International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

ORIGINAL ARTICLE

Comparison between Protective Effects of Resveratrol and Atorvastatin against Atherogenic Dyslipidemia in Rats

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ARTICLE INFO

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ABSTRACT

Background: Dyslipidemia puts patients at risk of cardiovascular diseases, which are the most cause of premature deaths worldwide. This study determined protective effects of resveratrol (RVL) and atorvastatin (ATV) in rats fed with a high-fat/high-fructose (HFHF) diet were compared for e treatment of atherogenic dyslipidemia.

Methods: Thirty-six adult male Sprague Dawley rats were divided into 4 groups, including a group fed with a standard diet and three groups fed with a HFHF diet for 12 weeks. In two groups, in addition to HFHF diet, animals received RVL (100 mg/kg) and ATV (10 mg/kg) by gavage. After 12 weeks, levels of body and heart weights, systolic blood pressure (SBP), serum biomarkers of atherogenic dyslipidemia, insulin resistance, and malondialdehyde (MDA) in the heart tissue were measured.

Results: Rats received the HFHF diet showed an elevation ($p<0.05$) in body and heart weight, SBP, serum total triglycerides (T-TGs), total cholesterol (T-CHOL), low-density lipoprotein CHOL (LDL-C), insulin resistance, aspartate aminotransferase (AST), and tumor necrosis factor-alpha (TNF-α), and also, elevated MDA content in the heart tissue. The administration of RVL significantly reduced ($p<0.05$) heart weight, SBP, serum T-TGs levels, insulin resistance, TNF-α, and cardiac MDA in rats received HFHF diet. On the other hand, the administration of ATV significantly decreased ($p<0.05$) heart-weight, and serum levels of T-TGs, T-CHOL, LDL-C, and TNF-α.

Conclusion: RVL at a dose of 10 mg/kg was not a better protective medication against atherogenic dyslipidemia; but it may be applicable as a complementary medication with ATV.

Introduction

Atherogenic dyslipidemia is defined as an increase in serum levels of triglycerides (T-TGs), total cholesterol (CHOL), low-density lipoprotein CHOL (LDL-C), and a reduction in the serum levels of high-density lipoprotein CHOL (HDL-C) (1). In severely obese patients, the existence of this abnormal lipid profile condition is associated with an imbalance in weight distribution, insulin resistance (IR), impairment in glucose tolerance, and immune dysfunction (2). It also puts patients at risk of cardiovascular diseases (CVDs), which are the most cause of premature deaths in the world (3, 4).

Statins are a class of drugs that are widely used against atherogenic dyslipidemia. They can decrease CHOL and subsequently LDL-C in the serum (5). The mode of action of statins is by interacting with and inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase that participates in the biosynthesis of CHOL (6). For decades, it has been assumed that statins are generally safe and well tolerated, but in recent years reports on their side effects have increased alarmingly (5, 7). Statin-associated muscle symptoms are the most adverse effects of these drugs that have been reported (5, 8). Besides, there is evidences that statins may trigger diabetes mellitus (DM) and increase the risk of hemorrhagic stroke (5). Moreover, neurotoxicity, hepatotoxicity, and renal toxicity of statins have been recorded in the literature (7, 9). These side effects can lead to the limit or discontinuation of prescribing statins against dyslipidemia (5, 9). Hence, searching to find new non-statin medications for dyslipidemia seems useful.

Resveratrol (RVL, 3,5,4'-trihydroxy-stilbene) is a natural polyphenol found in red grapes, peanuts, apples, and some berries. In recent years, studies have revealed that RVL has therapeutic effects on dyslipidemia and various CVDs (10, 11). Several mechanisms appear to be involved in the protective function of RVL against dyslipidemia and CVDs (10, 12). RVL has the ability to prevent the differentiation of fat cells into adult cells, inhibiting the proliferation of fat cells, reducing lipogenesis, and increasing lipolysis (13). RVL also ameliorates glucose tolerance and insulin sensitivity through several mechanisms. These mechanisms can modulate glucose uptake by increasing glucose transporter-4 expression, control glucose by increasing sirtuin-1 (SIRT-1) expression, regulate the insulin signaling pathway by increasing Akt (protein kinase B) expression, prevent inflammation, and increase peroxisome proliferator-activated receptor-gamma activity by inhibiting inflammatory markers (10, 12). RVL

