**CHANGES IN PENTRAXIN-3 LEVEL AND ITS INTERACTION**

**WITH METABOLIC INDICES IN PATIENTS WITH CORONARY**

**ARTERY DISEASE AND TYPE 2 DIABETES MELLITUS**

**ZMIANY STĘŻENIA PENTRAKSYNY 3 I JEJ INTERAKCJE ZE**

**WSKAŹNIKAMI METABOLICZNYMI U PACJENTOW Z CHOROBĄ**

**WIEŃCOWĄ ORAZ CUKRZYCĄ TYPU 2**

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**ABSTRACT**

**Introduction:** Recently great attention is paid to studying of coronary artery disease (CAD) pathogenesis against the background of the diabetes mellitus (DM). First of all, the

question of an inflammatory component role in development of atherosclerosis in patients with DM 2 types is studied. One of new perspective markers of immune inflammation

is pentraxin-3 (PTX-3).

**The aim** of the study was to evaluate the nature of changes in the level of pentraxin-3 in patients with coronary artery disease, depending on the presence of type 2 diabetes

mellitus and to investigate the nature of the relationship with metabolic parameters.

**Materials and methods:** Comprehensive examination of 110 patients with CAD was conducted. Patients were divided into groups depending on presence of type 2 DM: to

the first group (n = 75) entered patients with CAD and type 2 DM , the group of comparison was made by 35 patients with CAD without type 2 DM. 25 almost healthy persons

entered into control group.

**Results:** As a result of a research it is established the reliable increase in PTX-3 level in all patients with CAD in comparison with group of control for 65.40% . And in the

conditions of the combined current of CAD and type 2 DM, PTX-3 level is for 80.14% higher, than in persons of control group. Also interrelation between PTX-3 and indicators

of dcarbohydrate and lipidic exchanges were defines. According to the carried-out correlation analysis there was revealed existence of direct integral probable connections

between PTX-3 level and levels of glucose (r = 0.41; p <0,05), insulin (r = 0.36; p <0,05), index of HOMA (r = 0.89; p <0,05), TG level (r = 0.74; p <0,05) and the return with

the HDL (r = - 0.54; p <0,05).

**Conclusions:** In patients with CAD with the accompanying type 2 DM it is established higher PTX-3 level, than in patients without type 2 DM and control group that demonstrates

autoimune link activation. In the examined patients PTX-3 level increase was associated with violation of lipid and carbohydrate exchanges.

**KEY WORDS:** coronary artery disease, type 2 diabetes mellitus, metabolic violations, pentraxin-3

**INTRODUCTION**

Coronary artery disease (CAD) is one of the most common causes of mortality in developed countries, stipulating the attention paid to the study of the pathogenesis of ischemic

heart disease. In Ukraine, the prevalence and incidence of CAD increases annually and comprises 53.8% of the circulatory system diseases. Mortality from ischemic heart

disease is about 650 per 100 thousand of population [1]. A major risk factor for CAD is diabetes mellitus (DM), which became one of the leading medical and social problems of modern society, due to high morbidity and its prevalence, frequent development of chronic micro- and

macrovascular complications [2, 3]. CAD develops 2-4 times more often in patients with

type 2 diabetes than in patients of the same age without diabetes [4]. Cardiovascular diseases is the main reason for disability and mortality of patients with diabetes, and these diseases are to a considerable extent preconditioned by CAD [5]. It should be noted that 3 of 4 patients with

DM die from causes associated with atherosclerosis, and in most cases (75%) from CAD.

