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Lipid Lowering Therapy and Endothelial Function in Patients with Metabolic Syndrome

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Abstract

Introduction: Endothelial dysfunction (ED) plays an important role in the development and clinical manifestation of atherosclerosis. Endothelial dysfunction has been defined as the barometer of vascular health. Therefore, the development of reliable, safe, and noninvasive methods of endothelial function assessment is important for their use in cardiovascular risk stratification. We investigated the effects of lipid lowering therapy on endothelial dysfunction in patients with metabolic syndrome.

Methods: 74 patients (36 men, 38 women) with metabolic syndrome treated with atorvastatin monotherapy not reaching plasma target levels of LDL cholesterol were enrolled to trial. In first group up titration with atorvastatin, in second group combination therapy atorvastatin+fenofibrate and in third group atorvastatin+omega 3-fatty acid were used to reach plasma target levels of LDL cholesterol for follow up of 3 months treatment. The endothelial function/dysfunction was assessed by laboratory biomarkers according to change of the lipid levels.

Results: After 3 months of follow up we observed statistically significant changes in laboratory biomarkers of endothelial dysfunction in all patients. We observed increase in glutation peroxidase (48.53 ± 10.52 vs 45.61 ± 10.50, p <0.05), as well as the decrease in hsCRP (2.96 ± 2.20 vs 2.49 ± 1.77, p <0.05), Lp (a) (0.30 ± 0.38 vs 0.35 ± 0.46, p <0.05), apo B (0.97 ± 0.34 vs 1.18 ± 0.36, p <0.05) and homocysteine (12.99 ± 3.48 vs 17.54 ± 5.42, p <0.05).

Conclusion: The lipid lowering therapy improved endothelial function in patients with metabolic syndrome. Based on the currently available evidence, combination therapy may provide similar beneficial effects on endothelial function as statin monotherapy.

Keywords: Endothelial function; Lipid lowering therapy; Metabolic syndrome

Introduction

Cardiovascular diseases are the main cause of death worldwide. Metabolic syndrome with its components is one of the most important risk factors for cardiovascular disease. The principal consequence of the syndrome elements and cause of death is atherosclerosis. Treatment of each components of the metabolic syndrome delays the development of cardiovascular complications. It is very important to provide prevention and treatment of those risk factors, to achieve the reduction of cardiovascular morbidity and mortality [1].

Metabolic syndrome has been commonly defined by IDF classification [2]. These factors all lead to endothelial dysfunction. Endothelial dysfunction plays an important role in the development and clinical manifestation of atherosclerosis. The aim of this work is to compare the efectiveness and impact of hypolipidemics on endothelial function in the patients with metabolic syndrome [3].

Endothelial dysfunction

Peripheral endothelial function correlates well with coronary endothelial vasodilation and is reduced in patients with cardiovascular risk factors such as obesity, hypercholesterolemia, hypertension and diabetes [4,5]. We can clinically diagnose of endothelial dysfunction using special laboratory markers (hsCRP, superoxide dismutase, glutathione peroxidase, interleukin [6], invasive (quantitative coronary angiography) and non- invasive methods [6].

Methods

74 patients (36 men, 38 women) with metabolic syndrome treated with atorvastatin monotherapy not reaching plasma target levels of LDL cholesterol were enrolled to trial. In first group up titration with atorvastatin, in second group combination therapy atorvastatin+fenofibrate and in third group atorvastatin+omega 3-fatty acid were used to reach plasma target levels of LDL cholesterol for follow up of 3 months treatment. The baseline data was collected between June 2012 and March 2014.

Exclusion criteria: history of myositis/myopathy, creatine kinase (CK) level >10.0 times the upper limit of normal, alanine aminotransferase (ALT), aspartate aminotransferase (AST) or bilirubin 3.0 times the upper limit of normal, malignancy, no active endocrine disease (excluded were patients with thyroid gland disorders) and/or increased level of TSH, neuromuscular and joint disease and reluctance to discontinue statin therapy. Lipid lowering therapy was taken once daily in the evening. The endothelial function/

dysfunction was assessed by laboratory biomarkers according to change of the lipid levels. Fasting venous blood samples were collected for plasma glucose and serum lipid profile (total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol [HDL-C]). TG, TC, HDL-C, and glucose levels were measured by enzymatic reference method on an automated analyzer. Glutathione peroxidase (GPX) was measured by set RANSEL on an automated analyzer. Blood samples for lipid profiles, hsCRP, Lp (a), apoB, homocysteine, glutathione peroxidase and safety assessment (aspartate aminotransferase, alanine aminotransferase, and creatine kinase) were collected at least two times before study and after 3 months of treatment. TSH level was determined in every patient. Appropriate ethics committees approved the trial, and all participants gave their written, informed consent before any study procedure. Anthropometrical measures which included waist circumference (WC) and blood pressure (BP) were obtained.

