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# FEATURES OF CHANGES IN INSULIN-LIKE GROWTH FACTOR-1 IN PATIENTS WITH CORONARY HEART DISEASE IN COMBINATION WITH TYPE 2 DIABETES MELLITUS

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*The purpose of the study* was to study the level of insulin-like growth factor-1 in the blood of patients with coronary heart disease with type 2 diabetes mellitus, in patients with coronary heart disease without type 2 diabetes mellitus and in almost healthy individuals.

*Materials and methods.* We examined 73 patients (30 men, 43 women) with coronary heart disease aged 49 to 75 years (mean age –58.3 ± 1.8). All patients were treated in the therapeutic department of the prof. A. A. Shalimov Kharkiv Municipal Clinical Hospital No. 2. Examination of patients was performed using clinical, laboratory and instrumental methods. All patients had ischemic heart disease in the form of stable angina pectoris of I – II functional classes, I functional class was diagnosed in 27 patients, II – in 46 patients. From the group of examined patients in 36 patients the disease was accompanied by concomitant type 2 diabetes mellitus (group 1). Mild diabetes was detected in 15 people, moderate – in 21 patients. 37 patients did not have diabetes mellitus (group 2). Diagnosis of diabetes was based on the criteria of the World Diabetes Federation. The control group consisted of 20 people of the same age, who according to the results of clinical and additional studies were found to be practically healthy. Determination of insulin-like growth factor-1 and insulin levels in the blood was performed by enzyme-linked immunosorbent assay on a «Humareader photometer-analyzer». DRG kits (USA) were used to study the level of insulin-like growth factor-1.

*Results and discussion.* It was found that patients with coronary heart disease with concomitant type 2 diabetes had higher levels in serum triglycerides ($p < 0.05$) and very low density lipoprotein cholesterol ($p < 0.05$) compared with patients with coronary heart disease without diabetes. Patients with coronary heart disease and concomitant type 2 diabetes showed a statistically significant increase in blood insulin levels compared with patients with coronary heart disease without diabetes. The results of the analysis of insulin-like growth factor-1 showed that the content of insulin-like growth factor-1 in the blood of patients with coronary heart disease and type 2 diabetes was probably lower compared with patients with coronary heart disease without diabetes and with practically healthy individuals ($p < 0.01$). At the same time, the levels of insulin-like growth factor-1 in almost healthy individuals and patients with coronary heart disease without type 2 diabetes did not differ significantly.

*Conclusion.* In patients with coronary heart disease with type 2 diabetes the level of insulin-like growth factor-1 is probably lower than in patients with coronary heart disease without diabetes and almost healthy individuals. Given the antiapoptotic, antiatherosclerotic, anabolic properties of this growth factor, it can be argued that the development of relative insulin-like growth factor-1 deficiency in the combination of coronary heart disease with type 2 diabetes causes a significant increase in the risk of cardiovascular complications in this category of patients.

**Keywords:** insulin-like growth factor-1, indicators of lipid metabolism, coronary heart disease, type 2 diabetes mellitus.

**Connection of work with scientific programs, plans, topics.** The work was performed within the framework of the topic «Cellular and molecular mechanisms of development and correction of pathological conditions», state registration No. 0115U000966.

**Introduction.** Coronary heart disease (CHD) is one of the main causes of high mortality and disability in Ukraine and many countries around the world. It is a serious medical and economic problem, the solution of which depends on understanding the mechanisms of disease development, the ability to predict complications and the results of the effectiveness of therapy [1]. According to official statistics, the prevalence of coronary heart disease among the adult population of Ukraine is about 25%, including among people of working age – about 10% [1, 2]. In Ukraine the adult mortality rate from cardiovascular pathology among all causes of death is 66.5%. Moreover, in the majority of deaths from cardiovascular diseases (68.1%) the cause of death is coronary heart disease [3].

The problem of combining coronary heart disease and type 2 diabetes mellitus is also one of the most important for modern medical science [4]. These diseases pose an increased risk of developing cardiovascular complications [5, 6]. The urgency of this problem is due not only to the steady increase in the prevalence of this nosological combination, but also to the fact that coronary heart disease and type

