Statins improve myocardial perfusion in metabolic syndrome patients who have perfusion defects on myocardial perfusion imaging and angiographically normal coronary arteries

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Abstract. – Objective: Previous studies in hypercholesterolemic patients with coronary artery disease (CAD) have demonstrated that lipid lowering therapy restores coronary endothelium dependent vasodilatation and increases myocardial perfusion. However, there is not enough data showing the effects of statins on myocardial perfusion in metabolic syndrome (MetS) patients who have perfusion abnormalities but not evident CAD, which are attributed to microvascular dysfunction. We aimed to evaluate whether or not statin therapy improves myocardial perfusion, as assessed by Technetium (Tc)-99m single-photon emission computed tomography (SPECT), in patients with MetS and angiographically normal epicardial coronary anatomy.

Materials and Methods: The study population consisted of 55 selected patients (mean age: 52, 72% female) with MetS who have perfusion defect on exercise stress Tc-99m SPECT and normal coronary arteries. Patients were treated with 20 mg atorvastatin for six months regardless of baseline lipid levels and SPECT study was repeated after the therapy. The summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS), and left ventricular (LV) volumes and ejection fractions (EF) at rest and stress were obtained.

Results: We found significant improvements in SSS, SRS and SDS after six months of statin therapy (p = 0.001, 0.001 and 0.002, respectively). In addition, end-diastolic volumes at rest and stress, and stroke volume at rest were significantly decreased (p = 0.001, 0.001 and 0.026, respectively). Also, LV EF at stress was significantly increased (p = 0.035).

Conclusions: Statin therapy in patients with MetS who have perfusion defects on Tc-99m SPECT and normal coronary arteries produces significant improvements in myocardial perfusion abnormalities.

Key Words: Metabolic syndrome, Statins, Myocardial perfusion.

Introduction

Metabolic syndrome (MetS) is a complex disease characterized by the clustering of several metabolic disorders. Increased waist circumference and body weight, insulin resistance (IR), alterations of plasma lipids and glucose homeostasis and increased blood pressure are the principal components of the cluster. The MetS has been shown to be associated with increased risk of cardiovascular disease and also three meta-analyses reported an increased risk for cardiovascular events (CVE) including all causes of mortality in patients with MetS.

Coronary microvascular endothelial dysfunction has been demonstrated in MetS patients with normal epicardial coronary arteries, which is implicated in the pathogenesis of coronary artery disease (CAD) and is a well-known contributing factor for CVEs. Accordingly, impaired coronary flow reserve (CFR) have also been found in MetS patients without CAD, which are attributed to coronary microvascular dysfunction.

Previous clinical studies have clearly showed that statin therapy significantly decreases CVE in MetS patients. Several studies have also suggested beneficial pleiotropic effects of statins which may be important in reducing cardiovascular risk in these patients. Statins have been shown to restore endothelial function by stimu-
lating endothelial nitric oxide synthase (eNOS) activity, reducing adhesion molecules like soluble vascular cell adhesion molecule (s-VCAM-1), and proinflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) in high risk patients and patients with advanced atherosclerosis or heart failure. In addition, previous studies demonstrated that statins attenuated the biological function of angiotensin-2 (AT-2), and decreased oxidative stress and reactive oxygen sources (ROS) production. As reported before, technetium (Tc)-99m tetrofosmin single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) may be used for noninvasive evaluation of microvascular function and positive effects of statins on microcirculation in patients with CAD. Currently, there is not enough data showing the effects of statin therapy on myocardial perfusion in MetS patients who have perfusion abnormalities, especially without evident CAD. Therefore, we aimed to investigate whether or not statin therapy regardless of baseline lipid levels improves myocardial perfusion abnormalities in MetS patients without CAD using SPECT MPI.

Materials and Methods

Patients
We prospectively evaluated 166 patients with MetS, admitted to our Cardiology Department. The diagnosis of MetS was made based on the definition by Adult Treatment Panel III Final Report criteria (3 or more of the following abnormalities): waist circumference >102 cm in men and >88 cm in women; triglyceride level >150 mg/dl; high-density lipoprotein cholesterol (HDL-C) level < 40 mg/dl in men and <50 mg/dl in women; blood pressure >130/85 mmHg; or fasting glucose level >110 mg/dl. The patients with history of CAD, cardiomyopathy or severe valvular diseases, and who were on statin therapy or failed exercise stress were excluded from the study. Coronary artery disease was defined as coronary artery stenosis on previous coronary angiography, typical angina, ST-segment or T-wave changes specific for myocardial ischemia, pathological Q waves on electrocardiogram, regional wall motion abnormalities on echocardiography, a history of myocardial infarction or coronary revascularization. Thus, the 139 patients who met the enrollment criteria underwent exercise stress Tc-99m sestamibi gated SPECT study. Sixty-one patients had perfusion abnormalities in stress scintigraphic studies and these patients underwent diagnostic coronary angiography. Fifty-five patients have been found to have normal coronary arteries and they were included in the study. The study protocol was approved by the Ethics Committee of the institution. Written informed consent was obtained from all of the patients before the study.

