Effects of Rosuvastatin Alone or in Combination with Omega-3 Fatty Acid on Adiponectin Levels and Cardiometabolic Profile

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ABSTRACT

Background: Adiponectin is an important adipocyte-related protein that has been postulated to participate in prevention of the development of metabolic syndrome. The relationship between adiponectin serum levels and risk of coronary artery disease (CAD) has been widely investigated and remains controversial. The aim of the present study was to evaluate the effects of rosuvastatin and/or omega-3 fatty acid on adiponectin serum levels in patients with insulin resistance (IR) and CAD. **Patients and Methods:** This study involved 87 patients with CADs and IR of different etiology, the patients were divided into three groups; 24 patients on treatment with rosuvastatin, 22 patients on treatment with omega-3 fatty acid, 23 patients on treatment with omega-3 fatty acid and rosuvastatin, 18 patients were not previously or currently treated with either rosuvastatin or omega-3 fatty acid, those regarded as control patients. Anthropometric measures, adiponectin serum levels, and other biochemical parameters were assessed in each treated group. **Results:** Rosuvastatin therapy leads to a significant elevation in adiponectin serum levels from 4.1 ± 0.99 ng/mL to 6.76 ± 1.03 ng/mL compared to control $P < 0.01$. Omega-3 fatty acid therapy leads to a significant elevation in adiponectin serum levels from 4.1 ± 0.99 ng/mL to 6.11 ± 1.29 ng/mL compared to control $P < 0.01$. Rosuvastatin plus omega-3 fatty acid therapy lead to a significant elevation in adiponectin serum levels from 4.1 ± 0.99 ng/mL to 7.99 ± 1.76 ng/mL compared to control $P < 0.01$. **Conclusions:** Rosuvastatin and/or omega-3 fatty acid lead to significant cardiometabolic protection through an increment in adiponectin serum levels.

Key words: Adiponectin, omega-3 fatty acid, rosuvastatin

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INTRODUCTION

Coronary artery disease (CAD) is one of the most common causes of mortality and morbidity worldwide, caused by coronary atherosclerosis that mediated by dyslipidemia and inflammatory processes; CAD presented as stable angina or acute coronary syndrome that includes acute myocardial infarction and unstable angina.[1] The relationship between adiponectin serum levels and risk of CAD has been widely investigated and remains controversial.[2]

Adiponectin is an adipocytokine secreted from adiposities; it possesses significant insulin-sensitizing, anti-inflammatory, and antiatherogenic effects.[3]

Adiponectin accounts for 0.01% of plasma protein with a half-life of 2.5 h; normal adiponectin plasma level is 5–10 μg/mL with higher levels in female than males due to sexual dimorphism.[4] Adiponectin plasma forms are of two types, high-molecular weight (biological active form) and low-molecular weight. In addition, high-molecular weight adiponectin levels are positively associated with CAD and negatively associated with risk of type 2 diabetes mellitus (DM), but this is not true to the low-molecular weight adiponectin.[5] Adiponectin serum levels are inversely correlated with body mass index (BMI), visceral obesity, and insulin resistance (IR); thus, it regarded as an indicator and predictor of noninsulin dependent DM, insulin resistant, and overt hyperglycemia. Since adiponectin is responsible for provoking of fatty acid oxidation and skeletal muscles glucose uptake, inhibition of liver gluconeogenesis, and stimulation of pancreatic β-cells for insulin secretion, thereby adiponectin plays an important role in linking glucose metabolism with visceral adiposity.[6] Reduction of adiponectin levels in obesity predisposes for the development of CAD due to the reduction of adiponectin-mediated antioxidative, anti-inflammatory, antiapoptotic, and antiatherogenic effects.[7] High adiponectin levels considered as protective against the development of CAD in younger populations, but there is controversy regarding its cardioprotective role in elderly.[8]

IR is a failure of cells to respond the normal insulin action leading to high insulin levels and hyperglycemia, it may be uncertain and undetected until the development of overt diabetes commonly progressing into metabolic syndrome.[9] In IR, there are downregulations of adiponectin and adiponectin receptors leading to a reduction of insulin sensitivity and augmentations of vascular endothelial dysfunctions.[10]

Adiponectin and adiponectin receptors may be a target for different drugs and herbs, berberine, and other herbs such as gingerol, curcumin, and capsaicin have been shown to augment and stimulate adiponectin, which *per se* explain the potential antidiabetic effects of berberine.[11,12] Furthermore, studies with animal model demonstrated that mice that are fed with the docosahexaenoic acid and omega-3 fatty acid have been shown to stimulate adiponectin gene expression.[13]

Many previous studies have been revealed that statins are valuable in increasing the adiponectin levels and reduction of cardiovascular complications, but lipophilic statins such as atorvastatin were failed in improving the optimal high-molecular weight adiponectin while

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hydrophilic statins such as rosuvastatin increase the high-molecular weight adiponectin.[14]

The aim of the present study was to evaluate the effects of rosuvastatin and/or omega-3 fatty acid on adiponectin serum levels in patients with IR and CAD.