The prevalence of DM in Ukraine is 3041.6 per 100 thousand of population, and the primary morbidity is 272.0 per 100 thousand of population [4]. And this is a medical and social problem in terms of cardiovascular morbidity, which requires the improvement of diagnostic approaches

and determines the relevance of the study. Generalized or chronic inflammation is one of the pathogenic mechanisms of atherosclerosis. This is confirmed by recent clinical and experimental data obtained by determination of inflammation markers (C-reactive protein

(CRP), proinflammatory cytokines, such as interleukin-1, interleukin-6 (IL-6), interleukin-12, tumor necrosis factor- α (TNF-α), serum amyloid A, haptoglobin, fibrinogen) [6-12]. First of all, the role of inflammatory component in the development of atherosclerosis in patients with type 2 diabetes is being studied. One of the new markers of immune inflammation is pentraxin-3, overexpressed in endothelial and smooth muscle cells, monocytes and macrophages, which are components of the vascular wall and atherosclerotic plaque [12-15]. Pentraxin-3 (PTX-3), also known as TNF-inducible gene 14 protein, is related to pentraxin super-family, which includes classical short pentraxins CRP and serum amyloid P component, long pentraxin PTX-4, and a group of neuronal pentraxins. Its role in atherosclerosis has not yet been clarified. However, some scientific studies indicate an increased secretion of PTX-3 in patients with CAD [16, 17].

Other researchers reported that its increased expression was associated with acute coronary syndrome, and high plasma levels of PTX-3 were predictors of adverse clinical outcomes in patients with heart failure [18, 19]. However, the pathogenic role of PTX-3 in the development of CAD in patients with type 2 diabetes has not yet been studied, which requires further research in this direction.

**THE AIM**

The purpose of the study was to evaluate the nature of changes in the level of pentraxin-3 in patients with coronary artery disease, depending on the presence of type 2 diabetes mellitus and to investigate the nature of the relationship with metabolic parameters.

**MATERIALS AND METHODS**

The study involved comprehensive examination of 110 patients with CAD, who were treated at the Department of Cardiology of the Municipal Non-Profit Enterprise “City Clinical Hospital No.27” of Kharkiv City Administration, which is the basic medical institution of Academician L.T. Malaya Department of Internal Medicine No.2, Clinical Immunology and Allergology of Kharkiv National Medical University of the Ministry of Health of Ukraine. The patients were divided into groups depending on the presence of type 2 diabetes: the first group (n = 75) included patients with CAD and type 2 diabetes, the comparison group comprised 35 patients with CAD without diabetes. The control group included 25 practically healthy persons. The study did not include patients with severe concomitant disorders of the respiratory and digestive organs, kidneys and cancer. The diagnosis was made in accordance with the effective

orders of the Ministry of Health of Ukraine. All the patients underwent general clinical and instrumental examination. In order to control carbohydrate metabolism, glucose

levels were determined by glucose oxidant method, the content of glycosylated hemoglobin (HbA1c) in whole blood was determined by photometric reaction with thiobarbituric acid using commercial test system produced by the company Reagent (Ukraine) in accordance with the attached instruction. The concentration of insulin was determined by the immunoassay method using the commercial test system Insulin ELISA Kit produced by the company DRG (Germany). The HOMA Index (Homeostasis Model Assessment) was calculated using the formula:

insulin (mU/ml) × fasting glucose (mmol/l)/22.5 In HOMA index > 2.77 the patients were considered insulin-resistant. Biochemical study included determination of total cholesterol (TC) and high density lipoprotein (HDL) by peroxidase method using Cholesterol Liquicolor reagent kit produced by company Human (Germany) in heparin-stabilized blood serum. Triglycerides (TG) were determined by enzymatic colorimetric method using Triglycerides

GPO reagent kit produced by company Human (Germany). Atherogenicity factor (AF) was calculated by A.M. Klimov’s formula: AF = (TC - HDL)/HDL; very low density lipoprotein (VLDL) = TG/2.2 × 0.45, (mmol/l); low density lipoprotein (LDL) = TC - (VLDL + HDL),

(mmol/l). Obesity was characterized by the body mass index (BMI) (the Kettle Index), which was calculated by the formula:weight (kg)/height (m2) Pentraxin-3 concentration was determined by the immunoassay method using the commercial test system Human pentraxin 3 (PTX3) Elisa Kit produced by SUNLONG BIOTECH (China) in accordance with the attached instruction. Statistical data was processed using Statistica software, version 6.0. The differences between the groups in the distribution close to normal were evaluated by Pearson’s criterion. The differences were considered statistically significant at p<0.05.

