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RELATIONSHIP BETWEEN CARBOHYDRATE EXCHANGE PARAMETERS AND INTERLEUKIN-22 IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION WITH REGARD TO CONCOMITANT TYPE 2 DIABETES MELLITUS*

M. I. Zhuravleva[1], N. G. Ryndina[1], I. P. Dunaeva[2]

[1] Kharkiv National Medical University, Kharkiv, Ukraine
[2] Kharkiv Postgraduate Medical Academy, Kharkiv, Ukraine
mzhuravleva2017@gmail.com

Worldwide, ischaemic heart disease is the single most common cause of death and its frequency is increasing. However, in Europe, there has been an overall trend for a reduction in ischaemic heart disease mortality over the past three decades [1]. Ischaemic heart disease now accounts for almost 1.8 million annual deaths, or 20 % of all deaths in Europe, although with large variations between countries [2, 3].

Basu et al. found that althrought IL-22 was secreted by various types of cells, Th22 (CD4 + IL – 22 + T) cells were the critical source of IL-22 during the later stages of inflammation, indicating that Th22 may be essential for controlling chronic inflammation. The effector cytokine of Th22 cells is IL-22, which belongs to the IL-10 cytokine family and binds to the heterodimeric receptor complex consisting of the IL-10 receptor (IL-10R) ß chain and IL-22R.

Because IL-22R is expressed almost exclusively on nonimmune cells, IL-22 acts primarily on tissue cells such as epithelial cells and smooth muscle cells [4]. After binding to its receptor complex, IL-22 activates numerous signaling pathways including the Janus kinase/signal transducers and activators of transcriptions (JAK/STAT) pathway, predominantly STAT 3, and the three major MAPK pathways [5]. IL-22 is upregulated in a number of chronic inflammatory and autoimmune disease, and the exact role of IL-22 appears to depend on specific inflammatory microenvironments: the protective role of IL-22 has been found in a myocarditis model [6]

By information of Ogyi Park IL-22 reduses glucose level in serum as a result of inhibition of gluconeogenesis in liver, which is medicated VIA blocking signal transducer and activator of transcription 3 (STAT 3) pathway.

Role of IL-22 in cardial disease was shown in Ying-zolong Lin study [6]. IL-22 plays role in atherosclerosis as a marker of inflammatory process, there was significant increasing of IL-22 serum level in patients with acute forms of ischemic heart disease.

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Aim is to assess the state of immune inflammation based on the study of serum calprotectin level, as well as to analyze the presence and character of links with carbohydrate metabolism parameters based on the study of blood glucose, insulin and insulin resistance in patients with acute MI and DM type 2.

MATERIALS AND METHODS

The study involved examination of 110 patients (mean age 65.25 ± 0.09 years) who underwent treatment at myocardial infarction department of Kharkiv City Clinical Hospital № 27 and Kharkiv Railway Clinical Hospital № 1. The main group included 64 patients (average age 65.31 ± 1.62 years) with acute MI and concomitant DM type 2. The comparison group consisted of 46 patients with acute MI without DM type 2 (mean age 65.19 ± 1.22 years). Groups were matched according to age and gender.

The design of the study implied primary laboratory examination of patients during the first day of the acute MI with ST segment elevation onset prior to percutaneous intervention or thrombolytic therapy and their distribution into groups depending on the presence or absence of concomitant DM type 2.

Press of coronary stenosis, location of the occlusion in patients with acute MI, DM type 2 and isolated acute MI was estimated by coronary angiography showed that the most frequently occlusion was diagnosed in left anterior descending coronary artery (LAD). Infarction — depended artery was LAD in 85 % of patients with comorbidity of acute MI and DM type 2. In the remaining 15% of patients with acute MI and DM type 2 the infarction was registered in right coronary artery (RCA). The patients of comparison group showed the same results. 75 % of patients of this cohort had MI in LAD, 20 % of patients — in RCA and remaining 5 % of patients — in left circumflex artery (LCX).

Arterial hypertension was diagnosed either in 100 % of patients in the main group or the comparison group. Duration of the DM type 2 according to the outpatient card was 3–10 years.

A complicated course of acute MI in the form of acute heart failure (pulmonary oedema) was found in 12 patients with DM type 2 and 8 patients of comparison group. Rhythm disturbances in patients with acute MI and DM type 2 were detected in the form of atrial fibrillation in 4 cases, extrasystolic arrhythmia was seen in 6 patients of this group. Patients with isolated acute MI, extrasystolic arrhythmia was found at the same number of patients (6 cases). Atrial fibrillation was observed in 3 patients with acute MI. Conduction disturbances were detected in the form of AV block of different degree, bundle branche block in 10 patients with comorbidity of DM type 2 and acute MI and in 12 patients with isolated acute MI.

Blood glucose concentration was determined by glucose oxidase method. Insulin level was determined by immunoassay using test system EIA-2935, Insulin ELISA (Germany). Serum interleukin-22 level was established by immunoassay using the MRP8/14 ELISA KIT (Switzerland) test system.

