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The effect of statin therapy on oxidative stress indices in patients with arterial hypertension and type 2 diabetes mellitus

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Key words: hypertension, diabetes mellitus type 2, statins, oxidative stress.

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Objective: to study the effect of statin therapy on the oxidative and antioxidant systems parameters in patients with arterial hypertension (AH) and cocomitant type 2 diabetes mellitus (DM2T).

Materials and methods. 126 patients (55 males and 71 females, average age was 57.8 ± 6.2 years) with AH stage II and compensated DM2T were divided into 2 groups: the 1 group – with AH and DM2T (n = 69), who were constantly taking statins (rosuvastatin 10 mg/day or atorvastatin 20 mg/day) for at least 1 year; the 2 group – patients with AH and DM2T (n = 57) who did not take statins. The control group included 20 healthy volunteers. The parameters of lipid and carbohydrate metabolism, the degree of insulin resistance (HOMA-IR), the state of the oxidant system (malonic dialdehyde level –MDA), the antioxidant system (the activity of glutathione peroxidase (GPO) and the level of sulfhydryl groups -SH-groups) were evaluated. The statistics was carried out using the Statistica software package, version 8.0.

Results. In the 1st group only the levels of LDL cholesterol significantly differed from the control group ($P < 0.05$). In the 2nd group the levels of total cholesterol and LDL cholesterol were expected to be higher than in the 1st group ($P < 0.05$) and the control group ($P < 0.05$). Despite the higher level of fasting glucose in the 2nd group than in the 1st group, HOMA-IR in the 1st group was higher than in the 2nd group (7.48 ± 1.76 and 7.17 ± 1.54, respectively, $P > 0.05$). In the 1st group in comparison with the 2nd group unreliable increase in GPO and SH-groups levels on the background of the increase in MDA levels ($P > 0.05$) were observed.

Conclusions. The use of statins in low doses in AH combined with DM2T was accompanied by a nonsignificant improvement of antioxidant protection parameters on the background of increased insulin resistance and increased activity of lipid peroxidation.

Ключові слова: артеріальна гіпертензія, цукровий діабет 2 типу, статини, оксидативний стрес.

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Вплив статинотерапії на показники окислювального стресу в пацієнтів з артеріальною гіпертензією та цукровим діабетом 2 типу

В. Д. Немцова

Мета роботи – вивчити вплив терапії статинами на параметри оксидантної та антиоксидантної систем у пацієнтів з артеріальною гіпертензією (АГ) у поєднанні з цукровим діабетом 2 типу (ЦД2Т).

Матеріали та методи. 126 пацієнтів (55 чоловіків і 71 жінка, середній вік – 57,8 ± 6,2 року) з АГ II стадії та ЦД2Т у стадії компенсації поділили на дві групи: 1 – пацієнти з АГ і ЦД2Т (n = 69), які постійно приймали статини (розувастатин 10 мг/добу або аторвастатин 20 мг/добу) принаймні 1 рік, 2 група – пацієнти з АГ і ЦД2Т (n = 57), які не приймали статини. 20 здорових добровольців становили контрольну групу. Досліджувались параметри ліпідного та вуглеводного обміну, ступінь інсулінорезистентності (HOMA-IR), стан оксидантної системи (за рівнем малонового діальдегіду – МДА), стан антиоксидантної системи (активність глутатіонпероксидази (ГПО) та рівень сульфгідрильних груп – SH-груп). Статистика опрацьована за допомогою програмного забезпечення Statistica версії 8.0.

Результати. У 1 групі тільки рівень холестерину ЛПНЩ вірогідно відрізнявся від контрольної групи ($p < 0,05$). У 2 групі рівень загального холестерину та холестерину ЛПНЩ, як очікувалось, був вищим, ніж у першій групі ($p < 0,05$) та контрольній групі ($p < 0,05$). Незважаючи на вищий рівень глюкози натщесерце у хворих 2 групи порівняно з 1 групою, індекс HOMA-IR у 1 групі був вищим, ніж у 2 (7,48 ± 1,76 і 7,17 ± 1,54 відповідно, $p > 0,05$). У 1 групі порівняно з 2 визначили невірогідне підвищення рівня ГПО та SH-груп на тлі підвищення рівня МДА ($p > 0,05$).

