UDC: [616.379-008.64-008.9: 616.12] -078: 57.083.3

The influence of proinflammatory cytokines on the formation of cardiometabolic disorders in type 2 diabetes mellitus

Sokolnikova N.V., Filonenko M.V.
Kharkiv National Medical University
Kharkov, Ukraine

INTRODUCTION

It is a well-known fact that diabetes mellitus (DM) is an independent risk factor for the development of heart failure (HF), which was first convincingly shown in the Framingham study. In patients with diabetes aged 45–74 years, the risk of heart failure development was 2 times higher for men and 5 times higher for women, compared to the general population. This suggests that the risk of HF development in patients with diabetes is at least 2.5 times higher than in the general population [Kannel W. B., Hjortland M., Castelli W. P.2015].

The observed association of diabetes and heart failure can be explained by several obvious mechanisms. Patients with diabetes are characterized by the high prevalence of the most significant risk factors for heart failure: arterial hypertension (AH) and coronary heart disease (CHD). However, other predictors of the formation of HF have also been established for patients with type 2 diabetes: elevated HbA1c levels, overweight or obesity, older age, secondary insulin therapy, the presence of microangiopathy and macroangiopathy. [Campbell P., Krim S., Ventura H.2015]. Thus, the development of HF in diabetic patients is only partially explained by the increased risk of atherosclerotic and cardiovascular complications. The aggravating effect of type 2 diabetes on the development and prognosis of HF is due to a number of closely related mechanisms, including modulation of insulin signaling pathways and mitochondrial dysfunction, oxidative stress, accumulation of the end products of excess glycolysis and lipids [Belovol A., 2013]. The situation is significantly complicated by the frequent presence of overweight in such patients, which accelerates the formation of cardiovascular diseases, and, above all, the development of an independent diabetic cardiomyopathy - a specific diabetic myocardial damage.

Diabetic cardiomyopathy is a pathology of the heart muscle in patients with diabetes, unrelated to age, presence of hypertension, valvular heart disease, obesity, hyperlipidemia, and pathology of the coronary vessels, which manifests as a wide spectrum of biochemical and structural defects that lead to the systolic and diastolic dysfunction, and ultimately causes the development of congestive heart failure.

Diabetic cardiomyopathy is divided into primary and secondary. Primary one is the result of the accumulation of glycoprotein complexes, glucuronates and abnormal collagen in the interstitial tissue of the myocardium. The secondary one develops as a result of the extensive damage of the capillary bed of the myocardium by the microangiopathic process. As a rule, these two processes develop in parallel. Histological examination reveals a thickening of the basement membrane of capillaries, as well as the proliferation of endothelial cells, microaneurysms, myocardial fibrosis, degenerative changes of muscle fibers [Guanghong Jia, Michael A. Hill, James R. Sowers, 2018, https: // n.cc.nlm.nih .gov / pubmed / 29449364].

On the other hand, the prevalence of diabetes among patients with HF is higher than in the general population, according to some data - 25% and 9%, respectively. Even higher prevalence of diabetes (up to 40%) is registered among patients with acute decompensation of HF and among patients with signs of HF with a preserved ejection fraction (HF-PEF) [Campbell P., 2015]. Obviously, the relationship between DM and HF is bidirectional. The combination of diabetes and HF significantly complicates the prognosis: diabetes is a marker of a worse prognosis and an independent predictor of mortality in a population of patients with heart disease, on the other hand, the development of heart failure in patients with diabetes increases the mortality rate by 12 times compared with patients with diabetes without heart failure [Mareev V.Y, 2013].

Currently, there is increasing evidence of the role of inflammation in the formation of metabolic syndrome, type 2 diabetes and numerous diabetic complications [Low C. C. Wang, 2016]. There are increasing reports that activation of pro-inflammatory cytokines (C-reactive protein, tumor necrosis factor-α, interleukin-6 (IL-6), interleukin-8) is detected in diabetes [Zhou W., 2018]. Some

researchers believe that systemic inflammatory mediators can contribute to the development of insulin resistance (IR) and be predictors of the development of type 2 diabetes [Ohkuma T., 2017].

Therefore, it can be fairly assumed that activation of pro-inflammatory interleukins in type 2 diabetes in overweight patients can be associated not only with impaired carbohydrate metabolism, but also with dyslipidemia, and it might have additional pathogenetic consequences, such as the development of diabetic target organ damage.

