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LIPID DISORDERS AND INFLAMMATION IN PATIENTS WITH DIABETES MELLITUS TYPE 2 TREATED WITH STATINS

LIPIDNI POREMEĆAJI I INFLAMACIJA KOD BOLESNIKA S DIABETES MELLITUSOM TIPA 2 NA TERAPIJI STATINIMA

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Summary: The research focused on 40 patients (22 women and 18 men) with DM type 2, 26 of who underwent statin therapy and 14 of them followed a hygienic-dietetic regime. After a year of careful observation, the concentration of triglycerides (TG) was determined, as well as the overall cholesterol (TC), LDL-C, HDL-C, nonHDL cholesterol and atherogenic indices. As far as inflammatory indicators are concerned, the concentrations of highly sensitive C reactive protein (hsCRP), intracellular adhesion molecule (ICAM-1) and vascular adhesion molecule (VCAM-1) were determined; they were also compared among the therapy groups. The average TC and LDL-C values were considerably lower in the group treated by statins (5.6 ± 1.2 vs. 6.3 ± 1.4 mmol/L and 3.5 ± 0.9 vs. 4 ± 1.3 mmol/L, $p<0.05$). The values of TG, HDL-C, atherogenic indices LDL-C/HDL-C and TC/HDL-C and inflammatory indicators ICAM-1 and VCAM-1 did not differ significantly among the groups. The values of nonHDL-C were considerably lower in the group treated by statins (4.5 ± 1.1 vs. 5.1 ± 1.3 mmol/L, $p<0.05$), as well as the values of hsCRP (3.3 ± 2.2 vs. 5.6 ± 2.17 mg/dl, $p<0.01$). Parallel analysis showed a significant correlation between the concentration of TC and LDL-C and the values of ICAM-1 ($C=0.55$ and $C=0.65$, $p<0.05$). Anti-lipoid effects of statins are complemented with their significant anti-inflammatory influence on the reduction of the value of hsCRP, which proved to be the most important prognostic factor for the onset of atherosclerosis. Antiinflammatory effects of statins are supplemented by a significant decrease in the concentration of ICAM-1 in the conditions where the value of TC and LDL-C is reduced in patients with DM type 2.

Keywords: diabetes mellitus, statins, lipoprotein, hsCRP, ICAM-1, VCAM-1

Kratak sadržaj: Ispitivanjem je obuhvaćeno 40 bolesnika (22 žene i 18 muškaraca) sa DM tipa 2, pri čemu je 26 bilo na terapiji statinima a 14 na higijensko-dijetetskom režimu. Nakon praćenja od godinu dana određivane su koncentracije triglicerida (TG), ukupnog holesterola (TC), LDL-C, HDL-C, nonHDL holesterola i aterogenih indeksa. Od inflamatornih pokazatelja određivana je koncentracija visokosenzitivnog C-reaktivnog proteina (hsCRP), intracelularnog adhezionog molekula (ICAM-1) i vaskularnog adhezionog molekula (VCAM-1), pri čemu su komparirani rezultati terapijskih grupa. Prosečne vrednosti TC i LDL-C bile su značajno manje u grupi na terapiji statinima (5,6 ± 1,2 vs. 6,3 ± 1,4 mmol/L i 3,5 ± 0,9 vs. 4 ± 1,3 mmol/L, $p<0,05$). Vrednosti TG, HDL-C, aterogenih indeksa LDL-C/HDL-C i TC/HDL-C i inflamatornih pokazatelja ICAM-1 i VCAM-1 nisu se značajnije razlikovale između grupa. Vrednosti nonHDL-C značajno su manje u grupi na statinima (4,5 ± 1,1 vs. 5,1 ± 1,3 mmol/L, $p<0,05$), kao i vrednosti hsCRP (3,3 ± 2,2 vs. 5,6 ± 2,17 mg/L, $p<0,01$). Korelaciona analiza je pokazala značajnu povezanost koncentracije TC i LDL-C sa vrednostima ICAM-1 ($C=0,55$ i $C=0,65$, $p<0,05$). Antilipemični efekti statina upotpunjeni su njihovim značajnim antiinflamatornim delovanjem na smanjenje vrednosti hsCRP, koji se pokazao kao najvažniji prognostički faktor za pojavu ateroskleroze. Antiinflamatorni efekti statina su upotpunjeni značajnim padom koncentracije ICAM-1 u uslovima redukcije vrednosti TC i LDL-C kod bolesnika sa DM tipa 2.

Ključne reči: diabetes mellitus, statini, lipoproteini, hsCRP, ICAM-1, VCAM-1

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Introduction

Diabetes Mellitus type 2 (DM Type 2) is a complex metabolic disease accompanied by specific lipid disorders which include not only the concentration

change but also lipoprotein composition changes. The newest studies show that DM type 2 is accompanied by an increase of the inflammatory activity which leads to a rapid and diffuse atherosclerosis along with the existing diabetic dyslipidemia. Antilipemic and antiinflammatory effects of statins are, therefore, of vital importance with these patients.