Statistical Analysis

The statistical data are expressed as mean values ± SE. For statistical hypothesis testing of the diameter differences between the treatment groups were used Wilcoxon test for paired values (before and post treatment) or Kruskall Wallis test for differences in the unpaired variables between more groups with the post hoc analysis of LSD test. Significance level was set at P value of <0.05.

Results

A total of 74 patients (36 men, 38 women) participated in this study. The mean age of the participants was 60.74 years (between 31-82 years). Patient receiving combination treatment of atorvastatin and omega-3 polyunsaturated fatty acids (n-3 PUFAs) represented group of 27 patients (36.49%). In group of patients treated by atorvastatin monotherapy was 24 patients (32.43%): 15 patients on atorvastatin at a dose of 20 mg, 5 patients at a dose of 40 mg, 2 patients in the 60 mg and 2 patients at a dose of 80 mg. 23 patients (31.08%) represented group of patients treated by combination treatment with atorvastatin+fenofibrate at a dose of 145 mg.

IDF Criteria	Prevalence	%
Abdominal obesity	74	100
Art.hypertension/↑ BP	72	97.78
Diabetes mellitus of type 2/High FPG	55	74.33
High TG	47	63.51
Low HDL-C	21	28.38

Table 1: Prevalence of components contributed to metabolic syndrome in patients.

Table 1 outlines the prevalence of components contributing to MetS. Low HDL-C level was the least frequent component contributing to MetS while abdominal obesity was the most common component in patients.

Effect of lipid-lowering therapy on lipid profile

For all studied 74 patients after 3 months, we observed a significant reduction in total cholesterol (4.26 ± 0.92 vs 5.37 ± 1.38, p <0.05), LDL-C (2.22 ± 0.80 vs 3.22 ± 1.19, p<0.05), TG (1.61 ± 1.04 vs 2.42 ± 2, 19, p <0.05), HDL-C (1.31 ± 0.26 vs 1.17 ± 0.29, p<0.05) and CK (2.67 ± 1.09 vs 2.32 ± 1.13, p <0.05) (Table 2).

	Patients	Before treatment	After treatment	P
TC	74	5.37 ± 1.38	4.26 ± 0.92	0.000
LDL-C	74	3.22 ± 1.19	2.22 ± 0.80	0.000
TG	74	2.42 ± 2.19	1.61 ± 1.04	0.000
HDL-C	74	1.17 ± 0.29	1.31 ± 0.26	0.000
FPG	74	6.89 ± 2.16	6.71 ± 2.38	NS
bilirubin	74	9.98 ± 3.86	9.84 ± 3.73	NS
AST	74	0.37 ± 0.14	0.38 ± 0.13	NS
ALT	74	0.47 ± 0.38	0.48 ± 0.20	0.055
GMT	74	0.75 ± 0.68	0.70 ± 0.41	NS
ALP	74	1.35 ± 0.37	1.35 ± 0.31	NS
CK	74	2.32 ± 1.13	2.67 ± 1.09	0.000

Table 2: Comparison of laboratory parameters before and after 3 months of treatment in all patients.

	Patients	Before treatment	After treatment	P
TC	24	5.68 ± 1.38	4.26 ± 0.98	0
LDL-C	24	3.51 ± 1.15	2.24 ± 0.83	0
TG	24	2.04 ± 1.15	1.42 ± 0.28	0.001
HDL-C	24	1.26 ± 0.32	1.30 ± 0.21	0.005
FPG	24	6.61 ± 2.14	6.81 ± 2.91	NS
bilirubin	24	8.76 ± 3.06	9.08 ± 3.23	NS
AST	24	0.35 ± 0.09	0.33 ± 0.07	NS
ALT	24	0.40 ± 0.22	0.39 ± 0.17	NS
GMT	24	0.71 ± 0.72	0.59 ± 0.27	NS
ALP	24	1.44 ± 0.41	1.45 ± 0.36	NS
CK	24	2.43 ± 1.29	2.45 ± 1.10	NS

Table 3: Comparison of laboratory parameters before and after 3 months of treatment in patients with atorvastatin monotherapy.

