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Key words: chronic non-specific lung diseases, pulmonary heart disease, heart failure, hypertrophy of the myocardium, myocardial atrophy, lipid peroxidation, antioxidant defense.

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RELATION OF GROWTH-DIFFERENTIATION FACTOR-15 LEVELS AND NUMBER OF CIRCULATING ENDOTHELIAL PROGENITOR CELLS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Background: risk stratification of patients with established type 2 diabetes mellitus (DM) is under scientific discussion and appears to be controversial issue.

The objective: to investigate relationship between levels of growth differentiation factor-15 (GDF-15) and circulating number of endothelial progenitor cells (EPCs) with angiopoetic phenotypes: $CD34^+CD14^+CD309^+$, and $CD34+CD14^+CD309^+Tie2^+$ in patients with type 2 DM.

Materials and Methods. The study retrospectively involved 76 patients with type 2 DM aged 38 to 55 years and 30 healthy volunteers. Data collection included demographic and anthropometric information, hemodynamic performances and biomarkers of the disease. EPCs' populations were determined by flow cytometry.

Results. The levels of GDF-15 in peripheral blood of diabetics associated with age (r = 0.31, P = 0.044), high-sensitive C-reactive protein [hs-CRP] (r = 0.40, P = 0.001), smoking (r = 0.38, P = 0.001), body mass index [BMI] (r = 0.34, P = 0.001), LDL cholesterol (r = 0.28, P = 0.001), glycated hemoglobin [HbA1c] (r = -0.28, P = 0.001), number of CV risk factors (r = 0.26, P = 0.001). In univariate logistic regression analysis we found that level of GDF-15 ≥ 618 pg/mL, hs-CRP ≥ 7.12 mg/L, HbA1c ≥ 6.4%, fasting glucose ≥ 6.7 mmol/L, and BMI ≥ 27.3 kg/m^2 predicted deficiency of both angiopoetic phenotypes of EPCs. In multivariate logistic regression model GDF-15 ≥ 618 pg/mL demonstrated the best odds ratio values for declining of EPCs in diabetics in comparison with other predictors including BMI, HbA1c and hs-CRP.

In conclusion, GDF-15 was extremely evaluated in type 2 DM population to healthy volunteers and it was an independent factor that contributes to mobilization and probably proliferation of endothelial precursors with high angiopoetic activity.

Key words: growth differentiation factor-15; endothelial progenitor cells; type 2 diabetes mellitus.

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MARKERS OF ENDOTHELIAL INJURIES IN PATIENTS WITH CORONARY HEART DISEASE AND AUTOIMMUNE THYROIDITIS

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According to WHO, coronary heart disease (CHD) has been on the top of the list of 10 leading causes of death in the world over the years, and its share is 12.8% [1,2]. CHD mortality among working age population is 28.3% [2]. At the same time, there is a significant increase in autoimmune thyroiditis (AIT) in society: particularly, in Ukraine the prevalence of AIT has increased by 68% over the past 10 years [3,4]. Today, endothelial dysfunction (ED) is considered to be the pathogenetic basis for the formation of atherosclerotic vascular lesions. ED, formed in conditions of chronic systemic inflammation (CSI), is the earliest stage of atherogenesis, and it plays a leading role in the progression of

vascular changes and development of atherothrombosis[5]. At the same time, CSI is the pathogenetic basis of AIT[3]. AIT potentiates the development of atherosclerosis (ASVD), creating an immune-inflammatory environment, regardless of the development of hypothyroidism, which is an indispensable consequence of AIT and results in the progression of cardiovascular disease[6]. The above-mentioned determines the relevance of the search for indicative markers of endothelial injuries in conditions of the specified pathology for optimization of diagnosis, evaluation of the course and efficacy of therapeutic measures. Lately, significant scientific experience has been accumulated on the determination of ED by the level of circulating endothelial microparticles (EMP) in the bloodstream[7,8]. By the number of EMPs with the corresponding types of molecular antigenic markers classified by the CD system (from the English "cluster designation"), it is possible to make a conclusion about the condition of the cells producing them[7]. The purpose of our study was to study the condition of vascular endothelium in patients with CHD and CHD in combination with AIT at the level of EMP $CD32^+CD40^+$ and to compare the obtained data with the level of systemic inflammation.

Materials and methods. One-time, open-label clinical trial was conducted — single group study. It involved 175 people of both sexes: 115 patients with CHD: stable angina pectoris, FC II, HF 0-I (Study Group 1), 30 patients with AIT in euthyroid state (Study Group 2) and 30 healthy individuals, amounted to the control group. The criteria for inclusion into the research were men and women`s age of 40-74, the presence of CHD: angina pectoris, FC II, absence of destabilizing flow of CHD for at least two months, as well as the presence of concomitant AIT in the stage of euthyroidism, and the patient's informed consent to participate in the research. The exclusion criteria were the presence of Stage 2 hypertension, Stage 1 chronic heart failure (CHF), complications of cardiac rhythm and conduction, rheumatic diseases, anemia, diabetes mellitus, chronic liver and kidney disease with functional impairment, cancer. To all participants of the study a determination of the amount of EMPs in peripheral blood with expression of CD32 and CD40 antigens was made by flow cytometry using monoclonal antibodies[9]. CD32 (FCγRIIB) is an immunoglobulin superfamily receptor, CD40 belongs to the tumor necrosis factor alpha (TNFa) superfamily, both antigens play an important role in inflammatory signaling[10, 11]. TNFa was studied as a CSI marker by the immune-enzymatic method[12].