2 diabetes mellitus are aggravating diseases because they affect common target organs [7, 8, 9]. The combination of CHD and type 2 diabetes mellitus significantly increases the risk of macrovascular complications (stroke, myocardial infarction, sudden death, peripheral vascular atherosclerosis) and microvascular (nephropathy, retinopathy, etc.) [10, 11, 12]. Currently, research is underway to study the role of new biologically active substances that affect carbohydrate and fat metabolism. Such substances include insulin-like growth factor-1 (IGF-1), which is one of the representatives of polypeptide growth factors, close in its physiological effects to insulin, which plays an important role in regulating the structure and function of myocardium and blood vessels [13, 14, 15]. There are data on the participation of IGF-1 in the processes of cardiovascular hypertrophy [16]. A number of authors attribute IGF-1 to prognostically significant biological markers of heart failure [9, 17]. Excessive secretion of this growth factor has been shown to be associated with an increased risk of developing malignancies, and a significant reduction in this growth factor in the blood accelerates the mechanisms of premature aging and increases mortality [14, 18, 19]. To date, the pathogenetic role of IGF-1 in the development of cardiovascular lesions, including hypertension, type 2 diabetes mellitus and their combination remains unclear and requires further study.

**The purpose of the study** was to study the level of IGF-1 in the blood of patients with coronary heart disease with type 2 diabetes mellitus, in patients with coronary heart disease without type 2 diabetes mellitus and in almost healthy individuals.

**Materials and methods.** We examined 73 patients (30 men, 43 women) with CHD aged 49 to 75 years (mean age – 58.3 ± 1.8). All patients were treated in the therapeutic department of the Prof. A. A. Shalimov Kharkiv Municipal Clinical Hospital No. 2. Examination of patients was performed using clinical, laboratory and instrumental methods. All patients had ischemic heart disease in the form of stable angina pectoris of I – II functional classes, I functional class was diagnosed in 27 patients, II – in 46 patients. From the group of examined patients in 36 patients the disease was accompanied by concomitant type 2 diabetes mellitus (group 1). Mild diabetes was detected in 15 people, moderate – in 21 patients. 37 patients did not have diabetes mellitus (group 2). Diagnosis of diabetes was based on the criteria of the World Diabetes Federation [20].

All experiments were conducted in accordance with the Council of Europe Convention “On the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine Application of Biological and Medicine Achievements (ETS No. 164)” dated 04.04.1997, and the Helsinki Declaration of the World Medical Association (2008). Each study patient signed an informed consent to participate in the study and all measures to ensure anonymity of patients were taken.

The duration of CHD was from 4 to 15 years, the duration of type 2 diabetes mellitus – from 5 to 15 years. Hypertension was detected in 20 patients, which was within 1-2 degrees (according to the criteria of the Ukrainian Association of Cardiologists, 2008).

The study did not include patients with CHD of III functional class, grade III hypertension, symptomatic hypertension, type 1 diabetes mellitus, patients with severe kidney and liver damage.

The control group consisted of 20 people of the same age, who according to the results of clinical and additional studies were found to be practically healthy.

Blood lipid spectrum was determined by enzymatic method on a biochemical analyzer «Humareazer 2000» (Germany). The level of glycemia was determined by glucose oxidase method on a biochemical analyzer «Humareazer 2000» (Germany).

Determination of IGF-1 and insulin levels in the blood was performed by enzyme-linked immunosorbent assay on a «Humareader photometer-analyzer». DRG kits (USA) were used to study the level of IGF-1.

Statistical processing of the obtained data was performed using the general-purpose data processing software package Statistica for Windows version 6.0.

**Research results.** Groups of patients with coronary heart disease with type 2 diabetes and without it were compared by age, sex, duration and severity of CHD. The analysis of the complex of basic anthropometric, clinical-anamnestic and hemodynamic indicators revealed that the groups of patients with CHD with type 2 diabetes and CHD without diabetes did not differ statistically significantly in such indicators as height, weight, overweight and obesity, levels of systolic and diastolic blood pressure. There was a probable increase in baseline heart rate in patients with CHD on the background of type 2 diabetes (88.7 (1.08) beats per minute) compared with patients with CHD without diabetes (80.8 (1.54) beats per minute), $p < 0.05$). In the group of men with CHD, regardless of the presence or absence of diabetes, the initial values of heart rate did not differ significantly – 86.7 (1.69) and 84.5 (2.14) beats per minute ($p > 0.05$), and in women with CHD and concomitant type 2 diabetes, this figure was significantly higher than in women with CHD without diabetes – 89.5 (1.53) and 81.2 (1.43) beats per minute ($p < 0.0001$). The examined groups of patients with CHD on the background of type 2 diabetes and without it had some differences in lipid metabolism. The overall incidence of dyslipoproteinemia (DLP) in both groups of patients probably did not differ: in the group of patients with coronary heart disease on the background of type 2 diabetes, DLP

was detected in 26 patients (72%), and in the group of patients with coronary heart disease without diabetes – in 30 people (81%), p >0.05. The incidence of isolated hypercholesterolemia was significantly higher in patients with CHD without diabetes compared with patients with CHD with type 2 diabetes (p <0.01). At the same time, the frequency of isolated hypertriglyceridemia in patients with CHD in combination with type 2 diabetes and in patients with CHD disease without diabetes did not differ significantly (p> 0.05).

