fasting hyperglycemia and impaired glucose tolerance was determined according to the criteria of WHO [9].

Exclusion criteria included: symptomatic character of arterial hypertension; presence of concomitant endocrine, autoimmune, renal and oncologic pathology; exacerbation of chronic inflammatory processes or presence of acute inflammatory diseases, acute myocardial infarction or stroke, acute left or right ventricular failure; acquired valvular heart diseases;

traumatic injuries of central nervous systems; concomitant mental illnesses, alcoholism, drug addiction; diffuse diseases of connective tissues; as well as chronic heart failure NYHA III or IV.

Blood for biochemical investigation and enzyme immunoassay was drawn out of the cubital vein in the morning in a fasting state. For assessment of carbohydrate metabolism, the levels of glucose and glycated hemoglobin (HbA_{1c}) were measured. Oral glucose tolerance test (OGTT) was carried out after an overnight fast after standard oral loading with 75 g of glucose dissolved in 200 ml of water in patients not yet diagnosed with concomitant type 2 DM. Concentration of glucose in blood plasma in fasting state and after OGTT was determined with the help of enzymatic method. Determination of insulin concentration in fasting state and after OGTT was carried out using ELISA assay kit DRG® Insulin (EIA-2935), (DRG Instruments GmbH, Germany).

As a quantitative criterion of insulin resistance, the homeostasis model HOMA was utilized (Homeostasis model assessment). When Insulin Sensitivity Index (ISI) HOMA is 2.77 or higher the patient is considered insulin resistant [10].

The level of total cholesterol (TC), fractions of lipoproteins and TG was determined with the help of enzymatic method with the use of standard kits. The level of LDL-C, very low-density lipoprotein cholesterol (VLDL-C) and atherogenic index (AIP) of plasma was calculated according to the standard formulas.

For determination of the level of oncostatin M and IL-6, the enzyme immunoassay was used with the use of ELISA assay kit RayBio® Human Oncostatin M ELISA Kit (ELH-OSM-001), Ray Biotech, Inc. and the assay kit INTERLEUKIN-6-IFA-BEST (A-8768), (“Vektor-Best”, Russia). The level of IL-6 in blood plasma of healthy persons varies from 1 to 2 pg/ml.

Statistical analysis

Statistical analysis was carried out with the use of the program “STATISTICA for Windows”. In samplings with nonparametric data distribution the results are represented in the form Me (Q_{25}-Q_{75}), where Me is median (50th percentile), Q_{25} and Q_{75} – 25th and 75th percentiles respectively (the upper and lower quartiles). For comparison of the results the Wilcoxon test; Kolmogorov-Smirnov and Mann-Whitney U tests, median test were used. For assessment of measure of dependence, the Spearman's rank correlation coefficient was utilized. The null hypothesis was rejected at the level of certainty ($p<0.05$).

Results

The EH patients were divided into 3 groups depending on presence of the carbohydrate metabolism disorders. Thus, 30 EH patients (31.9%) without glucometabolic disorders were included into the 1st group, of which 14 (46%) were men and 16 (54%) were women. Age of the examined patients of this group varied from 40 to 69 years, the median being 57.50 years.

A total of 34 EH patients (36.4%) with prediabetes were included into the 2nd group. Prediabetes included fasting hyperglycemia (fasting glucose level ≥ 6.1 mmol/l, but ≤ 6.9 mmol/l; and glucose level 2 hours after the loading test < 7.8 mmol/l according to the result of OGTT) and impaired glucose tolerance (fasting glucose level < 7.0 mmol/l; and glucose level 2 hours after the loading test ≥ 7.8 mmol/l but < 11.1 mmol/l according to the result of OGTT). From the 34 patients, 14 (41%) were men and 20 (59%) were women. Age of the examined patients varied from 46 to 69 years, the median was 56 years.

The third group included 30 EH patients (31.9%) with concomitant type 2 DM, of which 11 (37%) were men and 19 (63%) were women.

Age of the examined patients varied from 52 to 69 years, the median being 61.87 years. Comparative characteristics of the glycemic profile in these groups of patients are set out in the Table 1.