**RESULTS AND DISCUSSION**

Our study showed a statistically significant increase in PTX-3 level in all patients with CAD as compared to the control group (Fig. 1). Thus, PTX-3 level in the control group was 1.18Ѓ}0.54 ng/ml, which was 65.40% less than in patients with CAD, where the value of this index was

3.41Ѓ}0.68 ng/ml (p <0.05). In patients with a concomitant course of CAD and DM 2,

the PTX-3 level was 80.14% higher than that of the control group and was 5.94Ѓ}0.57 ng/ml (p<0.05). Comparative analysis demonstrated a statistically significant increase in PTX-3 level by 57.41% in patients with CAD, subject to the presence of type 2 diabetes, which indicated an activation of PTX-3 inflammatory marker, which can be considered a predictor of the

concomitant course. The findings of the study are in agreement with the results

obtained by other researchers. Haibo L. [20] performed examination of 596 patients (467 men, 129 women, mean age 65.9Ѓ}8.1 years), showing that PTX-3 could be considered an inflammatory predictor of CAD. The level of PTX-3 in patients with CAD was 3.12Ѓ}0.63 ng/ml, which was higher than in the control group. The Cardiovascular Health Study (CHS) conducted by the National Heart, Lung, and Blood Institute involved examination of 5 888 men and women aged 65. PTX-3 was associated with cardiovascular disease and mortality, and its concentration was higher in patients with stable angina pectoris (p<0.001), as well as in patients with myocardial infarction (p=0.005) and ischemic stroke (p≤0.001), than

in the control group [21]. In our opinion, taking into account the association of type 2 diabetes with changes in the lipid and carbohydrate profile, which leads to an increase in the incidence of

cardiovascular complications in patients with CAD [22], it was expedient to study the features of lipid and carbohydrate metabolism in patients with CAD in the presence of concomitant type 2 diabetes. In groups of patients with CAD with concomitant type 2 diabetes, fasting glucose level reached 7.19Ѓ}0.31 mmol/l, and in the group of patients with CAD without diabetes it comprised 4.37Ѓ}0.08 mmol/l (p<0.05). The level of fasting insulin was 27.16Ѓ}0.48 mcU / ml in first

group patients and was significantly higher than the level of fasting insulin in second group patients, namely 8.32Ѓ}0.21 mcU/ml (p<0.05). First group patients were found to have higher values of glycosylated hemoglobin than in the second group, 10.42Ѓ}0.28% and 4.68Ѓ}0.25%

respectively (p<0.05). Determination of the HOMA index showed its significant increase in patients of the first group (8.87Ѓ}0.71) as compared to the second group (1.67Ѓ}0.25) (p<0.05) (Table 1). Assessment of lipid profiles revealed an increase in the level of LDL cholesterol (3.09Ѓ}0.07 mmol/l as compared to 2.67Ѓ}0.06 mmol/l), VLDL cholesterol (1.57Ѓ}0.03 mmol/l as compared to 1.14Ѓ}0.02 mmol/l) (p>0.05); an increase in TG level (1.81Ѓ}0.07 mmol/l versus 1.58Ѓ}0.04 mmol/l, respectively), and a decrease in HDL cholesterol (0.91Ѓ}0.02 mmol/l compared to 1.51Ѓ}0.03 mmol/l, respectively) (p<0.05) in patients with CAD and type 2 diabetes as compared to patients without diabetes (Table I). Taking into account the association of chronic inflammation markers with metabolic parameters in patients with CAD and type 2 diabetes, we identified a relationship between PTX-3 and carbohydrate and lipid metabolism

indices in our patients. Correlation analysis showed the presence of direct integral potential links between the level of PTX-3 and glucose levels (r=0.41; p<0.05), insulin (r=0.36; p<0.05), HOMA index (r=0.89; p<0.05), the level of TG (r=0.74; p<0.05) and reverse with HDL cholesterol (r= -0.54; p<0.05) (Table II). In the multiethnic study of the University of Vermont

Medical College including 2383 patients an increase in PTX-3 was positively associated with age (p<0.045), obesity (p<0.045), insulin levels (p<0.045), systolic blood pressure

(p<0.045), CRP (p<0,045) and the thickness of carotid intima-media (p<0.045) [23].