PATIENTS AND METHODS

This study was conducted at the Department of Clinical Pharmacology and Therapeutic in conjunction with the Department of Internal Medicine, College of Medicine, Al-Mustansiriya University from June to November 2015, Baghdad, Iraq. This study was permitted and approved by the Ethical and Scientific Committee; all enrolled patients gave informed written consent for initiation of the study (study permission no. 229/A2).

This was a cross-sectional study involved 87 patients with CADs and IR of different etiology. The patients were recruited from the Coronary Care Unit at Al-Yarmouk Teaching Hospital. The patients were included using the New York Heart Association classification,[15] and categorized according to the treatment history into three groups; Group (A): 24 patients on treatment with rosuvastatin 20 mg/day, Group (B): 22 patients on treatment with omega-3 fatty acid 400 mg/day (180 mg EPA + 120 DHA), Group (C): 23 patients on treatment with omega-3 fatty acid and rosuvastatin, Group (D): 18 patients were neither previously nor currently treated with either rosuvastatin or omega-3 fatty acid were regarded as control patients.

An exclusion criterion included patients with chronic liver disease, chronic renal failure, sepsis, stroke, and rheumatic and connective tissue diseases.

Biochemical measurements

after an overnight fasting, 10 ml of venous blood was drained from antecubital site, 7 ml put into planar tubes for routine investigations, and 3 ml put into ethylenediaminetetraacetic acid tubes and centrifuged at 2000 r/min for insulin, adiponectin, and cardiac troponin-I (cTnI) assessments. cTnI serum levels were estimated by ELISA kit method catalog (kit number E-ELRI1253 pg/mL, Elbascience, China), adiponectin serum levels were assessed through ELISA kit method (Cat. No. AG-45A-0001EK-KI01 ng/mL, Incheon, Korea), insulin serum levels were measured by ELISA kit method (ACS-180 mU/L, Ciba Corning Diagnostics, Medified, USA). Total cholesterol, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-c) were estimated by specific enzymatic colorimetric kits while low-density lipoprotein cholesterol (LDL-c) was determined by Friedewald *et al.* method;[16] then from lipid profile, different measures could be estimated through specific equations. Atherogenic index = log (TG/HDL),[17] atherogenic coefficient (AC) = total cholesterol-HDL/HDL,[18] very LDL (VLDL) = TG/5, and cardiac risk ratio CCR = total cholesterol/HDL.[19] Fasting and postprandial blood glucose were determined by ELISA kit method (Glucose Colorimetric Assay kit, K686-100, BIOVISION, China).

Anthropometric measurements

weight and height were measured through stadiometer and BMI with formula; BMI = body weight (kg)/height (m^2).[20]

Waist circumference was estimated in the standing position at midpoint between the upper border of the iliac crest and lower border of the last rib through graduated tape in centimeters.[21]

Hip circumference was estimated in the standing position, the largest distance between the greater trochanters,[22] also measured waist–hip ratio and a waist height ratio.

Basal adiposity index (BAI) is calculated by the following formula:[23]

$$BAI = \left(\frac{100 \times \text{hip circumference(m)}}{\text{Height (m)} \times \sqrt{\text{Height}}} \right) - 18$$

Lean body mass (LBM) was calculated according to the Boer formula as LBM = (0.32810 × body weight) + (0.33929 × height) − 29.5336,[24] and body fat % = (1.2 × BMI) + (0.23 × age) − (10.8 × gender) − 5.4, (1 for male and 0 for female).[25]

Cardiometabolic measurements

Blood pressure measurements of enrolled patients were assessed by standard mercury sphygmomanometer after rest at sitting position at the right arm. A resting twelfth leads electrocardiography (ECG) was assessed through digital ECG portable device recorder (GE Marquette Mac 800 Ecg-EkgMachine, USA).

Criteria for IR include, fasting serum insulin >25 μIU/L and postprandial blood glucose PPG 140–197 mg/dl.