However, a greater decrease in total cholesterol (4.26 ± 0.98 vs 5.68 ± 1.38, p <0.05) and LDL-C (2.24 ± 0.83 vs 3.51 ± 1.15, p <0.05) was observed in group 1 patients (atorvastatin monotherapy) and a higher increase in HDL-C was observed in combination treatment of atorvastatin and omega-3 polyunsaturated fatty acids (1.35 ± 0.29 vs 1.11 ± 0.23, p <0.05), although there were not statistically significant changes. Triglycerides were significantly reduced in patients in (atorvastatin + fenofibrate) group (2.39 ± 2.22 vs 4.31 ± 4.63, p <0.05) (Table 3-5).

	Patients	Before treatment	After treatment	P
TC	23	5.54 ± 1.50	4.30 ± 1.03	0.004
LDL-C	23	3.11 ± 1.31	2.06 ± 0.86	0.002
TG	23	4.31 ± 4.63	2.39 ± 2.22	0.003
HDL-C	23	1.14 ± 0.35	1.21 ± 0.23	NS
FPG	23	8.38 ± 2.70	8.02 ± 2.74	NS
bilirubin	23	9.88 ± 3.97	10.32 ± 3.80	NS
AST	23	0.37 ± 0.12	0.38 ± 0.06	NS
ALT	23	0.47 ± 0.25	0.50 ± 0.20	NS
GMT	23	0.69 ± 0.27	0.74 ± 0.43	NS
ALP	23	1.36 ± 0.38	1.36 ± 0.32	NS
CK	23	2.16 ± 0.87	2.76 ± 1.41	0.046

Table 4: Comparison of laboratory parameters before and after 3 months of treatment in patients with combination therapy atorvastatin +fenofibrate.

	Patients	Before treatment	After treatment	P
TC	27	5.04 ± 1.30	4.24 ± 0.87	0
LDL-C	27	3.03 ± 1.17	2.26 ± 0.77	0
TG	27	2.04 ± 0.67	1.45 ± 0.47	0
HDL-C	27	1.11 ± 0.23	1.35 ± 0.29	0
FPG	27	6.58 ± 1.74	6.18 ± 1.57	NS
bilirubin	27	11.02 ± 4.18	10.17 ± 4.02	NS
AST	27	0.39 ± 0.18	0.41 ± 0.17	NS
ALT	27	0.52 ± 0.51	0.53 ± 0.19	0.002
GMT	27	0.80 ± 0.74	0.76 ± 0.46	NS
ALP	27	1.28 ± 0.32	1.29 ± 0.26	NS
CK	27	2.29 ± 1.10	2.78 ± 0.95	0.001

Table 5: Comparison of laboratory parameters before and after 3 months of treatment in patients with combination therapy atorvastatin +omega-3 fatty acids.

Effect of lipid-lowering therapy on laboratory markers and risk factors of endothelial dysfunction. After 3 months of taking lipid-lowering therapy we observed the statistically significant changes in laboratory biomarkers and risk factors of endothelial dysfunction in all patients. There was increase of GPX (48.53 ± 10.52 vs 45.61 ± 10.50, p <0.05) and the decrease of hsCRP (2.96 ± 2.20 vs 2.49 ± 1.77, p <0.05), Lp (a) (0.30 ± 0.38 vs 0.35 ± 0.46, p <0.05), apoB (0.97 ± 0.34 vs 1.18 ± 0.36, p <0.05) and homocysteine (12.99 ± 3.48 vs 17.54 ± 5.42, p<0.05) (Table 6).

	Patients	Before treatment	After treatment	P
hsCRP	74	2.96 ± 2.20	2.49 ± 1.77	0.002
Lp(a)	74	0.35 ± 0.46	0.30 ± 0.38	0
apoB	74	1.18 ± 0.36	0.97 ± 0.34	0
HCYS	74	17.54 ± 5.42	12.99 ± 3.48	0
GPX	74	45.61 ± 10.50	48.53 ± 10.52	0

Table 6: Comparison of laboratory biomarkers and risk factors of endothelial dysfunction before and after 3 months of treatment in all patients.

No significant change was noted in hsCRP level in first group (atorvastatin monotherapy) (Table 7).

	Patients	Before treatment	After treatment	P
hsCRP	24	3.13 ± 2.14	2.53 ± 1.95	NS
Lp (a)	24	0.29 ± 0.28	0.24 ± 0.28	0.035
apoB	24	1.23 ± 0.38	1.02 ± 0.36	0.001
HCYS	24	15.93 ± 5.56	12.20 ± 4.18	0
GPX	24	51.37 ± 9.99	55.75 ± 10.60	0

Table 7: Comparison of laboratory biomarkers and risk factors of endothelial dysfunction before and after 3 months of treatment in patients with atorvastatin monotherapy.