Results. In patients from Study Group 1 (CHD) and Study Group 2 (CHD in combination with AIT), the content of EMP $CD32^+CD40^+$ in peripheral blood was significantly higher than in healthy individuals, who had the value of this index of 1.3 (1.05-2.11) x 10^7/L. At the same time, the content of EMP $CD32^+CD40^+$ in patients from Study Group 2 was significantly higher than in Study Group 1, and was 2.62 (1.50-6.10) x 10^7/L versus 1.8 (1.12-4.96) x 10^7/L (p=0.036). It indicates a high level of inflammatory activation of the endothelium in conditions of chronic autoimmune inflammation. When comparing the results of study of EMP $CD32^+CD40^+$ in all the groups, it was found that a value greater than 2.5 x 10^7/L indicates endothelial injury. The sensitivity (Se) and specificity (Sp) of the endothelial injury detection method were calculated using EMP $CD32^+CD40^+$ in AIT in combination with CHD: Se was 82%, Sr – 83%. In patients of both groups, the level of TNFa in the blood was elevated, while with the combination of CHD and AIT the level of TNFa was significantly higher than in patients with CHD alone (10.54±2.42 pg/mL versus 8.53±3.24 pg/mL). A close correlation between values of EMP $CD32^+CD40^+$ and TNFa in patients with CHD in combination with AIT (r=0.81, $p<0.05$) was found out. According to the data, the value of EMP > 2.5 x 10^7/L corresponds to the value of TNFa > 7.9 pg/mL. Se and Sr showed an increase in TNFa > 7.9 pg/mL as a marker, confirming the presence of endothelial injury in CHD in combination with AIT: Se was 100%, Sr – 82%.

The amount of EMP $CD32^+CD40^+$ in the blood is a reliable marker of inflammatory activation and destruction of vascular endothelium in CHD and CHD in combination with AIT. With a combination of CHD and AIT, increasing the TNFa content is a probable marker of inflammatory endothelial injury.

The use of the indicator of EMP $CD32^+CD40^+$ in the blood, as well as the study of EMP with other antigenic molecular markers, will expand the understanding the mechanisms of development and course of diseases with vascular injuries in the pathogenesis, and develop effective diagnostic approaches.

Determining the amount of EMP $CD32^+CD40^+$ in the blood is a highly sensitive method for verifying inflammatory endothelial injury, with CHD and CHD in combination with AIT in particular, and may be recommended for widespread use with the aim of early diagnosis of vascular injury, its progression, and to evaluate the efficacy of therapeutic measures.

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Key words: coronary heart disease, autoimmune thyroiditis, endothelial dysfunction, chronic systemic inflammation, circulating endothelial microparticles, tumor necrosis factor a.

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PREDICTIVE RELATIONSHIP BETWEEN DOPAMINE AND SEROTONIN ON EFFECT OF *GINKGO BILOBA* EXTRACT-761 IN THE TREATMENT OF OBSESSIVE COMPULSIVE DISORDER

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Drugs of herbal origin have proven to be effective in many anxiety disorders. EGb-761, EGB-761, a standardized extract of the *Ginkgo biloba* [Leaf] containing 24% of flavone glycosides (quercetin, kaempferol and iso rhamnetin) and 6% of terpenes (gingkolides and bilobalides) is an effective anxiolytic, neuroprotective and nootropic agent, despite its influential roles in various ailments of central nervous system, the data available in the treatment of obsessive compulsive disorder (OCD), a debilitating anxiety disorder and fourth most common forms of mental illness with server memory impairment, is scarce.

Materials and Methods. In this study, we evaluated the effect of *Ginkgo biloba* extract, EGb-761 50, 100 and 200 mg/kg on OCD using quinpirole (0.5 mg/kg) induced compulsive checking in rats and marble burying behaviour in mice, Rats were trained using Morris water maze apparatus before the induction of OCD and was used to evaluate the effect on spatial memory, the compulsions induced with quinpirole were assessed using an open field, on the last day of the treatment various behavioural parameters at each object were analysed such as: Frequency and duration of stops, Number of visits to other objects on successive return to each object and ritualistic behaviour for a period of 55 min.

Results. The effect on memory was evaluated based on the retention of the learned task i.e. time taken for the identification of the platform in Morris water maze apparatus and the underlying mechanisms are predicted based on the studies of brain monoamines such as dopamine and serotonin. EGb-761 at 100 and 200 mg/kg had shown significant improvement against quinpirole induced compulsions, a protective effect on memory task was observed in EGb treated rats. This could be attributed to the increase in serotonin and decrease in the dopamine levels. The interaction between the dopaminergic and serotonergic systems in the mid-brain regions i.e. substantia nigra and ventral tegmentum, with dopaminergic neurons being targets for serotonin cells explains the involvement of serotonin and dopamine in OCD. Activation of $5HT_{1A}$ (autoreceptor) inhibits dopamine release in the dorsal striatum and enhances dopamine release in nucleus accumbens. This explains the possible mechanism of the effect of SSRI's in the treatment of DA agonist induced OCD, as quinpirole is agonist to D_2 and D_3 receptors in the striatum which in turn increases the dopamine levels. The increase in the serotonin concentration with EGb-761, its role on $5HT_{1A}$-auto-receptors, which inhibit dopamine release and studies, on sertraline that it decreases the extracellular dopamine in the striatum, further supports the observation and the resulting decrease in dopamine levels observed in the present study, contributes to the protective effect of EGb and paroxetine in OCD. The protective effect of EGb-761 in the treatment of OCD is evident with both the performance on the open field and marble burying behaviour. The number of marbles buried by the end of 10 min was calculated after 1, 14, 28 days of treatment for all the groups.

Key words: Obsessive-compulsive disorder, Ginkgo biloba, memory, serotonin and dopamine.

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