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Research Article

Effects of Rosuvastatin on the Histopathological and Inflammatory Markers of Hyperlipidemic Rat Kidneys

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Abstract

Background: Hyperlipidemia is a significant cause of cardiovascular disease and global death by inducing endothelial dysfunction and narrowing blood vessels. The kidney is the first organ damaged by hyperlipidemia that distracts endothelial capillaries and increases glomerulosclerosis due to decreased renal blood flow. Rosuvastatin has an anti-hyperlipidemic effect and also improves endothelial function and reduces inflammation and oxidative stress. ***Objectives***: The present study aimed to investigate the impact of rosuvastatin on histopathological and inflammatory marker changes induced by hyperlipidemia in male rats. ***Methods***: Forty-six normal male rats were randomly divided into three main groups: the control negative group, ten rats that received a standard diet and water. In the hyperlipidemic group, eighteen rats were fed a high cholesterol (atherogenic) diet (79% standard diet and 21% ghee fat) for seven weeks. The treatment group includes eighteen rats that received a high cholesterol (atherogenic) diet (79% standard diet and 21% ghee fat) for seven weeks and were then treated with rosuvastatin 10 mg/kg/day orally by gastric gavage for 4 weeks. ***Results***: Rosuvastatin significantly decreased the proinflammatory markers (Interleukin-1, Interleukin-6, Tumor Necrosis Factor, and Cystatin C) and the pathological changes in the kidneys (p<0.005) compared with the hyperlipidemic group, while they were significantly increased in the hyperlipidemic group compared to the control group (p<0.005). However, rosuvastatin or hyperlipidemia did not significantly affect the body and the testicular weight. ***Conclusions***: Rosuvastatin modulates the histopathological changes and decreases the proinflammatory cytokine levels in hyperlipidemic male rats.

Keywords: Hyperlipidemia, Histopathology, Inflammatory markers, Kidneys.

آثار روزوفاستاتين على العلامات النسيجية المرضية والالتهابية لكلى الجرذان فرط شحميات الدم

الخلاصة

الخلفية: يُعد فرط شحميات الدم سبباً رئيسياً لأمراض القلب والأوعية الدموية والوفيات على مستوى العالم، من خلال تحفيز الخلل الوظيفي البطاني وتضييق الأوعية الدموية. وتُعد الكلى أول عضو يتضرر من فرط شحميات الدم، حيث يتسبب ذلك في تدمير الشعيرات البطانية وزيادة حدوث التصلب الكبيبي نتيجة انخفاض تدفق الدم الكلوي. يتمتع دواء روزوفاستاتين بتأثير مضاد لفرط شحميات الدم، كما يُحسن من وظيفة البطانة الوعائية ويقلل من الالتهاب والإجهاد التأكسدي. **الأهداف**: تقييم تأثير روزوفاستاتين على التغيرات النسجية والواسمات الالتهابية الناتجة عن فرط شحميات الدم في ذكور الجرذان. **الطرائق:** تم تقسيم ستة وأربعين جرذاً ذكراً سليماً بشكل عشوائي إلى ثلاث مجموعات رئيسية: المجموعة السلبية الضابطة (10جرذان) تناولت الغذاء والماء القياسيين. مجموعة فرط شحميات الدم (16 جرذاً) تم تغذيتها على نظام غذائي عالي الكوليسترول (تصلب الشرايين) مكوّن من 79% غذاء قياسي و21% دهن السمن لمدة سبعة أسابيع. مجموعة العلاج (20 جرذاً) تناولت نفس النظام الغذائي عالي الكوليسترول لمدة سبعة أسابيع، ثم تم معالجتها بدواء روزوفاستاتين (10 ملغم/كغم يومياً) عن طريق أنبوب المعدة لمدة أربعة أسابيع. **النتائج:** أدى روزوفاستاتين إلى انخفاض ملحوظ في الواسمات الالتهابية والتغيرات النسجية المرضية في الكلى عند مستوى معنوية (p<0.005) مقارنة مع مجموعة فرط شحميات الدم، في حين كانت هذه المؤشرات مرتفعة بشكل ملحوظ في مجموعة فرط شحميات الدم مقارنة مع المجموعة الضابطة. ومع ذلك، لم يُلاحظ أي تأثير معنوي للروزوفاستاتين أو فرط شحميات الدم على وزن الجسم أو وزن الخصيتين. **الاستنتاجات**: أن روزوفاستاتين يساهم في تعديل التغيرات النسجية ويقلل من السيتوكينات الالتهابية في الجرذان الذكور المصابة بفرط شحميات الدم.