The data obtained in different populations are of different nature, but today we can consider PТX-3 as a new marker that will be used to improve diagnostic efficiency in patients with CAD and type 2 diabetes.

**CONCLUSIONS**

1. Patients with CAD were found to have a higher level of РТХ- 3 (5.94Ѓ}0.57 ng/ml) than patients without type 2 diabetes (3.41Ѓ}0.68 ng/ml) and control group (1.18Ѓ}0.54 ng/ml),

indicating activation of the immune-inflammatory link. 2. Metabolic disorders in patients with CAD and type 2 diabetes are manifested by hyperinsulinemia, hyperglycemia, hypertriglyceridemia, increased insulin resistance and decreased LDL cholesterol levels. 3. In the examined patients, an increase in the level of РТХ-3 was associated with an increase in triglycerides, glucose, insulin, HOMA index, and a decrease in HDL cholesterol.

REFERENCES

1. Kovalenko V.M., Dorogoy A.P. Sercevo-sudinny khvorobi: medichnosocialne

znachennya ta strategiya rozvitku cardiologii v Ukraini [Cardiovascular diseases: medical and social significance and strategy of cardiology development in Ukraine]. Ukrainian Cardiology Journal. 2016; 3: 5-14. (In Ukrainian).

2. Pogrebnyak О.О. Vpliv simvastatinu і corurginu na klinichniy perebig ishemichnoi khvorobi sercya, masu tila ta kharakter rozpodilu jirovoi tkanini u khvorih na cukroviy diabet 2 tipu [Effect of simvastatin and corurgin on the clinical course of coronary heart disease, body weight and the distribution of fatty tissue in patients with type 2 diabetes mellitus]. Zaporozhye Medical Journal 2013; 3(78): 57-59. (In Ukrainian).

3. Kravchun N.A. Osoblyvosti formuvannya sercevo-sudynnyh uskladnen’ cukrovogo diabetu 2 tipu u khvorih z riznimi proyavami metabolichnogo sindromu ta ih pharmacologichna corecciya [Features of formation of cardiovascular complications of type 2 diabetes in patients with various

manifestations of metabolic syndrome and their pharmacological correction]. Diss. … doc. med. sciences. 14.01.14. Kharkiv, 2007. 323 p. (In Ukrainian).

4. Citowskiy М.N. Statistichniy, klinichniy ta morphologichniy aspect vplivu cukrovogo diabetu na stan sercevo-sudinnoi systemi [Statistical, clinical and morphological aspects of the influence of diabetes mellitus on the state of the cardiovascular system]. Scientific Herald of Uzhgorod University, series ≪Medicine≫ 2017; 1(55): 168-177. (In Ukrainian).

5. Illyash М.G., Bazyka О.E., Dovganich N.V. et al. Arterialna hypertensiya ta cukroviy diabet: suchasni aspecti licuvannya [Arterial hypertension and diabetes mellitus: modern aspects of treatment]. Practitioner 2016; 5(2): 5-9. (In Ukrainian).

6. Hajsadeghi S., Chitsazan M., Chitsazan M. et al. Changes of High Sensitivity C-Reactive Protein During Clopidogrel Therapy in Patients Undergoing Percutaneous Coronary Intervention. Res Cardiovasc Med 2015; 5(1): e28997, http://dx.doi.org/10.5812/

cardiovascmed.28997.

7. Poredos P., Spirkoska A., Lezaic L., Mijovski M.B. and Jezovnik M.K. Patients with an Inflamed Atherosclerotic Plaque have Increased Levels of Circulating Inflammatory Markers. J Atheroscler Thromb 2017; 24(1):
8. Xiong G.L., Prybol K., Boyle S.H. et al. Inflammation markers and Major Depressive Disorder in Patients with Chronic Heart Failure: Results from the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) study. Psychosom Med 2015; 77(7): 808–815, http://dx.doi.org/10.1097/PSY.0000000000000216.

9. Taleb S. Inflammation in atherosclerosis L’inflammation dans l’atherosclerose. Archives of Cardiovascular Diseases 2016; 109(12): 708-715.