THE PURPOSE OF WORK

Thus, the purpose of our work was to determine the relationship between pro-inflammatory cytokines: interleukin-1β (IL-1β), IL-6 and the indicators of carbohydrate and lipid metabolism in patients with diabetic cardiomyopathy against the background of type 2 diabetes with normal body mass and overweight.

MATERIALS AND METHODS

The examination of patients was performed on the basis of endocrinological department of Kharkiv Regional Clinical Hospital and the Department of Internal Medicine No. 3 of Kharkiv National Medical University. A total of 102 patients with type 2 diabetes were examined, as well as 20 healthy volunteers, comparable by age and gender, who formed the control group.

The mean age of the examined patients was 50.45 ± 0.59 years, the average age of control group was 50.35 ± 1.74 years. Duration of diabetes ranged from 1 to 9 years and averaged 4.77 ± 0.22 years. Patients included in the study neither had severe diabetic complications, nor clinically significant coronary heart disease or arterial hypertension.

Verification of diabetic cardiomyopathy was performed on the basis of clinical-anamnestic and laboratory-instrumental studies using criteria recommended by experts of the National Scientific Center "Institute of Cardiology named after M.D. Strazhesko" Academy of Medical Sciences of Ukraine (2008). The verification of the diagnosis of type 2 diabetes was performed according to the Order of the

Ministry of Healthcare of Ukraine, 05.08.2009, No. 574 "On approval of protocols for providing medical care to patients with endocrine diseases."

The following measurements were done for all of examined patients: waist circumference (WaistC) and hip circumference (HC), as well as body weight and height, followed by the calculation of body mass index (BMI) according to the formula: BMI (kg / m2) = body mass (kg) / body height2 (m).

The average BMI in patients with diabetic cardiomyopathy was 30.54 ± 0.61 kg / m2, and in the control group - (23.73 ± 0.29) kg / m2. In the main group 18 patients (17.64%) had BMI <24.99 kg / m2; 33 patients (32.39%) had BMI between 24.99 and 29.99 kg / m2; 32 patients (31.37%) had BMI 30 - 34.99 kg / m2, 12 patients (11.74%) had BMI 35 - 39.99 kg / m2, 7 patients had BMI above 40 kg / m2 (6.86%).

To determine the state of carbohydrate metabolism, all patients and volunteers of the control group had their fasting plasma glucose test done using the Hagedorn-Jenson method (FeliCit reagent kit (Ukraine)); as well as determination of immunoreactive insulin (IRI) by solid-phase method using the “sandwich” principle by ELISA reagent kit, produced by “DRG” (USA). Glycosylated hemoglobin (HbA1c) was determined by the kinetic method using a DAC-SpectroMed kit (Moldova) and a biochemical analyzer. The IR index was calculated using the Homeostasis Model Assessment (HOMA-IR) algorithm according to the following formula: HOMA-IR = Serum glucose (mmol / ml) × Insulin (μU / ml) / 22.5.

The state of lipid metabolism was determined by the biochemical method: the determination of total cholesterol (TC) was performed by enzymatic-photometric method with cholesterol oxidase / peroxidase using the DAC-Spectro Med kit. The level of triglycerides (TG) was determined by the enzymatic-photometric method using the DAC-Spectro Med kit. High-density lipoprotein cholesterol (HDL) was determined by the precipitating / enzymatic-photometric method using the DAC-Spectro Med kit. Low density lipoprotein cholesterol (LDL) was calculated by the Friedwald’s formula.

The levels of proinflammatory cytokines IL-1β and IL-6 were determined by the immunoassay solid-phase “sandwich” method using Vector-Best reagent kits.

The echocardiographic method according to the generally accepted method in accordance with the recommendations of the European Society of Cardiology [European Cardiology Association Recommendations, 2008] and the American Cardiographic Society [Douglas PS, 2011] was used to assess the markers of diabetic cardiomyopathy, namely the indicators of diastolic function of left ventricle: peak velocity of early filling of left ventricle E, peak velocity of late filling of left ventricle A, E/A ratio, deceleration time DT of early diastolic filling. The study included patients with left ventricle ejection fraction above 50%.

When the normal values of the diastolic function were detected, an additional analysis of the Valsalva maneuver was performed to determine the pseudonormal pattern.

