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THE INFLUENCE OF INTERLEUKIN-1β, CARBOHYDRATE AND LIPID METABOLISM ON FORMATION OF MYOCARDIAL DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES MELLITUS

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Abstract. *A total of 102 patients with type 2 diabetes and preserved left ventricular systolic function were examined in the endocrinology department of Kharkiv Regional Hospital. The following indexes were evaluated: body mass index, waist circumference, hip circumference, indexes of carbohydrate and lipid metabolism, and the concentration of IL-1β. All patients underwent echocardiography along with the determination of parameters of diastolic function. The results of statistical analysis showed that level of interleukin-1β, age, body mass index, waist to hip circumference ratio and the level of low-density lipoprotein take part in the formation of diastolic dysfunction.*

Keywords: *type 2 diabetes mellitus, body mass index, interleukin-1β, diastolic dysfunction.*

Type 2 diabetes mellitus (T2DM) is one of the major risk factors for cardiovascular disease. This effect is realized by a deterioration of the coronary arteries and myocardium as a result of the development of diabetes-specific microangiopathy, macroangiopathy, metabolic disorders and diabetic autonomic neuropathy [1, 2].

Diabetic cardiomyopathy is the specific myocardial injury, which develops in patients with T2DM independently of coronary heart disease and hypertension. The early manifestation of diabetic cardiomyopathy is left ventricular diastolic dysfunction (DD) [3, 4, 5]. The main role in the development of cardiovascular lesions in T2DM, due to the development of micro- and macroangiopathy belongs to insulin resistance, hyperinsulinemia and compensatory hyperglycemia, which launch a number of pathological mechanisms [6, 7]. As a result of these changes the basic

metabolic processes in the body are deranged, including metabolism of carbohydrates, fats and proteins. Also growth and differentiation of cells, DNA synthesis, regulation of gene transcription, etc., are broken. [8, 9]. The risk of myocardial pathology increases several times when T2DM is combined with other metabolic disorders.

A large group of cytokines, including interleukins, along with other systems provides a regulation of the basic functions in normal and pathological conditions. Interleukin-1β (IL-1β) belongs to the group of pro-inflammatory interleukins that are directly involved in the pathogenesis of cardiovascular disease because of their cytotoxic effect on the myocardium [10]. According to the experimental studies, IL-1β inhibits the contractility of myocardium in vitro models of isolated heart as well as in the culture of cardiomyocytes, promotes left ventricular remodeling, induces apoptosis of cardiomyocytes, and deranges the heart muscle function in heart failure. IL-1β is able to quickly suppress the potential-dependent calcium channels in rat ventricular cardiomyocytes and to decrease myocardial contractile function [11]. In recent years, evidence appeared that DM-2 is associated with an imbalance of certain cytokines, including the rise of IL-1β [12]. In addition, some scientists believe that activation of cytokines from the early stages of the formation of insulin resistance syndrome is the severity marker and predictor of metabolic disorders and cardiovascular disease [13]. Therefore, in recent years, considerable attention of researchers is focused on the elucidation of pathophysiological role of cytokines in the pathogenesis of cardiomyopathy in patients with T2DM [13, 14]. However, the role of IL-1β in the development and progression of diabetic cardiomyopathy in its early stages as well as in the stages of active formation of complications remains poorly understood.

Even the initial metabolic abnormalities contribute to the development and progression of diabetic cardiomyopathy in patients with T2DM who are overweight or have an abdominal obesity [7, 15]. However, the combination of various pathological factors of myocardial damage is still poorly understood in patients with T2DM and overweight.

The **purpose** of our study was to determine the correlation between the state of lipid and carbohydrate metabolism, proinflammatory IL-1β and indices of diastolic myocardial function in patients with T2DM.

Methods. A total of 102 patients at the age between 35 and 65 years with moderately severe T2DM were examined in endocrinology department of Kharkiv Regional Hospital. Duration of diabetes: 1-9 years, no severe diabetic complications were observed. The control group included 20 healthy individuals of corresponding age.

The following parameters were determined in examined patients: body weight, height, waist and hip circumference with subsequent calculation of body mass index (BMI) using the formula:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} / \text{height (m}^2\text{)}$$

Type of adipose tissue distribution was defined according to the waist to hip circumference ratio (WHR).

For the purpose of our research all patients were tested for serum glucose by glucose-oxidase Somogyi-Nelson assay by the standard method; the level of glycosylated hemoglobin (HbA1c) - kinetic method using a set of reagents «DAC-Spectro Med»; total cholesterol (TC) and triglycerides (TG) - enzymatic photometric method using a set of «DAC-Spectro Med»; high density lipoprotein (HDL) - precipitation/enzymatic-photometric method using a set of «DAC-Spectro Med»; the level of low density lipoprotein (LDL) was calculated by the Friedewald's formula. The content of IL-1β was determined by immune-enzyme assay using "Vector-Best" set of reagents.

The following DD indices were determined as markers of diabetic myocardial injury by echocardiography by universally recognized method according to the recommendations of the American Cardiology Society [16]: maximum peak of diastolic filling velocity during rapid filling of the left ventricle E, the maximum peak of diastolic filling velocity of the left ventricle during systole of the left atrium A, E/A ratio, duration of isovolumetric relaxation of myocardium IVRT, deceleration time DT. The study included patients with ejection fraction above 50%.

Examined patients were divided into 2 groups that differed by the degree of left ventricular DD according to the classification by cluster analysis methods. Classification tree method has revealed that the threshold for the distribution of patients into groups was BMI 28.47 kg/m^2. In case of BMI <28.47 kg / m^2 and systolic blood pressure below 150 mm Hg patient was attributed to the group 1 (n = 38). Group 2 included patients with BMI > 28.47 kg/m^2 and average hemodynamic blood pressure above 97.38 mm Hg (n = 64 patients) [17].