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INTRODUCTION

High-fat diets are becoming more popular in many countries, contributing to the increased incidence of chronic noncommunicable diseases (NCDs) such as hypertension, obesity, and chronic kidney disease (CKD), which account for 41 million annual deaths worldwide and 71% of total global fatalities [1]. Fats are estimated to represent 20 to 35% of total calorie intake, while they reach up to 50% in some countries [2]. The

type of dietary fat is a major risk factor, since saturated fat is more associated with positive lipid balance and the accumulation of visceral adipose tissue than other types of fat. Therefore, one of the global strategies to reduce mortality from NCD is to minimize the consumption of saturated fat [3]. The prevalence of hyperlipidemia, which encompasses elevated cholesterol and triglyceride levels and reduced high-density lipoproteinemia, has risen continuously as lifestyles and dietary habits have changed. It is among the most prominent risk factors for cardiovascular disease and morbidity and is one of the leading causes of death worldwide due to changes in lipoprotein transport and metabolism, creating atherosclerosis and contributing to endothelial dysfunction in many vital organs, including the kidneys [4]. Changes in fat metabolism are associated with renal aging, which is marked by enhanced glomerulosclerosis, tubular degeneration, fibrosis of the interstitial space, and diminished kidney function. These changes can damage tubular and glomerular excretion and decrease renal blood flow, glomerular filtration, and ultrafiltration, which can lead to the buildup and development of atherosclerosis and stenosis of blood vessels, particularly in the heart, brain, kidneys, and eyes, as demonstrated in experimental studies [5]. In addition, the kidneys receive 22% of the cardiac output, which puts them at risk for endothelial capillary injury and kidney damage, as they are considered the first organ to suffer damage from aging and degenerative diseases [6]. Most research has centered on Moorhead's lipid nephrotoxicity theory [7]. Advocates of this theory argue that elevated lipid levels can trigger inflammation, ROS generation, and internal electrical stress. Evidence suggests that the buildup of lipids in the kidneys can alter the structure and function of mesangial cells, podocytes, and proximal tubule cells, collectively affecting nephron function [8]. Studies have shown an association between the disruption of lipid metabolism and the occurrence of kidney damage in mice fed a high-fat diet [9, 10], as well as a significant association between the accumulation of renal lipids and the increase of pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin 1 (IL-1) [11]. Furthermore, excessive accumulation of lipids in the kidneys can lead to the damage of the renal tubular cells [12], tubulointerstitial fibrosis [13], podocyte damage, mesangial sclerosis [14], and structural changes in the glomeruli [15,16]. Recently, more focus has been placed on managing dyslipidemia and repairing kidney changes, as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA), enzymes that are involved in cholesterol synthesis, and statins are presently the most often prescribed medications for the primary and secondary prevention of cardiovascular disease in cases of dyslipidemia [17]. Beyond regulating lipid levels and hydrophilic properties, rosuvastatin has garnered increasing interest among medical scientists. Clinical and experimental studies have demonstrated that it exhibits various additional effects, including anti-inflammatory, antiproliferative, and antithrombotic properties, reduction of NADPH oxidase-mediated superoxide production, and enhancement of endothelial vasomotor function. Data also shows potential protective effects on hepatic, skeletal, and renal tissues [18]. To our knowledge, there is no literature indicating that rosuvastatin can reduce and alleviate damage in kidney hyperlipidemia. Therefore, the aim of the present study is to investigate the protective impact of rosuvastatin on histopathological, inflammatory biomarker changes and kidney functions in hyperlipidemic rats.

METHODS

Animals

Forty-six normal male Sprague-Dawley (SD) rats were used in this study. Their weights ranged between 110 and 120 grams, and their ages spanned from five to six weeks. The rats were sourced from the animal house of the College of Pharmacy at Hawler Medical University. They were housed in polypropylene cages under a 12-hour light/12-hour darkness cycle, with *ad libitum* access to food and water.

Experimental design

Forty-six animals were randomly allocated into three main groups; the control negative group consisted of 10 animals that received a standard diet and water throughout the experiment without any treatment. In the hyperlipidemic group, eighteen animals were fed by a high-cholesterol (atherogenic) diet (79% standard diet and 21% ghee fat) for seven weeks. The treatment group, eighteen animals, was fed by a high-cholesterol (atherogenic) diet (79% standard diet and 21% ghee fat) for seven weeks, then treated with rosuvastatin 10 mg/kg/daily orally by gastric gavage for 4 weeks. Throughout the experimental period, the body weights of all rats were recorded weekly, and their clinical status was monitored daily.

Blood samples

5.0 ml of blood samples were collected via cardiac puncture after anesthetizing the rat by using ketamine and xylazine intraperitoneally at doses of 35 mg/kg and 5.0 mg/kg BW. Then the blood centrifuged, and serum was used for the following serological tests: estimation of serum lipids and lipoproteins (total cholesterol, triglycerides TG, LDL-c, and HDL-c) by the Roche/ Hitachi Cobas 6000 analyzer series. Estimation of inflammatory markers by ELISA using Rat IL1 (Abcam kits, ab255730, USA), Rat TNF-alpha (Abcam kits, ab236712, USA 236712), Rat IL-6 (Abcam Kits, ab 234570), and cystatin-C (Abcam kits, ab 202181).