increases the expression of glutathione peroxidase, co-oxygenase, and superoxide dismutase genes, especially in cardiovascular cells and the vascular system, by increasing the expression of genes associated with intracellular antioxidant enzymes (10). RVL also statistically reduces tumor necrosis factor-alpha (TNF-α) expression in the endothelium of the arterial wall and heart muscle (14, 15). Due to these beneficial effects, RVL can be a suitable alternative to statins. Therefore, this study was designed and conducted to evaluate protective effect of RVL on some indicators related to the atherogenic dyslipidemia and CVDs in comparison to atorvastatin (ATV), the most globally prescribed statin (16), in rats fed with a high-fat/high-fructose (HFHF) diet (Figure 1).

Materials and Methods

Thirty-six adult male Sprague Dawley rats weighing 200-210 g were purchased from the Center of Comparative and Experimental Medicine of Shiraz University of Medical Sciences, Shiraz, Iran. The animals were maintained under a 12h light/dark cycle, at 23±2ºC and 60% humidity with free access to water and laboratory animals' standard food pellets. They were adapted to the new environment for two weeks before the experiments began. The care and use of the animals, as well as all animal experiments, were performed under the Animal Rights Monitoring Committee of Larestan University of Medical Sciences (IR.LARUMS.REC.1397.006).
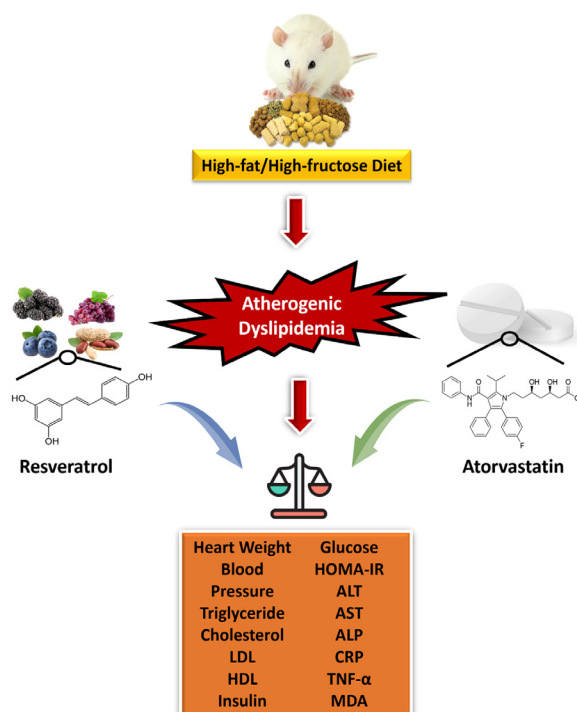

Figure 1: Schematic illustration of the design of the present study.

After 2 weeks of maintenance and feeding with a standard diet, rats were randomly divided into four groups (n=9) including (i) Standard (STD) food recipient group, (ii) HFHF diet, (iii) HFHF diet group which received RVL (HFHF+RVL), and (iv) HFHF diet group which received atorvastatin (HFHF+ATV). The STD diet contained 28% of calories from protein, 60% from carbohydrates, and 12% from fat. This diet was purchased from Pars Animal Fedd Co. (Tehran, Iran). High fat and high fructose (HFHF) diets were used to induce dyslipidemia. This diet contained 26.2% protein, 26.3% carbohydrates, and 34.9% fat, as well as 5% moisture. The energy content of the HFHF diet was 5.24 Kcal/g and 60% of its calories were provided by fat.

In addition, rats except in the STD group were given water containing 10% fructose, which had 40 Kcal per 100 mL of water. This formulation was prepared by Behsazan Haft Exir Danesh Co. (Shiraz, Iran). The intervention groups were daily treated with RVL and ATV at doses of 100 mg/kg and 10 mg/kg by gavage, respectively, from the beginning of the study at the same time and the intervention was continued for 12 weeks (17). RVL (100% pure trans resveratrol) was provided from NutriVita Co. (Lake Forest, California, USA).

