Effect of Rosuvastatin on Dyslipidemia and other Parameters Associated with Metabolic Syndrome in Saudi Patients

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ABSTRACT

Context: Metabolic syndrome (MS) is a constellation of metabolic irregularities consisting of dyslipidemia, hypertension, hyperglycemia, chronic inflammatory, and hypercoagulable state predisposing to diabetes and cardiovascular events. Statins are first-line drugs to treat the associated atherogenic dyslipidemia.

Aim: Effect of rosuvastatin on MS in Saudi patients was studied. Settings and Design: Prospective, open label, randomized clinical study. Materials and Methods: Patients of either sex ≥18 years (n = 153) having MS as per modified National Cholesterol Education Program Adult Treatment Panel III criteria were prescribed rosuvastatin 10 mg OD for 24 weeks. Serum lipids, biochemical, clinical, and anthropometric parameters were studied before and after treatment. Statistical Analysis Used: Statistical Package for Social Sciences version 17 was used. Descriptive analysis was used for all variables and documented as mean ± SD. Normality checked by Shapiro–Wilk test, Kurtosis and Skewness Z-score, and visualization of histograms. Lipid levels and other parameters before and after treatment were evaluated by paired t-test for parametric data and Wilcoxon signed rank test for nonparametric data. Pre- and post-test values were correlated by Pearson’s correlation coefficient. Multiple regression analysis was performed to see effect of other variables. Results: Highly significant reduction was observed in low density lipoprotein cholesterol, total cholesterol, triglycerides; very low density lipoprotein cholesterol, non-high density lipoprotein cholesterol and atherosclerotic index with an elevation in high density lipoprotein cholesterol. A total of 86% patients reached low density lipoprotein cholesterol goal of ≤100 mg/dL. Beneficial response was observed on other associated parameters. There was a strong correlation between pre- and post values. No significant effect was observed for any of the variables on cholesterol reduction. No serious/severe adverse effect was observed. Conclusion: Rosuvastatin markedly improved atherogenic dyslipidemia of MS.

KEYWORDS: Goal, insulin resistance, lipid, obesity, statin

INTRODUCTION

Metabolic syndrome (MS) is a collection of risk factors and metabolic irregularities that includes dyslipidemia, hypertension, hyperglycemia, or impaired glucose tolerance, insulin resistance, and central obesity predisposing to increased risk for progression to diabetes mellitus and atherosclerotic vascular disease. The current National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria includes any three of the following: (a) Waist circumference ≥102 cm in males and ≥88 cm in females; (b) serum triglycerides (TG) ≥150 mg/dL or antihyperlipidemic drug therapy for increased TG; (c) serum high density lipoprotein cholesterol (HDL-C) <40 mg/dL in males and <50 mg/dL in females or drug therapy for low HDL-C; (d) blood pressure ≥130/85 mmHg or antihypertensive therapy;

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(e) fasting plasma glucose ≥100 mg/dL or drug therapy for hyperglycemia. Various other organizations like IDF: International Diabetes Federation World Health Organization, European Group for the Study of Insulin Resistance, and AACE: American Association of Clinical Endocrinologists have laid down similar criteria and definitions with minor amendments.

Earlier it was considered a disease of west, but with dietary imbalance and lifestyle modifications, it is increasing at a rapid pace throughout the world. The current estimated age adjusted prevalence from 2003 to 2012 in US was about 33%. The IDF: International Diabetes Federation estimated the prevalence to be around 22–25% and the global prevalence of MS ranged from 10% to 84% taking into consideration ethnicity and race, age and sex, region, environment and socioeconomic status, and the defining criterion. In Saudi Arabia, the situation is not different and according to a study in Qassim region, the prevalence of MS is approximately 31.4%. Another study by Al-Qahtani and Imtiaz conducted on soldiers showed an age adjusted prevalence of about 20.8%. Other studies reported the prevalence from 16% to 21% based on different criteria. Moreover, the increasing burden of MS is not only limited to adults but is also involving adolescents at a rapid pace. A recent database screening from RIYADH cohort documented a prevalence of 94% in adolescents and 35.3% in adults by applying modified ATP III criteria.