The homeostatic model assessment-IR (HOMA-IR) was measured by specific equation that depends on fasting blood glucose (mg/dl) and insulin (μIU/L), the HOMA-β cell function.[26]

$$\text{HOMA-IR} = \frac{\text{glucose} \times \text{insulin}}{405} \quad \text{HOMA-}\beta = \frac{360 \times \text{insulin}}{\text{glucose}} \%\ .[26]$$

Insulin sensitivity was assessed by Quantitative Insulin Sensitivity Check Index (QUICKI),

$$\text{QUICKI} = \frac{1}{\left[\begin{array}{l} \log(\text{fasting insulin}\,\mu\text{U/mL}) \\ +\log(\text{fasting glucose mg/dL}) \end{array} \right]}\ .[27]$$

Statistical analysis

Data were presented as mean ± standard deviation and variables were compared by ANOVA test which determined the significance among groups followed by *post hoc* test, considering $P < 0.05$ statistically significant. Data were statistically analyzed through statistical package for social sciences software version 19.0 (SPSS 19.0, 2010, IBM Corp., NY, USA).

RESULTS

A total number of 97 patients were recruited in this study, ten patients were withdrawn due to personal reasons. Thus, 87 patients continued in this study. They were 24 (27.58%) patients treated with rosuvastatin, 22 (25.28%) patients on treatment with omega-3 fatty acid, 23 (26.43%) patients on treatment with omega-3 fatty acid and rosuvastatin, and 18 (20.68%) patients treated with neither of rosuvastatin nor omega-3 fatty acid. Majority of the patients were well compliant with treatment, with 57:30 male:female ratios, respectively. The patients in this study were associated with disease condition hyperlipidemia (94.25%), hypertension (90.80%), and IR (51.72%). The main duration of CAD was 4.55 ± 1.49 years with 64.36% of them having a positive family history for CAD. The patient characteristics are presented in Table 1.

There were no significant differences in anthropometric profiles between rosuvastatin-treated patients, omega-3 fatty acid-treated patients, rosuvastatin plus omega-3 fatty acid-treated patients, and control ($P > 0.05$) [Table 2].

Rosuvastatin therapy leads to a significant elevation in adiponectin serum levels from 4.1 ± 0.99 ng/mL to 6.76 ± 1.03 ng/mL compared to control $P < 0.0001$. Similarly, rosuvastatin significantly improved IR, fasting blood glucose, and HOMA-IR compared to control $P < 0.05$. Rosuvastatin also significantly reduced the levels of total cholesterol, total

Table 1: Baseline patient characteristics

Patient characteristics	Mean±SD, *n* (%)
Number	87
Age	48.38±11.73
Gender	
Male	57 (65.51)
Female	30 (34.48)
Hyperlipidemia	82 (94.25)
Hypertension	79 (90.80)
Insulin resistance	45 (51.72)
CAD	87 (100)
Stable angina	17 (19.54)
Unstable angina	12 (13.79)
STEMI	44 (50.57)
NSTEMI	14 (16.09)
Types of MI	
Anterior	12 (13.79)
Posterior	11 (12.64)
Anterioseptal	13 (14.94)
Inferior	17 (19.54)
Anteriolateral	5 (5.74)
Onset of chest pain	3.77±1.23
Duration of chest pain	8.71±1.62
Troponin-I	
Positive	70 (80.45)
Negative	17 (19.54)
CAD management	
Aspirin	67 (77.011)
Clopidogrel	55 (63.21)
Enoxaparin	86 (98.85)
Rosuvastatin	24 (27.58)
Omega-3 fatty acid	22 (25.28)
Rosuvastatin + Omega-3 fatty acid	23 (26.43)
Metoprolol	45 (51.72)
ACEI	22 (25.28)
Calcium channel blockers	10 (11.49)
Morphine	79 (90.80)
DC shock	2 (2.29)
Duration of rosuvastatin therapy (month)	9.77±2.12
Duration of omega-3 fatty acid therapy	4.83±1.83
Duration of combination therapy	5.29±1.55
Rosuvastatin off therapy	18 (20.68)
Family history of CAD	
Positive	56 (64.36)
Negative	31 (35.63)

Results are expressed as mean ± SD, *n* (%). CAD: Coronary artery disease, STEMI: ST-elevation myocardial infarction, NSTEMI: Non-ST-elevation myocardial infarction, ACEI: Angiotensin converting enzyme inhibitor, MI: Myocardial infarction

TG, VLDL, LDL-c, atherogenic index, and AC ($P < 0.0001$) and showed a significant elevation in HDL-c ($P < 0.05$). Moreover, rosuvastatin reduced systolic and diastolic blood pressures (DBPs) with a significant reduction in cardiac risk ratio compared to control ($P < 0.05$) [Table 3].

Omega-3 fatty acid therapy leads to a significant elevation in adiponectin serum levels from 4.1 ± 0.99 ng/mL to 6.11 ± 1.29 ng/mL compared to control ($P < 0.0001$), also omega-3 fatty acid significantly improved IR, fasting blood glucose, HOMA-β, and HOMA-IR compared to control ($P < 0.01$). Regarding the effect of omega-3 fatty acid on lipid profiles, it reduced the total cholesterol level, total TG, VLDL, LDL-c, atherogenic index, and AC significantly ($P < 0.01$) with no significant elevation in HDL-c compared to control [Table 3].