According to the Recommendations of the European Society of Cardiology for the management and treatment of patients with cardiovascular diseases (2008), the following types of diastolic dysfunction were distinguished: the type of delayed relaxation, which is determined by the decrease of E / A ratio <1, a restrictive type characterized by the increase of E / A ratio > 2 with a reduction of DT to 115-150 ms, and a pseudo-normal type that occupies an intermediate position between the slow relaxation type and restrictive type and is characterized by E / A ratio > 1 [8].

Statistical processing of the results of the study was conducted using the program Statistica 6.0 (StatSoft). The normal distribution of the studied interval indices was determined using the Shapiro-Wilk test, Kolmogorov-Smirnov test. Depending on the distribution law, the validity of the differences between the central tendencies (median, median) in two or more groups was verified using Mann-Whitney's criterion and the one-factor dispersion analysis. All comparisons were performed at a significance level of $p < 0.05$.

Correlation between interval variables was estimated using Spirman R or Gamma correlation coefficients. The reliability of the differences was determined by the Mann-Whitney’s criterion with a significance level of $p < 0.05$.

RESULTS AND THEIR DISCUSSION

After obtaining the results of all studies, a natural classification of patients with diabetic cardiomyopathy against the background of type 2DM was performed, which took the following indices into consideration: BMI, age, WaistC, WaistC / HC, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), serum glucose, HbA1c, IRI, HOMA-IR index, TC, TG, HDL cholesterol, LDL cholesterol, IL-1β, IL-6, echocardiography data, etc. and others (a total of 31index). The natural classification was performed by cluster analysis after preliminary standardization of indicators according to the formula: X = (B-C) / D, where X is the standardized value of the indicator, B is the measured value of the indicator, C and D are the mean value and the mean square deviation of the indicator, respectively.

As a result of classification, the patients were divided into 2 groups (clusters) that differed by severity of cardiometabolic lesions. The severity of cardiometabolic lesions can be explained as the severity of clinical manifestations of heart failure (HF) (NYHA) and the degree of diastolic dysfunction.

The following mean E / A values were obtained on echocardiography: 1st group - 0.93 ± 0.04, 2nd group - 0.82 ± 0.022, control group - 1.4 ± 0.075. The mean value of DT in the studied groups was the following: 1st group - 232.47 ± 3.54 ms, 2nd group - 239.75 ± 2.25 ms, control group - 182.2 ± 3.68 ms. At the same time, a significant differences between the values of diastolic function were found in the studied groups. Tree classification method has revealed that the threshold for distribution of patients into groups was BMI 28.47 kg / m2. Patients with BMI <28.47 kg / m2 and MAP <150 mm. Hg. were assigned to a group of moderate diabetic cardiomyopathy (1st group of patients). Patients with BMI> 28.47 kg / m2 and MAP> 97.38 mm Hg were included in the group of marked cardiomyopathy (2nd group of patients). In case of increased body weight, even with low values of mean arterial pressure (MAP <97.38 mm Hg), the WaistC / HC ratio played a decisive role in determining the severity of diabetic cardiomyopathy: if its value was more than 0.84, patient was assigned to the group of severe cardiomyopathy (Fig.

1). Thus, it was found that the threshold for distribution of a patient to a group of either moderate or severe cardiomyopathy is BMI 28.47 kg/m2. Secondary impact on the classification of such patients is performed by SBP, MAP and WaistC/HC.