Study Protocol
We recorded all of the 55 patients' demographic and clinical characteristics, including age, sex, height (cm), weight (kg), waist circumference (cm), hypertension, diabetes mellitus, smoking, dyslipidemia, and medications. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg or using antihypertensive medication. Dyslipidemia was defined as total cholesterol level >200 mg/dl, low-density lipoprotein cholesterol (LDL-C) level >130 mg/dl or triglyceride level >150 mg/dl. Atorvastatin 20 mg was given and continued for six months in all patients. Laboratory values measured from fasting blood samples before and after six months of atorvastatin therapy were as follows: glucose, uric acid, total cholesterol, HDL-C, LDL-C, triglyceride, fibrinogen, high sensitive C-reactive protein (hs-CRP) and insulin. The homeostasis model assessment-insulin resistance (HOMA-IR) was also calculated as follows: fasting glucose level (mg/dl) × insulin / 22.5. Insulin resistance was considered as HOMA-IR >3.5 and the patient number with HOMA-IR >3.5 were noted.

SPECT Imaging
The SPECT protocol was performed according to ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging. Technetium-99m sestamibi gated SPECT MPI at rest and exercise stress was performed in one day protocol using a dual head gamma camera (Marconi Axis 2000 Prism, General Electric, GE 400 AC/T, Milwaukee, WI, USA) equipped with a low energy, high resolution, collimator. After a 12 hours of fasting, 259-370 Mbq (7-10 mCi) and 777-1110 Mbq (21-30 mCi) Tc-99m sestamibi were administered intravenously 45-60 min before the acquisition of the study at rest and 1-2 min before completion of the exercise stress, respectively. Tomographic imaging was per-
formed during a state of rest and immediately after the exercise stress using a gamma camera with a computer interface. Data were acquired in a 64 × 64 matrix using 64 projections over a 180° semicircular orbit.

Exercise testing was performed using the Bruce protocol. Beta-adrenergic blocking agents or calcium antagonists were withdrawn 48-72 hours before the test. Patients were informed to avoid caffeine consumption for 24 hours before the stress test. Test endpoints were achievement of the target heart rate, horizontal or down-sloping ST-segment depression of >2 mm, ST-segment elevation of >1 mm, severe chest pain, the development of hypotension or severe hypertension (blood pressure >240/120 mmHg) or severe arrhythmias.

All scans were interpreted by two experienced nuclear cardiologists blinded to the study using a semi-quantitative 20-segment myocardial model. Each of the myocardial segments was scored using a 5-point scoring system (0: normal perfusion to 4: absent perfusion)23. Summed stress score (SSS), summed rest score (SRS) and summed difference perfusion scores (SDS) were obtained by adding the scores of the eight segments of each patient at stress and rest-reinjection, respectively. The quantitative gated SPECT software was applied to reconstructed short-axis data for edge detection and estimation of LV ejection fractions (EF), end-diastolic volumes (EDV), end-systolic volumes (ESV), and stroke volumes (SV) at rest and stress24.

We compared biochemical and scintigraphic results which were obtained before and after six months of atorvastatin therapy.

**Statistical Analysis**

The analyses were performed using SPSS software (Statistical Package for the Social Sciences, Version 10.0, SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean±SD. Differences between before and after six months of atorvastatin therapy for normally and non-homogenously distributed variables were compared using paired and unpaired t-tests and Mann-Whitney U test. All p values were 2-sided, and a p value of <0.05 was considered significant.

**Results**

Fifty-five patients with MetS were included in the study. Baseline clinical characteristics and medications of the patients are presented in Table I. None of the patients experienced significant elevations (>2 × upper normal limits) in liver function tests, myalgia, fatigue, or other adverse effects attributable to atorvastatin.

Compared to the baseline levels, we found statistically significant decreases in total cholesterol (16%), LDL-C (26%), triglyceride (27%), glucose (4%), hs-CRP (21%) and fibrinogen (7%) levels, and a significant increase in HDL-C (16%) after six months of statin therapy (Table II).