Rosuvastatin plus omega-3 fatty acid therapy lead to significant elevation in adiponectin serum levels from 4.1 ± 0.99 ng/mL to 7.99 ± 1.76 ng/mL compared to control ($P < 0.01$); rosuvastatin plus omega-3 fatty acid also improved IR, fasting blood glucose, HOMA-IR, and improved lipid profile significantly $P < 0.01$. Moreover, rosuvastatin plus omega-3 fatty acid also reduced the systolic and DBPs $P < 0.05$ with a significant reduction in cardiac risk ratio compared to control ($P < 0.01$). All treated groups with rosuvastatin and/or omega-3 fatty acid showed no significant effects on cTnI [Table 3].

There was significant differences in adiponectin serum levels between treated groups and nontreated group (control), this difference was highly significant between omega-3 fatty acid and rosuvastatin plus omega-3 fatty acid ($P = 0.00001$), whereas less significant between rosuvastatin and rosuvastatin plus omega-3 fatty acid-treated group and insignificant between rosuvastatin and omega-3 fatty acid-treated group [Table 4].

Rosuvastatin plus omega-3 fatty acid therapy revealed more significant elevation in adiponectin serum levels compared to control and other treated groups [Figure 1].

Adiponectin serum levels in patients with CAD that were not treated with either rosuvastatin or omega-3 fatty acid showed significant negative correlation with HOMA-β, QUICKI, total TG, VLDL, CCR, and DBP. Omega-3 fatty acid-treated patients' adiponectin serum levels were negatively correlated with insulin levels, fasting blood glucose, postprandial glucose, HOMA-β, total cholesterol, total TG, VLDL, LDL-c, atherogenic index, AC, CCR, diastolic and systolic blood pressure (SBP), whereas showed significant positive correlation with HDL-c. The same results were observed in rosuvastatin-treated patients except this correlation was insignificant with VLDL, atherogenic index, and SBP. Finally, adiponectin serum levels in rosuvastatin plus omega-3 fatty acid-treated patients had significant negative correlations with insulin levels, total cholesterol, total TG, VLDL, LDL-c, CCR, SBP, and DBP, and significant positive correlation with QUICKI and HDL-c [Table 5].

DISCUSSION

Adiponectin is known for an important physiological effects such as anti-inflammatory, vascular protection, antidiabetic, and cardioprotective effects.[28] Thus, hypoadiponectinemia may predispose patients to the cardiovascular complications and augment the risk of type 2 DM[29] which corresponds with results of the present study. Our study demonstrated a low adiponectin serum levels in patients with CAD and IR.

In acute CAD, the role of protective and beneficial effects of adiponectin remained obscure and uncertain due to various cellular and molecular mechanisms. Earlier studies by Sattar *et al.* failed to reveal cardiometabolic protection afforded by adiponectin in CAD,[30] therefore, many clinical studies were conducted by stimulating adiponectin effects using drugs or recombinant adiponectin to exert cardioprotection.[31]

The present study showed significant effect of rosuvastatin in elevation of adiponectin serum level with amelioration of cardiometabolic risk factors of CAD patients.

Animal model study reported by Shibata *et al.*, 2005 demonstrated that statin therapy leads to increase adiponectin serum levels and improvement of HOMA-IR in patients with acute coronary syndrome and IR through inhibition of tumor necrosis factor-induced myocardial ischemia and upregulation of myocardial adiponectin gene that regulates cardiac fatty acid oxidation and glucose uptake.[32] In addition, oxidative stress during myocardial infarction leads to myocardial IR and cardiac dysfunction, thus rosuvastatin acts as a direct antioxidant or indirectly through stimulation of adiponectin which is a potent antioxidant.[33,34]

Moreover, rosuvastatin in therapeutic doses in the present study decreased serum insulin levels and improved HOMA-IR. However, study by Thongtang *et al.*, revealed that the highest rosuvastatin dose leads to a moderate increment in the insulin levels.[35]

Table 2: The differences in anthropometric profiles between rosuvastatin-treated, omega-3 fatty acid-treated and rosuvastatin-omega 3 fatty acid-treated patients compared with control

