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I. M. Fushtey, S. L. Podsevahina, O. I. Palamarchuk, O. V. Tkachenko, I. A. Kulinich
State Institution «Zaporizhzhia Medical Academy of post-graduate education Ministry of Health of Ukraine»
Zaporizhzhia, Ukraine

І. М. Фуштей, С. Л. Подсеваxіна, О. І. Паламарчук, О. В. Ткаченко, І. А. Кулініч
Державний заклад «Запорізька медична академія післядипломної освіти Міністерства охорони здоров'я України»
Запоріжжя, Україна

INFLUENCE OF ROSUVASTATIN ON VASCULAR ENDOTHELIUM FUNCTIONAL STATE AND SYSTEMIC INFLAMMATION IN PATIENTS WITH ISCHEMIC HEART DISEASE AND DIABETES MELLITUS

Вплив розувастатину на функціональний стан ендотелія судин і системне запалення у хворих ішемічної хвороби серця та цукрового діабету

Abstract

Purpose of the study. *The goal of the present study was to evaluate the effect of low dosed statins (rosuvastatin 10 mg/day) on the state of lipid and carbohydrate metabolism, insulin levels, vascular endothelial function, and markers of systemic inflammation in patients with ischemic heart disease in combination with diabetes mellitus.*

Materials and research methods. *We examined 83 patients with ischemic heart disease and type 2 diabetes mellitus aged 44 to 78 years (mean age was (56,8 ± 3,4) years). For all patients, the fasting glucose level was determined, the HOMA index, the levels of total cholesterol, low density lipoproteins, very low density lipoproteins, high density lipoproteins and triglycerides in the blood, the concentration of C-reactive protein, and the content of pro-inflammatory cytokines in the blood serum were calculated. To study the function of the endothelium, dopplerography of the brachial artery was used according to the D.S. Celermajer. All patients received IHD therapy according to generally accepted standards. The drugs were used against the background of stable oral hypoglycemic therapy. As cholesterol-lowering therapy, rosuvastatin was prescribed at a dose of 10 mg/day for 3 months.*

Results. *During the study, it was noted that in patients with coronary artery disease in combination with type 2 diabetes mellitus on the*

Реферат

Мета дослідження. *Оцінити вплив низьких доз статинів (розувастатину в дозі 10 мг/добу) на стан ліпідного та вуглеводного обмінів, рівень інсуліну, функцію ендотелію судин та маркери системного запалення у хворих на ішемічну хворобу серця (ІХС) у поєднанні з цукровим діабетом (ЦД) 2-го типу.*

Матеріали та методи дослідження. *Обстежено 83 пацієнти з ІХС та ЦД 2-го типу віком від 44 до 78 років (середній вік склав (56,8 ± 3,4) років). Всім хворим визначали рівень глюкози натще, розраховували індекс HOMA, рівні загального ХС, ліпопротеїдів низької щільності, ліпопротеїдів дуже низької щільності, ліпопротеїдів високої щільності та тригліцеридів у крові, концентрацію С-реактивного білка (СРБ), вміст у сироватці крові прозапальних цитокінів. Для вивчення функції ендотелію використовували доплерографію плечової артерії за методом Д. С. Селермайер. Всім хворим проводилася терапія ІХС відповідно до загальноприйнятих стандартів. Препарати застосовували на фоні стабільної пероральної цукрознижувальної терапії. У якості холестерин знижувальної терапії призначався розувастатин у дозі 10 мг на добу протягом 3-х місяців.*

Результати. *У ході дослідження зазначено, що у хворих на ІХС у поєднанні з ЦД 2-го типу на тлі гіпер- та дисліпідемії, підвищеного*

background of hyper- and dyslipidemia, elevated levels of insulin and glucose, dysfunction of the vascular endothelium was revealed. Vascular endothelial dysfunction had a close correlation with markers of systemic inflammation, which was exacerbated by the presence of insulin resistance. While taking rosuvastatin at a dose of 10 mg/day, in addition to a sufficient lipid-correcting effect, there was a decrease in the level of IR, activity of systemic inflammation and improvement in the function of the vascular endothelium, which ensures the correction of additional risk factors in patients with coronary artery disease in combination with type 2 diabetes.