10. Solomon S., Pasarin L., Ursarescu I. The effect of non-surgical therapy on C reactive protein and IL-6 serum levels in patients with periodontal disease and atherosclerosis. Int J Clin Exp Med 2016; 9(2): 4411-4417.

11. Ammirati E., Moroni F., Norata G.D., M. Magnoni, and P.G. Camici. Markers of Inflammation Associated with Plaque Progression and Instability in Patients with Carotid Atherosclerosis. Mediators of Inflammation 2015; Article ID 718329, 15 pages, http://dx.doi.org/10.1155/2015/718329.

12. Shindo A., Tanemura H., Yata K., Hamada K. Inflammatory Biomarkers

in Atherosclerosis: Pentraxin 3 Can Become a Novel Marker of Plaque Vulnerability. PLoS One 2014; 9(6): e100045, http://dx.doi.org/10.1371/journal.pone.0100045.

13. Zhou Q., Chai X.-P., Fang Z.-F., Hu X.-Q. and Tang L. Association of Plasma Pentraxin-3 Levels on Admission with In-hospital Mortality in Patients with Acute Type A Aortic Dissection. Chin Med J (Engl) 2016; 129(21): 2589–2595, http://dx.doi.org/10.4103/0366-6999.192785.

14. Chodkowski A., Nabrdalik K., Kwiendacz H., Gumprecht J. Association of pentraxin 3 with atherosclerotic cardiovascular diseases – general knowledge in 2018. Clinical Diabetology 2018; 7(4): 203-206, http:// dx.doi.org/10.5603/DK.2018.0015.

15. Agilli M., Aydin F.N., Cayci T., Kurt Y.G. Pentraxin 3 (PTX3) plasma levels and carotid intima media thickness progression in the general population: A methodological approach. Nutrition, Metabolism & Cardiovascular Diseases 2014; 24(12): e38–e39, https://doi.org/10.1016/j.numecd.2014.08.011.

16. Fornai F., Carrizzo A., Forte M. The inflammatory protein Pentraxin 3 in cardiovascular disease. Immun Ageing 2016; 13(1): 25, http://dx.doi.org/10.1186/s12979-016-0080-1.

17. Liu H., Guan S., Fang W. Associations between pentraxin 3 and severity of coronary artery disease. BMJ Open 2015; 5(4): e007123, http://dx.doi.org/10.1136/bmjopen-2014-007123.

18. Akgul O., Baycan O.F., Bulut U., Somuncu M.U. Long-term prognostic value of elevated pentraxin 3 in patients undergoing primary angioplasty for ST-elevation myocardial infarction. Coron Artery Dis 2015; 26(7):592-7, http://dx.doi.org/10.1097/MCA.0000000000000280.

19. George M., Shanmugam E., Srivatsan V. Value of pentraxin-3 and galectin-3 in acute coronary syndrome: a short-term prospective cohort study. Ther Adv Cardiovasc Dis 2015; 9(5): 275-84, http://dx.doi.org/10.1177/1753944715578405.

20. Haibo L., Xiaofang G., Chunming W. et al. Prognostic value of plasma pentraxin-3 levels in patients with stable coronary artery disease after drug-eluting stent implantation. Mediators Inflamm 2014; 2014:963096.

21. Jenny N.S., Arnold A.M., Kuller L.H. Associations of Pentraxin 3 with Cardiovascular Disease and All Cause Death: The Cardiovascular Health Study. Arterioscler Thromb Vasc Biol 2009; 29(4): 594–599, http://dx.doi.org/10.1161/ATVBAHA.108.178947.

22. Parhofer K.G. Interaction between Glucose and Lipid Metabolism: More than Diabetic Dyslipidemia. Diabetes Metab J 2015; 39(5): 353–362, http://dx.doi.org/[10.4093/dmj.2015.39.5.353].

23. Jenny N.S., Blumenthal R.S., Kronmal R.A. Associations of pentraxin 3 with cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. J Thromb Haemost 2014; 12(6): 999-1005, http://dx.doi.org/10.1111/jth.12557.

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**Authors’ contributions:**

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*The Authors declare no conflict of interest.*

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