The main pathophysiological features of MS include insulin resistance, atherogenic dyslipidemia, hypertension, proinflammatory, and prothrombotic state and an additional risk for atherosclerotic vascular disease. The atherogenic dyslipidemia of MS is identified by decreased, increased TG; and predominance of low density lipoprotein (LDL-C) particles predisposing to cardiovascular events.

The statins are safe and effective drugs in treating dyslipidemia. Several large studies in different populations have documented their beneficial effects in reducing atherosclerotic cardiovascular mortality and morbidity by reduction of lipids. Besides cholesterol reduction, statins have many “pleiotropic” effects, for example, decreasing oxidative stress; plaque stabilization; decrease in hsCRP; High Sensitivity C-Reactive Protein factor VII, fibrinogen, hsCRP, PAI-1 and adipokine release; increased NO: Nitric Oxide availability and modulation of inflammation; and collectively or individually, these actions benefit in reduction of MS associated risks. Thus, patients with MS should be considered for an early statin therapy as a component of multidisciplinary approach.

Statins inhibit hepatic cholesterol synthesis by inhibiting HMG-CoA reductase, an important enzyme involved in de novo synthesis of cholesterol in liver ultimately increasing the expression of LDL receptors which increase cholesterol uptake from blood. Rosuvastatin is relatively newer statin marketed as ‘Crestor’ by AstraZeneca in 2004 and is also called as super statin due to its distinct pharmacokinetic profile and efficacy over other statins in large multicentric studies. This study is done to investigate the effect of rosuvastatin on lipids and other variables associated with patients of MS in Saudi Arabia. To our best knowledge, no study has been reported from Saudi Arabia on this aspect.

**Materials and Methods**

**Study design and protocol**

It was a prospective, open label randomized clinical study. Ethical clearance was granted by Research Ethics Committee. Informed consent was taken and study protocol explained to the participants. Screening of MS patients was done by taking detailed history and examination including measurement of blood pressure, anthropometric parameters, and relevant laboratory investigations including serum lipid measurements, fasting blood glucose, and liver and renal function tests as and when required.

Patients satisfying the inclusion criteria entered a 6-week dietary run-in phase, in which they were recommended a standardized NCEP ATP III-therapeutic lifestyle change diet. Hypolipidemic drugs (if any) were stopped at least 2 weeks prior to the end of this period. Eligible patients then received rosuvastatin 10 mg for a period of 24 weeks. They were also prescribed L-carnitine 500 mg OD for the entire study duration.

Laboratory investigations were done at the screening, beginning of dietary lead-in period (-6 week), beginning (0 week), and at the completion (24th week) of study duration. Interim investigations were performed on a case per case basis as and when required. Concomitant medications like erythromycin, azole antifungals, immunosuppressive, systemic steroids, glitazones, vitamin K antagonists, or any medication interacting with the statin metabolism were not permitted during the study.

**Study population**

Newly diagnosed Saudi patients of either sex ≥18 years having MS in accordance with the modified NCEP ATP-III guideline were enrolled for the study.

**Inclusion criteria**

MS characterized by existence of any three of the following abnormalities: Abdominal/central obesity [waist
circumference >102 cm (men) and >88 cm (women)]; TG ≥ 150 mg/dL; HDL-C < 40 mg/dL for men and < 50 mg/dL for women; blood pressure ≥130/85 mmHg or receiving antihypertensive treatment; and fasting blood glucose ≥ 110 mg/dL or taking antidiabetic medicines. Patients were also essential to have LDL-C ≥ 130 mg/dL.