Conclusions. *In patients with ischemic heart disease in combination with type 2 diabetes mellitus on the background of hyper- and dyslipidemia, elevated levels of insulin and glucose, dysfunction of the vascular endothelium was revealed. Dysfunction of the vascular endothelium is closely correlated with markers of systemic inflammation, which is exacerbated by the presence of insulin resistance. Against the background of taking rosuvastatin at a dose of 10 mg/day, in addition to a sufficient lipid-correcting effect, a decrease in the level of IR, activity of systemic inflammation and an improvement in the function of the vascular endothelium were noted, which ensures the correction of additional risk factors in patients with coronary artery disease in combination with type 2 diabetes.*

Keywords: *ischemic heart disease, diabetes mellitus, endothelial dysfunction, inflammation.*

рівня інсуліну та глюкози виявлено порушення функції ендотелію судин. Дисфункція ендотелію судин мала тісну кореляційну залежність із маркерами системного запалення, що посилювалося наявністю інсулінорезистентності. На фоні прийому розувастатину в дозі 10 мг/добу крім достатнього ліпідокорегуючого ефекту було відзначено зниження рівня ІР, активності системного запалення та покращення функції ендотелію судин, що забезпечує корекцію додаткових факторів ризику у хворих на ІХС у поєднанні з ЦД 2-го типу.

Висновки. *Використання розвастатину в дозі 10 мг на добу протягом 3-х місяців у пацієнтів з ІХС у поєднанні з ЦД 2-го типу знижувало рівень інсулінорезистентності, активність системного запалення та покращувало функцію ендотелію судин.*

Ключові слова: *ішемічна хвороба серця, цукровий діабет, дисфункція ендотелію, запалення.*

Over recent years in all countries there has been a constant increase in the incidence and prevalence of diabetes mellitus (DM) [1]. The majority of such patients (90–95%) suffer from type 2 diabetes, which is based on a genetic predisposition and a sedentary lifestyle. Cardiovascular diseases, in particular ischemic heart disease (IHD), are the main cause of death in these patients [4]. The reasons for atherosclerosis accelerated development, which is considered as the morphological basis of ischemic heart disease and cerebral diseases in patients with DM, have not yet been fully determined. Recent literature data indicates that not one, but several pathological factors are able to accelerate the development of ischemic heart disease. These include: atherogenic dyslipidemia, compensatory hyperinsulinemia, insulin resistance (IR), arterial hypertension, left ventricular hypertrophy, abdominal obesity, increased platelet aggregation, increased activity of tissue plasminogen activator inhibitor, activation of lipid peroxidation [6, 7].

At present time there is a great attention paid to the role of vascular endothelial dysfunction and immune inflammation in atherogenesis development. Thus, it is believed that endothelial dysfunction is an independent risk factor in the development of coronary artery atherosclerosis and it is often detected long before the manifestation of clinical symptoms of the disease, contributing to the progression of coronary artery disease and the development of its complications [2].

An increased blood levels of C-reactive protein (CRP) and of specific markers of inflammation – cytokines now considered as endothelial damage biological markers. Endothelium-dependent vascular dilatation disturbances (vasomotor endothelial dysfunction) considered as endothelial dysfunction functional marker [11, 14].

Hence, the treatment of patients with ischemic heart disease should be targeting not only at reducing the number and severity of symptoms of the disease, but also a correction of risk factors. Recent years, a large amount of data from multicenter studies has been accumulated, convincingly proving the effectiveness of intensive cholesterol-lowering therapy, in particular statins, in reducing of cardiovascular morbidity and mortality rates [13]. Currently, more and more attention is paid to the statins pleiotropic effect: the effect on endothelial function, inflammation

mechanisms, fibrinolytic properties of blood. However, literature data concerning the effects of statins on insulin levels are rather contradictory [8, 9]. The question of which dosage of statins is a priority, minimum or maximum, in patients with comorbidity also remains actual [10].

PURPOSE OF THE STUDY

The goal of the present study was to evaluate the effect of low dosed statins (rosuvastatin 10 mg/day) on the state of lipid and carbohydrate metabolism, insulin levels, vascular endothelial function, and markers of systemic inflammation in patients with ischemic heart disease in combination with diabetes mellitus.

MATERIALS AND RESEARCH METHODS

We examined 83 patients with ischemic heart disease and type 2 diabetes mellitus aged 44 to 78 years (mean age 56,8 ± 3,4 years); of these, 58 (67,5%) men and 35 (32,5%) women. The diagnosis of ischemic heart disease: stable effort angina functional class (FC) II-III was verified on the basis of anamnesis and instrumental investigation methods (veloergometry, ECG Holter monitoring, stress test). Diagnosis of diabetes mellitus type 2 (DM-2) was based on anamnestic data and repeated detection of fasting glycemia levels of 7,0 mmol/l and above and glycosylated hemoglobin levels of more than 7%. According to the New York Heart Association classification, heart failure FC I was diagnosed in 18 (25,6%) patients, FC II – in 46 (48,3%), FC III – in 19 (27,1%) patients.