In combination therapy atorvastatin+fenofibrate group we observed the most significant decrease in Lp (a) (0.48 ± 0.61 vs 0.61 ± 0.91, p=0.008) (Table 8).

	Patients	Before treatment	After treatment	P
hsCRP	23	3.15 ± 1.98	2.74 ± 1.82	0.016
Lp(a)	23	0.61 ± 0.91	0.48 ± 0.61	0.008
apoB	23	1.20 ± 0.32	0.96 ± 0.22	0.001
HCYS	23	16.36 ± 4.12	12.17 ± 2.93	0.002
GPX	23	43.35 ± 10. 34	44.11 ± 10.08	0.009

Table 8: Comparison of laboratory biomarkers and risk factors of endothelial dysfunction before and after 3 months of treatment in patients with combination therapy of atorvastatin and fenofibrate.

Combination therapy of statin and n-3 PUFAs shown the most significant decrease in apoB (0.94 ± 0.36 vs 1.13 ± 0.35, p = 0.0001) and homocysteine (13.78 ± 3, 05 vs 19.31 ± 5.29, p= 0.0001) from the all study groups (Table 9).

Discussion

The present study showed that all 3 groups of lipid lowering therapy significantly reduced total cholesterol, LDL-C and increased HDL-C. Treatment with combination therapy atorvastatin+fenofibrate

produced greater improvement in TG and total than other two groups, what is also in line with several major study, including ACCORD (Action to Control the Cardiovascular Risk in Diabetes Study Lipid) and FIELD (Fenofibrate Intervention and Event Lowering in Diabetes Study), which confirmed that a large number of patients with atherogenic dyslipidemia mainly benefit from a combination therapy of a statin with fenofibrate [7-9]. Statin therapy lead to similar decrease of TCH, LDL-C and HDL-C irrespective administered either in monotherapy or in combination (with n-3 PUFA or fenofibrate). In other words, no additional positive significant effects on TCH, LDL-C and HDL-C were observed when n-3 PUFA or fenofibrate were added to statin monotherapy.

	Patients	Before treatment	After treatment	P
hsCRP	27	2.76 ± 2.36	2.37 ± 1.65	NS
Lp (a)	27	0.30 ± 0.29	0.29 ± 0.33	0
apoB	27	1.13 ± 0.35	0.94 ± 0.36	0
HCYS	27	19.31 ± 5.29	13.78 ± 3.05	0
GPX	27	41.65 ± 8.90	45.20 ± 8.01	0

Table 9: Comparison of laboratory biomarkers and risk factors of endothelial dysfunction before and after 3 months of treatment in patients with combination therapy of atorvastatin and n-3 PUFAs.

Statins also have significant non-lipid lowering effects. Statins modulate series of processes leading to reduction of the accumulation of esterified cholesterol into macrophages, increase of endothelial NO synthetase, reduction of the inflammatory process, increased stability of the atherosclerotic plaques, restoration of platelets activity and of the coagulation process. HMG- CoA reductase, and only statins were suggested to improve endothelial function and proinflammatory cytokines. Inflammation plays a vital role in the development and progression of atherosclerosis [10]. Statins modulate series of processes leading to reduction of the accumulation of esterified cholesterol into macrophages, increase of endothelial NO synthetase, reduction of the inflammatory process, increased stability of the atherosclerotic plaques, restoration of platelets activity and of the coagulation process. In addition, statins can inhibit tumor cell growth and enhance intracellular calcium mobilization. Statins have also been suggested to inhibit hsCRP, the most reliable and accessible inflammation marker for clinical use [11]. In our study, in all treated patients, we shown statistically significant decrease of plasma hs-CRP (p=0.002). The most significant difference (p=0.016) was observed using combination therapy of a statin + fenofibrate. Furthermore, hsCRP showed a positive correlation with the LDL-C.

For other risk factors of endothelial dysfunction (Lp (a), apoB and homocysteine) we also observed a statistically significant difference after three months treatment with lipid-lowering agents. The decrease of homocysteine level was significant but still it has to be regarded as not optimal.

Statins also have significant role in reduction of oxidative stress. In our study we observed significantly increased of glutathione peroxidase (48.53 ± 10.52 vs 45.61 ± 10.50, p <0.0001). However, there was no statistically significant difference between treatment groups, a slight higher increase was observed using monotherapy or combination therapy statin with an n-3.