Exclusion criteria
High TG ≥ 500 mg/dL; high LDL-C ≥ 250 mg/dL; known history of CHD: Coronary Heart Disease/atherosclerotic disease; familial hypercholesterolemia; uncontrolled hypertension; uncontrolled hypothyroidism; statin hypersensitivity; acute or active hepatic dysfunction indicated by elevation of liver enzymes or bilirubin ≥1.5 times upper normal limit; inexplicable elevation of serum creatine kinase (CK) ≥3 times upper normal limit; use of nonrecommended concomitant drugs and pregnancy.

Biochemical laboratory measurements
Lipids in total serum were measured using automated enzymatic methods. Measurement of total cholesterol was done by CHOD-PAP: cholesterol oxidase-phenol aminophenazone method[38] HDL-C, LDL-C, and VLDL-C by modified PEG: Poly Ethylene Glycol-PAP method[37,40] and TG by modified GPO: glycerol-3-phosphate oxidase-PAP method[41,42] by commercially available kits from Pointe Scientific Inc, USA. Other tests, such as glucose tolerance tests, urine analysis, and renal and liver function tests were also done accordingly on as required basis.

Safety and tolerability
Spontaneous reports of adverse events (if any) by the patients revealed by observation or extracted by asking an open question were recorded. Laboratory measurements for safety assessment included: haemoglobin, leucocyte count, platelet count, bilirubin, and hepatic enzymes like alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, CK, and serum creatinine. Elevated levels of enzymes ≥3 times upper normal limit and CK values 5–10 with muscular symptoms or ≥10 times upper normal limit with or without muscular symptoms were taken as predefined safety variables. Increase of CK ≥10 times upper normal limit associated with muscular symptoms with no other reasonable cause was prospectively considered myopathy. Causality assessment of all the adverse events (if any) was done according to Naranjo scale.[43] It was documented that any adverse event would result in discontinuation of the patient from the study and the patient managed by university hospital.

Endpoint assessments
The primary efficacy endpoint was percentage change in serum LDL-C from baseline to 24 weeks. Secondary endpoints included the following:

(a) Percentage change in TC, TG, HDL-C, VLDL-C, and other indices from baseline to 24 weeks
(b) Patients attaining the LDL-C ≤100 mg/dL after 24 weeks
(c) Change in other associated parameters like atherosclerosis index, body mass index (BMI), waist-to-hip ratio, hypertension, and hyperglycemia, etc.

Statistical analysis
The data was statistically analyzed using Statistical Package for Social Sciences software for windows version 17. Continuous variables were documented as mean ± SD. Descriptive analysis was used for demographic and biochemical laboratory variables. Normality of data was checked by Shapiro–Wilk test, Kurtosis and Skewness Z-score, and visualization of histograms. Mean percentage change in lipid levels before and after treatment was compared by paired t-test for parametric data, while Wilcoxon signed rank test was applied in case of nonparametric data. Pearson’s correlation coefficient was evaluated for lipid parameters before and after treatment. Multiple regression analysis was performed to see the effect of other covariates. A P value <0.05 was considered statistically significant.

Results
Out of the total 153 participants enrolled, 142 completed the study. [Table 1] depicts the baseline measurements of the study population, while Table 2 shows the baseline values of lipid parameters. The mean age was about 50 years. There were 63.4% males and 36.6% females.

Figure 1 shows the (primary efficacy endpoint) percentage change in LDL-C from the start of therapy at 0 week to 24 weeks of treatment. There was a highly significant reduction in LDL-C levels (P < 0.001).

Moreover, as depicted in Figure 2, a total of 85.9% patients achieved the goal of LDL-C ≤ 100 mg/dL. Out of this, 62.3% were males and 37.7% were females.

Other lipid parameters beside LDL-C like TC, non-HDL-C, VLDL-C, TG, and LP (a) were also significantly reduced in addition to a statistically significant improvement in HDL-C levels as demonstrated in Figure 3.

Table 3 shows that there were highly significant moderate and strong correlations between pre-treatment and post-treatment lipid values implying that higher baseline lipid values showed a lesser reduction.