Висновки. Використання невисоких доз статинів при АГ у поєднанні з ЦД2Т супроводжувалось невірогідним поліпшенням параметрів антиоксидантного захисту на тлі підвищеної інсулінорезистентності та підвищеної активності перекисного окислення ліпідів.

Ключевые слова: артериальная гипертензия, сахарный диабет 2 типа, статины, окислительный стресс.

Запорожский медицинский журнал. – 2018. – Т. 20, № 1(106). – С. 26–30

Влияние статинотерапии на показатели окислительного стресса у пациентов с артериальной гипертензией и сахарным диабетом 2 типа

В. Д. Немцова

Цель работы – изучить влияние терапии статинами на параметры оксидантной и антиоксидантной систем у пациентов с артериальной гипертензией (АГ) в сочетании с сахарным диабетом 2 типа (СД2Т).

Материалы и методы. 126 пациентов (55 мужчин и 71 женщина, средний возраст 57,8 ± 6,2 года) с АГ II стадии и СД2Т в стадии компенсации были разделены на 2 группы: 1 группа – больные с АГ и СД2Т (n = 69), которые постоянно принимали статины (розувастатин 10 мг/сутки или аторвастатин 20 мг/сутки) не менее 1 года; 2 группа – пациенты с АГ и СД2Т (n = 57), которые не принимают статины. 20 здоровых добровольцев составили контрольную группу. Исследовались параметры липидного и углеводного обмена, степень инсулинорезистентности (HOMA-IR), состояние оксидантной системы (по уровню малонового диальдегида – МДА), состояние антиоксидантной системы (по активности глутатионпероксидазы (ГПО) и уровню сульфгидрильных групп – SH-групп). Статистика проводилась с помощью программного обеспечения Statistica версии 8.0.

Результаты. В 1 группе только уровень холестерина ЛПНП достоверно отличался от контрольной группы ($p < 0,05$). Во 2 группе уровень общего холестерина и холестерина ЛПНП, как и ожидалось, был выше, чем в первой группе ($p < 0,05$) и контрольной группе ($p < 0,05$). Несмотря на более высокий уровень глюкозы натощак у больных 2 группы по сравнению с 1, индекс HOMA-IR в 1 группе был выше, чем во 2 (7,48 ± 1,76 и 7,17 ± 1,54 соответственно, $p > 0,05$). В 1 группе по сравнению со 2 было выявлено недостоверное повышение уровня ГПО и SH-групп на фоне повышения уровня МДА ($p > 0,05$).

Выводы. Использование невысоких доз статинов при АГ в сочетании с СД2Т сопровождалось недостоверным улучшением параметров антиоксидантной защиты на фоне повышенной инсулинорезистентности и повышенной активности перекисного окисления липидов.

Arterial hypertension (AH) and diabetes mellitus (DM) and related complications remain one of the main problems of modern medicine. The results of numerous studies in recent decades confirm the key role of the endothelium in regulation of vascular homeostasis. At the same time, it is known that when oxidative stress (OS) increases, endothelial function is disturbed, which causes a progression of atherosclerosis and other cardiovascular complications [1,2]. Currently, many authors consider oxidative stress as a «universal framework» for the development of all diabetes complications, associated with the impaired endothelial function [1–3]. Another important component of oxidative stress development is the decrease in the antioxidant protection by hyperglycemia induced inactivation of antioxidants.

In patients with hypertension, especially in the presence of concomitant diabetes, an atherogenic dyslipidemia is commonly observed. A large number of multicenter studies have proved the efficiency of lipid-lowering therapy in patients with hypertension for the purpose of primary and secondary prevention [4,5]. The relevance of dyslipidemia correction in patients with hypertension is explained by the fact that antihypertensive drugs effect intensity depends on the cholesterol level in blood plasma. The use of statins as the most effective means to reduce LDL cholesterol levels and prevent cardiovascular complications in patients with hypertension has been justified by recommendations of the European Society for the Study of Hypertension and the European Society of Cardiology (ESH/ESC, 2013) [4]. However, current criteria for statin initiation are based not on actual levels of lipidemia, but on patient's individual cardiovascular risk assessment. Unified clinical Protocol of patients' health care with hypertension, approved by the Order of the Ministry of Health of Ukraine of 24.05.2012 # 284, also contains clear instructions regarding the obligatory statins prescription to persons with hypertension of high and very high risk in the absence of contraindications [5].