Fasting glucose levels were determined in all patients using standard glucose oxidant ELISA method. The HOMA index (characterizes insulin resistance (IR) was calculated according to the formula: fasting insulin level · fasting blood glucose (mol/l/22,5). IR was set at the HOMA index > 3 units. The levels of total cholesterol, low density lipoproteins (LDL), very low density lipoproteins (VLDL), high density lipoproteins (HDL) and triglycerides (TG) in the blood were determined by enzyme immunoassay on a biochemical analyzer from Cobas Mire (Poland). The concentration of C-reactive protein (CRP) was determined by a highly sensitive enzyme immunoassay (F. Hoffman-LaRoche, Austria). TNF-α, IL-1β and IL-6 levels in blood serum were determined by enzyme-linked immunosorbent assay using VectorBest Ukraine test systems in accordance with the attached instructions.

In order to investigate endothelium function, of the brachial artery (BA) dopplerography in the middle third was used according to the D.S. Celermajer method before and after occlusion with a tonometer cuff and sublingual administration of nitroglycerin 500 μg with an assessment of endothelium-dependent vasodilation (EDVD) parameters, according to the results of a test with reactive hyperemia, and endothelium-independent vasodilation (EIVD), according to the results of the test with nitroglycerin (NTG), vasodilation. The presence of endothelial dysfunction was verified when the EDVD of brachial artery decreased by less than 10% of the initial level.

All patients received IHD therapy according to generally accepted standards with the inclusion of aspirin (95,4%), β-blockers (93,5%), if necessary, calcium antagonists (45,2%), and long-acting nitrates (69,2%). The drugs were used against the background of stable oral hypoglycemic therapy. As a cholesterol-lowering therapy, rosuvastatin (Crestor, AstraZeneca UK Limited) was prescribed at a dose of 10 mg/day for 3 months against the background of a cholesterol-lowering diet. The comparison group without statin prescription was not selected for ethical reasons, as this would entail a predicted decrease of therapy effectiveness.

Statistical processing of the obtained data was carried out using the PSPP application package (version 1.0.1, GNUProject, 1988–2017). During the analysis, methods of parametric and nonparametric variational statistics were used. Distribution type of the variants was determined by the Kolmogorov-Smirnov test, the equality of general variances was controlled using the Fisher F-test. The results obtained are presented as mean values (M) ± standard deviation (s). To assess the relationship between quantitative parameters, the Spearman rank correlation test (r) was used.

RESULTS AND ITS DISCUSSION

The dynamics of the studied parameters under the influence of the therapy in patients with coronary artery disease in combination with type 2 diabetes is presented in the table.

All patients initially showed an increase levels of fasting glycemia, which is probably due to increased production of glucose by the liver due to IR (HOMA index of more than 3 units was revealed in 76,3% of patients). A significant increase in LDL, VLDL and TG was revealed, which is consistent with the literature data that LDL is a significant biochemical marker of a high risk of ischemic heart disease [9]. And an increase in the level of triglycerides is the most characteristic sign of impaired lipoprotein metabolism in DM-2, and according to the literature data, they are among the most aggressive remnant particles on the atherogenesis side of [5].

Table 1

The dynamics of the studied parameters under the influence of therapy in patients with coronary artery disease in combination with type 2 diabetes

Parameter	Parameter value (M ± m)	
Total cholesterol, mmol/L	6,12 ± 0,25	4,55 ± 0,16*
LDL, mmol/L	4,13 ± 0,71	2,98 ± 0,24*
VLDL, mmol/L	1,69 ± 0,21	1,0 ± 0,12*
HDL, mmol/L	1,01 ± 0,03	1,06 ± 0,02
TG, mmol/L	2,97 ± 0,36	1,82 ± 0,18*
Fasting glucose level, mmol/L	9,78 ± 0,81	7,12 ± 0,38*
Fasting insulin level, mmol/L	20,36 ± 2,48	12,74 ± 2,15*
Index HOMA, conventional units.	8,9 ± 1,6	5,1 ± 1,1*
CRP, mg/L	5,86 ± 1,24	3,15 ± 1,36*
TNF-α, pg/L	27,6 ± 2,12	13,25 ± 1,18*
IL-6, pg/L	6,99 ± 0,38	4,11 ± 0,61*
IL-10, pg/L	1,92 ± 0,17	3,56 ± 0,22*
EDVD, %	6,98 ± 1,12	9,27 ± 1,57*
EIVD, %	21,15 ± 3,76	27,38 ± 3,45*