Table 4 depicts the influence of variables on the cholesterol lowering response by rosuvastatin using multiple regression analysis. When the mean total
Table 1: Baseline characteristics of study population. All values are expressed as mean ± SD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.60 ± 7.06</td>
<td>50.92 ± 8.11</td>
<td>50.72 ± 7.40</td>
</tr>
<tr>
<td>Gender (n)</td>
<td>90</td>
<td>52</td>
<td>142</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.84 ± 7.69</td>
<td>62.84 ± 5.43</td>
<td>71.71 ± 9.69</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.93 ± 6.52</td>
<td>155.23 ± 6.14</td>
<td>163.91 ± 9.18</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>26.87 ± 2.13</td>
<td>26.09 ± 2.31</td>
<td>26.58 ± 2.21</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>98.42 ± 8.32</td>
<td>92.15 ± 8.27</td>
<td>96.12 ± 8.79</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>100.06 ± 7.80</td>
<td>105.19 ± 5.85</td>
<td>101.94 ± 7.52</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>1.01 ± 0.06</td>
<td>0.91 ± 0.07</td>
<td>0.97 ± 0.08</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>104.44 ± 12.16</td>
<td>104.30 ± 12.80</td>
<td>104.39 ± 12.31</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131.84 ± 11.70</td>
<td>136.61 ± 13.17</td>
<td>133.59 ± 12.38</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83.93 ± 8.14</td>
<td>86.19 ± 7.39</td>
<td>84.76 ± 7.90</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SD

Table 2: Baseline lipid parameters of study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sex</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>M 258.42 ± 38.21</td>
<td>256.59 ± 36.44</td>
</tr>
<tr>
<td></td>
<td>F 253.42 ± 33.63</td>
<td></td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>M 179.13 ± 37.28</td>
<td>174.69 ± 34.11</td>
</tr>
<tr>
<td></td>
<td>F 167.00 ± 26.71</td>
<td></td>
</tr>
<tr>
<td>VLDL-C (mg/dL)</td>
<td>M 36.15 ± 6.08</td>
<td>35.28 ± 6.13</td>
</tr>
<tr>
<td></td>
<td>F 33.76 ± 6.03</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>M 41.40 ± 9.37</td>
<td>44.84 ± 10.36</td>
</tr>
<tr>
<td></td>
<td>F 50.80 ± 9.36</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>M 195.00 ± 31.25</td>
<td>191.53 ± 28.77</td>
</tr>
<tr>
<td></td>
<td>F 185.53 ± 23.22</td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>M 217.28 ± 40.22</td>
<td>211.91 ± 37.49</td>
</tr>
<tr>
<td></td>
<td>F 202.61 ± 30.74</td>
<td></td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>M 25.26 ± 8.03</td>
<td>25.14 ± 7.70</td>
</tr>
<tr>
<td></td>
<td>F 24.92 ± 7.23</td>
<td></td>
</tr>
<tr>
<td>LDL-C / HDL-C ratio</td>
<td>M 4.64 ± 1.86</td>
<td>4.18 ± 1.66</td>
</tr>
<tr>
<td></td>
<td>F 3.37 ± 0.73</td>
<td></td>
</tr>
</tbody>
</table>

*LDL-C = Low density lipoprotein cholesterol; TG = Triglycerides; HDL-C = High density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); VLDL-C = Very low density lipoprotein cholesterol

Table 3: The correlations between pre- and post-treatment values

<table>
<thead>
<tr>
<th>Lipid parameters</th>
<th>Correlation coefficient (r)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL1 and LDL2</td>
<td>.652</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC1 and TC2</td>
<td>.626</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL1 and VLDL2</td>
<td>.230</td>
<td>0.054</td>
</tr>
<tr>
<td>HDL1 and HDL2</td>
<td>.974</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG1 and TG2</td>
<td>.509</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL1 and non-HDL2</td>
<td>.625</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp(a)1 and Lp(a)2</td>
<td>.842</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4: Analysis of influence of independent variables on the lipid lowering response of rosuvastatin by multiple linear regression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>0.117</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.063</td>
<td>0.690</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.072</td>
<td>0.565</td>
</tr>
<tr>
<td>WHR</td>
<td>0.054</td>
<td>0.729</td>
</tr>
<tr>
<td>Baseline TC</td>
<td>-0.239</td>
<td>0.104</td>
</tr>
<tr>
<td>Atherosclerosis Index</td>
<td>-0.151</td>
<td>0.345</td>
</tr>
</tbody>
</table>