After the experimental period, the animals were anesthetized by an intraperitoneal ketamine/xylazine injection. Then, rats were weighed, and after that, the systolic blood pressure (SBP) of each animal was measured by a tail cuff attached to a pneumatic pulse transducer (Narco Bio-Systems Inc., Houston, TX, USA) (18). The blood sample of each rat was collected from the heart and subsequently, the anesthetized animals were euthanized by cervical dislocation. The serum was separated by centrifugation of blood samples at 3000 rpm for 5 minutes at 4°C and lipid, insulin, and blood glucose profile tests, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), C-reactive protein (CRP), and TNF-α. Also, the heart tissue of animals was removed from the body and weighed. Thereafter, the heart tissue was stored at -20°C for further measurement of lipid peroxidation (LPO) in the heart tissue.

Levels of lipid parameters, including total CHOL (T-CHOL) and T-TGs, HDL-C, and LDL-C, as well as blood glucose, ALT, AST, and alkaline phosphatase (ALP) were analyzed spectrophotometrically in serum using commercial kits (Pars Azmoon, Tehran, Iran). Serum insulin was determined by radioimmunoassay kit (Shanghai Crystal Day Biotech Co., LTD, China). High-sensitivity C-reactive protein (hs-CRP) and TNF-α were assessed using commercial enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Crystal Day Biotech Co., LTD, China) according to the manufacturer's instructions. IR was estimated by homeostasis model assessment (HOMA) as an index of insulin resistance and calculated by the following formula:

$$HOMA - IR = \frac{insulin(U/mL) \_ glucose(mmol/L)}{22.5}$$

Malondialdehyde (MDA) as the indicator of LPO was assayed calorimetrically in the heart homogenate samples by using 1 mL of trichloroacetic acid (10%) and 1 mL of thiobarbituric acid (0.67%). Subsequently, samples were then heated in a boiling water bath for 30 min. Thiobarbituric acid reactive substances (TBARS) were determined by the absorbance at 535 nm. All the chemicals were of the highest grade and obtained from Merck Group (Darmstadt, Germany). All values were expressed as mean±SD. Data were statistically analyzed using one-way ANOVA for multiple group comparison followed by Tukey post hoc test using GraphPad Prism (version 9.5.0, GraphPad Software, San Diego, California, USA). Significance was set at $p<0.05$.

Results

Data from the measurements of body and heart weight were summarized in Figure 2 (A, and B, respectively). After 12 weeks, the body weight significantly ($p<0.01$) increased in the HFHF group (372.4±0.14.66) in comparison to the STD group (334.7±21.72). Meanwhile, the heart weight was significantly ($p<0.0001$) elevated in the HFHF group (1.40±0.11) in comparison to the STD group (1.06±0.08). Also, the administration of RVL significantly ($p<0.05$) reduced heart weight in the HFHF+RVL group (1.29±0.07) compared to the HFHF group (1.40±0.11).