The Tc-99m sestamibi gated SPECT perfusion findings were presented in Table III. Six-months of statin therapy resulted in statistically significant decreases in SSS (22%), SRS (36%) and SDS (36%) (p = 0.001, 0.001 and 0.002, respectively) (Figure 1). Also, analysis of Tc-99m sestamibi gated SPECT showed a significant increase in LV EF at stress (p = 0.035). In addition, statin therapy has been found to decrease EDV during rest, EDV during stress and SV during rest (p = 0.001, 0.001 and 0.026, respectively) (Table III).

**Discussion**

Metabolic syndrome comprises a cluster of metabolic risk factors and confers an increased risk for type 2 diabetes mellitus and cardiovascular diseases1-4. Coronary microvascular endothel-
Statins improve myocardial perfusion in metabolic syndrome patients

Table II. Biochemical parameters during atorvastatin therapy.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Six months</th>
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<tr>
<td>Glucose (mg/dl)</td>
<td>112.8 ± 4.6</td>
<td>107.4 ± 4.1</td>
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<td>Total cholesterol (mg/dl)</td>
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<td>HDL (mg/dl)</td>
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<td>56.1 ± 1.8</td>
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<td>LDL (mg/dl)</td>
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<td>Triglycerides (mg/dl)</td>
<td>209.8 ± 11.6</td>
<td>152.0 ± 9.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Hs-CRP (mg/L)</td>
<td>0.64 ± 0.07</td>
<td>0.50 ± 0.05</td>
<td>0.016</td>
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<tr>
<td>Fibrinogen (mg/dl)</td>
<td>392.3 ± 11.4</td>
<td>362.5 ± 10.9</td>
<td>0.006</td>
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<tr>
<td>Uric acid (mg/dl)</td>
<td>5.4 ± 0.2</td>
<td>5.1 ± 0.2</td>
<td>0.297</td>
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<td>HOMA-IR &gt; 3.5 (n)</td>
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HDL: high-density lipoprotein; LDL: low-density lipoprotein; Hs-CRP: high-sensitive C-reactive protein; HOMA-IR: homeostasis model assessment-insulin resistance.

Statins have pleiotropic effects on lowering CRP, other biomarkers of inflammation beyond its lipid lowering effect. Statins have been shown to improve endothelial function by scavenging superoxide anion, increasing eNOS activity, reducing endothelin-1 secretion, decreasing serum levels of s-VCAM, TNF-α and IL-6. Ichiki et al demonstrated that statins downregulated AT-2 type 1 receptor expression and reduced the biological function of AT-2. In addition, because statins increase eNOS activity and have a beneficial effect on endothelial cell integrity, they have antithrombotic effects and decrease fibrinolytic system activity. These result in reduction in hypertrophy and production of extracellular matrix, and prevention of left ventricular remodelling. Another important property of statins is a decrease in oxidative

Table III. Single photon emission computed tomography myocardial perfusion imaging during atorvastatin therapy.

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<th>Six months</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Rest EF (%)</td>
<td>53.6 ± 0.9</td>
<td>55.4 ± 1.1</td>
<td>0.198</td>
</tr>
<tr>
<td>Stress EF (%)</td>
<td>47.6 ± 1.0</td>
<td>50.2 ± 0.8</td>
<td>0.035</td>
</tr>
<tr>
<td>Rest LV EDV (ml)</td>
<td>96.6 ± 2.9</td>
<td>80.2 ± 2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Stress LV EDV (ml)</td>
<td>92.2 ± 3.4</td>
<td>76.1 ± 3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Rest LV ESV (ml)</td>
<td>60.7 ± 2.6</td>
<td>57.2 ± 2.4</td>
<td>0.271</td>
</tr>
<tr>
<td>Stress LV ESV (ml)</td>
<td>51.8 ± 1.8</td>
<td>48.9 ± 2.7</td>
<td>0.319</td>
</tr>
<tr>
<td>Rest LV SV (ml)</td>
<td>45.3 ± 3.4</td>
<td>37.7 ± 2.6</td>
<td>0.026</td>
</tr>
<tr>
<td>Stress LV SV (ml)</td>
<td>44.7 ± 2.7</td>
<td>44.4 ± 2.9</td>
<td>0.906</td>
</tr>
<tr>
<td>SSS</td>
<td>14.6 ± 1.4</td>
<td>11.4 ± 0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>SRS</td>
<td>13.1 ± 1.1</td>
<td>8.4 ± 0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>SDS</td>
<td>7.2 ± 1.1</td>
<td>4.6 ± 0.6</td>
<td>0.002</td>
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EF: ejection fraction; LV: left ventricle; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; SRS: summed rest score; SSS: summed stress score; SDS: summed difference score.

