EFFICIENCY OF ATORVASTATIN THERAPY FOR DECREASING THE LEVEL OF HIGHLY SENSITIVE C- REACTIVE PROTEIN (HSCRP) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Although cardiovascular morbidity and mortality are high in patients with type 2 diabetes mellitus, no more than 25% of the high risk level for a cardiovascular disease can be explained by traditional risk factors: high blood pressure, dislipidaemia and obesity by central mechanism. A great amount of data suggests that chronic inflammation is a major factor that leads to the progression of atherosclerosis and atherotrombosis. ***Materials and Methods****: there were included in the study 84 patients with type 2 diabetes mellitus, with no manifesting cardiovascular disease (CVD) and with acute cardiovascular events (CVE), treated with oral antidiabetics (biguanides and sulfonylureas) who were administered the treatment with Atorvastatin in doses of 10mg/day and 20mg/day, in two administration stages: a period of 4-8 weeks and one of 12-24 weeks.* ***Results and Discussions****: Within the whole group of patients in the study, there prevails the age group of 51-60 years old (41%), followed by the age group of 61-70 years old (28%). The hs-CRP values were significantly high in diabetic patients not treated with hypolipemiants comparatively to those treated with Atrovastatin, both in diabetic patients with acute cardiovascular events 10,92 ± 1,59mg/l vs. 4,75 ± 1,02mg/l, and in those without any manifesting cardiovascular disease 7,16 ± 3,79mg/l vs. 1,41 ± 0,64mg/l; hs-CRP decreased significantly with the increase of Atorvastatin dosis, not being influenced by the treatment duration (4-8 weeks vs. 12-24 weeks).* ***Conclusions****: In patients with acute myocardial heart attack or stroke, hs-CRP had significantly high values comparatively to those with no manifesting cardiovascular disease, no matter the patient's lipidic profile is. The statins treatment reduces the level of hs-CRP in a way mainly independent of the LDL cholesterol level.*

keywords*: hsCRP, Atorvastatin, type 2 diabetes mellitus.*

Introduction

The cardiovascular risk factors like smoking, high blood pressure (HBP), dislipidaemia and hyperglycemia play a proinflammatory part in triggering the endothelial dysfunction and the formation of atherosclerotic plaque [1, 2]. The lipids accumulation in the artery wall is the result of a complex process that involves inflammation, who leads to other lipidic accumulations. The endothelial dysfunction is representative in diabetes mellitus (DM) and insulin resistance and is characterized by the reduction of effective action of nitric oxide (NO). The hyperglycemic status involves a range of

mechanisms that determine the intensification of vascular tonus.

In patients with DM statins improve the endothelial dysfunction by stimulating the NO production by the endothelial cells, by modulating the release of NO and by the action of vasoconstrictors. According to the meta-analysis of 14 randomized trials (including CARDS, HPS, ALLHAT and ASCOT), the statins therapy minimizes the risk for major coronary events in patients with DM, but with no present vascular pathology [3]. According to the data resulted from the meta-analysis of 5 trials with primary prevention, the statins therapy similarly reduces the risk for major coronary events, both in patients with DM and in those without DM [4].

These proofs represente the basis for the recommendations of the National Cholesterol Education Program (NCEP) and the American Diabetes Association (ADA), which support the administration of statins as the first line therapy in patients with DM and dislipidaemia.

Materials and Methods

The patients included in the study were recruted from the Clinic of Diabetes and Nutrition Diseases, from the Center of Cardiology and from the Clinic of Neurology within the Emergency County Clinical Hospital in Craiova, as well as from the specialty ambulatory after an informing consent signed by each patient.

The patients distribution on groups was performed based on the study protocole, approved by the Ethical Board of the University of Medicine and Pharmacy Craiova.

In our study, we assessed the efficiency of Atorvastatin in the decrease of cardiovascular risk on the lipidic, glycemic metabolism and on inflammatory biomarkers in patients with type 2 diabetes mellitus with no manifesting cardiovascular disease (CVD) and in diabetic patients with acute cardiovascular events (CVE), who get Atorvastatin in doses of 10 mg/day and 20 mg/day, in two administration stages: a period of 4-8 weeks and one of 12-24 weeks.