The BP was statistically ($p<0.05$) increased in animals received the HFHF diet (138±4.61), when compared to animals received the STD diet (132.8±2.24, Figure 2C). The RVL treatment significantly ($p<0.001$) decreased the BP (from 138.9±3.88 to 134.8±2.22), while the administration of ATV did not significantly change the BP in rats (Figure 2C). Rats that received the HFHF diet (122.7±13.54) showed a significantly ($p<0.001$) increase in serum levels of T-TGs, compared to the animals that received the STD diet (102.4±11.10, Figure 3A). The administration of RVL and ATV in rats that received the HFHF diet (109.1±6.53 and 109.8±7.12, respectively) significantly ($p<0.05$) decreased T-TGs levels in serum in comparison to the HFHF group (122.7±13.54). Also, both T-CHOL and LDL levels in serum were significantly ($p<0.05$) elevated in the HFHF group (60.89±5.95
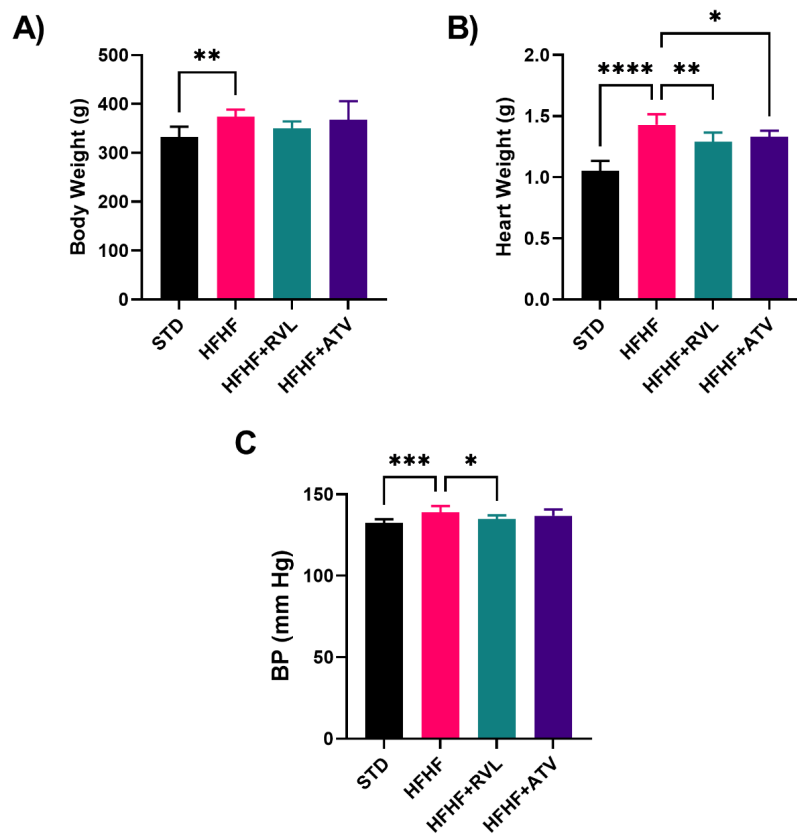
Figure 2: Body weight, heart weight and blood pressure in different groups (A-C, respectively). Data were shown as mean±SD (N=9). *$p<0.05$, **$p<0.01$, ***$p<0.001$, and ****$p<0.0001$, respectively.
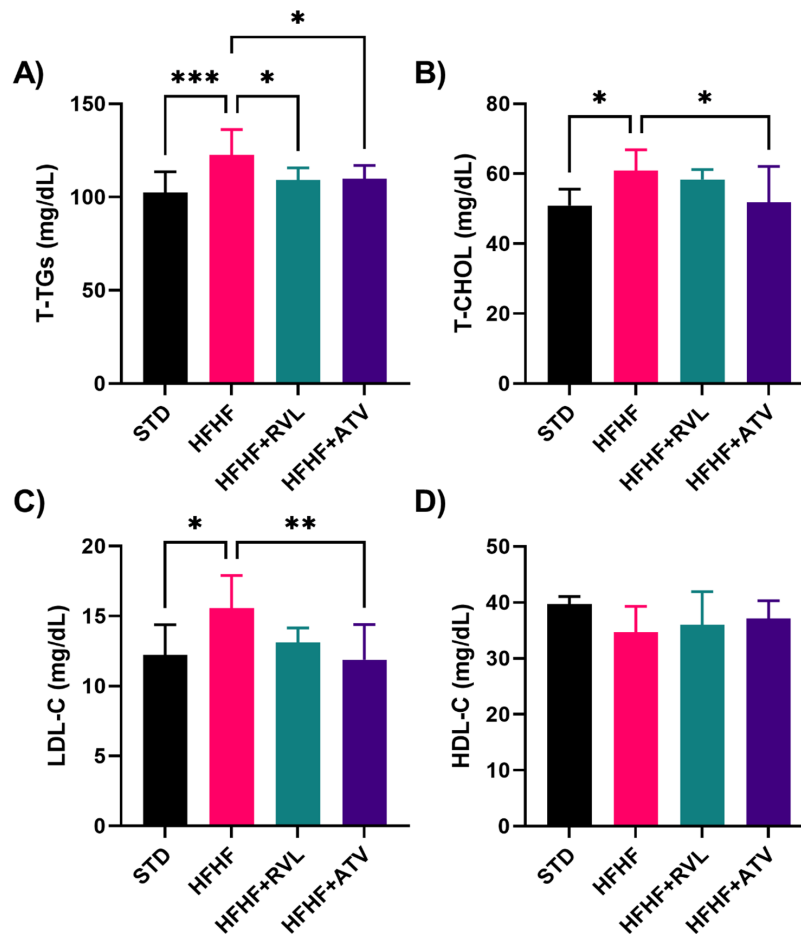