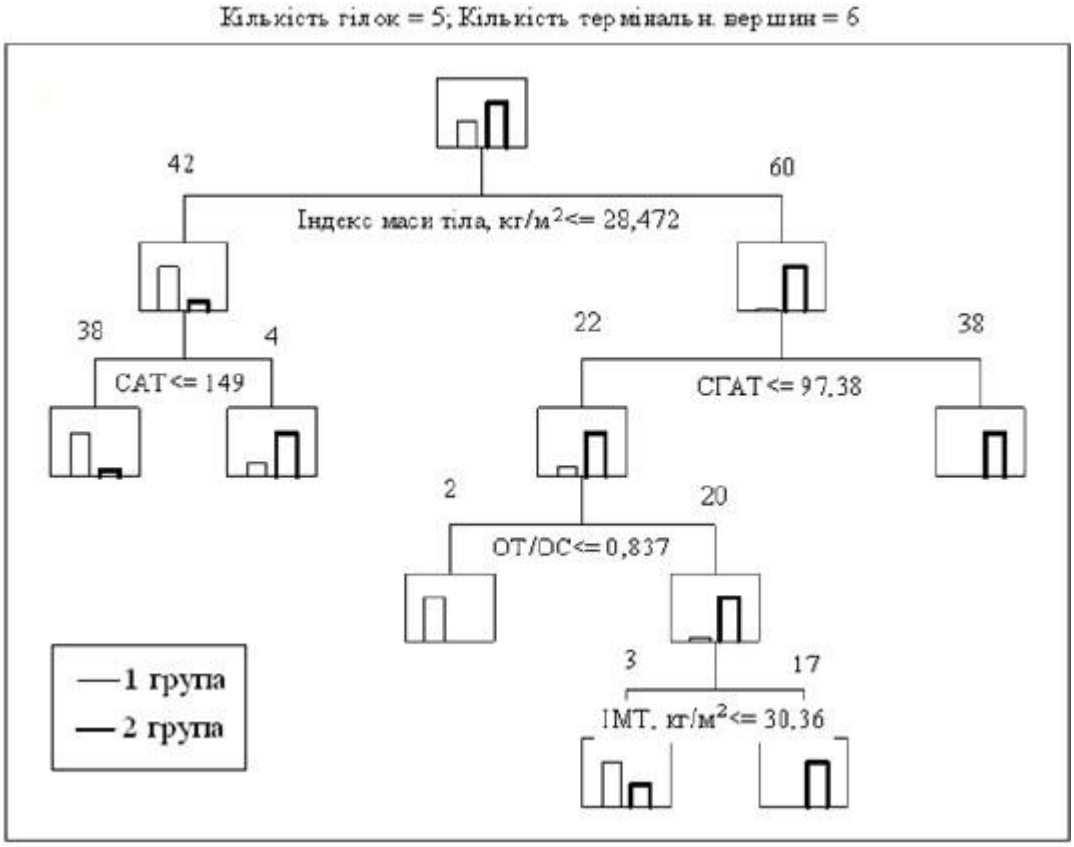

Fig. 1. Classification tree to determine the severity of cardiomyopathy against the background of DMD type 2.

It is interesting to note that the division into groups is not entirely determined by the value of BMI, since about 15% of patients with overweight (BMI> 25 kg / m2) were included in the group of moderate cardiomyopathy, and 17% of patients with BMI <25 kg / m2 were classified into the group of severe cardiomyopathy, which probably indicates the compensatory capacity of the body, even with an increase in BMI.

It is necessary to note the high adequacy of the received mathematical model of distribution of patients - 88,3% ($p < 0,05$), which indicates the high reliability of the received distribution.

Among patients of group 1 (n = 38), 32 (84.21%) had HF of functional class 1, and 6 patients (15.79%) had HF of functional class (FC) 2; the signs of diastolic

dysfunction with slow relaxation were detected in 35 patients (92.10%), and pseudonormal type of diastolic dysfunction was discovered in 3 patients (7.90%) by Valsalva maneuver.

Among patients of group 2 (n = 64), more patients with marked HF were detected: 7 patients (10.94%) with HF of FC 1 and 57 patients (89.06%) with HF of FC 2. In 48 patients (75.00%), a delayed relaxation of diastolic dysfunction was more pronounced than that of patients in group 1 ($p < 0.05$). In addition, the pseudonormal type of diastolic dysfunction was discovered by Valsalva maneuver in a larger number of patients (16 patients, 25.00%).

Thus, group 1 included 38 patients with moderate cardiomyopathy against the background of T2DM, group 2 included 64 patients with severe cardiomyopathy against the background of T2DM.

We performed a comparative analysis of serum glucose levels, HbA1c, IRI and HOMA-IR. Thus, we found that serum glucose and HbA1c levels significantly differed between the group of patients with cardiomyopathy against the background of T2DM and the control group, but there were no significant differences in the 1st and 2nd group of patients. The levels of IRI and HOMA-IR significantly differed in all studied groups (Table 1). The determined levels of serum glucose and HbA1c reveal insufficient compensation of carbohydrate metabolism, and the level of IRI and HOMA-IR allows us to conclude about the presence of hyperinsulinaemia and IR in patients of group 1 and 2, the changes were more marked in group 2.