Table 1. Glycemic profile in EH patients depending on presence of concomitant prediabetes and type 2 DM, Me (Q_{25}-Q_{75})

Group / Parameter	1st group Patients with EH, n=30	2nd group Patients with EH and prediabetes, n=34	3rd group Patients with EH and type 2 DM, n=30	p (Kruskal-Wallis ANOVA)
Fasting glucose, mmol/l	4.78 (4.26-5.14)	5.55 (5.55-6.13)	6.76 (5.56-7.00)	<0.001
Glucose 2 hours after OGTT, mmol/l	6.00 (5.60-6.33)	7.35 (7.02-8.00)	-	>0.05
Fasting insulin, uU/ml	13.14 (9.12-17.99)	24.16 (11.08-26.67)	24.16 (19.57-27.97)	<0.001
Insulin 2 hours after OGTT, uU/ml	41.12 (29.62-57.40)	72.34 (60.82-80.29)	–	<0.001
HbA_{1c} %	5.40 (4.70-6.97)	5.90 (5.20-7.10)	7.57 (6.10-9.20)	<0.001
HOMA – IR	2.82 (1.84-3.67)	5.99 (2.34-7.99)	7.58 (4.89-9.32)	<0.001

Table 2. Anthropometric measurements in examined patients, Me (Q_{25}-Q_{75})

Group / Parameter	Patients with EH, n=30	Patients with EH and prediabetes, n=34	Patients with EH and type 2 DM, n=30	p (Kruskal-Wallis ANOVA)
Body weight, kg	78.50 (52-138)	92.00 (66-125)	82.50 (56-120)	0.002
Body height, m	1.71 (1.62-1.75)	1.67 (1.6-1.73)	1.62 (1.58-1.72)	0.0001
WC (waist circumference),cm	94 (84-105)	107 (98-112)	101 (91-108)	0.0002
HC (hip circumference),cm	103 (98-109.5)	112(106-124)	105.5 (102-109)	0.00001
WC/HC,	0.91 (0.85-0.95)	0.92(0.90-0.96)	0.94 (0.9-0.98)	0.0001
Body mass index, kg/m^2	26.09 (24.86-30.82)	32.89 (29.01-36.26)	29.50 (26.30-33.46)	0.00001

We have detected consistent discrepancies between the groups according to such parameters as fasting glucose and insulin level, insulin level in 2 hours after OGTT. However, level of glucose in blood after OGTT in patients with EH and prediabetes, although surpassing the level EH patients with EH, yet these differences proved inconsistent.

HbA_{1c} level statistically differed consistently, gained maximum value in patients of the 2nd group with EH and prediabetes, insignificantly decreased in patients of the 3rd group of hypertensive patients with type 2 DM but was higher than the value in patients with EH of the 1st group.

Insulin resistance (IR) is characterized by impaired insulin sensitivity of tissues and is considered a predictor of the development of such pathological conditions and diseases as obesity, type 2 DM, atherosclerosis [11]. With the aim of detection of IR in our research we calculated HOMA index. As a result, among the examined patients of the 1st group IR was detected in 54% (n=21) persons, in the 2nd group – in 71% (n=24) persons, while in the 3rd group virtually all patients had IR, namely – 97% (n=29) persons.

We analyzed the anthropometric measurements in the groups of patients, the comparative characteristics of which are set out in the Table 2.

Intercomparison of anthropometric measurements in the comparison groups showed that EH patients with concomitant prediabetes were characterized by consistently higher body mass parameters) BMI, WC, HC as compared to EH patients without concomitant carbohydrate metabolism disorders and as compared to the patients with EH associated with type 2 DM. Thereafter we analyzed the absolute and relative count of patients with normal weight or overweight, as well as with presence of obesity of different degrees (Table 3).

Table 3. Distribution of the examined patients depending on presence and degree of obesity.

Group / Parameter		Patients with EH, n=30	Patients with EH and prediabetes, n=34	Patients with EH and type 2 DM, n=30
		abs. / %	abs. / %	abs. / %
Normal body weight		9/30	0/0	1/3
Overweight		13/43	12/35	16/54
Obesity	1st degree	4/14	8/24	12/40
	2nd degree	3/11	12/35	1/3
	3rd degree	1/2	2/6	0/0

Table 4. Lipid metabolism parameters, level of oncostatin M, IL-6 in examined patients, Me (Q_{25}-Q_{75})

