ANTI-INFLAMMATORY EFFECT OF STATINS THERAPY
IN PATIENTS WITH CORONARY DISEASE AND DIABETES MELLITUS TYPE 2

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Summary. *Cardiovascular disease (CVD) is the leading cause of death in the world. In 2001, total mortality in Serbia and Monte Negro due to CVD was 56%. Diabetes mellitus (DM) type 2 is an important risk factor for CVD in both men and women. The aim of the study was to determine anti-inflammatory effects of statins therapy in patients with coronary artery disease (CAD) and DM type 2 by monitoring the markers of the systemic inflammatory response. 70 patients suffering from coronary artery disease associated with DM type 2 were analyzed. In order to assess the anti-inflammatory effect of anti-lipemic therapy the leukocyte count, albumin, fibrinogen, highly sensitive C reactive protein (hsCRP), vascular cells adhesion molecule (VCAM-1) and intracellular adhesion molecule (ICAM-1) concentration were determined in a group on statins and a group without statins therapy. Biomarkers of the systemic inflammatory response, except for the concentration of VCAM-1, were significantly higher in female compared to male patients in the group under lifestyle modification. In diabetics on statins therapy, this sex-related difference disappears and only the concentration of ICAM-1 remains significantly higher in female diabetics. A long-term statins therapy significantly reduces the concentration of hsCRP (30%) and increases albumin concentration (5%) when compared to the group with lifestyle modification. There was a sex-related effect of statins therapy. A more favorable effect of statins therapy was registered in female patients who had a higher risk for development of CAD and additional coronary events. Statins therapy exerts a significant anti-inflammatory effect in diabetics and, through decreasing hsCRP, has a great impact on reducing the risk for CAD.*

Key words: *Atherosclerosis, statins, coronary artery disease, diabetes*

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the world (50% of total mortality). Ischemic cardiac disease is responsible for 30% of total mortality. In 2001, total mortality in Serbia and Monte Negro due to CVD was 56%. The mortality caused by coronary artery disease (CAD) has increasing in our country. There is a trend of decline in CVD mortality in developed countries and it is less than 50%. Especially, this trend is registered in mortality caused by myocardial infarction (1). This success is achieved by modification of atherosclerosis risk factors: prevention or cessation of smoking, increased physical activity, diet without cholesterol and saturated fatty acids, weight reduction, medication of hypertension and diabetes, and reduction of blood lipids levels with lipid lowering therapy (2).

Diabetes mellitus type 2 is an important risk factor for CVD in both men and women. The results of prospective studies have showed that the risk for CVD is 2-4 times higher in patients with DM type 2 than in patients without diabetes and that yearly 2-5% of patients with DM type 2 exhibit fatal or non-fatal cardiovascular event (3).

The incidence of myocardial infarction and mortality caused by coronary artery disease is the same in non-diabetics with CVD and patients with DM type 2 without CVD (4).

Atherosclerosis is a highly complex multifactorial process which occurs as excessive inflammatory fibro-proliferative response to different forms of arterial endothelium injury (5). A number of factors like cytokines and vasodillating substances mediated this multistep process through years. Endothelial dysfunction is a key event in lipid accumulation in arterial intimae, and is followed by leucocytes mobilization, fatty streaks formation, smooth muscle cells proliferation, extracellular matrix reorganization, and plaque formation (6).

Nowadays, it is well known that the immune system is early involved in atherosclerosis induction and formation of the plaque (7). Inflammatory reaction mediated by macrophages leads to matrix metaloproteinases releasing, collagen type I degradation, and fibrous cap rupture. At the same time, IL-6 releasing induces the

increase in production of C reactive protein (CRP) in the liver. The expression of the adhesion molecule in endothelial cells enables the binding of thrombocytes which produce PGDF responsible for development of endothelial procoagulant activity.