Variables	Control (*n*=18)	Rosuvastatin (*n*=24)	Omega-3 fatty acid (*n*=22)	Rosuvastatin and omega-3 fatty acid (*n*=23)	*F* statistic	*P*	95% CI
Age (year)	42.43±13.72	43.87±12.61	43.55±11.67	42.87±10.33	0.061	0.9802	8.4163-10.2238
Height (cm)							
Male	178.44±16.82	177.39±16.55	177.49±15.55	176.39±15.58	0.0553	0.9828	12.4698-13.3209
Female	165.66±13.73	166.84±12.94	166.81±13.88	166.75±13.99	0.0335	0.9917	9.9583-10.5135
Weight (kg)	93.63±19.43	97.55±17.29	95.73±16.44	97.55±16.29	0.2329	0.8732	10.2133-13.2263
BMI (kg/m^2)	31.76±8.62	33.02±8.22	32.41±9.66	33.04±6.72	0.1063	0.9562	5.5564-6.3590
WC (cm)							
Male	101.66±11.62	101.67±11.83	100.68±12.69	102.67±12.84	0.0984	0.9607	10.0317-8.3973
Female	90.42±10.53	91.88±10.62	92.66±10.75	91.81±11.29	0.144	0.9332	7.3822-8.2048
HC (cm)							
Male	102.29±14.93	102.33±11.69	103.62±13.78	103.71±16.82	0.0644	0.9785	11.7093-12.3753
Female	104.83±16.43	103.77±16.77	105.75±15.23	104.99±15.79	0.0596	0.9808	14.1910-13.5083
WH r							
Male	0.99±0.09	0.99±0.08	0.97±0.04	0.98±0.06	0.4132	0.7439	0.0566-0.0430
Female	0.86±0.061	0.88±0.063	0.87±0.07	0.87±0.054	0.3578	0.7836	0.0309-0.0376
W-Htr							
Male	0.56±0.09	0.57±0.04	0.57±0.09	0.57±0.08	0.0814	0.97	0.0525-0.0585
Female	0.54±0.06	0.55±0.02	0.55±0.07	0.55±0.05	0.173	0.9144	0.0329-0.0401
BAI							
Male	24.95±5.88	25.32±5.97	25.47±6.33	25.74±6.44	0.0574	0.9818	4.6753-5.1416
Female	31.07±9.62	30.16±9.05	31.09±9.33	30.63±8.77	0.4757	0.7001	15.2244-13.8659
Body fat (%)							
Male	19.8±3.88	20.0±5.75	19.3±3.61	20.7±3.69	0.3946	0.7572	3.3776-4.0480
Female	30.9±8.79	30.7±8.99	32.1±8.99	31.3±7.85	0.113	0.9523	7.2800-7.2256
Lean body mass							
Male	66.6±11.72	67.9±12.55	67.1±11.72	67.9±10.77	0.0611	0.9801	8.2783-8.9637
Female	53.7±9.33	55.2±9.97	54.7±9.44	55.2±8.33	0.1135	0.9519	−6.0950-7.1077

Results are expressed as mean ± SD. BMI: Body mass index, WC: Waist circumference, HC: Hip circumference, WH r: Waist-hip ratio, W-Ht r: Waist height ratio, BAI: Body adiposity index, CI: Confidence interval, SD: Standard deviation

Table 3: Variations in adiponectin serum levels, biochemical, and cardiometabolic profiles in three different treated groups compared to the control

Variables	Control (*n*=18)	Rosuvastatin (*n*=24)	Omega-3 fatty acid (*n*=22)	Rosuvastatin and omega-3 fatty acid (*n*=23)	*F* statistic	*P*	95% CI
Adiponectin (ng/mL)	4.1±0.99	6.76±1.03	6.11±1.29	7.99±1.76	30.371	0.0000*	1.5826-2.2382
Cardiac troponin-I (pg/mL)	75.33±13.29	73.67±12.72	74.88±12.48	73.22±11.83	0.1312	0.9413	−11.9201-9.1517
Insulin (μIU/L)	12.9±2.82	10.75±2.93	9.62±3.11	9.88±1.82	5.8307	0.0012*	−4.3638-1.2017
FBG (mg/dL)	109.66±12.65	100.63±6.83	90.54±7.63	97.64±10.52	13.8292	0.000*	−16.7755-4.2584
PPG (mg/dL)	144.73±12.83	143.99±14.69	136.83±13.73	137.83±14.83	1.7895	0.1555	−12.2870-4.6460
HOMA-IR	3.5±1.09	2.7±0.87	2.2±0.94	2.38±1.01	6.7561	0.0004*	−1.5956-0.4245
HOMA-β	99.52±9.81	102.84±12.66	125.75±11.59	102.67±12.66	22.5646	0.0000*	−6.3734-8.9013
QUICKI	0.32±0.055	0.33±0.042	0.34±0.045	0.34±0.011	1.1016	0.3533	−0.0232-0.0411
Total cholesterol (mg/dL)	321.77±22.91	199.65±12.71	244.63±11.62	164.88±15.79	363.287	0.0000*	−122.120-57.277
Total triglycerides (mg/dL)	221.73±13.85	164.63±13.62	141.69±22.52	133.82±13.89	113.15	0.0000*	−70.536-18.235
HDL-c (mg/dL)	44.76±7.89	51.66±8.94	46.73±6.86	53.83±9.61	5.2191	0.0024*	−0.0022-8.6292
VLDL (mg/dL)	44.34±8.83	32.92±6.33	28.33±4.72	26.76±5.99	28.9588	0.0000*	−16.7319--1.1890
LDL-c (mg/dL)	232.66±22.62	115.06±12.89	183.62±14.22	84.26±6.85	429.616	0.0000*	−129.5714-79.8924
Atherogenic index	0.335±0.044	0.143±0.023	0.122±0.031	0.035±0.0036	396.157	0.0000*	−0.2150-0.0865
Atherogenic coefficient	6.19±1.33	2.86±0.87	4.23±1.77	2.06±0.99	40.3314	0.0000*	−4.3720-0.1751
CCR	4.95±1.55	3.86±0.95	5.23±1.88	3.06±0.97	11.6826	0.0000*	−2.2126-0.2506
SBP (mmHg)	155.73±21.62	136.79±22.61	150.72±14.62	141.86±11.94	4.6652	0.0046*	−4.1058-18.9523
DBP (mmHg)	91.72±11.86	83.22±11.82	87.52±8.65	82.69±9.63	3.2324	0.0264**	−17.1144-7.5316