Baseline Six months

- Glucose (mg/dl): 112.8 ± 4.6, 107.4 ± 4.1
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- HDL (mg/dl): 48.3 ± 1.6, 56.1 ± 1.8
- LDL (mg/dl): 116.8 ± 4.4, 86.9 ± 4.5
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- Hs-CRP (mg/L): 0.64 ± 0.07, 0.50 ± 0.05
- Fibrinogen (mg/dl): 392.3 ± 11.4, 362.5 ± 10.9
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- HOMA-IR > 3.5 (n): 31, 30

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stress at the molecular level by reducing circulating levels of TNF-α, stimulating eNOS activity and local control of renin-angiotensin-aldosterone system\(^\text{15,16,35}\). Landmesser et al demonstrated simvastatin significantly improved endothelial function and substantially reduced oxidative stress despite the same LDL reduction as ezetimibe\(^\text{36}\). This effect appears to be exclusive to statins and not related to other lipid lowering agents like ezetimibe\(^\text{36}\).

On the other hand, many clinical trials clearly confirmed that statins have provided significant reductions in the risk of CVE in MetS patients\(^\text{11-13,37}\). Statins have been found to restore acetylcholine induced coronary vasodilatation in patients with CAD\(^\text{38}\). Several studies, using Tc-99m SPECT study, have demonstrated that statin therapy increases myocardial perfusion in hypercholesterolemic patients with CAD\(^\text{17,19}\).

The presence of perfusion abnormality detected by using MPI has been shown to be associated with a worse prognosis in patients with MetS and may be a marker of increased risk in such patients\(^\text{39}\). As reported previously, SPECT MPI makes noninvasive evaluation of microvascular function possible\(^\text{17,18}\). In addition, the SPECT study has revealed the protective effects of statins on microcirculation and myocardial perfusion in patients with CAD\(^\text{17,19}\). However, there is not sufficient data showing beneficial effects of statin therapy on myocardial perfusion in patients with MetS who have perfusion abnormalities and normal coronary arteries. Therefore, we aimed to evaluate if statin therapy improves myocardial perfusion in such patients using Tc-99m SPECT.

The results of this study clearly indicated significant improvements in myocardial perfusion abnormalities in the MetS patients who have perfusion defects on SPECT studies and normal coronary arteries after six months of atorvastatin therapy. In addition, we found significant improvements in LV volume parameters in EDV at rest and stress, and SV at rest and also LV systolic function in EF at stress at the end of the 6 months of statin therapy. These findings were compatible with a prior study reporting changes in ventricular function following lipid-lowering therapy in patients with MetS and without CAD\(^\text{40}\).

We also noted significant reductions in serum total cholesterol, LDL-C, triglyceride, glucose, fibrinogen, and hs-CRP levels, and a significant increase in HDL-C levels at sixth-month. Number of the patients with IR, defined by HOMA-IR >3.5, did not change with statin therapy indicating that statin therapy does not have any effect on IR.

In our study, we detected myocardial perfusion abnormalities in 39.5% of the MetS patients without CAD. After six months of statin therapy, the magnitude of the improvements of perfusion defects for SRS and SDS was more than the reduction in serum LDL-C levels (SSS was decreased by 22%, SRS and SDS were decreased by 36%). In addition, the improvements of perfusion defects were seen even in patients with normal mean LDL-C levels at the beginning. Our findings confirm previous studies showing that magnitude of improvements in the myocardial perfusion is more than improvements in serum LDL-C levels after six months of statin therapy\(^\text{18,19}\). These findings may be explained by pleiotropic and vascular protective effects of statins on microcirculation as reported in previous studies\(^\text{18,19}\). Statin-induced up-regulation of eNOS activity is an important mechanism of improvement of endothelial function and myocardial perfusion\(^\text{15}\).
Study Limitations

Our study did not have long-term follow-up outcome data related to the study population. The lack of placebo arm was the other potential weakness. Despite these, we excluded the patients who had structural cardiac disease and our study population had normal coronary arteries. Thus, the power of the study was not affected by the existence of any cardiac disease.

Conclusions

In patients with MetS who have perfusion defects on Tc-99m SPECT study and normal epicardial coronary arteries, statin therapy produces significant improvements in myocardial perfusion abnormalities. To clarify this matter, further studies containing the long-term outcome data in such patients are needed.

References


7) SEINÉ EH, DE JONGH RT, ERINGA EC, UZERMAN RG, STEHOUWER CD. Microvascular dysfunction: a potential pathophysiological role in the metabolic syndrome. Hypertension 2007; 50: 204-211.


