

Effects of rosuvastatin on metabolic profile: Versatility of dose-dependent effect

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ABSTRACT

Obesity refers to an excess of body fat content causing metabolic and inflammatory disorders. Therefore, the aim of the present study was to investigate dose-dependent effect of rosuvastatin on the metabolic profile of diet-induced obesity in mice model study. A total number of 40 male Albino Swiss mice were used which divided into Group I: Control group, fed normal diet for 8 weeks ($n = 10$); Group II: High-fat diet (HFD) group, fed on HFD for 8 weeks ($n = 10$); Group III: HFD + 20 mg/kg rosuvastatin for 8 weeks ($n = 10$); and Group IV: HFD + 40 mg/kg rosuvastatin for 8 weeks ($n = 10$). Anthropometric and biochemical parameters were estimated, including fasting blood glucose, lipid profile, fasting insulin, and glucose tolerance test (GTT). Mice on HFD fed showed a significant increase in the insulin resistance, body weight, deterioration of lipid profile and significant reduction in the β -cell function, and insulin sensitivity compared to the control $P < 0.05$. GTT and blood glucose level were significantly high in HFD fed group compared to the control group $P < 0.05$. Rosuvastatin in a dose of 40 mg/kg illustrated better effect than 20 mg/kg on the glucometabolic profile $P < 0.05$. Rosuvastatin may has a potential effect on reduction of glucometabolic changes induced by HFD with significant amelioration of pancreatic β -cell function in dose-dependent manner.

Key words: Fasting blood glucose, fasting insulin, glucose tolerance test, insulin tolerance test, lipid profile, obesity, rosuvastatin

INTRODUCTION

Obesity refers to an excess of the body fat content causing metabolic and inflammatory disorders.^[1] Large-scale studies have been performed to study the association between obesity with physical and mental health problems. Obesity is linked to metabolic syndrome that is characterized by visceral obesity, insulin resistance (IR), and hypertension.^[2]

Body mass index (BMI) was introduced as a valuable tool to assess overweight and obesity. The world health organization used BMI cutoff values to set the classification of obesity in adults.^[3]

It is evident that BMI varies with gender, age, and ethnicity; however, it is not considered as a sensitive measure for body fat content but still be considered as the most practical and simple tool in the epidemiological studies.^[4] A dose-related increase in body weight and risk of type 2 diabetes mellitus (T2DM) with statin therapy has been recognized.^[5]

Similar to other statins, rosuvastatin inhibits the active site of 3-hydroxy-3-methyl-glutaryl-coenzyme. A

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reductase (HMG-CoA). The efficacy of rosuvastatin is related to the fluorinated phenyl and methyl sulfonamide groups (polar group) which allow multiple affinity and interaction with HMG-CoA reductase enzyme.^{16,71}

Therefore, the aim of the present study was to investigate the dose-dependent effect of rosuvastatin on the metabolic profile of diet-induced obesity in mice model study.

MATERIALS AND METHODS

Animals

A total number of 40 male Albino Swiss mice were used with age and weight 2–3 months and 250–300 g, respectively, they kept in sterilized cages at 23°C temperature with 12/12 artificial light-dark cycle. Free access to normal chow and water was allowed, and they left for 1 week of adaptation. All mice were cared for in accordance and harmony with guide for the care and use of laboratory animals.¹⁸¹ The experimental protocol was approved and reviewed by the Animal Care Review Committee at College of Medicine, Al-Mustansiriyah University.

Drugs and chemicals

High-fat diet (HFD) (60% fat D12492 Research Diets, Inc., New Brunswick, NJ, USA), glucose solution 50% (glucose 50 ml vial, team medical supplies, Phebra, Ray RD), soluble insulin (Actrapid HM, neutral insulin injection 100 IU/ml, Novo Nordisk, IndiaMART), and rosuvastatin (rosuvastatin STADA 10 mg, IndiaMART) which were purchased from private pharmaceutical company.