@adjusted; #standardized; *significant; WHR = Waist-to-hip ratio, BMI = Body mass index, TC = Total cholesterol; no covariate showed a significant interaction with hypolipidemic response; model explained 7% of the variability
cholesterol reduction (as dependent variable) was regressed against the independent variables like age, gender, BMI, obesity, atherosclerosis index, and baseline cholesterol; no significant effect was observed for any of the variables and the model explained just 7% of the variability.

Concerning the other nonparametrically distributed measurements beside lipid parameters, significant change was observed only in case of blood pressure and atherosclerosis index. The fasting blood sugar, waist-to-hip ratio, and BMI showed non-significant Z-scores on Wilcoxon signed rank test as evidenced in Table 5.

Table 6 shows the adverse effect profile. No severe/serious adverse effect was detected or reported by the patient. All the adverse effects were nonspecific and were not related to study medication. Naranjo causality scores were either 0 or 1. No biochemical derangement or elevation of enzymes was noted in any case. Five patients were lost to follow-up and three other withdrew without any reason.

**Figure 1:** Change in LDL-C from baseline to 24 weeks of treatment, *P* < 0.001. LDL-C = Low density lipoprotein cholesterol

**Figure 2:** Percentage of patients attaining the goal of LDL-C ≤ 100 mg/dL. *Dark colored outer circle represents total percentage of patients reaching the lipid goal, while light colored circle demonstrates those not reaching the goal. Dark colored inner circle represents the total percentage of males and light colored inner circles represent total percentage of females reaching the LDL-C goal. LDL-C = Low density lipoprotein cholesterol.

**Figure 3:** Mean percentage change in other lipid parameters from baseline to 24 weeks, *indicates P < 0.001. LDL-C = Low density lipoprotein cholesterol; TG = Triglycerides; VLDL-C = Very low density lipoprotein cholesterol; HDL-C = High density lipoprotein cholesterol; Lp(a) = Lipoprotein(a)

**Table 5:** Difference between pre-treatment and post-treatment nonparametric variables by Wilcoxon signed rank test

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>-1.75*</td>
<td>0.085</td>
</tr>
<tr>
<td>WHR</td>
<td>-1.450*</td>
<td>0.147</td>
</tr>
<tr>
<td>BP (systolic)</td>
<td>-3.734*</td>
<td>0.001</td>
</tr>
<tr>
<td>BP (diastolic)</td>
<td>-3.316*</td>
<td>0.001</td>
</tr>
<tr>
<td>FBS</td>
<td>-2.356*</td>
<td>0.071</td>
</tr>
<tr>
<td>A. Index</td>
<td>-7.323*</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*based on positive ranks; *based on negative ranks; BP = Blood Pressure; FBS = Fasting blood sugar; BMI = Body mass index; WHR = Waist-to-hip ratio; A. Index = Atherosclerosis Index (LDL-C/HDL-C); Blood Pressure and Atherosclerosis Index showed a statistically significant reduction.
Doubtful (0)

So it seems that though there is

This may be explained by the

Probable (1)

Earlier studies with rosuvastatin have

found that rosuvastatin has additional

1

Doubtful (0)

2

Doubtful (1)

1

Doubtful (0)

1

Probable (1)

Table 6: This table shows adverse event

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients (n)</th>
<th>Naranjo category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>3</td>
<td>Doubtful (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>Probable (1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>Doubtful (1)</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>Doubtful (0)</td>
</tr>
<tr>
<td>Backache</td>
<td>1</td>
<td>Probable (1)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

MS is a multifactorial disorder predisposing to diabetes and atherosclerotic vascular disease. Statins are one of the best drugs to treat dyslipidemia associated with MS. Present study is undertaken to evaluate the effects of rosuvastatin in Saudi patients of MS.

