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ROLE OF GLYCAEMIA LEVEL IN THE DEVELOPMENT OF INTERSTITIAL COLLAGEN IN PATIENTS WITH CORONARY HEART DISEASE AND TYPE 2 DIABETES

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A role of blood glucose levels in the development of interstitial collagen has been studied in 84 patients (53 women and 31 men, average age 60 ± 2.4 years) with coronary heart disease (CHD). All patients were divided into twocomparable groups: a study group including patients with coronary heart disease andtype 2 diabetes mellitus (DM) and a control group consisting of patients with coronary heart disease without DM. All patients received standard medical therapy as recommended by the European Society of Cardiology. The level of blood glucose in both groups was assessed by the standard technique, a degree of interstitial collagen volume fraction (ICVF) was measured using the formula of J. Shirani et al. The data were processed by parametric and nonparametric statistical methods. It has been proved that hyperglycemia in type 2 diabetes contributes to the development of ICVF, the degree of which increases with the rise of blood glucose level. A high level ofICVF in patients with coronary heart disease and diabetes type 2 can be a predictor of myocardial dyssynchrony development and heart failure progression, therefore, a close monitoring and timely correction of changes of blood glucose levelsare recommended to prevent the complication development. ICVF evaluation should become a routine diagnostic method in all patients with type 2 diabetes.

KEY WORDS: interstitial collagen volume fraction, type 2 diabetes mellitus, coronary heart disease

РОЛЬ РІВНЯ ГЛІКЕМІЇ У РОЗВИТКУ ІНТЕРСТИЦІАЛЬНОГО КОЛАГЕНУ У ПАЦІЄНТІВ НА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ ТА ЦУКРОВІЙ ДІАБЕТ 2-ГО ТИПУ

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На 84 пацієнтах (53 жінок і 31 чоловіків, середній вік 60 ± 2,4 років) на ішемічну хворобу серця (ІХС) вивчена роль рівня глікемії у розвитку інтерстиціального колагену. Всі пацієнти були розділені на групу спостереження, де були пацієнти з ІХС та цукровим діабетом (ЦД) 2 типу та групу контролю - пацієнти з ІХС без ЦД. Всі пацієнти отримували стандартну медикаментозну терапію відповідно до рекомендацій European Society of Cardiology. Рівень глікемії в обох групах оцінювався згідно загальноприйнятої методики, ступінь наявності об'ємної фракції інтерстиціального колагену (ОФІК) вимірювали за допомогою формули J. Shirani та співавторів. Дані обробляли методами параметричної та непараметричної статистики. Доведено, що гіперглікемія при ЦД 2 типу сприяє розвитку ОФІК, ступінь наявності якої зростає зі зростанням рівня глікемії. Високий рівень ОФІК у пацієнтів з ІХС і ЦД 2-го типу може бути предиктором розвитку диссинхроній міокарда та прогресування ХСН, тому рекомендовано ретельний контроль і своєчасна корекція рівня глікемії для попередження розвитку ускладнень. Визначення ОФІК має стати рутинним методом діагностики у всіх пацієнтів на ЦД 2-го типу.

КЛЮЧОВІ СЛОВА: об'ємна фракція інтерстиціального колагену, цукровий діабет 2-го типу, ішемічна хвороба серця

РОЛЬ УРОВНЯ ГЛИКЕМИИ В РАЗВИТИИ ИНТЕРСТИЦИАЛЬНОГО КОЛЛАГЕНА У ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА И САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА

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На 84пациентах (53 женщин и 31 мужчин, средний возраст 60 ± 2,4 лет) с ишемической болезнью сердца (ИБС) изучена роль уровня гликемии в развитии интерстициального коллагена. Все пациенты были разделены на сопоставимые группу наблюдения, где были пациенты с ИБС и сахарным

диабетом (СД) 2 типа и группу контроля - пациенты с ИБС без СД. Все пациенты получали стандартную медикаментозную терапию согласно рекомендациям EuropeanSocietyofCardiology. Уровень гликемии в обеих группах оценивался по общепринятой методике, степень выраженности объемной фракции интерстициального коллагена (ОФИК) измеряли с помощью формулы J. Shirani и соавторов. Данные обрабатывались методами параметрической и непараметрической статистики. Доказано, что гипергликемия при СД 2 типа способствует развитию ОФИК, степень выраженности которой возрастает с ростом уровня гликемии. Высокий уровень ОФИК у пациентов с ИБС и СД 2-го типа может быть предиктором развития диссинхроний миокарда и прогрессирования ХСН, поэтому рекомендуется требуется тщательный контроль и своевременная коррекция уровня гликемии для предупреждения развития осложнений. Определение ОФИК должно стать рутинным методом диагностики у всех пациентов с СД 2-го типа.