Table 1.

The data of carbohydrate metabolism study in patients with diabetic cardiomyopathy and healthy volunteers

Indices	Control group	Group 1	Group 2
Plasma glucose, mmol/l	5,5±0,1	9,92±0,6*	9,61±0,3*
HbA1c, %	4,92±0,048	8,11±0,3*	8,11±0,3*
IRI, microU/ml	9,04±0,36	12,5±0,47*	18,3±0,4*/**
HOMA-IR	2,23±0,12	5,52±0,4*	7,07±0,38*/**

Notes:

1. * Significantly ($p < 0,05$) differs from the control group

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

The Tarasenko K.V. study also revealed a relation between overweight and an increase of IRI level. Thus, hyperinsulinemia reflects an imbalance of the regulation of metabolism and progression of IR in patients with overweight [Tarasenko K.V. 2012).

There is no consensus in the studied literature on the relationship between indices of carbohydrate metabolism (fasting plasma glucose and HbA1c) and the parameters of diastolic function of the left ventricule. According to some authors, the dependence of the parameters of the diastolic function is revealed only with quite a poor glycemic control. In the Vinereanu D. study, the significant correlation was obtained at a concentration of HbA1c of 9.2% [Vinereanu D. 2003]. In the Ametov O.S. study, the relationship between carbohydrate metabolism and diastolic dysfunction of the left ventricle was significant and reliable [AS Ametov, 2008].

In our study, the analysis of the relationship between glycemia and diastolic function in patients with diabetic cardiomyopathy against the background of type 2 diabetes did not show a relationship between plasma glucose, HbA1c and diastolic function, probably due to the small extent of glycemia fluctuations, which could possibly affect the results of the study. Currently, there is no consensus opinion regarding the association of insulin resistance markers and disorders of the diastolic function of the left ventricle. But there are interesting reports about the role of insulin resistance in the development of myocardial pathology in patients with T2DM and overweight, and this is the so-called "cardiac insulin resistance" [Grey S. 2011].

The analysis of the correlation between carbohydrate metabolism and diastolic dysfunction in our study showed that there was no reliable interrelationship in the group 1. A significant negative correlation was detected between IRI and E / A ratio in group 2.

When analyzing lipid metabolism data, we found that group 2 had the highest level of TC (5.68 ± 0.18 mmol / l) and it significantly differed from group 1 (4.58 ± 0.16 mmol / l) and control group (4.06 ± 0.05 mmol / l) (p <0.05). TG and LDL levels were significantly higher in patients of group 2 than in patients of both group1

and control group: TG level in control group was 1.3 ± 0.035 mmol / l, group 1 - 1.54 ± 0,05 mmol / l, group 2 - 1,87 ± 0,05 mmol / l ($p < 0,05$); LDL cholesterol level in control group was 2.01 ± 0.045 mmol / l, group 1 - 2.65 ± 0.16 mmol / l, group 2- 3.62 ± 0.17 mmol / l ($p < 0.05$). The concentration of HDL was the highest in group 2 and significantly differed from that in the control group, however, it did not differ from that in group 1: the HDL level in the control group was 1.39 ± 0.02 mmol / L, in group 1 - 1,2 ± 0,02 mmol / l, group 2 - 1,19 ± 0,025 mmol / l ($p < 0,05$).

While studying the relationship between TC, TG, LDL, HDL, and diastolic function, a correlation was found between the TG level and the E / A ratio in group 1 ($R = -0.374$ ($p < 0.05$)), which indicates the importance of hypertriglyceridemia for the development of cardiometabolic complications in T2DM from the very beginning of cardiomyopathy formation in diabetes.

A comparative analysis of the levels of pro-inflammatory interleukins in patients with T2DM and in control group was performed and there were significant differences in the studied groups. The level of IL-1β was significantly higher in patients of group 2 compared with group 1 and the control group. However, an increase in the activity of pro-inflammatory IL-1β was already significant in patients of group 1 and significantly differed from the normal mean values of this cytokine in the control group. Fig. 2 shows the significant difference between levels of IL-1β in group 1, 2 and the control group.