As a result of the analysis of the average levels of lipid metabolism, it was found that patients with CHD with concomitant type 2 diabetes had higher levels in serum triglycerides (p <0.05) and very low density lipoprotein cholesterol (p <0.05) compared with patients with CHD without diabetes. Other indicators of lipid metabolism in both groups of patients did not differ significantly. Patients with CHD and concomitant type 2 diabetes showed a statistically significant increase in blood insulin levels compared with patients with CHD without diabetes – 17.2 (1.92) and 10.6 (1.24) μM O / ml, respectively (p <0.05).

Hyperinsulinemia (level of IGF-1 in the blood more than 25 μIU / ml) was detected in 23 (64%) patients with CHD and concomitant type 2 diabetes. When analyzing the content of insulin in the blood separately in men and women, it was found that in men with CHD and type 2 diabetes and in men with CHD without diabetes blood insulin levels did not differ significantly – 13.5 (1.43) and 11.8 (1.73) μIU / ml, p> 0.05. At the same time, in women with coronary heart disease and concomitant type 2 diabetes, blood insulin levels were significantly higher (19.9 (3.69) μIU / ml) than in women with coronary heart disease without diabetes (11.0 (1.68) μIU / ml), p <0.05). The results of the analysis of IGF-1 showed that the content of IGF-1 in the blood of patients with CHD and type 2 diabetes (129.5 (97.1 ÷ 157.1) ng / ml) was probably lower compared with patients with CHD without diabetes (188.0 (157.5 ÷ 199.3) ng / ml) and with practically healthy individuals (172.7 (146.0 ÷ 186.0) ng / ml) (p <0.01). At the same time, the levels of IGF in almost healthy individuals and patients with CHD without type 2 diabetes did not differ significantly. In the distribution of patients according to body mass index (BMI), a probable relationship was found between the content of IGF-1 in the blood of patients of both groups and the presence of excess body weight (EBW) or obesity. As BMI increased, IGF-1 levels decreased in both patients with CHD with concomitant type 2 diabetes and patients with CHD without diabetes. Thus, in patients with CHD with type 2 diabetes and normal body weight, the level of IGF-1 was 158.4 (145.2 ÷ 311.3) ng / ml, in patients with EBW – 132.6 (130.2 ÷ 172.3) ng / ml, with Stage I obesity – 124.6 (93.2 ÷ 136.4) ng / ml, with Stage II obesity – 120.3 (117.7 ÷ 142.5) ng / ml, with Stage III obesity – 70.9 (66.5 ÷ 157.1) ng / ml (p = 0.0233). In the group of patients with CHD without diabetes, the level of IGF-1 in the blood of patients with normal body weight was 168.9 (142.2 ÷ 311.3) ng / ml, in patients with EBW – 152.4 (150.7 ÷ 172, 9) ng / ml, with Stage I obesity – 142.7 (132.0 ÷ 155.5) ng / ml, with Stage II obesity – 95.4 (53.3 ÷ 135.8) ng / ml, with Stage III obesity – 86.6 (51.4 ÷ 130.2) ng / ml (p = 0.0026). In the distribution of patients with coronary heart disease and diabetes depending on the presence or absence of hyperinsulinemia, it was found that in patients with high blood insulin levels, the level of IGF-1 was significantly higher (143.4 (130.1 ÷ 322.9) ng / ml) compared with patients with normal bood insulin (65.6 (64.8 ÷ 112.7) ng / ml, (p <0.01).