Correlation analysis was performed among all studied parameters according to their distribution law using Statistica 6,0 licensed program.

During this clinical study we followed the safety precautions for the patients' health, the protection of their rights, human dignity and ethical standards in accordance with the principles of the Helsinki Declaration of Human Rights, the European Convention on Human Rights and Biomedicine, and applicable laws of Ukraine.

Results. While comparing the received data, we found significant differences in selected groups not only in comparison with the control group, but also between patients of the 1st and 2nd groups. The details are shown in the table 1.

In terms of the objectives and purpose of the study, of course, we were interested in 2nd group of patients. The determination of correlation dependencies in this group between parameters of diastolic function and BMI, WHR, serum glucose, HbA1c, TC, HDL, LDL, TG, and IL-1β showed the presence of significant negative relation between E/A and IL-1β (R = -0,27 (p <0.05)), and significant positive relation between DT and IL-1β (R = 0,274 (p <0.05)).

However, the correlation coefficients in this case were small (R <0,4), which corresponds to a weak link according to Chaddock's scale. Therefore, we used the method of multiple correlation - multiple regression in this study in order to determine the influence of IL-1β, lipid and carbohydrate metabolism, some data of objective examination on the formation of the basic indexes of diastolic function. The results of multiple regression can be represented as regression equation and the coefficient of determination R^2, which reflects the adequacy of the regression model.

Table 1.

Mean values of indices in the study groups

Investigated indices	Control group (n=20)	Group1 (n=38)	Group 2 (n=64)
Age, years	51,3±1,7	51,45±0,98	53,05±0,74
BMI, kg/m^2	23,73±0,29	25,42±0,51	33,6±0,69*/**
WHR	0,82±0,017	0,84±0,01	0,91±0,01*/**
Serum glucose, mmol/L	5,5±0,1	9,92±0,6*	9,61±0,3*
HbA1c, %	4,92±0,048	8,11±0,3*	8,45±0,23*
TC, mmol/L	4,06±0,05	4,58±0,16	5,68±0,18*/**
TG, mmol/L	1,3±0,035	1,54±0,05*	1,87±0,05*/**
HDL, mmol/L	1,39±0,02	1,2±0,02*	1,19±0,025*
LDL, mmol/L	2,01±0,045	2,65±0,16*	3,62±0,174*/**
IL-1β, pg/ml	8,12±0,24*	11,34±0,25*	14,76±0,28*/**
MV, E/A	1,4±0,075*	0,93±0,04*	0,82±0,022*/**
IVRT, ms	79,75±1,73*	102,84±1,47*	106,44±0,94*/**
DT, ms	182,2±3,68*	232,47±3,54*	239,75±2,25*

Note:
1. * significantly (p<0,05) differs from the control group
2. */** significantly (p<0,05) differs from group 1 and control group

Accordingly, the regression equations for them are as follows:

E/A = 0,75 -0,43 «Age» - 0,30 «BMI» - 0,27 «WHR» - 0,13 «IL-1β»

DT = 1,44 +0,32 «Age» +0,29 «LDL» - 0,11 «IL-1β»

The coefficient of determination R^2 in the first case was equal to 0.62, and in the second case - 0.66. This indicates a good adequacy of the regression model, i.e., 61% and 66% of changes of the dependent variables (E/A and DT) are stipulated by the influence of indices included in the equation.

Unfortunately, it didn't work to get regression equation with a high degree of adequacy for IVRT parameter. In addition, we didn't receive regression model with a reasonable degree of adequacy for the 1st group and control group.

Conclusions.

The activity of proinflammatory IL-1β increases at the beginning of T2DM and is probably one of the pathogenetic mechanisms of diabetic complications. The received data indicate that IL-1β may be considered as a mediator of myocardial damage and its progression marker in patients with T2DM and BMI above 28.47 kg/m^2, which extends the diagnostic and prognostic capabilities when examining these patients.

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Резюме: В ендокринологічному відділенні КЗОЗ «ОКЛ – ЦЕМД та МК» обстежено 102 хворих на цукровий діабет 2 типу зі збереженою систолічною функцією лівого шлуночка. Було визначено індекс маси тіла, окружність талії, окружність стегон, показники вуглеводного, ліпідного обмінів, а також концентрація інтерлейкіну-1β. Всім хворим було проведено ехокардіографічне дослідження з визначенням показників діастолічної функції. В результаті статистичного аналізу встановлено, що у формуванні діастолічної дисфункції беруть участь рівень інтерлейкіну-1β, вік, індекс маси тіла, відношення окружності талії до окружності стегон, а також рівень холестерину ліпопротеїнів низької щільності.
Ключові слова: цукровий діабет 2 тип, індекс маси тіла, інтерлейкін-1β, діастолічна дисфункція.

Резюме: В эндокринологическом отделении КУОЗ «ОКБ – ЦЭМП и МК» обследованы 102 больных сахарным диабетом 2 типа с сохраненной систолической функцией левого желудочка. Были определены индекс массы тела, окружность талии, окружность бедер, показатели углеводного, липидного обменов, а также концентрация интерлейкина-1β. Всем больным было проведено эхокардиографическое исследование с определением значений диастолической функции. В результате статистического анализа установлено, что в формировании диастолической дисфункции у больных сахарным диабетом 2 типа участвуют уровень интерлейкина-1β, возраст, индекс массы тела, отношение окружности талии к окружности бедер, а также уровень холестерина липопротеинов низкой плотности.
Ключевые слова: сахарный диабет типа 2, индекс массы тела, интерлейкин-1β, диастолическая дисфункция.

Received: 29.11.2014 *Accepted: 27.01.2015*