If atherosclerosis is considered an inflammatory process, it is hard to separate the role of infection from the inflammatory nature of the atherosclerotic process. Inflammation intensity in the atherosclerotic process may be measured through the activity of CRP as a marker of systemic inflammation in coronary syndromes. A recent clinical study has showed that increasing the concentration of CRP as a marker of systemic inflammatory response has an important role in development of acute coronary syndromes (8).

The idea that the inflammation process is the ground for pathogenesis of atherosclerosis has opened a new question: is there any connection between the inflammation markers which are parameters of endothelial activity and the progression of atherosclerotic disease?

One of the extensive studies, the 12-year long Edinburgh Artery Study, designed to address this question, has determined inflammatory response parameters: CRP, interleukin-6 (IL-6), ICAM-1, VCAM-1 and E-selectin. The results show that CRP, IL-6 and ICAM-1 are molecular markers accompanied by appearance and progression of atherosclerosis. IL-6 turned out to be the most important independent parameter of presence and progression of peripheral vascular and cerebrovascular disease compared to other parameters (9).

It has been proved that some other biomarkers may predict the risk of CV event not only in patients with CVD, but also in those without clinical manifestations of atherosclerosis. These markers include: fibrinogen, serum amyloid A, mieloperoxidase and soluble CD40 L receptor (10). Besides these, the prognostic value for the development of atherosclerosis is also typical of some other common inflammation parameters such as: albumins concentration, leucocytes count, antibody concentration and concentration of circulating immune complexes. These results confirm the importance of the inflammatory process in the pathogenesis of atherosclerosis (11).

Based on the results of six great 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 drugs which significantly reduce the risk of CD and decrease CVD mortality and the possibility of new coronary events in patients with CD (6). Their ability to inhibit 3-hydroxyl-3-methyl-glutaryl coenzyme A reductase is the primary mechanism of their action. This is the way how statins exhibit the anti-lipemic effect by decreasing total cholesterol and LDL-C.

However, there are many other useful secondary mechanisms of their action proved by experiments such as: direct anti-inflammatory effect, endothelial function repair mediated by NO increased production, cells proliferation inhibition, fibrous cap stabilization, oxidative modification of LDL particles decrease, and anti-oxidative effect (12).

The results of West of Scotland Coronary Prevention Study (WOSCOPS) have made it possible for statins therapy to be used in prevention of CAD and medication of metabolic syndrome. This study showed that pravastatin therapy prevents development of DM type 2 from metabolic syndrome in 30% of patients and reduces CVD by 36% (13). WOSCOPS study suggested that the anti-inflammatory action of statins and its effects on the endothelial function are of the same importance as anti-lipemic effects of statins in prevention of atherosclerosis in DM type 2.

Aim

The aim of the study was to determine anti-inflammatory effects of statins therapy in patients with coronary disease and diabetes mellitus type 2 by monitoring of the markers of systemic inflammatory response.

Patients and Methods

A total of 70 patients suffering from coronary artery disease associated with DM type 2 were analyzed at the Institute of Prevention, Treatment and Rehabilitation of Cardiovascular Diseases in Niška Banja and Department of Internal Medicine of Military Hospital in Nis. According to the type of anti-lipemic therapy, the patients were divided into two groups The first group comprised 35 patients under dietetic regime, while the second group of patients was on anti-lipemic therapy with statins (equivalent of 20mg simvastatin daily dose). Diabetes mellitus type 2 was confirmed in all of the patients and they also received a hypoglycemic therapy. The period from making diagnosis of CAD and duration of therapy with statins in both groups lasted minimally one year.

In order to assess the anti-inflammatory effect of anti-lipemic therapy with standard laboratory methods, the leukocyte count, albumin and fibrinogen concentration were determined. The reactants of acute phase which were determined are: concentration of highly sensitive hsCRP with the commercial test of Dade Behring company on a Dimension Expand analyzer. Cell adhesion molecules: vascular adhesion molecules (VCAM-1) and intracellular adhesion molecules (ICAM-1) were determined by ELISA method with the commercial test by Beckman Coutte Company on a Bio Systems-Elisa reader. The obtained results are expressed in ng/ml. Fibrinogen concentration was determined by turbidometric method and expressed in g/l.