Study design

After the acclimatization period, the mice were divided into the following:

- Group I: Control group, fed normal diet for 8 weeks ($n = 10$)
- Group II: HFD group, fed on HFD for 8 weeks ($n = 10$)
- Group III: Treated group, fed with HFD for 4 weeks and received single daily dose of 20 mg/kg rosuvastatin orally for 4 weeks ($n = 10$)
- Group IV: Treated group, fed with HFD for 8 weeks and received single daily dose of 40 mg/kg rosuvastatin orally for 4 weeks ($n = 10$).

Weight measurement, food intake, fasting blood glucose, glucose tolerance test (GTT), insulin tolerance test (ITT), lipid profile measurement, and fasting insulin levels were measured at baseline, 4 weeks, and 8 weeks after induction of obesity.

Measurement of food intake and body weight

The weighed food was poured in the cages and left for 24 h. The remaining food was collected, weighed, and the difference between food weights was calculated that represented the food intake in g/24 h. Measurement of mice weight was done by digital weight calculator.

In addition, glucose tolerance test (GTT) was done according to the previous methods.^{9,101}

Plasma sample collection

Blood samples were collected after mice decapitation in labeled-EDTA containing tubes. The blood samples were centrifuged at 5000 rpm for 10 min. The supernatant layer was stored at -20°C until the time of analysis.

Serum lipid profile was measured using ELISA kit method. Low-density lipoprotein (LDL) level was calculated according to Lee *et al.*, method. Very LDL (VLDL) = TG/5. Atherogenic Index of Plasma (AIP) was estimated using the equation $AIP = \log(\text{triglyceride [TG]}/\text{HDL-c})$.^{11,121}

Fasting insulin level was determined by ELISA kit (Mouse insulin [INS] kit, Shanghai Yehua biological technology, China). Homeostasis model assessment for IR (HOMA-IR) = fasting insulin concentration ($\mu\text{IU/ml}$) \times fasting glucose concentration (mg/dl)/405. $\text{HOMA-}\beta = (\text{fasting plasma insulin level } [\mu\text{IU/ml}] \times 360)/(\text{fasting plasma glucose level [mg/dl]} - 63)$. Insulin sensitivity was estimated using the quantitative insulin check index equation: $\text{QUICKI} = 1/(\log(\text{fasting plasma insulin } [\mu\text{IU/ml}]) + \log[\text{fasting plasma glucose [mg/dl]}])$.¹³¹

Statistical analysis

Data were expressed as mean \pm standard deviation. Students paired and unpaired *t*-test was used to compare values between baselines and follow-up values. One-way ANOVA test the differences between the groups. All statistical procedures were done by Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS 22.0, 2016, IBM Corp., NY, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Food intake and body weight were increased in HFD compared to the control ($P = 0.001$). HFD group showed a significant increase in total cholesterol (TC), LDL, and TG sera levels with elevated AIP ($P = 0.001$), and decrease in HDL-c level ($P = 0.001$) compared to the control while VLDL serum level was increased in HFD mice compared to the control ($P = 0.02$). HFD mice showed significant increase in the fasting blood glucose, fasting insulin level compared to the control ($P = 0.0001$ and $P = 0.05$), respectively. In addition, HFD mice showed significant increase in the IR with decrease in β -cell function and insulin sensitivity ($P < 0.05$). GTT and blood glucose level were significantly high in HFD mice compared to the control group ($P = 0.001$) [Table 1].

Food intake and body weight were high in HFD compared to HFD-rosuvastatin group ($P = 0.01$) and ($P = 0.02$), respectively. Body weight was not significant at a dose of 20 mg/kg compared to HFD-rosuvastatin group ($P = 0.07$). LDL and both TC and TG were high in