***Note:** * – difference in significance parameters compared to those before treatment (p = 0,015)*

Hyperinsulinemia, along with hyperlipidemia, is a risk factor for the development of IHD [3]. According to the scientific data, fasting insulin levels are among the parameters that affect the prognosis of myocardial infarction over the next 5 years [6]. In our study, positive correlations were found between the level of insulin and glucose (r = 0,68, p = 0,002), the level of TG and insulin (r = 0,58, p = 0,015), the level of total cholesterol and insulin (r = 0,68, p = 0,015).

Thus, chronic hyperinsulinemia leads to a decrease in insulin receptors, resulting in IR, hyper- and dyslipidemia, which contribute to the accelerated development of the atherosclerotic process.

Initially, all patients showed an increased levels of systemic inflammation markers: CRP, TNF-α and IL-6, as well as a decrease in the content of the anti-inflammatory cytokine IL-10. It is known that TNF-α and IL-6 interact with insulin receptors and inhibits the pathway of insulin signal transmission to the cell, as well as disrupt the function of the transport protein GLUT-4, which ensures the insulin-independent incorporation of glucose into muscle and adipose tissue [12]. It is assumed that atherosclerosis and IR have similar pathophysiological mechanisms, mainly due to the action of TNF-α and IL-6. We have established a direct correlation between CRP and HOMA (r = 0,36, p = 0,015), TNF-α and HOMA (r = 0,48, p = 0,015), IL-6 and HOMA (r = 0,32, p = 0,03) and inverse correlation between IL-10 and HOMA (r = –0,29, p = 0,03). So, IR leads to the activation of systemic inflammation in patients with coronary artery disease in combination with diabetes, which also contributes to the accelerated development of atherosclerosis in this category of patients.

In the examined patients, dysfunction of the endothelium was recorded according to the results of the test with reactive hyperemia – a decrease in EDVD and EIVD. A negative correlation was established between the level of total cholesterol and EDVD (r = –0,56, p = 0,015), LDL and EDVD (r = –0,62, p = 0,015). A significant direct correlation was established between EDVD and inflammation markers: CRP (r = 0,46, p = 0,015), TNF-α (r = 0,64, p = 0,015) and IL-6 (r = 0,36, p = 0,015). Thus, in patients with ischemic heart disease and type 2 diabetes, activation of systemic inflammation is closely related to endothelial dysfunction.

After 3 months of treatment period, there was a significant decrease in the level of total cholesterol by 15,2%, LDL – by 9,4%, VLDL – by 7,8% and TG – by 24,1%. In parallel, there was a decrease in the level of glycemia in 77,5% of patients and insulinemia in 81,2% of patients, as well as a decrease in the HOMA index by 36,6%. Under the influence of therapy, parameters there were significant decreasing of parameter reflecting the systemic inflammation activity: CRP – by 44,2%, TNF-α – by 29,6%, IL-6 – by 22,7%, and the content of IL-10 increased by 29,8%. At the end of the follow-up, against the background of favorable changes in blood lipid fractions, EDVD significantly increased by 72,2% (p = 0,015) and EIVD by 34,5%.

Thus, improvement of endothelial function provides antithrombotic activity of the vessel wall, normalization of vascular tone control, reduction

of lipid infiltration, which reduces the activity of systemic inflammation.

CONCLUSIONS

1. Effects of low dosed statins (rosuvastatin 10 mg/day) on the state of lipid and carbohydrate metabolism, insulin levels, vascular endothelial function, and markers of systemic inflammation in patients with ischemic heart disease in combination with diabetes mellitus was investigated and evaluated.

2. In patients with ischemic heart disease in combination with type 2 diabetes mellitus on the background of hyper- and dyslipidemia, elevated levels of insulin and glucose, dysfunction of the vascular endothelium was revealed.

3. Dysfunction of the vascular endothelium is closely correlated with markers of systemic inflammation, which is exacerbated by the presence of insulin resistance.

4. Against the background of taking rosuvastatin at a dose of 10 mg/day, in addition to a sufficient lipid-correcting effect, a decrease in the level of IR, activity of systemic inflammation and an improvement in the function of the vascular endothelium were noted, which ensures the correction of additional risk factors in patients with coronary artery disease in combination with type 2 diabetes.

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