Statins prescription in type 2 diabetes mellitus (DM) is one of the fundamental principles of modern antidiabetic therapy. Reduction of cardiovascular complications and cardiovascular mortality in type 2 diabetes patients with statins using for primary and secondary prevention has been repeatedly proven, as reflected in the recommendations of the American Diabetes Association (American Diabetes Association, ADA) and European Association for the Study of Diabetes (EASD) [1,3]. However, in clinical practice we are often faced with a topical problem of complexity in persistent medication adherence development in patients with chronic diseases by reason of the need for long-term use. This is particularly critical issue for patients with comorbid pathology due to the forced polypharmacy, especially in oligosymtomatic cases, feeling of well-being and lack of patients' knowledge about their disease. Low socio-economic patient's status is also rather important. According to the literature, statin therapy adherence is not high enough. In addition, convincing evidence regarding the beneficial effects of natural antioxidants on oxidative stress has not been received. Currently, there are more and more experimental data, conducted both in animals and humans, proving the overwhelming oxidative stress pleiotropic action of statins. However, available literature contains very few data on the statins effect on oxidative stress in comorbid pathology, most of which are obtained by the use of high doses of statins, that in routine practice is not very common.

Purpose

Thus, the purpose of this study was to investigate the influence of statin therapy on oxidative and antioxidant systems indices in patients with arterial hypertension and concomitant type 2 diabetes mellitus (DM2T).

Materials and methods

The study included 126 patients (55 males and 71 females), average age of 57.8 ± 6.2 years with stage II hypertension and type 2 diabetes in stage of compensation, who on the background of dietary recommendations received basic therapy according to international and national guidelines for management of patients with relevant pathology [3,4,6]. So at least 6 months before inclusion in the study all patients received ACE inhibitors /ARBs, diuretic (torasemide/indapamide) in individual dosages as antihypertensive therapy, some patients received calcium antagonists (amlodipine/lercanidipine). All patients received Metformin as antidiabetic therapy in individually defined doses of 1000 to 2000 mg/day; in addition 29 (of 23.02 %) patients received sulfonylureas. Patients with uncontrolled hypertension were not included in the study. All patients were divided into 2 groups: the first group consisted of patients with hypertension and type 2 diabetes (n = 69) who constantly received statins (rosuvastatin 10 mg/day or atorvastatin 20 mg/day) for at least 1 year, the second group – patients with arterial hypertension and type 2 diabetes (n = 57) who did not take statins.

The study did not include patients with symptomatic hypertension, type 1 diabetes and other endocrinologic disorders, clinical signs of ischemic heart disease or severe concomitant chronic diseases.

The diagnostic criteria of hypertension, endorsed by the European recommendations for the diagnosis and treatment of hypertension (2013), were used for the selection of patients [4]. The diagnosis of DM2T was applied according

to approved by the Order of the Ministry of Health of Ukraine of 22.05.2009 # 356, "On approval of protocols of medical care to patients with endocrine diseases" [6]. The control group consisted of 20 healthy volunteers comparable with age and gender of the investigated patients.

The study Protocol included assessment of anthropometric data, blood pressure (BP) average AP, obtained from the three measurements in 2-minute intervals in the sitting position.

Fasting blood glucose concentration measurement was performed by glucose oxidase method using analyzer *Humolizer* (manufactured in Germany). Measurement of total serum cholesterol (TC), triglycerides (TG) and cholesterol of high density lipoproteins (HDL cholesterol) were performed in serum enzymatically by photocolorimetric method with sets produced by *Human* (manufactured in Germany). The content of cholesterol in the low density lipoprotein (LDL cholesterol) was calculated by the formula of Friedewald W. T. with consideration of measurement in mmol/l: LDL cholesterol = cholesterol – (HDL cholesterol + TG/2.22).

The blood serum insulin concentration and the glycosylated hemoglobin level (HbA) ware measured by enzyme immunoassay using a set of reagents *Hummer* (USA). To determine the insulin resistance (IR) index, HOMA – IR was used, which was calculated by the following formula:

((Glucose fasting) × (fasting insulin)) mmol/ml/22.5.