КЛЮЧЕВЫЕ СЛОВА: объемная фракция интерстициального коллагена, сахарный диабет 2-го типа, ишемическая болезнь сердца

INTRODUCTION

Coronary heart disease (CHD) remains the leading cause of death and disability among the working-age population. According to P. Heidenreichet al., by 2030 the prevalence of coronary heart disease will increase by 9.3 %, which will be associatedwith the direct medical cost grow by 198 % compared to year 2010 [1]. Concomitant type 2 diabetes significantly increases the severity of patient'sconditiondue to formation ofmyocardial dyssynchrony, progression of heart failure (HF) and a number of other pathological conditions [2]. The cause is hyperglycemia, which triggers the activation of the systemic immune inflammation and mediates the degradation of extracellular matrix and formation of myocardial fibrosis [2-4] with the increase of interstitial collagen volume fraction (ICVF) [5-6].

However, there are no data in the literature on the dependence of glycaemia level from the ICVF levels in patients with coronary heart disease and type 2 diabetes, which makes this study relevant.

Current work was performed according to the scientific research planof the Chair of Therapy and Nephrology of Kharkiv Medical Academy of Postgraduate Education «Cardiac and neurohumoral mechanisms of chronic heart failure in patients with concomitant diseases» (№ DR 0111U003579).

OBJECTIVE

To study the influence of glycaemia on the formation of interstitial collagen in patients with coronary heart disease and type 2 diabetes mellitus.

MATERIALS AND METHODS

57 patients (42 women (73 %), 15 men (27 %)) of average age 63 + 2.4 years were enrolled in this study. The enrollment criteriawere coronary heart disease and type 2 diabetes, chronic heart failure of I-III Functional Class according to NYHA with preserved systolic function (ejection fraction > 55 %). Patients were excluded from the analysis in case they had acute coronary disease or chronic renal failure.

The control group consisted of patients with coronary heart disease without DM – 27 participants (16 men (59 %), 11 women (41 %)) of average age 57 + 2.3 years.

The diagnosis of ischemic heart disease was established according to the recommendations of European Society of Cardiology (ESC) on the basis of anamnesis, results of clinical and laboratory examinations, specificfeatures on the ECG, echocardiography [7-8].

The diagnosis of type 2 diabetes was establishe daccording to the recommendations of American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) considering the diagnostic criteria for type 2 diabetes.

According to the recommendations of European Society of Cardiology [9-10], all patients with ischemic heart diseasewere prescribed ACE inhibitors Ramipril 10 mg, β-blocker Nebivolol 5 mg, antiplatelet Acetylsalicylic acid 75 mg, potassium-sparing diuretic Eplerenone50 mg, HMG-CoA reductase inhibitor Rosuvastatin 10 mg, and metabolic drug Trimetazidine 60 mg.

Patients with type 2 diabetes mellitus additionally received oral hypoglycemic agents: Metformin 1500 mg and Glimepiride 4 mg as a daily doseregarding the level of blood glucose. Plasma glucose levels were measured in the fasted state after an 8-14-hour

period of overnight fast. Glucose concentration in the capillary whole blood was measured by enzymatic method using standard kits.

The degree of interstitial collagen volume fraction was calculatedfrom the formula of J. Shirani et al [8]: ICVF (%) = $(1\text{-}1{,}3*\frac{totalQRS(mm)\,x\,height\,(m)}{LVMM\,(g)})*100$, wherein the normal level of ICVF was set within the range of 1 % and 2 %.

A 12-lead electrocardiogram registration was performed using the apparatus CardioLab (STC «HAI – Medica», Kharkov, Ukraine) according to the standard calculation procedures and guidelines.

LVMMI was calculated as the ratio of the left ventricular myocardial mass (LVMM) to body surface area, the LVMM was evaluated using the echocardiography (Echo-CG) on the following equipment: Siemens Ac USONSC 2000 (Siemens Medical Solution, Mountain View, USA) and ULTIMA PRO-30 («Radmir», Ukraine) applying a 3.5 MHz-probe with synchronous ECG registration in four cardiac cycles from the standard approaches in accordance with conventional procedure described in the guidelines of American Society of Echocardiography.

