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Interrelation between statins and endothelial dysfunction marker in male and female patients with coronary atherosclerosis

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Summary

Objective

To analyze the interrelation between the marker of endothelial dysfunction endothelin and hypolipedemic drugs administration in patients with verified coronary arteries (CA) lesions

Materials and methods

This study included 429 patients (302 males and 127 females) in the age of 62,7±8,8 years with CA lesions verified with coronary angiography. Endothelin levels in serum were measured with immune-enzyme assay ELISA.

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Results

Negative correlation between statins therapy and endothelin levels was identified in male patients (r= -0,11, P=0,04). We revealed that males undergoing statin therapy (n=294) had 1,8 times less endothelin levels comparing with the men who did not receive statins. The interrelation between statin administration and endothelin levels in female patients with CA lesions was not found.

Conclusion

In male patients with CA lesions, as opposed to females, statin administration correlates negatively with endothelin levels and is associated with its 2-fold decrease. Interrelation between endothelin concentration and administration of other drugs was not found.

Keywords

Atherosclerosis, endothelial dysfunction, endothelin, statins.

Introduction

Atherosclerosis that develops asymptomatically during many years underlies many cardiovascular diseases(CVD). Endothelial dysfunction of vascular wall is an initial step of atherogenesis, because of that it is considered to be the marker of early atherosclerosis development [1, 2]. Endothelial dysfunction(ED) is caused by impaired functional activity of vascular endothelium accompanied with unbalanced vasodilators' and vasoconstrictors' production that changes vascular tone. Endothelin is studied better than other known vasoconstrictors produced by endothelium from the point of view of signaling pathways regulation [3]. High endothelin levels are observed in such disorders like acute myocardial infarction, cardiac rhythm abnormalities, myocardial hypertrophy, coronary heart disease (CHD) and it is associated with main cardiovascular disease (CVD) risk factors [4,5]. Thus, misbalanced endothelin production can indicate endothelial dysfunction and other associated abnormalities determining atherosclerosis development.

Big consideration is given to the possibility of ED correction with pharmacological therapy. Wide spectrum of medicines is used for CVD treatment. The most effective groups between them are statins, beta-blockers, anticoagulants, antiaggregants, diuretics, nitrates, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers ets. Particular attention is paid to pleiotropic effects of statins – HMG-CoA reductase inhibitors [6, 7]. Apart of hypolipidemic and antiatherogenic activity positive effect of statins on endothelium can be explained by their antioxidant and endothelium-protective action [8-10]. Investigation of statins pleiotropic effects and particularly their influence on vascular endothelium is of high scientific interest.

The aim of this work was to analyze the interrelation between endothelin as the marker of endothelial dysfunction and administration of statins and other drugs in patients with verified coronary arteries (CA) lesions.

Materials and methods

This study included male and female patients in the age of 30-80 years who were admitted to the National Research Centre for Preventive Medicine for diagnostics and treatment of suspected CHD and who were referred for coronary angiography (CAG) during 2011-2012.

CA lesions verified by CAG were considered as the inclusion criteria for this study. Exclusion criteria for this study were: history of myocardial infarction or stroke less than 6 months ago, any acute inflammatory disease, 3 or more stage of chronic kidney disease (glomerular filtration rate less than 60ml/min/1,73m^2), decompensated diabetes mellitus, both types (glycated hemoglobin levels >7,5%), left ventricle ejection fraction <40%, cancer, hematological diseases including trombocytopathies and coagulopathies, immune system disorders, pregnancy and lactation.

This study was performed according with the principles of Helsinki Declaration. Study protocol was approved by Ethic Committee of the National Research Centre for Preventive Medicine. All patients gave written informed consent for participation in the study and personal data proceeding.

Blood pressure was measured on the right arm in the sitting position after 5-10 minutes of rest twice after 5-minutes break, and the average of 2 measurements was analyzed. Heart rate (HR) was estimated during 60 seconds in the sitting position of patient after rest.

Blood sampling was performed from cubital vein after 12 h of starvation. Blood serum was obtained from blood after centrifugation at 4 ºC degree, 1000 g, for 10 minutes. Blood serum was aliquotated and stored at -26 ºC before analysis.

Then we measured total cholesterol (TC), triglycerides (TG) and high density lipids (HDL) cholesterol levels (after low density lipids (LDL) sedimentation with sodium phosphovolframate and $MgCl_2$) were obtained using enzymatic kits provided by company"Human"(Germany) and automatic analyzer "Konelab 20i" (Finland). LDL lipids concentrations was quantified using Friedewald formula.

Endothelin 1-21 concentration was measured with the kit provided by "Biomedica" (Austria) using solid-phase immunoenzyme assay ELISE according with manufacturer's instruction.

Statistical analysis of the results was performed using Statistica 8.0 software. For each continuous quantity depending on distribution type we measured average value and standard deviation (SD). To estimate the differences between two groups we used non-parametric Mann-Whitney test. To identify correlation between different characteristics we used Spearman's rank correlation analysis. Differences with p-value <0,05 were considered statistically significant.