Table 1: Baseline characteristics at starting of the study

Variables	Control (n=10)		P	HFD (n=10)		P
	Before	After		Before	After	
Food intake (g/24 h)	3.57±0.14	3.67±0.16	0.15	3.53±0.17	4.85±0.18*	0.0001
Body weight (g)	29.14±2.672	31.34±2.65	0.08	29.57±2.76	37.00±2.94*	0.0001
TC (mg/dl)	144.021±10.01	146.12±12.28	0.68	144.597±9.92	209.947±39.16*	0.0001
TG (mg/dl)	87.571±12.31	89.71±13.450	0.71	88.00±12.34	125.29±19.99*	0.0001
HDL (mg/dl)	71.921±13.72	68.76±13.67	0.61	71.53±13.59	47.10±9.115*	0.0002
LDL (mg/dl)	54.585±20.53	59.891±7.89	0.45	54.889±18.79	137.79±30.51*	0.0001
VLDL (mg/dl)	17.51±5.33	17.94±5.89	0.86	17.60±5.56	25.05±7.98*	0.02
AIP	0.107±0.107	0.136±0.11	0.55	0.104±0.10	0.428±0.10*	0.0001
FBG (mg/dl)	75.14±6.89	75.29±7.653	0.96	80.29±10.97	115.43±9.59*	0.0001
FSI	7.45±2.215	7.59±2.36	0.89	7.02±2.151	11.03±1.46*	0.0001
HOMA-IR	0.92±0.040	0.94±0.053	0.23	0.88±0.033	1.51±0.049*	0.0001
HOMA-β	134.1±63.59	135.4±63.22	0.96	112.9±11.18	75.2±9.18*	0.0001
QUICKI	0.37±0.026	0.36±0.026	0.79	0.36±0.074	0.32±0.079	0.22
GTT (AUC)	15,382.43±1837.60	15,093.57±1583.43	0.33	14,569.29±1868.28	21,064.29±3087.98*	0.0001

Data are expressed as mean±SD, unpaired t-test. * $P < 0.05$ compared to the control. TC: Total cholesterol, TG: Triglycerides, HDL: High-density lipoprotein; LDL: Low-density lipoprotein, VLDL: Very LDL, AIP: Atherogenic Index of Plasma, FBG: Fasting blood glucose, FSI: Fasting serum insulin; HOMA-IR: Homeostatic model assessment of insulin resistance; QUICKI: Quantitative insulin sensitivity check index, AUC: Area under the curve, GTT: Glucose tolerance test, SD: Standard deviation, HFD: High-fat diet

HFD compared to HFD-rosuvastatin group either at 20 mg/kg or 40 mg/kg ($P = 0.001$). There was no significant change in HDL levels in the treated groups ($P = 0.28$). Atherogenic Index was high in HFD (0.428 ± 0.010) group compared to HFD-rosuvastatin 20 mg/kg (0.28 ± 0.011) and (0.22 ± 0.082) in HFD-rosuvastatin 40 mg/kg ($P = 0.001$). Fasting blood glucose was high in rosuvastatin 20 mg/kg (171.00 ± 24.98 mg/dl) ($P = 0.001$) and low in rosuvastatin 40 mg/kg (124.71 ± 13.66 mg/dl) compared to HFD mice ($P = 0.09$). Moreover, there were no significant differences regarding fasting specific insulin, QUICKI, and HOMA-IR between HFD and HFD-rosuvastatin treated groups ($P = 0.47$, $P = 0.66$, 0.42), respectively. Besides, insulin sensitivity and β -cell function were improved in rosuvastatin group at 40 mg/kg ($P = 0.04$) but not in rosuvastatin at 20 mg/kg ($P = 0.06$) compared to HFD group. GTT was low in HFD group compared to HFD + rosuvastatin at 20 mg/kg ($P = 0.03$) and high compared to HFD + rosuvastatin at 40 mg/kg ($P = 0.0001$) [Table 2 and Figures 1-3].

DISCUSSION

The present study illustrated that intake of HFD for 2 consecutive months increase body weight significantly compared to the control, which coincides with the previous findings.^[14]

HFD-induced obesity is linked with the development of central insulin and/or leptin resistance in rodent model within a short duration. Besides, HFD leads to peripheral IR that provokes brain glucose uptake which *per se* stimulate appetite and food intake.^[15]

Fasting insulin and fasting blood glucose were elevated in HFD mice since chronic intake of HFD is associated with significant