Results are expressed as mean±SD, *P<0.05, **P<0.01. FBG: Fasting blood glucose, PPG: Postprandial glucose, HOMA-IR: Homeostatic model assessment insulin resistance, HOMA-β: Homeostatic model assessment β cell function, QUICKI: Quantitative Insulin Sensitivity Check Index, HDL-c: High-density lipoprotein-cholesterol, LDL-c: Low-density lipoprotein-cholesterol, VLDL: Very low-density lipoprotein, CCR: Cardiac risk ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, CI: Confidence interval

Rosuvastatin therapy also leads to significant amelioration in lipid profile, atherogenic index, AC, cardiac risk ratio, and reduction in blood pressure compared to patients not taking rosuvastatin; these findings correspond with many previous studies that revealed significant lipid lowering effects of rosuvastatin with preservation of endothelial function through stimulation of vascular endothelial nitric

Table 4: Variations in adiponectin serum levels, biochemical, and cardio-metabolic profiles in treated groups compared to the control

Biochemical parameters	*Post-hoc* test (Tukey HSD) (*P*)						ANOVA test	
	C versus R	C versus O	C versus OR	R versus O	R versus OR	O versus OR	*F*	*P*
Adiponectin (ng/mL)	0.0000*	0.0000*	0.0000*	0.3455	0.0104‡	0.0000*	30.37	0.0000*
Cardiac troponin-I (pg/mL)	0.0602	0.0015*	0.0036*	0.4944	0.6899	0.9884	5.830	0.0012*
Insulin (μIU/L)	0.0156‡	0.0000*	0.0007*	0.0029*	0.7017	0.0652	13.82	0.0000*
FBG (mg/dL)	0.9983	0.3000	0.4114	0.3213	0.4454	0.9953	1.7895	0.1555
PPG (mg/dL)	0.0482‡	0.0004*	0.0025*	0.3095	0.6741	0.9253	6.756	0.0004*
HOMA-IR	0.8059	0.0000*	0.8332	0.0000*	0.9683	0.0000*	22.56	0.0000*
HOMA-β	0.8593	0.4140	0.4051	0.8385	0.8338	0.8355	1.1016	0.3533
QUICKI	0.0820	0.0000*	0.8862	0.0000*	0.0000*	0.0000*	363.28	0.0000*
Total	0.0000*	0.0000*	0.0000*	0.0001*	0.0000*	0.3811	113.15	0.0000*
Triglycerides (mg/dL)	0.0501	0.8831	0.0054*	0.2045	0.8148	0.03‡	5.2191	0.0024*
HDL-c (mg/dL)	0.0000*	0.0000*	0.0000*	0.0863	0.0089*	0.8495	28.95	0.0000*
VLDL (mg/dL)	0.1859	0.0000*	0.9111	0.0000*	0.0000*	0.0051*	429.61	0.0000*
LDL-c (mg/dL)	0.0010*	0.0302‡	0.9316	0.0623	0.0000*	0.0000*	396.15	0.0000*
Atherogenic index	0.0000*	0.0000*	0.0000*	0.0026*	0.1458	0.0000*	40.33	0.0000*
Atherogenic coefficient	0.0603	0.9182	0.0002*	0.0060*	0.1976	0.0000*	11.68	0.0000*
SBP (mmHg)	0.0066*	0.8209	0.0795	0.0527	0.7738	0.3636	4.66	0.0046*
DBP (mmHg)	0.0545	0.5945	0.0387‡	0.5138	0.9982	0.4203	3.232	0.0264‡