Figure 3: Serum levels of T-TGs, T-CHOL, LDL, and HDL (A-D, respectively). Data were shown as mean±SD (N=9). *$p<0.05$, **$p<0.01$, ***$p<0.001$, and ****$p<0.0001$, respectively.

and 15.56±2.35, respectively) when compared to the STD group (50.89±4.68 and 12.22±2.17, respectively; Figure 3B and C, respectively). Administration of ATV significantly reduced serum levels of both T-CHOL and LDL (51.78±10.32 and 11.89±2.52, respectively) in comparison to the HFHF group (Figure 3B and C, respectively). Animals that received HFHF diet and RVL did not exhibit alterations in either of these variables (Figure 3B and 3C, respectively). No statistically significant changes were found in levels of serum HDL between groups (Figure 3D).

The effects of RVL on the serum levels of insulin and glucose as well as HOMA-IR were summarized in Figure 4 (A, B, and C, respectively). There were no statistically significant changes in serum levels of insulin between groups (Figure 4A). Glucose levels were significantly elevated in the serum of rats received the HFHF diet, when compared to rats received the STD diet (213.9±31.72 vs. 173.2±8.18; $p<0.05$, Figure 4B). Both RVL and ATV treatments did not significantly change serum levels of insulin and glucose in rats that received the HFHF diet (Figure 4A and 4B). HOMA-IR showed a statistically significant increase in the HFHF-fed rats compared to STD diet-fed rats (4.38±0.78 vs. 3.28±0.43, $p<0.001$). On the other hand, administration of RVL significantly decreased HOMA-IR in comparison to the HFHF group (3.65±0.52 vs. 4.38±0.78, $p<0.05$; Figure 4C). No significant changes were observed in levels of ALT and ALP between groups (Figure 4D and 4E). AST levels in serum significantly increased in the HFHF group in comparison to the STD group (162.7±17.58 vs. 137.2±21.08; $p<0.01$, Figure 4F).
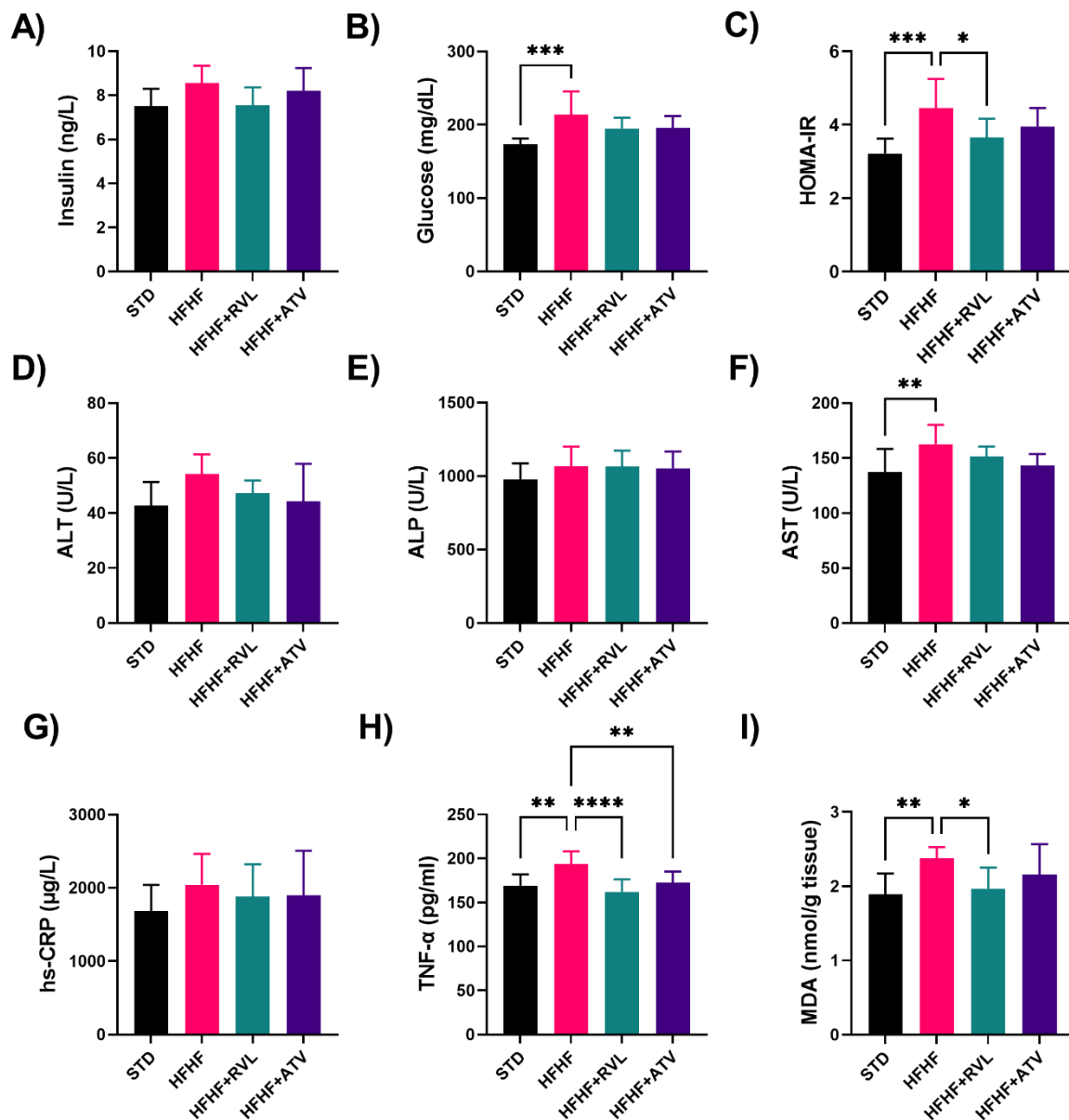