The statistical analysis was done using the following programs: Excel 7.0 and SPSS 11.0. We employed standard descriptive methods and the data analysis was done using a Student's t-test and the Fischer test of exact probability.

Results

The general characteristics of patients under lifestyle modification therapy are given in Table 1.

There is a significantly greater number of male patients in the group of diabetics under lifestyle modification therapy ($Hi^2 = 6.3$; $p < 0.05$). The Student's t test shows a significantly longer period of clinically manifest CAD and a shorter period of dyslipidemia in men (Table 1).

The values of inflammatory biomarkers in diabetics under lifestyle modification therapy are shown in Table 2.

The data shown in Table 2 indicate that female patients in this group have an unfavourable profile of inflammatory indicators compared to males. This is manifested in a significantly greater number of leukocytes ($p < 0.001$), and a higher concentration of albumin ($p < 0.01$), fibrinogen ($p < 0.05$), hsCRP and ICAM-1 molecules ($p < 0.01$). Only the concentration of VCAM-1 molecules was not significantly different between the genders.

The general characteristics of diabetics on statins therapy are shown in Table 3.

The average age, duration of clinically manifest DM type 2, coronary artery disease and dyslipidemia were not significantly different between males and females. There is a similar number of patients of both sexes in the group on statins therapy (Table 3).

The biochemical examination included measurement of different markers of inflammation which have a role in the pathogenesis of atherosclerosis. The values of these parameters in diabetics on statins therapy are shown in Table 4.

The data in Table 4 indicate a similar value of inflammatory biomarkers in both men and women, except for the concentration of ICAM-1 molecules, which is significantly lower in males compared to female diabetics (4.59 ± 2.47 vs. 9.99 ± 7.09 ng/ml, $p < 0.01$).

The anti-inflammatory effects of statins therapy and its significance in the reduction of risk for development of repetitive coronary events were determined by comparing the inflammatory biomarkers between these groups with different therapeutic anti-lipemic regiments (Table 5).

Table 1. Characteristic of diabetics under lifestyle modification therapy

	N	(%)	Age (years)	Duration of DM (years)	Duration of CAD (years)	Duration of dyslipidemia (years)
Women	12	34*	63.00 ± 1.10	16.5 ± 2.64	2.01 ± 1.2	7.65 ± 2.73
Men	23	66	62.75 ± 5.97	13.7 ± 9.83	7.50 ± 2.73 *	2.10 ± 0.75 *
Total	35	100	62.83 ± 4.84	14.6 ± 8.07	5.61 ± 2.1	6.95 ± 2.25

* $p<0.05$;

Table 2. Inflammatory risk biomarkers for CAD

	Women	Men	Total
Total leukocyte count (G/l)	9.63 ± 1.02***	5.38 ± 0.73	6.23 ± 1.87
Albumin (g/l)	48.00 ± 1.20 **	45.25 ± 0.86	46.6 ± 1.05
Fibrinogen (g/l)	2.89 ± 0.60 *	2.11 ± 0.54	2.26 ± 0.58
HsCRP (mg/l)	10.50 ± 2.60***	3.73 ± 1.67	5.10 ± 3.20
VCAM-1 (ng/ml)	8.47 ± 0.95	9.57 ± 1.30	9.30 ± 1.21
ICAM-1 (ng/ml)	9.22 ± 1.01 **	6.91 ± 1.00	7.48 ± 1.35

* $p<0.05$; **$p<0.01$; ***$p<0.001$

Table 3. Characteristics of diabetics on statins therapy

	N	(%)	Age (years)	Duration of DM (years)	Duration of CAD (years)	Duration of dyslipidemia (years)
Women	20	57	65.00 ± 5.86	7.35 ± 8.02	8.05 ± 6.36	9.00 ± 7.40
Men	15	43	62.57 ± 6.04	7.72 ± 4.67	6.75 ± 2.43	7.71 ± 4.14
Total	35	100	63.93 ± 5.97	7.51 ± 6.67	7.61 ± 5.34	8.40 ± 6.13