Results and Discussions

The average age of the patients included in the study was of 61,12 ± 11,38 years old (age limits - 39 and 84 years old), with a significant difference between the two groups: in Group A (without any manifesting cardiovascular disease) the average age was of 53,61 ± 6,68 years old, while in Group B (with acute cardiovascular events) the average age was of 69,88 ± 9,27 years old. The sex distribution emphasized a prevalence of women in Group A of 61,9% vs. 38,1% and a high prevalence of men in Group B of 72.22% vs. 27,78%.

In the case of patients who were not treated with hypolipemiant drugs (A1,B1) the results of the glucose metabolism parameters showed that glycaemia and glicated hemoglobin (HbA1c) had higher values in patients with acute CVE (B1) in comparison to those without any manifesting CVD (A1) 165,5 ± 12,87mg/dl vs. 147,23 ± 22,39mg/dl, 7,4 ± 0,39% vs. 6,54 ± 0,41% respectively.

Total cholesterol, LDL cholesterol and Triglycerides had higher values in patients with no acute cardiovascular events comparatively to those who had suffered a myocardial heart attack or a stroke: 249,07 ±

38,26mg/dl vs. 223 ± 39,81mg/dl, 123,34 ± 33,32mg/dl vs. 119 ± 36,63mg/dl and 199,23 ± 36,97 vs.155,50 ± 15,46mg/dl, which demonstrates that acute cardiovascular events in diabetic patients may appear in normal values of the lipidic parameters (Tables 1, 2).

HDL cholesterol had a higher value in patients without any CVD in comparison to those with acute CVE 34,41 ± 2,26mg/dl vs. 32,75 ± 1,30mg/dl, but under the target level for patients with type 2 diabetes mellitus.

The concept according to which the inflammation governs atherosclerosis and its complications has given a new hypothesis regarding the connections between the risk factors, as well as cellular and molecular alterations that stand at the basis of this disease. This construction offers us not only a new perspective on the disease emergence mechanisms, but it has also started to produce changes within the clinical practice [5].

Most of present data supports the power of prediction of the inflammation biomarkers in large categories of individuals, both in those apparently healthy and in those with manifesting cardiovascular disease [5].

High levels of CRP are associated with the minimizing of the synthetase nitric-oxide expression, which may diminish the nitric-oxide (NO) production, promotes the oxidative alteration of LDL and favours the action of inhibitor-1 of the plasminogen activator [6].

The average values of the glycemic, lipidic metabolism parameters and hs-CRP in patients not treated with hypolipemiants are emphasized in Table 1.

Table 1. Characteristics of patients with type 2 DM not treated with hypolipemiants.

Characteristics	A1W	A1M	A1T	B1W	B1M	B1T
Glycaemia [mg/dl]	143,22 +-21,75	156,25 +-24,22	147,23 +-22,39	163,00 +-11,38	166,12 +-6,32	165,5 +-12,87
HbA1c [%]	6,45 +-0,39	6,75 +-0,43	6,54 +-0,41	7,29 +-0,30	7,43 +-0,20	7,4 +-0,39
Total Chol, [mg/dl]	255,66 +-28,77	234,25 +-56,80	249,07 +-38,26	270 +-9,17	211,25 +-15,12	223 +-39,81
LDL Chol, [mg/dl]	133,95 +-25,87	99,47 +-39,49	123,34 +-33,32	163,60 +-11,52	107,85 +-14,81	119 +-36,63
HDL Chol, [mg/dl]	34,71 +-2,10	33,75 +-2,79	34,41 +-2,26	32,3 +-0,53	32,86 +-3,12	32,75 +-1,30
Triglycerides [mg/dl]	189,77 +-30,44	220,5 +-46,11	199,23 +-36,97	161,5 +-13,21	154 +-6,94	155,50 +-15,46
hs-CRP [mg/l]	6,48 +-3,65	8,7 +-4,17	7,16 +-3,79	10,7 +-0,64	10,97 +-0,45	10,92 +-1,59

Note: A1= the subgroup without any manifesting CVD, B1= the subgroup with acute cardiovascular events, W= women, M= men, T= total.