Figure 4: Insulin and glucose serum levels, HOMA-IR values, serum levels of ALT, ALP, AST, CRP and TNF-α levels and MDA content in the heart tissue in the different groups (A-I, respectively). Data were shown as mean±SD (N=9). *$p<0.05$, **$p<0.01$, ***$p<0.001$, and ****$p<0.0001$, respectively.

No statistically significant changes were found in levels of serum CRP between groups (Figure 4G). Levels of TNF-α significantly increased in rats received the HFHF diet, when compared to animals that received the STD diet (191.2±15.67 vs. 167.4±13.19, $p<0.01$, Figure 4H). However, the administration of RVL and ATV in rats that received an HFHF diet (162.2±14.13 and 172.4±12.58, respectively) significantly ($p<0.001$ and $p<0.05$, respectively) decreased levels of TNF-α in serum in comparison to the HFHF group (2.37±0.14, Figure 4H). Also, the rats that received the HFHF diet showed a statistical significant increase ($p<0.001$) in the MDA content (172.4±12.58) in the heart tissue; but the administration of RVL decreased the MDA level (1.96±0.28), which was statistically significant ($p<0.05$, Figure 4H).

Discussion

Findings from the present study revealed that administration of RVL in animals fed with the HFHF diet statistically reduced heart weight, HOMA-IR, serum levels of T-TGs, and TNF-α, as well as decreased MDA levels in the heart tissue. Meanwhile, administration of ATV statistically decreased heart weight, T-TGs, T-CHOL, LDL-C, and TNF-α levels in the serum of animals that received the HFHF diet. The induction of dyslipidemia in experimental animals was successful following the use of the HFHF diet. After 12 weeks, a statistically significant increase in serum levels of T-TGs, T-CHOL, and LDL-C was observed. Treatment with both RVL and ATV significantly reduced serum levels of T-TGs, which indicates that similar to ATV, RVL can lower levels of T-TGs in the serum.

In line with our results, Raskovic et al. have reported that supplementation of RVL decreased serum levels of T-TGs in rats with induced hyperlipidemia and type 2 diabetes (19). Yan et al. (2018) also revealed that RVL reduced T-TGs levels of plasma in rats with diabetes (20). Lower serum T-TGs levels in the group received RVL can be due to the inhibiting role of RVL on fatty acid and triacylglycerol synthesis in the hepatocytes (21). Also, RVL increased lipolysis by up-regulation of adipose TG lipase and hormone-sensitive lipase proteins (22). In contrast with ATV, there were no statistically significant differences after 12 weeks in the levels of T-CHOL and LDL-C in the HFHF-fed animals that received RVL. Higher doses of RVL have shown to be capable of modulating these parameters (23, 24).