Significance of differences among treated groups presented via ANOVA test and Tukey HSD. *P<0.01, ‡P<0.05; C versus R: Control versus rosuvastatin, C versus O: Control versus omega-3 fatty acid, C versus OR: Control versus rosuvastatin + omega-3 fatty acid, R versus O: Rosuvastatin versus omega-3 fatty acid, R versus OR: Rosuvastatin versus rosuvastatin + omega-3 fatty acid, O versus OR: Omega-3 fatty acid versus rosuvastatin + omega-3 fatty acid. FBG: Fasting blood glucose, PPG: Postprandial glucose, HOMA-IR: Homeostatic model assessment insulin resistance, HOMA-β: Homeostatic model assessment β cell function, QUICKI: Quantitative Insulin Sensitivity Check Index, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, VLDL: Very low-density lipoprotein, HSD: Honestly significant difference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

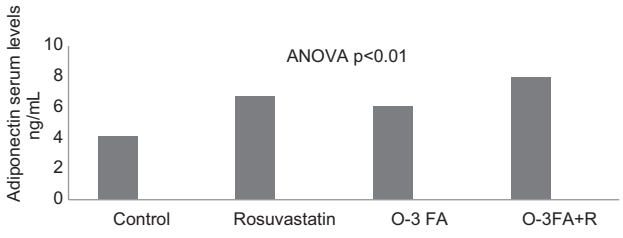

Figure 1: Effects of rosuvastatin and/or O-3FA on adiponectin serum levels in coronary heart disease compared to control. O-3FA: Omega-3 fatty acid; O-3FA + R: Omega-3 fatty acid plus rosuvastatin

oxide.[36] Rosuvastatin such as pitavastatin is hydrophilic, which exert potent cardiometabolic protection, glycemic control, and adiponectin activation more than lipophilic statins,[37] which further explains the cardioprotective and glucometabolic effects of rosuvastatin in the present study.

On the other hand, the patients with CAD treated with omega-3 fatty acid showed insignificant differences in the anthropometric parameters compared to the control, this finding was similar to study by Rafraf *et al.* which pointed out toward insignificant effects of omega-3 fatty acid therapy on anthropometrics profile.[38] Therapy with omega-3 fatty acid in patients with CAD led to significant increases in adiponectin serum levels compared to control with significant improvement in HOMA-IR, HOMA-β, insulin levels, and fasting blood glucose, these findings were inconsistent with Yamamoto *et al.* results which revealed that administration of omega-3 fatty acid produced significant anti-inflammatory effects in patients with CAD associated with hyperlipidemia through an increase in adiponectin serum levels.[39] Omega-3 fatty acid increases adiponectin serum levels through activation of adipocytes peroxisome proliferator-activated receptor gamma that augments adiponectin synthesis and secretion.[40] Lorente-Cebrián *et al.* in 2006 disclosed an increased in the adiponectin by omega-3 fatty acid lead to reduction of fasting insulin levels and attenuation of IR due to adiponectin-insulin-sensitizing property.[41]

Indeed, omega-3 fatty therapy in the present study led to a significant amelioration of lipid profile, atherogenic index, and AC with insignificant elevation in HDL-c levels while the effect on the cardiac risk ratio and blood pressures were insignificant, these observations were consistent with the finding of Dokholyan *et al.* study that displayed insignificant effects of omega-3 fatty therapy on the reduction of blood pressure in hypertensive patients.[42]

Furthermore, dual effects of omega-3 fatty acid plus rosuvastatin led to more pronounced effects on cardiometabolic risk profile through significant increases in adiponectin levels, amelioration of lipid profiles, cardiac risk ratio, atherogenic index, AC, reduction in blood pressure, and improvement of IR. As previously reported, combinations of rosuvastatin and omega-3 fatty acid therapy were associated with a higher reduction of cardiovascular risk scores compared to the either rosuvastatin or omega-3 fatty acid monotherapy.[43]

Moreover, Mindrescu *et al.* study observed that omega-3 fatty acid supplementation in rosuvastatin-treated patients lead to significant endothelial function and improvement in the vasoactive effect of rosuvastatin. Deficiency in free fatty acids upregulates HMG-CoA reductase activity, which leads to rosuvastatin resistance, subsequently downregulation of nitric oxide, endothelial dysfunction followed by IR.[44] Hence, combined therapy of omega-3 fatty acid and rosuvastatin lead to more cardiometabolic protection as presented in our study through reduction in the blood pressure and cardiac risk ratio.