The baseline measurements of the study population showed increased BMI and waist-to-hip ratio indicating obesity which put an additional risk to insulin resistance.

The baseline lipid parameters showed that TC values were greater in males as compared with females. A previous study on prevalence showed elevated levels in females. This discrepancy can be partly explained by the region, sampling methodology, large time gap (almost 20 years), changing lifestyle of males and disease profile. However, the most common age group in their study was 5th decade which is in accordance with our findings.

The primary efficacy endpoint (LDL-C) showed a highly significant reduction (P < 0.001) from baseline (57.53 ± 9.91) and approximately 86% patients reached the LDL goal of <100 mg/dL, with more males (62.3%) reaching the goal. This is very close to the manufacturer’s claim, AstraZeneca which summarizes the goal attainment by 84% of patients. Earlier studies with rosuvastatin have shown a marked decrease in LDL-C as compared with other statins. Rosuvastatin showed superiority even on the most recently launched pitavastatin. A meta-analysis by Law et al. 2003 showed a decrease of 37–59% in LDL-C by rosuvastatin in a dose range of 5–80 mg OD. Another study by Olsson et al. 2005 showed a 53% reduction in LDL-C and 82% patients reaching the goal after 52 weeks of rosuvastatin 10 mg OD treatment. These findings are in accordance with our findings with slight variations. The variability may be explained by differences in sampled population, disease patterns, and study designs.

The mean percentage reductions reported in our study concerning other lipid parameters also depicted a highly significant change which is in accordance in with previous studies discussed above. In a recent Cochrane meta-analysis, rosuvastatin showed superiority over other statins in different dose ranges. There were highly significant correlations between pre- and post-treatment lipid parameters implying that higher baseline values showed a lesser reduction and a less increase in HDL-C. This can be partly explained by a less stringent adherence to standard diet and protocol in patients having higher baseline values. Moreover, high baseline line values itself demonstrate deviations from healthy lifestyle and dietary regulations thus predisposing these patients less compliant to study medications.

Regression analysis showed a nonsignificant influence of variables on hypolipidemic response and a mere 7% of variability was attributed to these factors implying that there are other factors (may be genetics) playing an important role in variability of statin response.

Our study participants also demonstrated a statistically significant decrease in blood pressure. A study by Seki et al. found that rosuvastatin has additional antihypertensive effect, further reinforced by another large multicenter study. This may be explained by the phenomenon of increased release of endothelial nitric oxide, upregulation, and overexpression of NO synthase, decrease endothelin-1, and decreased expression of angiotensin II type-1 receptor.

However, our findings reported a slight escalation in blood glucose. There are equivocal studies addressing this issue. A meta-analysis by Sattar et al. involving 91140 patients from 13 studies concluded that long term statin therapy (>4 years) of 255 patients led to just one extra incidence of diabetes mellitus grossly outweighing the benefit of prevention of 5.4 cardiovascular events. Another pooled study data depicted an increase of 3 mg/dL when more than 345000 patients were studied. Additionally, Simsek et al. demonstrated no change in mean fasting blood sugar with rosuvastatin therapy. However, a dose-dependent increase in glucose impairment with rosuvastatin therapy was found by Kostapanos et al. So it seems that though there is a negative effect but the change is neither statistically nor clinically significant and more studies are needed to come to any conclusion.

There was also an improvement in waist-to-hip ratio and BMI but it was nonsignificant which may be attributed to measurement bias and other unexplained factors. The atherosclerosis index also decreased significantly. It is one of the best drugs to treat dyslipidemia associated with MS. Present study is undertaken to evaluate the effects of rosuvastatin in Saudi patients of MS.