In rats fed with HFHF, the heart weight statistically increased in comparison to the control group. Several studies attributed the increase in heart weight after the intake of a high-fat diet to cardiac hypertrophy (25, 26). Dyslipidemia is associated with left ventricular hypertrophy which increases the risk of cardiovascular mortality (27). Administration of RVL in the present study statistically decreased heart weight in animals fed with HDHF. Hence, RVL can be a cardioprotective drug against cardiac hypertrophy caused by dyslipidemia.

HOMA-IR is a validated model to assess insulin resistance and is an indicator of cardiometabolic risk (28). In this study, the administration of RVL in rats fed with an HFHF diet significantly reduced HOMA-IR; which shows that RVL improved insulin sensitivity in experimental animals. Similar to our findings, Asadi et al. have reported that RVL decreased HOMA-IR in rats with type-2 diabetes (29). Also, a recent randomized, placebo-controlled trial revealed that supplementation of RVL could decrease HOMA-IR (30). This may be due to the activating role of RVL on SIRT-1 and Akt which participate in decreasing hyperglycemia and enhancing insulin sensitivity (31, 32). On the other hand, supplementation of RVL increases circulation adiponectin, which is associated with improving insulin sensitivity (22). Unlike RVL, administration of ATV did not improve insulin sensitivity, which indicated that RVL is a better medication against insulin resistance.

MDA is a byproduct of LPO and its levels increase in patients with metabolic syndrome, obesity, and type 2 diabetes mellitus (33). Heart tissue is highly susceptible to the accumulation of LPO products, which are related to the onset of CVDs, primarily in atherosclerosis-based diseases (34). In our study, intake of HFHF diet in rats increased MDA level in the cardiac tissue. However, treatment of the animals with RVL decreased the cardiac MDA level while ATV did not reduce it. Therefore, RVL can have a cardioprotective effect by reduction of LPO in the heart tissue. In agreement with our results, other experimental studies have reported that RVL alleviates LPO in the heart tissue following cardiac damage (20, 35, 36). Mohajeri et al. indicated that intraperitoneally injection of 20 mg/kg RVL for 30 consecutive days in an experimental myocardial infarction rat model decreased MDA level in the heart tissue (36). Similarly, Fang et al. indicated that oral administration of RVL to diabetic rats for 16 weeks decreased the cardiac level of MDA (35).

Dyslipidemia, subsequent lipid oxidation, and inflammation cross-talk with each other in the development of atherosclerotic-based CVDs (37, 38). Oxidized lipoproteins can have a primary role in the biosynthesis of inflammatory cytokines, principally

TNF-α, interleukin 6, and 1β (37, 39). In the present study, serum level of TNF-α significantly increased in rats following intake of the HFHF diet. Meanwhile, administration of both ATV and RVL reduced the levels of TNF-α in the serum. Thereby, RVL like ATV can lower inflammation caused by dyslipidemia and decrease the risk of atherosclerotic-based CVDs. In line with the present results, Li *et al.* have indicated that the administration of RVL reduced serum and myocardial TNF-α production (40).

Conclusion

Based on our findings, administration of RVL in rats fed with the HFHF diet significantly reduced heart weight, HOMA-IR, serum levels of T-TGs and TNF-α, as well as decreased MDA level in the heart tissue. Also, administration of ATV significantly decreased the heart weight, serum levels of T-TGs, T-CHOL, LDL-C, and TNF-α levels in the animals that received the HFHF diet. Although, RVL has comparable effects with ATV; however, ATV was shown to have better protective effects against dyslipidemia. Hence, our suggestion is RVL at the dose of 10 mg/kg can be considered a complementary medication with statins for treating dyslipidemia.

Acknowledgment

Authors' Contribution

M.K., M.R.Z, H. A and M.N.; Contributed to writing the first draft. M.B, M.N, and S.A; Contributed to all data and statistical analysis, and interpretation of data. M.B and S.A.; Contributed to the research concept, supervised the work, and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

None declared.

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