Mente *et al.* observed that the variation in adiponectin serum levels was linked to the ethnicity, especially South Asian and Caucasian peoples. IR in these people was correlated low adiponectin levels, whereas this correlation was not observed with Indian peoples.[45] This observation corresponds with the findings of the current study since all enrolled patients were Iraqi patients.

The present study demonstrated a protective role of adiponectin against acute coronary heart disease (CHD) contrasting with the findings of

Table 5: Correlation of adiponectin levels with cardiometabolic profiles

Cardiometabolic Variables	Control (*n*=18)		Omega-3 FA (*n*=22)		Rosuvastatin (*n*=24)		Omega-3 FA + rosuvastatin (*n*=23)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Insulin (μIU/L)	−0.3321	0.062	−0.9616	<0.0001*	−0.3896	0.017‡	−0.4364	0.01‡
Cardiac troponin-I (pg/mL)	−0.0576	0.336	−0.1493	0.19	−0.1992	0.123	−0.0707	0.293
FBG (mg/dL)	−0.1524	0.213	−0.6049	0.001*	−0.9945	<0.0001*	−0.107	0.239
PPG (mg/dL)	−0.1753	0.188	−0.4862	0.006*	−0.4017	0.014‡	−0.2567	0.08
HOMA-IR	−0.1945	0.168	0.0863	0.439	−0.3693	0.022‡	−0.2075	0.121
HOMA-β	−0.7894	<0.0001*	−0.9814	<0.0001*	−0.4268	0.01‡	−0.2184	0.111
QUICKI	−0.4193	0.027‡	0.2498	0.187	−0.3693	0.022‡	0.9509	<0.0001*
Total cholesterol (mg/dL)	−0.1918	0.171	−0.4699	0.007*	−0.6202	<0.0001*	−0.5858	0.001*
Total triglycerides (mg/dL)	−0.777	<0.0001*	−0.6779	<0.0001*	−0.9458	<0.0001*	−0.5564	0.001*
HDL-c (mg/dL)	0.233	0.236	0.5666	0.005*	0.9652	<0.0001*	0.956	<0.0001*
VLDL (mg/dL)	−0.9791	<0.0001*	−0.521	0.003*	0.3621	0.066	−0.9509	<0.0001*
LDL-c (mg/dL)	−0.2741	0.099	−0.3242	0.046‡	−0.9896	<0.0001*	−0.3858	0.02‡
Atherogenic index	−0.1596	0.205	−0.6286	<0.0001*	−0.1448	0.183	−0.2075	0.121
Atherogenic coefficient	−0.0908	0.29	−0.3592	0.031‡	−0.6531	<0.0001*	−0.018	0.379
CCR	−0.9926	<0.0001*	−0.8892	<0.0001*	−0.3693	0.022‡	−0.9782	<0.0001*
SBP (mmHg)	−0.1652	0.199	−0.4155	0.016‡	−0.286	0.057	−0.8222	<0.0001*
DBP (mmHg)	−0.995	<0.0001*	−0.6145	<0.0001*	−0.9973	<0.0001*	−0.6656	<0.0001*

P value was calculated at 95% CI; **P*<0.01, ‡*P*<0.05, FBG: Fasting blood glucose, PPG: Postprandial glucose, HOMA-IR: Homeostatic model assessment insulin resistance, HOMA-β: Homeostatic model assessment β cell function, QUICKI: Quantitative Insulin Sensitivity Check Index, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, VLDL: Very low-density lipoprotein, CCR: Cardiac risk ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CI: Confidence interval, FA: Fatty acid

earlier study by Dekker *et al*. which showed an association between high adiponectin levels and high cardiovascular mortality risk.[46] This elevation might due to use of common medication that used in CHD such as statins, fibrate, and angiotensin converting enzyme inhibitors which generally increase serum adiponectin levels, or due to the elevation of brain natriuretic levels in patients with heart failure as natriuretic levels stimulate adiponectin secretion.[47]

Finally, adiponectin serum levels were positively correlated with plasma HDL-c and QUICKI and negatively correlated with other measured parameters consistent with the finding of Li *et al*.[48]

Limitation of the present study

The study had small sample size which might lead to over or under estimations of adiponectin serum levels. Gender differences in adiponectin serum levels were not evaluated since it is documented as higher in women,[49] we measured only total adiponectin levels not high-molecular weight adiponectin (which is more active and linked to insulin sensitivity). We also did not include hemoglobin A1c and brain natriuretic peptides in our estimations. Moreover, physical activity, dietary habit, and other adipocytokines were also not evaluated in this cross-sectional study. Our study also limited to only one type of ethnic population.

CONCLUSION

Rosuvastatin and/or omega-3 fatty acid lead to significant cardiometabolic protection through an increment in adiponectin serum levels in patients with CAD.

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Conflicts of interest

There are no conflicts of interest.

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