**Discussion.** The data obtained as a result of our work correlate with the results of a number of other studies. The role of IGF-1 in the development of cardiovascular disease continues to be actively studied. Thus, the results of numerous studies suggest that low levels of circulating IGF-1 significantly increase the risk of cardiovascular and cerebrovascular diseases [21, 22, 23]. Insulin-like growth factor-1 is an important regulator of cell growth, differentiation and apoptosis. IGF-I deficiency is known to be associated with premature atherosclerosis and elevated cardiovascular disease mortality. Low IGF-I levels have been shown to be a risk factor for myocardial infarction and other manifestations of coronary heart disease [24, 25, 26]. Insulin-like growth factor-I is homologous to proinsulin and possesses glucose reducing activity. The association between the level of IGF-I and diabetes has been highlighted. Type 2 diabetes mellitus is associated with lower levels of IGF-I regardless to the presence or absence of obesity. Low levels of IGF-1 correlate with an increased risk of vascular complications with diabetes [27, 28]. The antiatherogenic effects of IGF-1 in ApoE-deficient mice have been established [29]. In addition, the content of this growth factor in the blood was negatively correlated with the level of systolic blood pressure, cholesterol levels of high-density lipoproteins and glomerular filtration rate [30]. Currently, insulin and IGF-1 are considered as a single signaling system that regulates not only metabolic processes but also the processes of cell growth and differentiation [31].

Thus, based on the literature and the results of this work, we can conclude that the development of relative deficiency of IGF-1 in patients with CHD with type 2 diabetes can be used as a very informative marker of unfavorable prognosis of these diseases.

**Conclusions:**

1. In patients with coronary heart disease with type 2 diabetes the level of IGF-1 is probably lower than in patients with coronary heart disease without diabetes and almost healthy

individuals. Given the antiapoptotic, antiatherosclerotic, anabolic properties of this growth factor, it can be argued that the development of relative IGF-1 deficiency in the combination of coronary heart disease with type 2 diabetes causes a significant increase in the risk of cardiovascular complications in this category of patients.

2. In order to increase the informativeness of the assessment of the risk of cardiovascular complications and the nature of coronary heart disease in patients with type 2 diabetes, the complex of examination should include determination of serum levels of growth factor IGF-1.

**Perspectives of further research.** Further study of the importance of IGF-1 in the pathogenesis of coronary heart disease and diabetes is promising and relevant. It is also important to study the relationship between IGF-1 levels in patients' blood and morpho-functional parameters of the heart and blood vessels.

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**ОСОБЛИВОСТІ ЗМІН ІНСУЛІНОПОДІБНОГО ФАКТОРУ РОСТУ-1 У ХВОРИХ НА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ У ПОЄДНАННІ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ**

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**Резюме.** *Метою дослідження* було вивчення рівнів інсуліноподібний фактор росту-1 у крові хворих на ішемічну хворобу серця на фоні цукрового діабету 2 типу та без нього , а також у практично здорових осіб.

*Матеріал та методи.* Було обстежено 73 хворих на ішемічну хворобу серця в віці від 49 до 75 років (середній вік – 58,3 ± 1,8). Усі хворі знаходились на лікуванні в терапевтичному відділенні 2-ї міської клінічної лікарні міста Харкова. Обсяг обстеження охоплював загальноприйняті методи клінічного, лабораторного й інструментального обстеження. У всіх пацієнтів виявлена у вигляді стабільної стенокардії напруги I – II функціональних класів. З групи обстежених хворих у 36 пацієнтів захворювання супроводжувалось супутнім цукровим діабетом 2 типу (1 група ). 37 пацієнтів не мали цукрового діабету ( 2 група ). Діагностика цукрового діабету 2 типу проводилась на основі критеріїв Всесвітньої федерації цукрового діабету.

*Результати.* Було встановлено, що хворі 1 групи відрізнялись більш високими рівнями в сироватці крові тригліцеридів ($p < 0,05$) та холестерину ліпопротеїдів дуже низької щільності ($p < 0,05$) у порівнянні з хворими 2 групи. Також у хворих 1 групи виявлено статистично достовірне підвищення рівня інсуліну у крові у порівнянні з хворими 2 групи. Встановлено вірогідне зниження рівня інсуліноподібний фактор росту-1 у крові хворих на ішемічну хворобу серця на фоні цукрового діабету 2 типу в порівнянні з хворими на ішемічну хворобу серця без цукрового діабету.

*Висновки.* Враховуючи антиапоптотичні, антиатеросклеротичні, анаболічні властивості цього ростового фактору, можна стверджувати, що розвиток відносного дефіциту інсуліноподібний фактор росту-1 при поєднанні ішемічної хвороби серця з цукровим діабетом 2 типу обумовлює значне підвищення ризику виникнення кардіоваскулярних ускладнень у даної категорії хворих. Перспективне подальше вивчення значення інсуліноподібний фактор росту-1 у патогенезі ішемічної хвороби серця та цукрового діабету, а також взаємозв'язків між рівнем цього фактору у крові та морфо-функціональними показниками серця та судин.

**Ключові слова:** інсуліноподібний фактор росту-1, показники ліпідного обміну, ішемічна хвороба серця, цукровий діабет 2 типу.

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