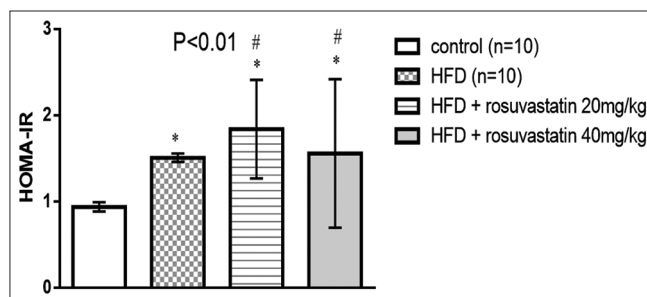


Figure 1: Dose-dependent effect of rosuvastatin on the insulin resistance compared to high-fat diet and control groups. * $P < 0.01$ compared to the control, # $P = 0.42$ compared to high-fat diet, one-way ANOVA test $P < 0.01$

hyperglycemia and hyperinsulinemia.^[16] Moreover, high fatty acid metabolites lead to reduction of glucose uptake. Besides, high glucose level stimulates the adaptive response of β -cell through insulin overproduction to compensate the IR.^[17,18]

In the present study, HFD led to significant glucose intolerance and impaired glucose disposal causing hyperglycemia due to the link between IR and dyslipidemia. As well, IR induces hepatic lipogenesis and hyperinsulinemia which accelerate *de novo* TG and VLDL synthesis.^[19,20]

The present study exposed a significant increment in HOMA-IR and the decrement in HOMA- β , QUICKI values within 8 weeks of HFD due to the development of IR and deterioration in β -cell function. These findings correspond with Wanchai *et al.*, a study that illustrated HFD leads to IR and reduction of insulin sensitivity.^[21]

Rosuvastatin in the current study led to a significant reduction of body weight since rosuvastatin may affects the

Table 2: Metabolic dose-dependent effect of rosuvastatin on high-fat diet-induced weight gain

Variables	HFD (n=10)	HFD + rosuvastatin 20 mg/kg (n=10)	HFD + rosuvastatin 40 mg/kg (n=10)	F	P
Food intake (g/24 h)	4.85±0.18	2.79±0.64	2.39±0.27 [#]	101.52	0.0001*
Body weight (g)	37.00±2.94	34.71±2.56	31.86±3.57 [#]	7.11	0.003*
TC (mg/dl)	209.947±39.16	141.54±28.55 [#]	123.11±21.93 [#]	22.19	0.0001*
TG (mg/dl)	125.29±19.99	102.57±17.21 [#]	94.29±12.83 [#]	8.99	0.001*
HDL (mg/dl)	47.10±9.115	49.14±12.12	53.80±6.097	1.32	0.28
LDL (mg/dl)	137.79±30.51	66.67±18.93 [#]	44.73±22.91 [#]	39.13	0.0001*
VLDL (mg/dl)	25.05±7.98	20.51±6.99	18.85±5.86	2.10	0.14
AIP	0.428±0.010	0.28±0.011 [#]	0.22±0.082 ^{#,s}	49.50	0.0001*
FBG (mg/dl)	115.43±9.59	171.00±24.98	124.71±13.66	29.45	0.0001*
FSI (μU/ml)	11.03±1.46	12.40±1.49	11.28±4.04	0.77	0.47
HOMA-IR	1.51±0.049	1.84±0.57	1.56±0.86	0.88	0.42
HOMA-β	75.2±9.18	38.8±8.20 [#]	65.81±8.43 ^{s,#}	48.13	0.0001*
QUICKI	0.32±0.079	0.302±0.009	0.317±0.02	0.41	0.66
GTT (AUC)	21,064.29±3087.98	27,537.86±3207.77 [#]	16,272.88±2394.67 ^{#,s}	37.51	0.0001*

One-way - ANOVA test; * $P < 0.01$, Tukey HSD *Post hoc* test; [#] $P < 0.05$ (compared to HFD), ^s $P < 0.05$ (compared to HFD + rosuvastatin 20 mg/kg). TC: Total cholesterol, TG: Triglycerides, HDL: High-density lipoprotein; LDL: Low-density lipoprotein, VLDL: Very LDL, AIP: Atherogenic Index of Plasma, FBG: Fasting blood glucose, FSI: Fasting serum insulin; HOMA-IR: Homeostatic model assessment of insulin resistance; QUICKI: Quantitative insulin sensitivity check index, AUC: Area under the curve, GTT: Glucose tolerance test, HFD: High-fat diet