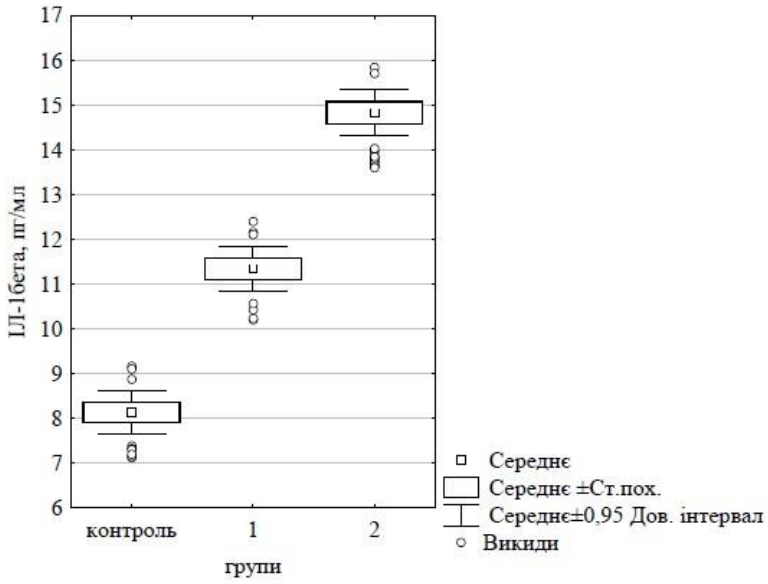

Fig. 2. Differences of IL-1β level in patients and controls.

The level of IL-6 was significantly higher in patients of group 1 compared with its mean parameters in the control group. The activity of IL-6 was even higher in patients of group 2and differed from the mean values of IL-6 in group 1and the control group. Fig. 2 demonstrates the significance of the difference between the mean values of IL-6 in group 1, 2 and the control group.

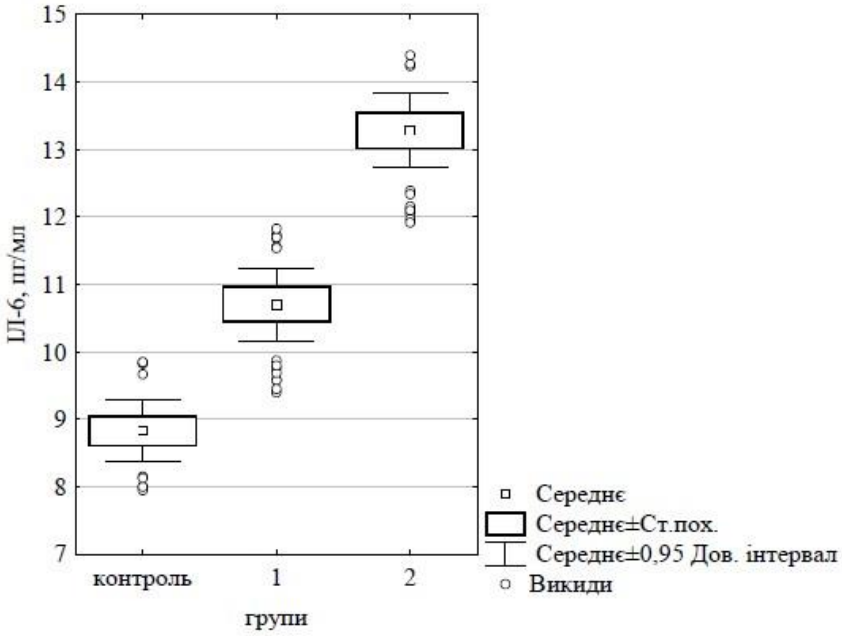

Fig. 3. The significance of IL-6 level differences between the groups of patients with T2DM and the control group.

When comparing the mean levels of activity of pro-inflammatory IL-1β and IL-6 in group 1, 2 and in the control group, we revealed a significant difference between interleukin levels the in the studied groups, which is described in Table 2.

Table 2.

The comparison of interleukin levels in studied groups

Studied indices	Control group (n=20)	Group 1 (n=38)	Group 2 (n=64)
IL-1β, pg/ml	8,12±0,24	11,34±0,25*	14,76±0,28*/**
IL-6, pg/ml	8,83±0,22	10,70±0,27*	13,28±0,27*/**

Notes:

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

Based on the purpose of our work, we revealed correlations between markers of systemic inflammation IL-1β and IL-6 and markers of obesity in selected groups.