The level of carbohydrate metabolism disruption was assessed by calculating homeostasis model assessment (HOMA), QUICKI, Caro indices of insulin resistance by the following mathematical formulas:

$$\text{HOMA Index: } (G_0 \times I_0) / 22.5$$

$$\text{Caro Index} = G_0 / I_0$$

where I_0 is fasting insulinemia (mcU/ml),
G_0 is fasting glycemia (mmol/l).

$$\text{QUICKI Index} = 1 / [\log (I_0) + \log (G_0)]$$

where G_0 is fasting glycemia (mg/dl),
I_0 is fasting insulinemia (mcU/ml).

The value of the insulin level ≥ 12 mcU/ml; HOMA index ≥ 2.6; QUICKI ≤ 0.331; Caro Index ≤ 0.33 indicates insulin resistance. Troponin I in serum was measured by ELISA.

Statistical analysis was performed using BIOSTAT 3.4 statistical software. Estimation of the difference between the groups in the distribution of close to normal was carried out by parametric methods using Fisher's test (F). The presence of interlinks between the studied indices was determined by Pearson's correlation (R). The differences were considered statistically significant in $p < 0.05$.

Table

Indices of carbohydrate metabolism, interleukin-22 in patients with acute MI in the presence or absence of DM type 2

Index, unit of Measurement	Patients with acute MI with DM type 2 n = 64	Patients with isolated Acute MI n = 46
Interleukin-22, ng/ml	26.58 ± 6.61 p < 0.01	49.73 ± 4.08 p < 0.01
Troponin I, ng/ml	5.43 ± 1.26 p > 0.05	3.96 ± 4.21 p > 0.05
Insulin, μlU / ml	29.57 ± 0.67 p > 12	2.46 ± 0.25 p < 0.01
Glucose, mmol/L	11.17 ± 0.56 p < 0.01	4.62 ± 0.16 p < 0.01
HOMA index	12.61 ± 0.87 p > 2.6	0.45 ± 0.05 p < 0.001
Caro index	0.32 ± 0.02 p < 0.33	2.49 ± 0.61 p < 0.001
QUICKI index	0.31 ± 0.005 p < 0.34	1.17 ± 0.12 p < 0.001

RESULTS AND THEIR DISCUSSION

Patients with acute MI in combination with DM type 2 were found to have a significant increasing of interleukin-22 by 25.9 % ($p < 0.001$) compared to patients with acute MI without DM type 2. The results are presented in Table.

As for the level of insulin in serum, the concentration of this parameter in patients with combined course of acute MI and DM 2 type significantly exceeded those in patients with acute MI without DM type 2.

Assessment of carbohydrate metabolism revealed changes in the form of statistically significant increase in the concentration of fasting glucose in patients with acute MI in combination with DM type 2 by 41.8 % when compared to patients with isolated acute MI.

In patients with acute MI and DM type 2 level of index HOMA was more than 2.6, index Caro < 0.33 and index QUICKI 0.0331. Insulin, index HOMA, Caro and QUICKI showed process of insulin resistance in patients with acute MI and DM type 2. Patients with isolated acute MI had insulin resistance indexes at normal range.

The level of HOMA index in patients with acute MI and concomitant DM type 2 when compared to patients with isolated acute MI was also higher (differences are statistically significant, $p < 0.01$). Caro index, reflecting the sensitivity of tissues to insulin, showed changes in the form of reduction of this parameter in comorbidity of acute MI and DM type 2 compared to patients with isolated acute MI. Similar changes were obtained in QUICKI index, which was significantly lower in patients of the main group with comorbidity of acute MI and DM type 2.

Concentration of troponin I did not show reliable differences, the level of this parameter in patients with acute MI and DM type 2 completely corresponded to that in patients with isolated acute MI.

The presence and character of the links between the studied parameters were assessed by correlation. Patients with acute MI in the presence of DM type 2 were found to have a negative correlation between serum interleukin-22 and insulinemia ($R = -0.32$; $p < 0.05$), HOMA index ($R = -0.43$; $p < 0.05$) and level of fasting glycemia ($R = -0.63$; $p < 0.05$). The obtained results indicate that changes of anti-inflammatory indicator interleukin-22 is accompanied by changes of carbohydrate homeostasis in the form of an increase in the insulin resistance degree in patients with acute MI and DM type 2.

The results obtained in our study do not contradict the data of other authors of the world medical community. Thus, the team of authors

led by Ortega F. provided information on a relationship between interleukin-22 with chronic inflammation and metabolic disorders, such as a decrease in tissue sensitivity to insulin [7]. In addition, there are data [8] regarding an association of the concentration of circulating interleukin-22 with excessive body weight and obesity.

The positive effect of IL-22 on the state of carbohydrates is shown in the work Sumaira Z Hasnain [9] due to the reduction of oxidative stress in pancreatic islet cells in obesity, along with the activation of the expression of antioxidant system genes. In addition, high levels of IL-22 resulted in decreased insulin secretion, which was equivalent to levels of insulin in the absence of metabolic abnormalities. That is, IL-22 can be considered as a mediator regulating insulin secretion and oxidative stress.