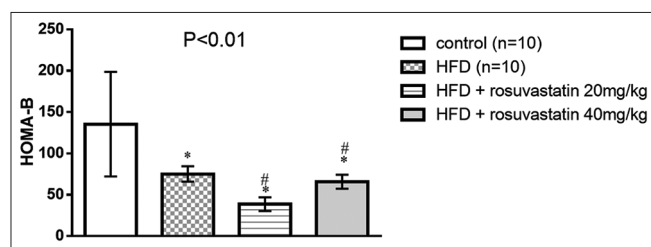


Figure 2: Dose-dependent effect of rosuvastatin on β -cell function compared to high-fat diet and control groups. * $P < 0.01$ compared to the control, [#] $P < 0.05$ compared to high-fat diet, One-way ANOVA test $P < 0.01$

satiety. Seif *et al.* study confirmed that rosuvastatin could counteract the effect of fatty acids on leptin receptors at the hypothalamus.^[22,23]

Indeed, rosuvastatin illustrated a dose-dependent effect in the improvement of lipid profile and Atherogenic Index suggesting that rosuvastatin may alleviate the bad influence of HFD on lipid metabolism.^[24]

As blood glucose elevated, it triggers the release of insulin in response to fasting hyperglycemia in HFD; however, this mechanism is impaired in rosuvastatin-treated group.^[25]

It has been reported that chronic depletion of cellular cholesterol in response to rosuvastatin-mediated inhibition of membrane fluidity/rigidity ratio might affect insulin carrier granules attachment to the lipid raft.^[26] This finding might explain the potential effect of rosuvastatin on the insulin levels in the present study.

Besides, results of the present study revealed that rosuvastatin improved insulin sensitivity in a dose-dependent manner

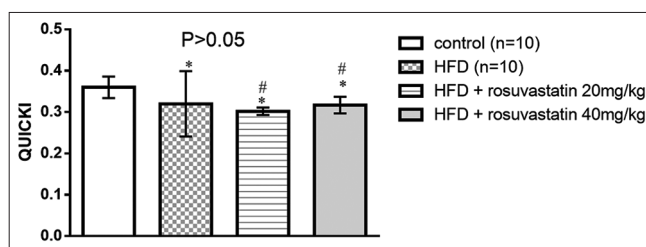


Figure 3: Dose-dependent effect of rosuvastatin on the insulin sensitivity compared to high-fat diet and control groups. * $P > 0.05$ compared to the control, [#] $P > 0.05$ compared to high-fat diet, One-way ANOVA test $P > 0.05$

as 40 mg/kg rosuvastatin led to the improvement of IR with reduction in the insulin release due to the inhibition of gluconeogenesis through the modulation of peroxisome proliferative-activated receptor- γ coactivator-1 (PGC-1 α) pathway.^[27,28]

The exact molecular mechanism of rosuvastatin effect on the β -cell is linked to membrane disorganization or isoprenoids inhibition, disturbed calcium current, and impaired β -cell mitochondrial ATP production.^[29] Therefore, rosuvastatin illustrated a dose-dependent effect in the amelioration of pancreatic β -cell during HFD-induced metabolic disturbances, unlike other statins types.^[30]

The present study revealed several limitations which are small sample size, short duration of rosuvastatin effect, lack the values of blood pressure measurement, and obesity-linked inflammatory biomarkers. However, this study may be regarded as a preliminary study for large-scale human study to assess the beneficial effect of rosuvastatin in patients with T2DM and associated overweight and/or metabolic syndrome.

CONCLUSION

Rosuvastatin may have a potential effect on reduction of glucometabolic changes induced by HFD with significant amelioration of pancreatic β -cell function in dose-dependent manner.

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Conflicts of interest

There are no conflicts of interest.

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