Group / Parameter	Patients with EH, n=30	Patients with EH and prediabetes, n=34	Patients with EH and type 2 DM, n=30	p (Kruskal-Wallis ANOVA)
TC, mmol/l	5.67(4.95-7.11)	5.02(4.63-6.00)	4.81(4.15-5.28)	0.001
TG, mmol/l	2.75(2.56-3.01)	2.48(2.35-2.88)	1.06(0.72-1.34)	0.0001
HDL-C, mmol/l	0.98(0.83-1.35)	1.14(0.95-1.35)	1.27(1.16-1.39)	0.002
LDL-C, mmol/l	3.51(2.77-4.54)	3.15(2.3-3.77)	3.04(2.55-3.44)	0.0299
VLDL-C, mmol/l	1.25(1.16-1.36)	1.13(1.07-1.31)	0.48(0.33-0.61)	0.0001
AIP	4.57(3.86-5.51)	4.26(3.03-4.88)	2.79(2.40-3.21)	0.0001
Oncostatin M (pkg/ml)	28.42 (17.56-42.77)	25.65 (17.65-30.65)	10.45 (9.16-11.34)	<0.001
IL-6 (pkg/ml)	18.81 (13.14-26.69)	13.94 (11.00-16.94)	7.53 (6.93-9.86)	<0.001

As a result, it was established that in the 1st group the majority of patients had overweight (43%) and normal body weight (30%), and an insignificant percentage of obesity of the 1st degree (14%), 2nd degree (11%), 3rd degree (2%). As to the 2nd group of hypertensive patients with prediabetes, in most cases with the same frequency obesity of the 2nd degree and overweight were established (35% in both cases), while obesity of the 2nd degree was present in 24% of patients, and obesity of the 3rd degree only in 6%. In the 3rd group of EH patients with concomitant type 2 DM patients with overweight (54%) and obesity of the 1st degree (40%) prevailed, normal body weight and obesity of the 2nd degree was ascertained only in 3% of patients (in both cases).

The results of comparative characteristics of lipid metabolism parameters in EH patients depending on presence of carbohydrate metabolism disorders in them are set out in the Table 4.

According to our results, in EH patients of the 1st group the maximum increase of the level of TC, HDL-C, VLDL-C, AIP and decrease of the level of HDL-C was detected.

According to our data, maximum level of oncostatin M was registered in the 1st group of patients with EH the course of which was not accompanied by carbohydrate metabolism

disorders (Table 4). While in EH patients with prediabetes and type 2 DM a consistent decrease of the plasma content of oncostatin M ($p<0.001$(Kruskal-Wallis ANOVA)) was registered.

During comparative characteristics of the level of IL-6 in groups of EH patients a similar tendency was detected, i.e., in the 1st group with isolated EH the maximum level of IL-6 was detected, in the 2nd group of patients with EH and prediabetes the level of IL-6 was consistently lower, and in the 3rd group of patients with EH and type 2 DM the value of IL-6 was minimal ($p<0.001$, Kruskal-Wallis ANOVA) (Table 4).

We carried out the correlation analysis with the aim of revealing interrelations between the level of oncostatin M, IL-6 and carbohydrate metabolism parameters. As a result, in the 1st group of EH patients, a direct dependence was established between oncostatin M and IL-6 ($r=0.523$; $p=0.0001$). Inverse consistent dependence was revealed as to the level of oncostatin M and HbA_{1c} ($r=-0.292$; $p=0.046$). Negative relation was also present between the level of IL-6 and glucose after OGTT ($r=-0.337$; $p=0.019$) and insulin after OGTT ($r=-0.281$; $p=0.052$).

In the 2nd group (patients in whom the course of EH was accompanied by prediabetes) a closer direct connection was established between oncostatin M and IL-6 ($r=0.807$; $p=2.18E-07$). The level of IL-6 correlated negatively with HbA_{1c} ($r=-0.452$; $p=0.009$), insulin ($r=-0.424$; $p=0.024$).

In the 3rd group (patients with EH and type 2 DM) an interrelation was established between oncostatin M and IL-6 ($r=0.614$; $p=0.002$).

Since oncostatin M is a member of the family of IL-6, and we have detected changes of its plasma content similar to that of IL-6, as well as close consistent correlational interrelations between these cytokines in all groups under analysis, we consider it possible to extrapolate the conclusions concerning IL-6 to oncostatin M, as well.

According to the results of correlation analysis with calculation of Spearman's correlation coefficient we have established the presence of positive relation between the level of oncostatin M and level of TC ($R=0.719$; $p=1.65x10^{-5}$), TG ($R=0.380$; $p=0.046$), LDL cholesterol ($R=0.719$; $p=1.65x10^{-5}$).