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M. I. Zhuravleva[1], N. G. Ryndina[1], I. P. Dunaeva[2]

[1] Kharkiv National Medical University, Kharkiv, Ukraine;
[2] Kharkiv Postgraduate Medical Academy, Kharkiv, Ukraine
mzhuravleva2017@gmail.com

In patients with acute myocardial infarction in combination with type 2 diabetes mellitus, a significant increase in the level of interleukin-22 was found by 25.9% ($p < 0.001$) compared with patients with AMI without type 2 diabetes.

Analysis of carbohydrate metabolism revealed changes in the form of a possible increase in fasting glucose concentration in patients with AMI in combination with type 2 diabetes by 41.8 % ($p < 0.001$) when compared with patients with isolated AMI.

The negative correlation was found between serum interleukin-22 and insulinemia ($R = –0.32$, $p < 0.05$), HOMA index ($R = –0.43$; $p < 0.05$) and the level of fasting glucose ($R = –0.63$; $p < 0.05$).

The results indicate that the increase in autoimmune activity due to the anti-inflammatory parameter of interleukin-22 is accompanied by an increase in the degree of insulin resistance in patients with AMI and type 2 diabetes.

Keywords: diabetes mellitus, acute myocardial infarction, interleukin-22, insulin resistance.

ВЗАЄМОЗВ'ЯЗОК ПАРАМЕТРІВ ВУГЛЕВОДНОГО ОБМІНУ ТА ІНТЕРЛЕЙКІНУ-22 У ХВОРИХ НА ГОСТРИЙ ІНФАРКТ МІОКАРДА З УРАХУВАННЯМ КОМОРБІДНОГО ЦУКРОВОГО ДІАБЕТУ 2 ТИПУ.

Журавльова М. І.[1], Риндіна Н. Г.[1], Дунаєва І. П.[2]

[1] Харківський національний медичний університет, м. Харків, Україна;
[2] Харківська медична академія післядипломної освіти, м. Харків, Україна
mzhuravleva2017@gmail.com

У хворих на гострий інфаркт міокарда у поєднанні з цукровим діабетом 2 типу знайдено достовірне підвищення рівня інтерлейкіну-22 на 25.9% ($p < 0,001$) у порівнянні з хворими на ГІМ без ЦД 2 типу.

Аналіз показників вуглеводного обміну виявив зміни у вигляді вірогідного зростання концентрації глюкози натще, у хворих на ГІМ у поєднанні з ЦД 2 типу на 41,8% ($p < 0,001$) при зіставленні з хворими на ізольований ГІМ.

Знайдено зворотній кореляційний зв'язок між інтерлейкіном-22 сироватки крові та інсулінемією ($R = –0.32$; $p < 0,05$), індексом HOMA ($R = –0.43$; $p < 0,05$) та рівнем глікемії натще ($R = –0.63$; $p < 0,05$).

Отримані результати свідчать про те, що зростання імунозапальної активності за рахунок протизапального параметра інтерлейкіну-22 супроводжується зростанням ступеня інсулінорезистентності у хворих на ГІМ та ЦД 2 типу.

Ключові слова: цукровий діабет, гострий інфаркт міокарду, інтерлейкін-22, інсулінорезистентність.

ВЗАИМОСВЯЗЬ ПАРАМЕТРОВ УГЛЕВОДНОГО ОБМЕНА И ИНТЕРЛЕЙКИНА-22 У БОЛЬНЫХ ОСТРЫМ ИНФАРКТОМ МИОКАРДА С КОМОРБИДНЫМ САХАРНЫМ ДИАБЕТОМ 2 ТИПА.

Журавлева М. И.[1], Рындина Н. Г.[1], Дунаева И. П.[2]

[1] Харьковский национальный медицинский университет, г. Харьков, Украина;
[2] Харьковская медицинская академия последипломного образования, г. Харьков, Украина
mzhuravleva2017@gmail.com

У больных с острым инфарктом миокарда в сочетании с сахарным диабетом 2 типа найдено достоверное повышение уровня интерлейкина-22 на 25,9 % ($p < 0,001$) по сравнению с больными ОИМ без СД 2 типа.

Анализ показателей углеводного обмена обнаружил изменения в виде возможного роста концентрации глюкозы натощак у больных ОИМ в сочетании с СД 2 типа на 41,8 % ($p < 0,001$) при сопоставлении с больными изолированным ОИМ.

Найдена обратная корреляционная связь между интерлейкином-22 сыворотки крови и инсулинемии ($R = –0.32$, $p < 0,05$), индексом HOMA ($R = –0.43$; $p < 0,05$) и уровнем гликемии натощак ($R = –0.63$; $p < 0,05$).

Полученные результаты свидетельствуют о том, что рост аутоиммунной активности за счет противовоспалительного параметра интерлейкина-22 сопровождается ростом степени инсулинорезистентности у больных с ОИМ и СД 2 типа.

Ключевые слова: сахарный диабет, острый инфаркт миокарда, интерлейкин-22, инсулинорезистентность.