PUFAs therapy compared to statin and fibrate combination. On the other hand, 12 weeks study of atorvastatin and simvastatin suggested that an important role of oxidative stress lowering as possible pleiotropic effect of atorvastatin and simvastatin is questionable [12].

Statins are generally well tolerated. The most common possible adverse effects during treatment with statins is asymptomatic elevation of liver enzymes and myopathy. Myopathy associated with statin therapy represents a wide variety of conditions, ranging from myalgia (muscle pain without elevation of creatine kinase), myositis (also present elevation of creatine kinase) and ending with rhabdomyolysis (creatine kinase levels increased significantly, often more than ten times over the upper limit of normal also associated with an increase in creatinine). In large clinical trials, the occurrence of severe myopathy described by 0.1-0.5%, while the incidence of rhabdomyolysis is 0.02 to 0.04%.

Mechanism of statin myopathy is not fully explained yet, but most likely involves the reduction of coenzyme Q10 (CoQ10). The objective of this study was to evaluate the possible benefits of coenzyme Q and selenium supplementation administered to patients with statin-associated myopathy (SAM). In conclusion, supplementation of statin-treated patients with CoQ10 resulted in a decrease in the symptoms of SAM, both in absolute numbers and intensity. Additional selenium supplementation was not associated with any statistically significant decrease of SAM. However, it is not possible to draw any definite conclusions, even though this study was carried out in double-blind fashion, because it involved a small number of patients [13].

In addition, examination of the safety profiles of the treatment groups showed that all three groups were well tolerated in patients with metabolic syndrome over a 3-months-period. No patient discontinued the study because of an adverse event. Clinically relevant increases in CK or hepatic transaminases, indicative of myotoxicity or hepatotoxicity, were not observed within either trial group (Table 3-5) [14].

Of course, a longer follow up would be needed in order to test more relevant functional parameters such as arterial stiffness. Nevertheless, tested biochemical systemic biomarkers along with evaluation of endothelial dysfunction (ENDOPAT 2000) could provide important information non-lipid modifiable effects of different lipid-lowering drugs used either in monotherapy or in combination.

Our trial has several limitations. It was pilot trial with limited number of patients, with no homogenic group for comparism and different number of patients in group and the results should be also seen in light of limitations.

References

1. Vaughan CJ, Gotto AM Jr, Basson CT (2000) The evolving role of statins in the management of atherosclerosis. J Am Coll Cardiol 35: 1-10.
2. Ghosh A (2011) The metabolic syndrome: a definition dilemma. Cardiovasc J Afr 22: 295-296.
3. Reiner Ž, Catapano AL, De Backer G (2011). ESC/EAS Guidelines for the management of dyslipidaemias. The task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). In European Heart Journal 32: 1769-1818.
4. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, et al. (2000) Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 101: 948-954.

5. Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, et al. (2002) Prognostic value of coronary vascular endothelial dysfunction. Circulation 106: 653-658.
6. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, et al. (2010) Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J 31: 1142-1148.
7. Scott R, O'Brien R, Fulcher G, Pardy C, D'Emden M, et al. (2009) Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care 32: 493-498.
8. Moutzouri E, Kei A, Elisaf MS, Milionis HJ (2010) Management of dyslipidemias with fibrates, alone and in combination with statins: role of delayed-release fenofibric acid. Vasc Health Risk Manag 6: 525-539.
9. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, et al. (2010) Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 362: 1563-1574.
10. Catapano AL, Chapman J, Wiklund O, Taskinen MR (2011) The new joint EAS/ESC guidelines for the management of dyslipidaemias. Atherosclerosis 217: 1.
11. Ceska R, Kvasilová M, Procházková R, Smelková G, Vrablík M (2010) Hyperlipoproteinaemia and dyslipoproteinaemia I. Classification, diagnostics, cardiovascular, cardiometabolic and residual risk. Vnitr Lek 56: 526-531.
12. Scheffer PG, Schindhelm RK, van Verschuer VM, Groenemeijer M, Simsek S, et al. (2013) No effect of atorvastatin and simvastatin on oxidative stress in patients at high risk for cardiovascular disease. Neth J Med 71: 359-365.
13. Fedacko J, Pella D, Fedackova P, Hänninen O, Tuomainen P, et al. (2013) Coenzyme Q(10) and selenium in statin-associated myopathy treatment. Can J Physiol Pharmacol 91: 165-170.
14. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B (2005) Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovasc Drugs Ther 19: 403-414.