The very idea that inflammatory processes can be the basis of atherosclerosis development has lead to the question whether there is a connection between the inflammatory markers, inner wall activity markers and advancement of the atherosclerotic process. One of the larger studies designed to answer this question – Edinburgh Artery Study – has been determining the parameters of the inflammatory response of CPR, IL-6, ICAM-1, VCAM-1, and E-selectin during a period of 12 years. The results have shown that the CRP, IL-6, and ICAM-1 molecular markers can be found in the atherosclerotic process. IL-6 has proved to be the single most significant indicator of the development and progress of peripheral and cerebrovascular disease when compared to the rest of the measured parameters (1). It has been noticed that some other markers are able to predict the cardiovascular risk, not only with the patients who have a coronary disease, but also with those who do not have any manifestations of atherosclerosis. These markers are: fibrinogen, serum amiloid A, myeloperoxydase and soluble CD40L receptor (2). Among these indicators, some other constant markers have a prognostic value for the development of atherosclerosis: albumin concentration, white blood cell count, antibody and circulating immuno-complex concentration, which all together indicates that the inflammatory component has a huge significance in the pathogenesis of atherosclerosis (3).

Based on the results of the six key studies (Heart Protection Study – HPS, AFCAPS/TexCAPS, Scandinavian Simvastatin Survival Study – 4S, West of Scotland Coronary Prevention Study – WOSCOPS, Cholesterol and Recurrent Events – CARE, Long-Term Intervention with Pravastatin in Ischaemic Disease – LIPID), statins are defined as medicines which most significantly reduce the risk of CD appearance and lower CV mortality rate and recurrent coronary onset in patients with existing CD (4). The primary mechanism of their activity is the ability to inhibit 3-hydroxy--3-metil glutaryl coensime A reductaze, the key enzyme in the endogen cholesterol synthesis. In accordance with this effect, they achieve an antilipemic impact because they reduce the amount of total LDL-C. However, there exist numerous secondary useful mechanisms, out of which many have been scientifically examined. These pleotropic effects of statins include direct antiinflammatory activity, recovering the endothelium, and inhibition of cell proliferation, stabilization of the fibrous cover of the atherosclerotic plaque, reduction of the oxydative LDL particle modification, and antioxydative effect (5).

The goal of research was to examine the lipid disorders and their relation to the inflammatory indicators in DM type 2 patients treated with statins.

Patients and Methodology

This research included 40 patients (22 women, 18 men) with the diagnosis of DM type 2. All the patients were treated and examined at the Niška Banja Institute and the Military Hospital in Niš. The patients were divided into two groups according to the administration of antilipemic therapy. The first group consisted of 26 patients treated with statins during a period of one year. The second included 14 patients subjected to a controlled hygienic-diet antilipemic method.

All these patients were evaluated for the parameters of lipid status: triglyceride concentration (TG), total cholesterol (TC), LDL-C and HDL-C cholesterol. Non-HDL cholesterol and atherogenic indices (LDL-C/HDL-C; TC/HDL-C) were also calculated. The inflammatory indicators were noted, too: highly sensitive C reactive protein concentration (hsCRP), intracellular adhesive molecule (ICAM-1), and vascular adhesive molecule (VCAM-1), and these were compared between the therapy groups.

Lipid markers were calculated with the Dimension Xpand, Behring Company. HsCRP was calculated by the Turbitimer aparatus, Behring Company. ICAM-1 and VCAM-1 concentrations were measured by ELISA method, Cellcom Company.

The static analysis included usage of standard descriptive methods and the analysis by appropriate tests, during which the SPSS 11.0 software package was used.

Results

General characteristics of the hygienic-diet treatment patients are shown in *Table I*.

The average patient age was 61.42 ± 7.1, and there was no significant difference in the duration of diabetes mellitus type 2 and dyslipidemia among the members of the target group.

The average values of TC and LDL-C were significantly lower in the statin treated group (5.6 ± 1.2 vs. 6.3 ± 1.4 mmol/L and 3.5 ± 0.9 vs. 4±1.3 mmol/L, $p<0.05$). The TG and HDL-C values did not show much variation among the therapy groups (*Table II*).

The values of the atherogenic indices LDL-C/HDL-C and TC/HDL-C did not show much variation among the patients in the target group. The values of nonHDL-C were significantly lower in the statin treated group (4.5 ± 1.1 vs. 5.1 ± 1.3 mmol/l, $p<0.05$) (*Table III*).

The values of inflammatory indicators VCAM-1 and ICAM-1 did not show much variation among the groups. The values of hsCRP were significantly reduced in the statin treated group (3.3 ± 2.2 vs. 5.6 ± 2.17 mg/mg/L, $p<0.01$) (*Table IV*).

The correlation analysis has shown a significant connection between the concentration of TC and LDL-C, and ICAM-1 values (C=0.55 i C=0.65, $p<0.05$).

Table I Characteristics of patients with atherosclerosis and the hygienic-diet treatment.

	Num.	(%)	Age (years)	Diabetes duration	Dyslipidemia duration
Statins	26	65	60.8 ± 8.33	7.05 ± 5.14	5.65 ± 3.73
Hygienic -diet	14	35	62.75 ± 4.77	9.7 ± 6.4	3.1 ± 2.75
Total	10	100	61.42 ± 7.1	7.9 ± 5.9	4.72 ± 3.25

Table II Lipid status parameters.