Table 2. Characteristics of patients with DM type 2 treated with Atorvastatin

Characteristics	A2W	A2M	A2T	B2W	B2M	B2T
Glycaemia [mg/dl]	136,750 +-12,72	132 +-13,70	134,37 +-8,89	148 +-10,14	179,60 +-21,73	167,75 +-23,80
HbA1c [%]	6,77 +-0,26	6,59 +-0,42	6,68 +-0,25	6,91 +-0,33	7,94 +-0,75	7,55 +-0,80
Total Chol, [mg/dl]	204,25 +-2,82	199,25 +-35,33	201,75 +-11,88	203,33 +-7,57	196,80 +-15,72	199,25 +-13,00
LDL Chol, [mg/dl]	90,65 +-4,80	88,4 +-31,80	89,52 +-12,34	88,27 +-7,91	80,28 +-19,27	83,27 +-15,72
HDL Chol, [mg/dl]	38,9 +-0,42	37,65 +-1,45	38,27 +-2,17	38,83 +-2,66	36,68 +-1,78	37,49 +-2,25
Triglycerides [mg/dl]	163 +-0,42	159,75 +-17,11	161,37 +-9,92	166,33 +-3,78	174,200 +-16,67	171,25 +-13,40
hs-CRP [mg/l]	1,05 +-1,37	1,77 +-1,61	1,41 +-0,64	4,4 +-1,35	4,96 +-0,87	4,75 +-1,02

Note: A2= the subgroup without any manifesting cardiovascular disease,
B2= the subgroup with acute cardiovascular events, W= women, M= men, T= total.

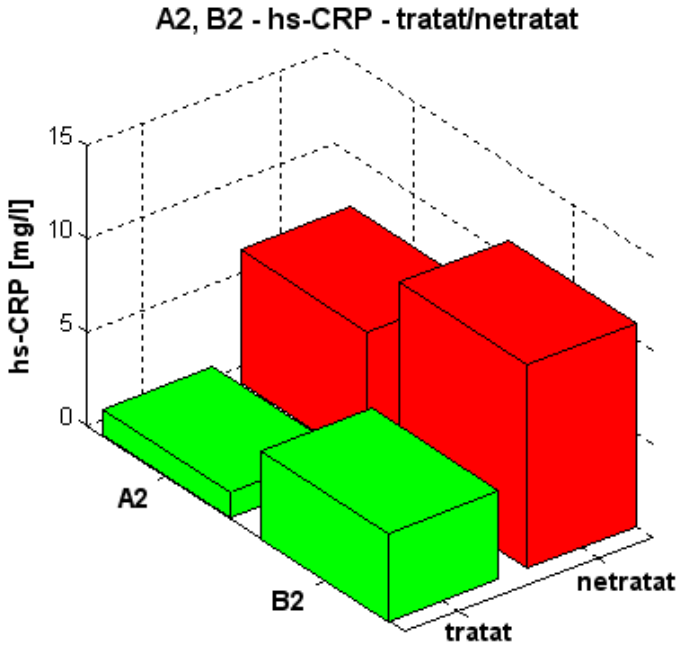

Figure 1. Graphic representation of hs-CRP values in patients treated with Atorvastatin (A2MB2) and not treated with hypolipemiants (A1B1).

In both subgroups of patients, the women registered higher values of total cholesterol and LDL cholesterol, while men presented high values of glycaemia, oxidate LDL and hsCRP, in comparison to women.

In our research study, the hs-CRP values were significantly high in diabetic patients not treated with hypolipemiants in comparison to those treated with Atorvastatin, both in diabetic patients with acute cardiovascular events (CVE) (B2) and also in those without any manifesting cardiovascular disease (CVD) (A2), (Figure 1); hs-CRP significantly decreased along with the increase of Atorvastatin dosis, not being influenced by the duration of treatment (4-8 weeks vs. 12-24 weeks).