The baseline measurements of the study population showed increased BMI and waist-to-hip ratio indicating obesity which put an additional risk to insulin resistance.

The baseline lipid parameters showed that TC values were greater in males as compared with females. A previous study on prevalence showed elevated levels in females. This discrepancy can be partly explained by the region, sampling methodology, large time gap (almost 20 years), changing lifestyle of males and disease profile. However, the most common age group in their study was 5th decade which is in accordance with our findings.

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The mean percentage reductions reported in our study concerning other lipid parameters also depicted a highly significant change which is in accordance in with previous studies discussed above. In a recent Cochrane meta-analysis, rosuvastatin showed superiority over other statins in different dose ranges. There were highly significant correlations between pre- and post-treatment lipid parameters implying that higher baseline values showed a lesser reduction and a less increase in HDL-C. This can be partly explained by a less stringent adherence to standard diet and protocol in patients having higher baseline values. Moreover, high baseline line values itself demonstrate deviations from healthy lifestyle and dietary regulations thus predisposing these patients less compliant to study medications.

Regression analysis showed a nonsignificant influence of variables on hypolipidemic response and a mere 7% of variability was attributed to these factors implying that there are other factors (may be genetics) playing an important role in variability of statin response.

Our study participants also demonstrated a statistically significant decrease in blood pressure. A study by Seki et al. found that rosuvastatin has additional antihypertensive effect, further reinforced by another large multicenter study. This may be explained by the phenomenon of increased release of endothelial nitric oxide, upregulation, and overexpression of NO synthase, decrease endothelin-1, and decreased expression of angiotensin II type-1 receptor.

However, our findings reported a slight escalation in blood glucose. There are equivocal studies addressing this issue. A meta-analysis by Sattar et al. involving 91140 patients from 13 studies concluded that long term statin therapy (>4 years) of 255 patients led to just one extra incidence of diabetes mellitus grossly outweighing the benefit of prevention of 5.4 cardiovascular events. Another pooled study data depicted an increase of 3 mg/dL when more than 345000 patients were studied. Additionally, Simsek et al. demonstrated no change in mean fasting blood sugar with rosuvastatin therapy. However, a dose-dependent increase in glucose impairment with rosuvastatin therapy was found by Kostapanos et al. So it seems that though there is a negative effect but the change is neither statistically nor clinically significant and more studies are needed to come to any conclusion.

There was also an improvement in waist-to-hip ratio and BMI but it was nonsignificant which may be attributed to measurement bias and other unexplained factors. The atherosclerosis index also decreased significantly. It is one of the best drugs to treat dyslipidemia associated with MS. Present study is undertaken to evaluate the effects of rosuvastatin in Saudi patients of MS.
of the most reliable indicators of increased cardiovascular risk. Rosuvastatin is known to positively affect the reverse cholesterol transport pathway. MS patients have increased CETP activity leading to shift of cholesteryl esters from HDL to TG. Rosuvastatin has been found to inhibit CETP activity reversing this process and increasing the HDL-C level.[67,68] A study in cardiovascular patients by Jukema et al.[69] reinforces our findings of statistically and clinically significant decrease of LDL-C/HDL-C ratio.

No adverse events were linked to the prescribed study drug and only of minor nature. All the events were either doubtful or probable category according to Naranjo scale. Biochemical parameters were within normal ranges. Most common adverse event was constipation followed by headache. One patient experienced myalgia which was not related to rosuvastatin (no elevation of markers) but led to patient withdrawal. Five patients changed addresses and were lost to follow-up. Additionally, three patients withdrew without any reason.

**Conclusion**

Rosuvastatin significantly reduced the lipid parameters with a beneficial effect on associated comorbidities of MS without any severe or serious side effect. More studies are needed with larger samples and multiple study sites to establish a localized therapeutic guideline for rosuvastatin use in MS.

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**Conflicts of interest**

There are no conflicts of interest.

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