	Statins	Hygienic-diet	Total
TG (mmol/L)	2.6 ± 1.22	2.8 ± 1.03	2.67 ± 1.15
TC (mmol/L)	5.69 ± 1.2*	6.33 ± 1.48	5.91 ± 1.33
LDL-C (mmol/L)	3.49 ± 0.89*	4.01 ± 1.29	3.66 ± 1.05
HDL-C (mmol/L)	1.27 ± 0.36	1.21 ± 0.33	1.21 ± 0.35

*$p<0.05$

Table III Atherogenic indicators.

	Statins	Hygienic-diet	Total
nonHDL-C (mmol/L)	4.47 ± 1.12	5.12 ± 1.34*	4.69 ± 1.22
LDL-C/HDL-C	3.01 ± 0.76	3.37 ± 0.95	3.14 ± 0.85
TC/HDL-C	4.94 ± 1.27	5.41 ± 1.41	5.1 ± 1.32

*$p<0.05$

Table IV Inflammatory risk factors for the development of atherosclerotic disorders.

	Statins	Hygienic-diet	Total
hsCRP (mg/L)	3.30 ± 2.20**	5.6 ± 2.17	4.04 ± 3.12
VCAM-1 (ng/mL)	11.41 ± 4.50	10.43 ± 4.73	11.05 ± 4.53
ICAM-1 (ng/mL)	7.9 ± 6.36	7.14 ± 2.7	7.62 ± 5.27

*$p<0.01$

Discussion

There were no significant differences between the target groups and among the patients concerning their age and DM type 2 duration (*Table I*). According to this fact, a difference in the inflammatory system response markers was not expected, taking into account that the change did not occur in the general population. The hypolipemic effect of statins and the importance of reducing cardiovascular disease induced mobidity and mortality has been known since the first large statin study – 4S (119PhD). Depending on the statin type and the administered dose, the effect on lipid parameters can vary. The usage of statins reduces total cholesterol by 17–40%, LDL cholesterol by 18–60%, and TG by 7–30%. Thus, the expected results involved the reduction of the lipid markers, total and LDL-C, together with an increase in HDL-C value.

The results confirm a significant reduction of the total and LDL cholesterol (*Table II*), but the statin effect on the increase of protective HDL-C has not been achieved after a long-term statin therapy.

The effect of statin therapy on atherogenic indices has been examined by determining the relation of LDL/HDL cholesterol, TC/HDL cholesterol, calculating the atherogenic index of plasma (AIP), and nonHDL cholesterol concentration (*Table II*). The relation between atherogenic and antiatherogenic lipids or lipoproteins, also known as atherogenic indices, are useful clinical risk indicators for the development of coronary diseases and other clinical manifestations of atherosclerosis. Numerous studies have shown good prognostic characteristics of the LDL-C/HDL-C and TC/HDL-C indices used to determine the onset of a CD (7, 8). However, this study did not show a significant reduction of these markers in the target groups, which points to the insufficient antilipemic potential of the applied statin therapy (*Table II*). Among the hygienic-dietetical method patients with dyslipidemia, drastically higher, negative nonHDL-C values were present (*Table II*), when compared to the patients treated with statins, which again confirmed that there was a reduction of the atherogenic risk with treated patients with DM type 2.

The well-known therapeutic effects of statins on the reduction of the lipid markers are completed by their significant antiinflammatory effects on the reduction of hsCRP values, which has proved to be the most important factor for the development of atherosclerosis.

It has been doubtful up to recently whether the hsCRP reduction during statin usage can additionally benefit the patient, beside the lipid decreasing effect. In two recently developed studies: »Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)« (2) and »Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22)« (9), the strongest

evidence of the independent effect of statin in cardiovascular risk reduction mediated by the CRP value reduction were presented.

The importance of hsCRP reduction in the secondary blood vessels atherosclerosis prevention can be found in the results which show that atherosclerosis is diminished with the decreased hsCRP value regardless of the LDL-C concentration value change (2).

The antiinflammatory effects of statins are completed with a drastic reduction of the ICAM concentration value in reduction conditions of TC/LDL-C values with DM type 2.

The ICAM-1 expression is not related to endothelial cells only, but can also be seen on the lymphocytes, monocytes, and various non-hematopoetic cells. VCAM is mostly an adhesive endothelial molecule, although its presence has been discovered in the lymphoid dendritic cells and tissue macrofagi. There are results that indicate an increased expression of these molecules in the conditions with higher risk for the development of thromboembolic atherosclerotic complications, such as diabetes mellitus type 2, hypertension, obesity, etc. In this research with the diabetic patients on a secondary coronary disease prevention treatment, the statin therapy did not show any change in the ICAM-1 and VCAM-1 values (*Table IV*). This is in accordance with the research of Wiklund et al., which indicates that the statin therapy does not reduce the ICAM-1 and VCAM-1 values with the DM type 2 patients (10).

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