In all 102 patients with T2DM, a significant correlation was detected between BMI and IL-1β (R = 0.76 (p <0.05)), as well as between BMI and IL-6 (R = 0.59 (p <0. 05)). In addition, the correlation between IL-1β and WaistC was found in group 1 (R = 0.37 (p <0.05)) as well as in group 2 (R = 0.32 (p <0.05)). A significant correlation was also found between IL-6 and Waist C in group 1 (R = 0.39 (p <0.05)).

It was shown in the study of Kovalyova Y.A., that in patients with coronary artery disease and obesity, the level of IL-β was significantly higher than that of control group. The author associates the obtained results with the pathogenetic effect of excessive accumulation of adipose tissue on the development of cardiovascular diseases due to the activation of pro-inflammatory mechanisms [Kovalyova Y.A., 2013].

The study of Kopitsa M.P. had revealed that the level of IL-6 was elevated in patients with acute myocardial infarction (AMI) and obesity in comparison to a group of patients with AMI and no obesity. In addition, the authors found a significant correlation between IL-6 and abdominal obesity, IR and dyslipidemia [Kopitsa M.P, 2009].

That is, the results we obtained on the hyperexpression of mediators of systemic inflammation IL-1β and IL-6 in patients of group 1 and 2 are significant and coincide with the results of other studies.

In patients of group 1, the correlation between E / A ratio and IL-6 (R = -0.328 (p <0.05) was detected in the realms of study of the relationships between the diastolic function and IL-1β, IL-6). There were no other significant reliable connections. In patients of group 2, the correlation between IL-1β and E / A ratio (R = -0.27, p <0.05) was revealed, as well as between IL-1β and DT (R = -0.27 , p <0.05). No other significant connections were found.

The analysis of interrelations between interleukins and carbohydrate and lipid metabolism indices in group 1 revealed significant correlations between IL-1β and IRI, IL-6 and IRI, IL-1β and TC, IL-1β and TG, IL-6 and TC , IL-6 and TG, IL-1β and LDL, IL-6 and LDL (Table 3).

Table 3.

The correlation between interleukins and indices of carbohydrate and lipid metabolism in group 1.

Inter-leukins	Glucose, mmol/L	HbA1c, %	IRI, mcU/ml	HOMA-IR	TC, mmol/L	TG, mmol/L	HDL, mmol/L	LDL, mmol/L
IL-1β, pg/ml	0,12	-0,03	0,47*	0,15	0,55*	0,27	-0,04	0,48*
IL-6, pg/ml	-0,04	-0,03	0,33*	-0,01	0,62*	0,41	0,02	0,54*

Note: * - significant correlations (p <0,05)

While studying the relationships between the mediators of systemic inflammation IL-1β, IL-6 and carbohydrate, lipid metabolism and markers of IR, we found significant correlations between IL-1β and IRI, IL-6 and IRI, IL-6 and TC, IL-6 and LDL, IL-6 and TG in group 2 of patients. The findings suggest that pro-inflammatory IL-1β and IL-6 are associated with dyslipidemia and hyperinsulinemia in patients with marked CMP against the background of T2DM. The detailed information is given in Table 4.

Table 4.

The correlation between interleukins and indices of carbohydrate and lipid metabolism in group 2.

Inter-leukins	Glucose, mmol/L	HbA1c, %	IRI, mcU/ml	HOMA-IR	TC, mmol/L	TG, mmol/L	HDL, mmol/L	LDL, mmol/L
IL-1β, pg/ml	0,06	-0,01	0,50*	0,18	0,24	0,15	-0,11	0,03
IL-6, pg/ml	0,23	0,14	0,41*	0,24	0,52*	0,30*	0,03	0,50*

Note: * - significant correlations (p <0,05)

While analyzing Table 2 and 3, we can conclude that patients of group 2 were characterized by more significant correlations between proinflammatory interleukins and basal hyperinsulinemia, whereas patients of group 1 had a more significant correlations between markers of systemic inflammation and dyslipidemia.