NS for all parameters

Table 4. Inflammatory risk biomarkers for CAD in the group on statins therapy

	Women	Men	Total
Total leukocyte count (G/l)	6.41 ± 0.8	6.22 ± 0.78	6.32 ± 0.78
Albumin (g/l)	48.6 ± 0.97	47.82 ± 2.36	48.4 ± 1.32
Fibrinogen (g/l)	2.82 ± 1.18	2.52 ± 0.5	2.69 ± 0.94
hsCRP (mg/l)	3.32 ± 2.44	3.89 ± 1.02	3.57 ± 1.94
VCAM-1 (ng/ml)	10.36 ± 4.71	10.37 ± 2.11	10.36 ± 3.67
ICAM-1 (ng/ml)	9.99 ± 7.09 **	4.59 ± 2.47	7.5 ± 6.03

**$p<0.01$

Table 5. Inflammatory risk biomarkers for CAD

	Statins therapy	Diet therapy
Total leukocyte count (G/l)	6.32 ± 0.78	6.23 ± 1.87
Albumin (g/l)	48.4 ± 1.32 *	46.60 ± 1.05
Fibrinogen (g/l)	2.69 ± 0.94	2.26 ± 0.58
hsCRP (mg/l)	3.57 ± 1.94	5.10 ± 3.20 *
VCAM-1 (ng/ml)	10.36 ± 3.67	9.30 ± 1.21
ICAM-1 (ng/ml)	7.50 ± 6.03	7.48 ± 1.35

* $p < 0.05$

The anti-inflammatory effects of statins therapy are best demonstrated by the lower concentration of hsCRP and the higher albumin concentration ($p < 0.05$) in the group on statins therapy. Other measured parameters did not show any difference between these groups (Table 5).

Discussion

There is no significant difference in the average age and duration of clinically manifest DM type 2 between the sexes in the analyzed groups. In the group under lifestyle modification therapy, duration of clinically manifest CAD was significantly longer, while duration of clinically manifest dyslipidemia was significantly shorter in male patients. In this context, we do not expect a significant difference in the values of systemic inflammatory biomarkers, having in the mind that this difference does not exist in the general population. However, almost all biomarkers of the systemic inflammatory response were significantly higher in females compared to males in the group under lifestyle modification. Only the concentration of VCAM-1 was not statistically different between the sexes. In the group of diabetics on statins therapy, the sex-related difference disappears and only the concentration of ICAM-1 remains significantly higher in female diabetics.

These results prove the existence of a higher risk for developing CAD and additional coronary events in females with DM type 2. There was a sex-related effect of statins therapy. A more favorable effect of statins therapy was registered in female patients. This leads to a greater decrease in values for inflammatory risk markers for CAD in males. In this way, statins therapy in diabetics nullifies the "excess" risk present in females, as opposed to males.

A long-term statins therapy significantly reduces the concentration of hsCRP and increases albumin concentration in secondary prevention of CAD in diabetics.

Two recently finished studies, "The Reversal of Atherosclerosis with Aggressive Lipid Lowering (RE-VERSAL)" (14) and "The Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22)" (15), have provided strong clinical evidence on independent effects of statins therapy on cardiovascular risk reduction mediated through decrease in hsCRP concentration. Many aspects about the strength and degree of the relation between inflammatory and metabolic disturbances in dia-

betics are still unknown. The FRISC study by Lindahl *et al.* was done on 917 diabetics with acute coronary syndrome. This study demonstrated that the initial concentration of CRP was a significant and independent predictor of the final outcome (16). Some other studies like TIMI-11A indicate that the higher concentration of CRP is associated with DM type 2 and suggest that it is a strong independent risk factor for the prognosis of disease (17).