After database formation the data were processed using Microsoft Excel and program «Statistica». Parametric (M, sd) and non-parametric (absolute and relative - proportions (p, %) and criterion χ^2) criteria were used for statistical evaluation of the results. The chance of differences between groups was calculated by nonparametric Mann-Whitney U-test criterion. The expected result was evaluated by the confidence level $p < 0.01$ and $p < 0.05$.

RESULTS AND DISCUSSION

The figure shows the dependence of the degree of ICVF from blood glucose levels in patients with coronary heart disease.

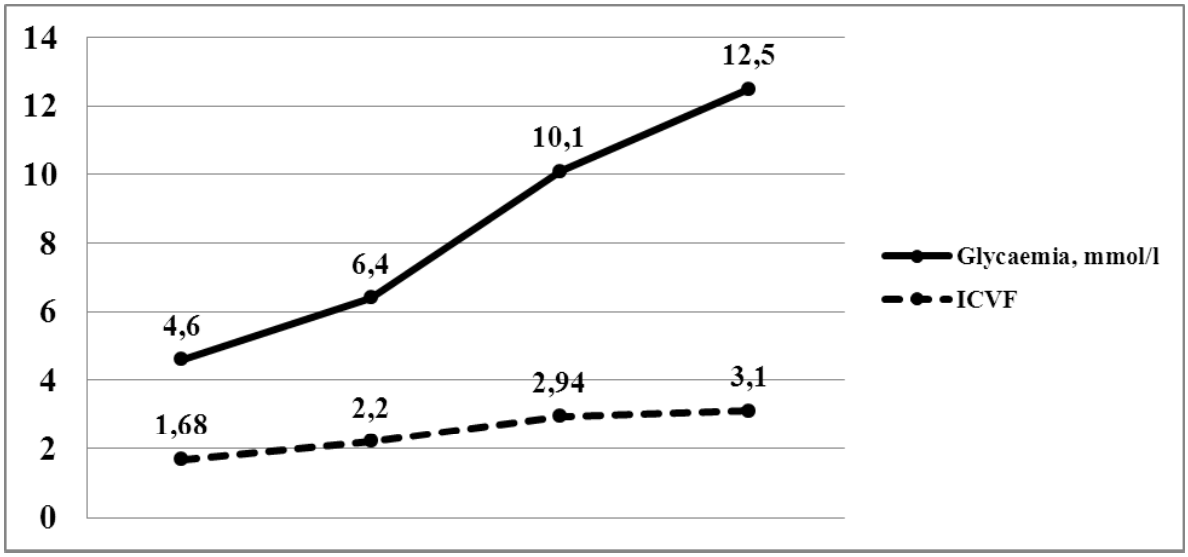

Fig. The effect of glycaemia on the level of ICVF in both groups of patients

In patients with a glucose concentration of 4.6 ± 1.2 mmol/l in the capillary whole blood in fasted state, a ICVF level remained within normal limits (1,68 ± 0.3 %), while the increase of glucose concentration to 6.4 ± 1,3 mmol/l was associated with ICVF level elevation to 2.2 + 0.51 %. At the blood glucose level of 10.1 + 1.16 mmol/l the ICVF level increased to 2.94 + 0.83 %.

These data confirm that hyperglycemia provokes the ICVF level elevation that, in turn, is a poor prognostic sign for coronary heart disease, heart failure and other related diseases.

The present study underscores the relevance of glycaemia control in patients with type 2 diabetes and timely determination of ICVF that will allow to prevent the occurrence of myocardial dyssynchrony and progression of heart failure [11-12].

CONCLUSIONS

1. The hyperglycemia in patients with type 2 diabetes contributes to the development of interstitial collagen volume fraction.

2. The study showed a significant increase of the level of interstitial collagen volume fraction associated with the glycaemia level elevation.

3. A high level of interstitial collagen volume fraction in patients with coronary heart disease and type 2 diabetes can be a predictor of myocardial dyssynchrony development and heart failure progression.

4. A close monitoring of blood glucose levels is required in patients with type 2 diabetes to prevent the complication development.

5. Determination of ICVF should become a routine diagnostic method in all patients with diabetes and subsequent correction of changes is necessary in the early stages of type 2 diabetes.

PROSPECTS FOR FUTURE STUDIES

It is necessary to investigate further the specificfeatures of interstitial collagen changes depending on the therapy application aimed to reduce myocardial fibrosis.

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