The study by Pavlovsky A.S. presented the data, which confirm the close relationships between IR and the activity of proinflammatory cytokines. The author demonstrates the positive dynamics of the pro-inflammatory IL-1β and IL-6 against the background of hypoglycemic therapy in patients with T2DM with concomitant

non-alcoholic fatty liver dystrophy [Pavlovsky A.S, 2018]. According to Kochubei O.A. data, the activation of the pro-inflammatory cytokine IL-6 is associated with the progression of dyslipidemia in patients with disorders of carbohydrate metabolism, and these changes are more marked in patients with T2DM rather than in patients with pre-diabetes [Kochubei O.A, 2012]. That is, the data we have received is comparable to the results of other researchers, which indicates the reliability of the results.

The control group demonstrated no correlations between proinflammatory cytokines and the indices of lipid and carbohydrate metabolism, as well as the markers of IR. Thus, the increase of IL-1β and IL-6 influences the development of dyslipidemia in patients with moderate diabetic cardiomyopathy against the background of T2DM. The hyperproduction of IL-1β and IL-6 promotes the progression of hyperinsulinemia in patients with severe cardiomyopathy against the background of T2DM.

CONCLUSION

In case of the development of diabetic cardiomyopathy against the background of type 2 diabetes, the threshold value for the body mass index, which determines the severity of myocardial damage, is more than 28.47 kg/m2. In patients with cardiomyopathy against the background of type 2 diabetes, the correlations between laboratory data and diastolic dysfunction, which is a marker of primary cardiometabolic lesion in patients with type 2 diabetes, were revealed, and these relationships are more weighty and numerous in patients with a body mass index more than 28.47 kg / m2.

In patients with cardiomyopathy against the background of type 2 diabetes, the development of diastolic dysfunction of the myocardium is associated with hypertriglyceridemia and hyperinsulinemia.

In patients with type 2 diabetes with BMI below 28.47 kg / m2, the hyperexpression of pro-inflammatory IL-1β and IL-6 potentiates the progression of dyslipidemia, and in patients with severe CMP against the background of type 2

diabetes, hyperproduction of IL-1β and IL-6 is likely to contribute to the increase in hyperinsulinaemia.

The expression of pro-inflammatory cytokines interleukin-1β and interleukin-6 rises from the very beginning of cardiometabolic disorder formation. Obviously, the activation of the pro-inflammatory cytokines contributes to the formation of cardiomyopathy against the background of type 2 diabetes.

We believe that IL-1β and IL-6 can be accepted as markers of cardiometabolic myocardial damage in patients with type 2 diabetes, which extends diagnostic and prognostic capabilities of examination of such patients.

SUMMARY

THE INFLUENCE OF PROINFLAMMATORY CYTOKINES ON THE FORMATION OF CARDIOMETABOLIC DISORDERS IN TYPE 2 DIABETES MELLITUS

Sokolnikova N.V., Filonenko M.V.

Kharkiv National Medical University

Kharkiv, Ukraine

The prevalence of type 2 diabetes mellitus is increasing every year, and with each year the number of patients suffering from cardiovascular complications caused by diabetes is increasing as well. Type 2 diabetes often goes along with obesity or overweight, which greatly impairs cardiovascular outcomes for such patients. Diabetic cardiomyopathy is a specific lesion of the myocardium that occurs on the background of diabetes due to the activation of numerous pathogenetic mechanisms.

None of the pathological processes in the body can sustain without the activation of proinflammatory cytokines. Therefore, we hypothesized that in patients with diabetic cardiomyopathy, especially in those with overweight, an increase of interleukin-1β and interleukin-6 contributes to the development of cardiometabolic complications and the formation of organic pathology of the myocardium.

A total of 102 patients with diabetes type 2 and no severe diabetic complications were examined in the endocrinology department of the Kharkiv Regional Clinical Hospital. The following data were analyzed: anthropometric measurements, indicators of carbohydrate and lipid metabolism, the level of activity of pro-inflammatory cytokines interleukin-1β and interleukin-6; as well as the intensity of cardiometabolic disorders, assessed by echocardiography. A statistical analysis revealed an increase of interleukin-1β and interleukin-6 activity, starting from the early stages of the disease, as well as the direct participation of these cytokines in the formation and progression of diabetic dyslipidemia and hyperinsulinemia, which allows us to consider them as the markers of metabolic disorders in patients with diabetes type 2.

Key words: diabetes type 2, interleukin-1β, interleukin-6, dyslipidemia, insulin resistance, diabetic cardiomyopathy.

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