In our study, the concentration of hsCRP was 30% lower, and albumin concentration was 5% higher in diabetics on statins therapy compared to the group under lifestyle modification therapy. This is an important reduction, which is in accord with the results in literature. The available literature shows a decrease in hsCRP by 30-40% in patients on statins therapy independently of the statins effect on lipid parameters, which indicates that this is the group drug effect (18). The concentration of hsCRP is the most important biomarker for development of CAD and its prognostic value is higher than LDL-C concentration in Framingham risk score (19). Besides its powerful prognostic significance for CAD it exerts proinflammatory and proatherogenic property. It is also a marker of the total inflammatory response due to which it is a good indicator of the anti-inflammatory therapeutic response.

The importance of hsCRP reduction in secondary prevention of CAD arises from the fact that atherosclerosis is stopped in patients with hsCRP reduction regardless of LDL-C concentration change (14).

The clinical study of secondary prevention CARE (18) has showed that the most important risk reduction is found in diabetics with a higher CRP concentration compared to diabetics with normal CRP concentration. Having in mind that CRP concentration is significantly increased in metabolic syndrome and DM type 2, we could expect a more prominent effect of statins in the reduction of risk for CAD and CRP concentration. We proved these expectations in our investigation. A similar study on diabetics under intensive 6-month statins therapy has showed a 15-47% decrease in CRP concentration (20).

In addition to endothelial cells, the expression of ICAM-1 can be observed in lymphocytes, monocytes, and different non-hematopoetic cells. VCAM is mainly expressed in endothelial cells, but it can also be expressed in lymphoid dendritic cells and tissue macrophages. Increasing concentrations of adhesion molecules are present in some pathologic conditions such as essential hypertension, cardiovascular diseases, and DM type 2 (21). In diabetics, the increased level of E-selectin, VCAM-1 and ICAM-1 present independent prognostic factors for cardiovascular mortality (22). However, some investigations among patients with DM type 2 show that only ICAM-1 has a significant correlation with the appearance of cardiovascular events 5 years after follow-up (23).

In this study, Statins therapy did not show any effects on ICAM-1 and VCAM-1 concentration among diabetics on secondary prevention of CAD.

Providing that all examined patients had a diagnosis of CAD for at least one year, this finding is consistent

with the results of other investigations, which have showed that ICAM-1 and VCAM-1 are markers of the initial phase of arteriosclerosis. At the same time, this is consistent with the results of Wiklund *et al.* They have demonstrated that statins therapy could not decrease the concentration of ICAM-1 in patients with DM type 2 (24).

In this study, there was no change in the total leukocyte count in patients on statins therapy. Framingham study has observed a clear correlation between the total leukocyte count and development of CAD. The increase in leukocyte number by 1×10^9/l raised the risk for CAD development by 32% in males and by 17% in females (25). The National Health and Nutrition Examination Survey (NHANES I) Epidemiological Follow-up study pointed out that male patients without CAD and with a total leukocyte count of more than 18.000/l had 1.55 relative risk for CAD development compared to those with a total leukocyte count between 8100-18000/l (26). In further analysis, they concluded that the main part of this additional risk originates from the neutrophile count, which shows the increased relative risk for CAD development to be 3.54 times in a higher quartile.

There was a significant increase in albumin concentration in patients on statins therapy. This has a prognostic importance because some population studies have showed a correlation between albumin concentration and development of CAD. Although albumin concentration is a negative reactant of the acute phase in the inflammatory response, cardiovascular risk decreases parallel with increase in albumin concentration. The results of NHANES I study (9-16 years of follow-up) indicate that albumin concentration is an important prognostic factor for CAD development (26). The relative risk was 0.51 in patients with albumin concentration higher than 44 g/l, compared to 0.70 in patients with lower albumin concentration. In Multiple Risk Factor Intervention Trial (MRFIT) patients with albumin concentration higher than 47 g/l had an 0.45 rela-

tive risk for cardiovascular mortality or CAD development, compared to patients with albumin concentration < 44 g/l (27). In a study designed to investigate the importance of different risk factors for cardiovascular mortality, there was an increase in the relative risk (2.5) in female patients with albumin concentration < 38 g/l, compared to females with concentration > 43 g/l (28).