Important data regarding the benefit of the hypolipemiant treatment on the improvement of the prognosis in patients with DM have been given by ASCOT-LLA and CARDS studies [7, 8]. In the ASCOT-LLA study, the administration of Atorvastatin in diabetic patients reduced the number of cardiovascular complications with 36% over a surveillance period of 3.3 years [7]. At the same time, the results of CARDS study have shown a reduction of cardiovascular complications by 37% when Atorvastatin was used by diabetic patients over a period of surveillance of 3.9 years [8].

In our study, we have found evidence for the benefit of patients in which the statins treatment led to hs-CRP concentrations under 2mg/l, independent of the LDL cholesterol levels reaching or not the target value under 70mg/l. In this matter, our data is in accordance with the research indicating that inflammation is a determining factor for plaque instability, as well as with the experimental data pointing out that statins, besides the decreasing effect for lipids, also present important antiinflammatory effects [9].

Although it was proven that the statins treatment reduces the hs-CRP level in a way mostly independent on the LDL cholesterol level, but is missing the evidence that connects a higher reduction of hs-CRP levels with a decrease in the number of cardiovascular events. The clinical necessity for the inflammatory biomarkers has generated a high interest and present investigations assess the cost-efficiency ratio for these to become a prediction instrument beyond the conventional risk factors.

The proposal that hsCRP levels should become a guide and/or a therapeutical target has been supported by the worldwide clinical studies.

The rapid transfer of inflammation biology within cardiovascular diseases, from laboratory to clinic, serves as a nice example of direct research near the patient's bed. Despite all these, a great deal of questions remain unsolved regarding this matter and in the future we can expect considerable challenges regarding the emergence of experimental and clinical studies meant to help solving some controversed aspects.

The application of inflammation biology within atherosclerosis has already provided a new perspective on the manner in which present interventions, both pharmacological and regarding life style, may reduce the cardiovascular risk. Finally, accepting the fact that inflammation plays a fundamental part in atherosclerosis may lead to new treatments, in which target aspects may be the subclinical inflammatory process from the inside of atheroma plaque [5].

Conclusions

1. The statins treatment reduces the hs-CRP level in a way mostly independent of the LDL cholesterol level, but is missing the

evidence that connect a more significant decrease in hs-CRP levels with the reduction of cardiovascular events.

2. The pro inflammatory status, characterized by high values of highly sensitive C-reactive protein also represents a marker for cardiovascular risk, alongside the other risk factors (obesity, HBP, smoking, dislipidaemia).

3. In patients with acute myocard heart attack or stroke, hs-CRP had significantly higher values than in those without any manifesting cardiovascular disease, disregarding the patients' lipidic profile, which suggests that it may be considered an independent predictive factor for cardiovascular risk.

REFERENCES

1. Yeh ETH, Palusinski RP: C-reactive protein: the pawn has been promoted to queen. *Curr Atheroscler* 2003; Rep 5: 101-105.

2. Cleland SJ, Sattar N, Petrie JR, Forouhi NG, Elliott HL, Connell JMC: Endothelial dysfunction as a possible link between C-reactive protein levels and cardiovascular disease. *Clin Sci* 2000; 98: 531-535.

3. Cholesterol Treatment Trialists' (CTT) collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90056 participants in 14 randomised trials of statins. *Lancet*, 2005; no. 366: 1267-1278.

4. Costa J. et al. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomized controlled trials. *BMJ* 2006; vol.332, 115-24.

5. Libby P, Ridker PM. Inflammation and atherothrombosis: from population biology and bench research to clinical practice. *J Am Coll Cardiol* 2006; 48: A33-A46.

6. Verma S, Wang C-H, Li S-H, Dumont AS, Fedak PWM, Badiwala MV, Dhillon B, Weisel RD, Li R-K, Mickle DAG, Stewart DJ: A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation* 2002; 106: 913 -919.

7. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Östergren J, for the ASCOT investigators: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. 2003; *Lancet* 361: 1149-1158.

8. Colhoun H, Betteridge D, Durrington P. et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2001; vol. 364, no. 9435, 685-696.

9. Shah P.K. Mechanisms of plaque vulnerability and rupture. *J Am Coll Cardiol* 2003; vol. 41, 15-22.

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