To study the antioxidative system the activity of glutathione peroxidase (GPO) and the level of sulfhydryl groups (SH-groups) were assessed. The level of malondialdehyde (MDA) was used as a marker of severity of oxidative system activity. The activity of GPO (KF 1.11.1.9) in EDTA-hemolysate was determined by the decrease in the content of reduced glutathione during a 5-minute incubation of a test sample of hemolysate in the presence of oxidizing substrate – cumene hydroperoxide by the photometric method [7]. The SH-groups and MDA were determined in serum using photometric method [7]. The following reagents were used: thiobarbituric acid (Organika, Germany), dithiobisnitrobenzoic acid (Merck, Germany), restored glutathione (Sigma-Aldrich, Germany), cumene hydroperoxide (Merck, Germany).

The results are presented as mean values ± standard deviation from the mean value (M ± SD). Statistical data processing was performed using software package Statistica, version 8.0. To assess differences between groups in the distribution close to normal, the criterion of Student was used. The differences were considered statistically significant when $P < 0.05$.

The present study was performed in compliance with the basic provisions of the World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects (1964–2000) and the Order of the Ministry of Health of Ukraine of 23.09.2009 # 690. The present article is a part of the research of Clinical Pharmacology Department of Kharkiv National Medical University # 0112U002385 "To Optimize the Diagnosis of Hypertension and Detection of Subclinical Lesion of Target Organs in Individuals of Young Age".

Results and discussion

The results of our work show that, despite the significant improvement of lipid indicators compared with individuals who do not take statins, the use of rosuvastatin in a dose 10 mg/day or atorvastatin 20 mg/day did not always provide sufficient normalization of cholesterol metabolism indicators (*Table 1*). The patients of the 1st group retained significant differences of the TG and LDL Cholesterol levels compared with the control group ($P < 0.05$). Nevertheless, the recommended target levels of TC, LDL Cholesterol, TG were got in many patients of this group. Patients of the 2nd group showed a more pronounced atherogenic dyslipidemia, which was manifested as significantly higher values of TC and LDL Cholesterol compared with the control group, and compared with the patients taking statins. It is constantly emphasized in the literature that doses of statins applied in routine practice are often too small to ensure the achievement of TC and LDL Cholesterol target levels recommended for patients with DM2T. However, these lipid indicators are important risk factors for cardiovascular disease (CVD). It is believed that DM2T is the most common cause of secondary hypertriglyceridemia, which in case of inadequate control of lipid disorders, leads to insulin resistance, hypertension and atherosclerosis. Although information on the relationships between TG and risk of CVD and its complications development is very controversial. The present study observed hypertriglyceridemia in both groups of patients, more pronounced in the second group, which was significantly different from the level in the control group (1 group – 1.75 ± 0.33 mmol/l, 2 group – 2.14 ± 0.28 mmol/l, control group – 1.03 ± 0.30 mmol/l, $P < 0.05$). The intake of statins in this study did not cause a significant decrease in TG levels.

Table 1. Comparative characteristics of lipid and carbohydrate metabolism and oxidant-antioxidant system in patients with hypertension and type 2 diabetes depending on the use of statin therapy

Indicator	Control (n = 20)	1 group (n = 69)	2 group (n = 57)
Cholesterol, mmol/l	4.77 ± 0.52	5.16 ± 0.29	5.85 ± 0.36*. **
TG, mmol/l	1.03 ± 0.30	1.75 ± 0.33*	2.14 ± 0.28*
VLDL cholesterol, mmol/l	0.54 ± 0.22	0.79 ± 0.17	0.89 ± 0.34
HDL cholesterol, mmol/l	1.45 ± 0.30	1.24 ± 0.18	1.20 ± 0.11
LDL cholesterol, mmol/l	2.6 ± 0.33	3.08 ± 0. 12*	3.76 ± 0.45*. **
Glucose, mmol/l	4.62 ± 1.08	7.62 ± 1.34 *	8.09 ± 1.16 *
HOMA-IR	2.23 ± 0.36	7.48 ± 1.76*	7.17 ± 1.54*
Glycated hemoglobin, HbA (%)	4.62 ± 1.08	7.28 ± 0.68 *	7.88 ± 0.54 *
Malonic dialdehyde (MDA) μmol/l	4.07 ± 0.22	6.75 ± 1.18 *	6.44 ± 1.03 *
Glutathionperoxidase (GPO) (μkat/GNF)	6.77 ± 0.52	5.30 ± 0.93 *	5.11 ± 0.87 *
The SH groups (μmol/l)	712.26 ± 11.08	570.56 ± 13.71*	555.24 ± 14.63*

*: $P < 0.05$ when compared with the control group; **: $P < 0.05$ when compared groups 1 and 2.