Circulating level of IL-6 and level in adipose tissue is permanently increased in case of obesity and correlates with fasting hypertriglyceridemia, plasma level of free fatty acids and systemic IR in humans [12]. In our research we obtained similar results, namely, consistent correlational relations between IL -6 and TG in fasting state ($R=0.433$; $p=0.021$), besides, IL-6 correlated with the level of TC ($R=0.697$; $p=3.81x10^{-5}$), LDL cholesterol ($R=0.644$; $p=0.0002$), VLDL cholesterol ($R=0.429$; $p=0.023$), AIP ($R=0.402$; $p=0.038$) in the group of patients with EH accompanied by prediabetes. In the 1st group of EH patients and in the 3rd group of EH patients with type 2 DM, the correlational relations between the level of IL-6 and lipid metabolism parameters proved to be inconsistent.

Therefore, oncostatin M and IL-6 belong to the same superfamily of cytokine IL-6, in our research we have detected their similar activity in EH patients depending on presence of glucometabolic disorders, which is confirmed by consistent interrelations between their levels in all groups under analysis: oncostatin M vs. IL-6 ($R=0.523$; $p=0.0001$) in the 1st group of EH patients, oncostatin M vs. IL-6 ($R=0.807$; $p=2.18 x10^{-7}$) in the 2nd group (EH patients with prediabetes), oncostatin M vs. IL-6 ($R=0.614$; $p=0.002$) in the 3rd group (EH patients with type 2 DM).

Discussion

Combination of EH and type 2 diabetes mellitus is a serious public health issue for Ukraine that, according to official statistics, lies in the fifth place in terms of prevalence of type 2 DM in Europe. At the same time, one should keep in mind the important fact that the results of official statistics based upon the data of epidemiological studies do not reflect the as-is-state of the morbidity rate of type 2 DM in our country, where for one case of detection of type 2 DM three to four cases of undiagnosed disease fall [13].

The development of overt type 2 DM is preceded by latent changes in carbohydrate metabolism that were named "prediabetes" – fasting hyperglycemia and impaired carbohydrate tolerance. At the present stage prediabetes is attached a particular diagnostic and prognostic value, given the fact that it is a predictor of the development not only of type 2 DM properly but also of a string of cardiovascular diseases [4].

Taking into account the value of latent carbohydrate metabolism disorders we carried out the screening of prediabetes in EH patients. Over recent years, a growing number of data are accumulating that postprandial blood glucose exceeds fasting hyperglycemia in its prognostic value. Based upon these results a proposal and recommendation have arisen that OGTT must be the basic method of prediabetes screening. This is confirmed in our research in which after the analysis of carbohydrate parameters, namely, of glucose and insulin level in fasting state and in 2 hours after OGTT, presence of prediabetes was diagnosed in 34 patients with EH, which made 36.2%.

Level of HbA_{1c} was used earlier only as an indicator of DM compensation. However, there exist communications as to utilizing this parameter with the aim of diagnosing prediabetes and type 2 DM [4]. Besides, in some clinical studies direct correlation was shown between the increased HbA_{1c} level and cardiovascular mortality. Thus, according to the results of Norfolk cohort of the European Prospective Investigation of Cancer and Nutrition, male mortality rate due to cardiovascular diseases in persons with type 2 DM and without it was interrelated with HbA_{1c} level. Even in case of HbA_{1c} level at the upper limit of normal (5-6 %) cardiovascular mortality rate was higher than in persons with HbA_{1c} level lower than 5 %. What is more, each 1% of HbA_{1c} increased the risk of death by 28% regardless of the age, AP level, body weight of the patients, cholesterol level and tobacco smoking [14]. The obtained results confirm the importance of singling out of patients with latent carbohydrate metabolism disorders, namely, prediabetes, as they, despite absence of overt type 2 DM, already have increased level of HbA_{1c}, which is of negative prognostic value.

Overweight and obesity are considered important risk factors for the development both of EH and type 2 DM. Presence of obesity is closely connected with formation of dyslipidemia and activation of the inflammatory component of immune response in case of these diseases [15].