Results

429 patients (302 males, 127 females) with average age 62,7±8,8 years were included in this study. Main demographic characteristics of cohort and endothelin levels are demonstrated in Table 1.

Age, weight, HR, TC, LDL cholesterol, HDL cholesterol values were different between male and female groups (p<0,05).

Average endothelin concentration in all cohort was 2,90±3,53 fmol/ml, no significant difference in relation with gender was identified.

97% of males and 93% of females received statins in such proportion: atorvastatin (78%), rosuvastatin (12%), simvastatin (10%). We estimated the interrelation between statins therapy and endothelin levels in patients and identified the negative correlation between statins therapy and endothelin levels in males (r=-0,11, p<0,05). More than that, males who were taking statins (n=294) had 1,8 times less levels of endothelin comparing with the males who did not receive them (2,80±3,48 vs 4,98±4,24 fmol/ml, p<0,05, respectively).

We did not observe the interrelation between statins administration and serum endothelin levels in the female patients.

Apart of statins, patients took the following medicines: anticoagulants (Warfarin), antiplatelet drugs (Clopidogrel, Aspirin), ACE inhibitors, calcium channel blockers, angiotensin type II receptor blockers, beta-blockers, nitrogen monoxide donors (organic nitrates), aldosteron antagonists, diuretics. The interrelation between endothelin concentration and administration of other drugs was not identified in both groups of patients.

Discussion

Our results evidence that the interrelation between statins therapy and the marker of endothelial dysfunction endothelin in patients with verified coronary atherosclerosis depends on gender. Statins administration in male patients is associated with almost 2-fold reduction of endothelin concentration in patients who received statins comparing with the ones

Table 1. **Main demographic characteristics, endothelin concentration and lipid profile**

Characteristics	Total (n = 429)	Males (n = 302)	Females (n = 127)
	Means (M) ± SD		
General characteristics			
Age, years	62,7±8,8	59,8±9,1	65,6±8,4*
Weight, kg	83,0±13,8	88,4±15,6	77,5±12,0*
Body mass index, kg/m^2	29,5±4,8	29,1±4,4	29,9±5,1
Systolic blood pressure, mmHg	131,6±15,3	130,3±15,2	132,8±15,3
Diastolic blood pressure, mm Hg	80,3±8,0	80,6±8,7	80,0±7,3
HR, beats per minute	69,9±7,8	68,7±7,8	71,0±7,8*
Biochemical marker of endothelial dysfunction			
Endothelin, fmol/ml	2,90±3,53	2,86±3,50	2,94±3,56
Lipide profile			
TC, mmol/L	5,02±1,33	4,83±-1,20	5,20±1,45*
LDL cholesterol , mmol/L	3,14±1,23	2,99±1,05	3,28±1,40*
HDL cholesterol, mmol/L	1,00±0,25	0,95±0,20	1,06±0,30*
TG, mmol/L	1,93±1,40	1,93±1,25	1,93±1,54

* differences between male and female groups, p<0,05

who did not receive statins. Endothelin concentration reduction after statins therapy goes along with the results of the meta-analysis of 155 independent studies demonstrating that statins reduce plasma endothelin levels [11].

In female patients there is no interrelation between statins therapy and endothelin levels. Females underwent the same pharmacological treatment as males in this study. It is possible that difference in statins action is related to hormonal status of patients. Sexual hormons influence endothelin plasma levels: male hormones (testosterone), unlike female hormones, increase endothelin concentration [12]. The results of meta-analysis proved that statins administration accompanied with testosterone levels reduction [13]. It can be explained with the fact that HGM-CoA reductase inhibition with statins causes the decrease of mevalonate concentration that is the precursor of sterols and isoprenoids that are necessary for steroid hormone synthesis including androgens. Thus, the association of statins with lowered endothelin levels in males is possibly linked with indirect action of statins through the reduction of testosterone levels that, in its turn, increases endothelin levels; otherwise, it can be related to the direct effect of statins on vascular endothelium, that causes endothelin levels reduction. We also cannot exclude the possibility of existence of different mechanisms underlying atherosclerosis development in males and females.

It is necessary to identify if endothelin levels reduction has a positive influence on cardiovascular events. Recent meta-analysis demonstrated that lipophilic statins including atorvastatin and simvastatin can reduce the risk of cardiovascular mortality [14], similar conclusion was obtained in large-scale prospective study of Pauriah, et al. [15]. Thus, it is likely that endothelin levels reduction has positive effect on organism in relation to undesirable cardiovascular events.

Conclusion

Statins obviously have endothelium-protective action. Their endothelium-protective effect can be related to gender. Males with CA lesions, unlike female patients, demonstrate negative correlation between statins administration and endothelin levels that indicate endothelial dysfunction. Male patients who took statins had 2 times less endothelin levels comparing with the males who did not receive statins.

Conflict of interest: None declared.

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