Despite the fact that the level of fasting glucose in patients of the 2 group was higher than in the 1 group, the index of insulin resistance – HOMA in a group of people, taking statins was higher, which confirms the opinion about the worsening of insulin resistance even when using low doses of statins. By now there are numerous data about the negative effects of statins on carbohydrate metabolism, insulin synthesis and cells receptor sensitivity. Data of randomized, placebo-controlled study published in 2010 showed the effect of 2-month therapy with atorvastatin at doses of 10, 20, 40 and 80 mg/day on the level of insulin, glucose, glycosylated hemoglobin, lipoprotein and apoproteins B in blood plasma compared to placebo in patients with hypercholesterolemia [8]. It has been noted, that despite the significant reduction in LDL cholesterol and apo B levels, atorvastatin treatment increased fasting insulin levels and glycated hemoglobin against the backdrop of increasing insulin resistance and increasing random glycaemia in patients with hypercholesterolemia. However, it should be noted that not all researchers have found the carbohydrate metabolism disorders on the background of atorvastatin use.

Regardless lipid-reducing activity in recent years some studies have appeared in which a great importance is paid to the statins ability to decrease in cardio-vascular risk by influencing OS, preventing or reducing endothelial dysfunction. For instance in the experimental study of Celal Kilit et al. (2017) it has been shown that lovastatin prevents endothelial dysfunction development by OS suppressing in various models with high CVD risk [9].

In earlier experiments, conducted mainly on animals, using fluvastatin and simvastatin, positive changes after statins prescription were observed, not only in inflammatory processes but also in indicators of peroxidation [8].

Despite the available data on the favorable influence of modern anti-hypertensive [10] and antidiabetic [2] therapy on oxidative stress, our results demonstrate the presence of strong OS in patients with combined course of AH and DM2T. This is manifested in a significant increase in the MDA levels ($P < 0.05$) and decrease in GPO ($P < 0.05$) and SH-groups ($P < 0.05$) levels compared to healthy volunteers. In the group of patients receiving atorvastatin/rosuvastatin, compared to patients not taking statins, we observed the following: on the background of tendency in antioxidant protection (GPO and SH-groups) indices improvement which does not reach accurate values, the oxidative system activation is observed, resulting in increased values of MDA (6.75 ± 1.18 mmol/l, 6.44 ± 1.03 mmol/l, respectively, $P > 0.05$). The oxidative system intension in patients of the 1st group may be explained by the increase in the degree of insulin resistance caused by statins, and improved antioxidant protection – confirmation of actual pleiotropic effect of this group of drugs. Also the authors of the present study suggest that insufficiency of the antioxidant actions of statins in the first group of patients is associated with the inadequate doses of drugs for this effect realization, which can be seen by the lipid indicators. Taking into account that the data of recent studies, according to results of which it is recommended to use the levels of MDA as risk of complications markers in patients with type 2 diabetes, especially poorly compensated [11], researches in this area have both significant scientific importance and practical value.

Conclusions

1. The combined course of arterial hypertension and type 2 diabetes mellitus is accompanied by the presence of marked oxidative stress, despite the presence of stable anti-hypertensive and anti-diabetic therapy.

2. The use of statins in patients with arterial hypertension and type 2 diabetes mellitus was accompanied by an improvement of antioxidant protection indicators on the background of increased insulin resistance and increased activity of lipid peroxidation — MDA.

3. The use of atorvastatin 20 mg or rosuvastatin 10 mg was accompanied by a slightly marked positive influence on oxidative stress in patients with arterial hypertension and type 2 diabetes mellitus.

4. Despite the presence of contradictory data regarding the negative impact of statins on particular parts of metabolism in patients with type 2 diabetes mellitus, the obtained results have demonstrated the undeniable benefits of statin therapy and the need to improve patient adherence, especially in cases of comorbid pathology that increases the risk of cardio-vascular complications development.

Prospects: since the majority of statins effects on oxidative stress in humans studies was performed using high doses of drugs, it is necessary to conduct a more detailed study of the most frequently used doses in practical medicine on oxidative stress indicators influence and their interaction with other metabolic systems in individuals with comorbid pathology, including type 2 diabetes mellitus.

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