According to the data of different researches, approximately in half of EH patients lipid metabolism disorders are observed, frequent association of which may be connected both with accidental combination of these widespread risk factors and with metabolic disorders common for both diseases underlying their development. Data exist concerning close interrelation of dyslipidemia and IR. Thus, it is considered that IR mechanisms may be enabled in the development both of dyslipidemia and EH [11]. Subject to the presence of IR, intensified lipolysis and increased delivery of free fatty

acids to liver take place in the adipose tissue, which is a reason of dyslipidemia appearance, namely, the production of LDL-C, TG increases and the level of HDL-C decreases [16]. According to our results, in EH patients of the 1st group the maximum increase of the level of TC, HDL-C, VLDL-C, AIP and decrease of the level of HDL-C was detected. This may confirm the assumption about direct or indirect involvement of dyslipidemia in the mechanisms of increase of AP and development of EH. Thus, hypercholesterolemia and dyslipidemia may directly influence the tonus of peripheral vessels and, consequently, the AP level. Besides, there exist evidences as to the role of LDL-C and VLDL-C in the formation of endothelial dysfunction, in the course of oxidizing of which a great quantity of active substances is released - tumor necrosis factor-α, interleukins, growth factors, etc. In the conditions of lipid loading these processes gain a pathological character, contribute to the development of endothelial dysfunction, which eventually results in disturbance of NO synthesis, increased production of endothelin-1 and vasoconstriction [16].

The results of experimental and clinical studies of effects of cytokines of the family of IL-6 are somewhat contradictory. Thus, increased secretion of IL-6 in the view of obesity, IR and type 2 DM, as well as a higher risk of the development of type 2 DM with in persons with high level of IL-6, which indicates the decreased insulin sensitivity under the action of this cytokine. In another research, it was shown that IL-6 exerts a dual effect: in the liver cells and adipocytes it inhibits the action of insulin, results in the formation of IR, while in the cells of skeletal muscles, vice versa, IL-6 enhances the effects of insulin and contributes to uptake and disposal of glucose and lipids [17]. Probably it accounts for the diversity and, at times, contradistinction of effects of IL-6 upon the metabolic processes, especially upon the action of insulin in tissues, as well as the data obtained by us as to decrease of IL-6 and oncostatin M in patients with EH and prediabetes and type 2 DM.

The reason of such dual action of IL-6 upon insulin in different tissues is not quite understandable. One of possible explanations may be a time dependent cytokine secretion: transient or permanent as in case of chronic inflammation characteristic of the metabolic syndrome, type 2 DM. In case of a short-term increased secretion of IL-6, as, for instance, in case of physical exertion, the increased level of cytokine serves as a signal of energy failure, enhances the action of insulin in muscular tissues and inhibits in liver and adipose cells [18].

Secretion of IL-6 is moderately increased in case of mild inflammatory process, which is peculiar to obesity, type 2 DM, and is stimulated to the maximum in case of an acute inflammation [18]. It is possible that chronic hemodynamic stress conditioned by the increased level of AP is a more powerful stimulus of hypersecretion both of IL-6 and oncostatin M, as evidenced by a more significant increase of levels of these cytokines in the 1st group of EH patients as compared to the patients of the 2nd group with concomitant prediabetes and of the 3rd group with type 2 DM.

There are experimental evidences as to the capacity of oncostatin M of modulating lipid metabolism. During investigation of in vivo activity of oncostatin M in experimental animals its influence upon the expression of receptors of LDL cholesterol in liver was determined. To this research hamsters with experimental dyslipidemia were enrolled, during administration of oncostatin M the decreased

level of TG and LDL cholesterol was registered [19].

Conclusions

Presence of prediabetes was found in our study cohort in 36.2% of EH patients, in 71% of which IR was present and consistent increase of the level of HbA_{1c} was registered. The obtained data confirm the necessity of prediabetes screening. Early detection of prediabetes is of great practical importance in the context of timely correction of carbohydrate metabolism disorders with the aim of preventing the development of micro- and macrovascular complications of type 2 DM in EH patients. We have detected the increase of circulating level of oncostatin M and IL-6 in EH patients, which confirms the pathogenetic value of hypertension as a stimulus of hyperproduction of these cytokines. In EH patients with concomitant prediabetes and type 2 DM the level of oncostatin M and IL-6 was decreased, which might be explained, on the one hand, by dual effects of the family of IL-6, the representatives of which either contribute to the development of IR or, vice versa, enhance the insulin sensitivity of tissues. On the other hand, one cannot rule out the possibility of the fact that hypertension is a more powerful stimulus which brings about hyperinterleukinemia in EH patients. We have detected consistent close interrelations between oncostatin M, IL-6 and lipid metabolism parameters (TC, TG, LDL-C) in EH patients with prediabetes, which is yet another proof of clinical value of this pathological condition and substantiates the necessity of screening the patients with latent carbohydrate metabolism disorders.

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