Fibrinogen has an important role in haemostatic processes and increases the atherotrombotic risk. It is an acute phase protein and has a significant impact on serum viscosity and sedimentation rate. Because of that, it presents an independent risk factor for CAD development and additional coronary events. A meta-analysis of six prospective studies shows that a high fibrinogen concentration increases 2.3-fold the relative risk for cardiovascular diseases. A study on the Scottish population, conducted on 11,000 persons with a 7.6-year follow-up, has showed a significant connection between fibrinogen concentration and CAD development. Persons with fibrinogen concentration in the upper tercile of the value range had a 1.8 relative risk compared to persons with fibrinogen concentration in the lower tercile of the value range. Generally, this increase in risk is analogous with a change in fibrinogen concentration to 1 g/l (28).

Conclusion

Women with DM type 2 have prominent lipids and inflammatory disorders that are more prominent, compared to men with DM type 2. Statins therapy nullifies the excess of cardiovascular risk between genders, which indicates a greater benefit of statins therapy in female patients. Besides the sex-related differences, statins therapy exerts important anti-inflammatory effects through hsCRP reduction and increase of albumin concentration.

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ANTIINFLAMATORNI EFEKTI STATINSKE TERAPIJE KOD BOLESNIKA SA KORONARNOM BOLEŠĆU I DIJABETES MELITUSOM TIP 2

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Kratak sadržaj: *Kardiovaskularna oboljenja (KVB) u čijoj osnovi leži ateroskleroza, su najčešći uzrok smrti u svetu. U 2001. godini u Jugoslaviji je smrtnost od KVB iznosila 56%. Dijabetes melitus (DM) tip 2 je značajan faktor rizika za nastanak KVB, u oba pola. Cilj rada bio je određivanje antiinflamatornih efekata stainske terapije kod bolesnika sa koronarnom bolescu i DM tip 2, kroz praćenje pokazatelja sistemskog inflamatornog odgovora.*
Analizirano je 70 bolesnika obolelih od koronarne bolesti sa DM tip 2. Da bi se odredio antiinflamatorni efekat hipolipemične terapije vršeno je određivanje broja leukocita, koncentracije albumina, fibrinogena, visoko senzitivnog-hsCRP i ćelijskih adhezionih molekula (vaskularni adhezioni molekul VCAM-1 i intracelularni adhezioni molekul ICAM-1) u grupama bolesnika na terapiji statinima i bez statina.
Biomarkeri sistemskog inflamatornog odgovora, osim koncentracije VCAM-1, bili su značajno viši kod žena u odnosu na muškarce u grupi sa higijensko dijetetskim režimom. U grupi na terapiji statinima ova polno uslovljena razlika se gubi i jedino koncentracija ICAM-1 ostaje značajno veća kod žena. Dugoročna primena statina dovodi do značajne redukcije koncentracije hsCRP (30%) i povećanja koncentracije albumina (5%) u odnosu na grupu bez statinske terapije.
Prisutan je znatno povoljniji efekat statinske terapije kod žena sa DM tip 2 koji dovodi do veće redukcije inflamatornih pokazatelja rizika za KVB na vrednosti slične onima nađenim kod muškaraca. Primena statinske terapije u bolesnika sa DM tip 2 anulira "višak" rizika koji postoji kod žena u odnosu na muškarce. Statini ispoljavaju značajan antiinflamatorni efekat u dijabetičara i smanjenjem koncentracije hsCRP značajno redukuju rizik za pojavu KVB.

Ključne reči: *Ateroskleroza, statini, koronarna bolest, dijabetes*