Samples were processed manually and used the Biotek ELx50 automated washer machine, Biotek ELx800 semi-automated reader Elisa machine. The standard curve was prepared by plotting the optical density of each calibrator with respect to the corresponding concentration values and used 4 parameters. Fit as the package insert of the kit recommended. The optical density (OD) of each calibrator, control, and sample (y-axis) with respect to the corresponding concentration IU/mL (x-axis).

Histopathologic score assessment

At the end of the experiment, the animals were euthanized, and the kidneys were removed for measurement and histopathological examination. The samples were preserved overnight in 10% neutral buffered formalin for microscopy [19], followed by paraffin infiltration and embedding. The 4.0 µm sections from each region were put on normal microscope slides (Fisher Scientific, PA). A light microscopic examination (Leica, Germany) of serial Hematoxylin and Eosin (H&E)-stained sections was performed. Histopathologic scoring assessment was conducted using AmScope ™ software (China) under magnification (100 and 400 X). The frequency of observing the following renal histological abnormalities was measured: glomeruli and tubular dilation, tubular degeneration or necrosis, interstitial hemorrhage, and inflammatory reaction. Microscopic grading was carried out by calculating the proportion of morphologically abnormal areas relative to the total surface area of each renal structure. The following scoring system was used: score 0: no lesion, score 1: 1–25%, score 2: 26–50%, score 3: 51–75%, and score 4: ≥76% [20,21] with modification (supplementary data).

Ethical approval

The study protocol was approved by the Research Ethics Committee and Institutional Animal Care of the College of Medicine, Hawler Medical University, Kurdistan Region, Iraq, ID (HMU 9,11) ethical norms for animal experimentation.

Statistical analysis

The data from the results were presented as the mean±SEM. For the comparison of two variable measurements, unpaired t-tests were employed. For three variables, a one-way ANOVA was utilized. A significance level of $p< 0.05$ was considered statistically significant. All statistical analyses were conducted using GraphPad Instat Version 8.02 (GraphPad Software, San Diego, California, USA).

RESULTS

In Table 1, the rats in the hyperlipidemic group showed a significant increase *(*$p< 0.001$*)* in total cholesterol (97.53 ± 0.87 mg/dl), LDL (57.75 ± 1.61 mg/dl), and TG (102.52 ± 0.93 mg/dl) compared to the control negative group (53.59 ± 0.76 mg/dl, 19.57 ± 0.38 mg/dl, and 44.13 ± 0.4470 mg/dl, respectively).

Table 1: The differences in serum levels of total cholesterol, HDL-c, LDL-c, and triglycerides of controls and hyperlipidemic rats.

Biomarker	Control	Hyperlipidemic group	*p*-value
Total cholesterol (mg/dL)	53.59±0.76	97.53±0.87	<0.001
HDL-c (mg/dL)	24.88±0.37	18.16±0.24	<0.001
LDL-c (mg/dL)	19.57±0.38	57.75±1.61	<0.001
Triglycerides (mg/dL)	44.13±0.45	102.52±0.93	<0.001

Values are presented as mean±SEM. Data evaluated using un-paired t-test at $p<0.05$.

Additionally, there was a highly significant *(*$p< 0.001$*)* decrease in HDL (24.88 ± 0.37 mg/dl) compared to the hyperlipidemic group (18.16 ± 0.24 mg/dl). In the hyperlipidemic group, total cholesterol increased significantly ($p< 0.001$) to 97.53 ± 0.87 mg/dl, which was approximately 1.8 times higher than in the control group (53.59 ± 0.76 mg/dl). Similarly, LDL levels were nearly 3.0 times higher (57.75 ± 1.61 mg/dl *vs*. 19.57 ± 0.38 mg/dl), and triglycerides were about 2.3 times higher (102.5 ± 0.93 mg/dl *vs*. 44.13 ± 0.45 mg/dl). In contrast, HDL levels significantly decreased ($p< 0.001$) in the hyperlipidemic group (18.16 ± 0.24 mg/dl), to approximately 0.73 times the level observed in the control group (24.88 ± 0.37 mg/dl). These findings indicate a strong statistical relationship between the hyperlipidemic condition and altered lipid parameters. The body weight in the hyperlipidemia group significantly increased *(*$p< 0.001$*)* compared to the control negative group. Rosuvastatin treatment decreased body weight compared to the hyperlipidemic group non-significantly (Figure 1A).

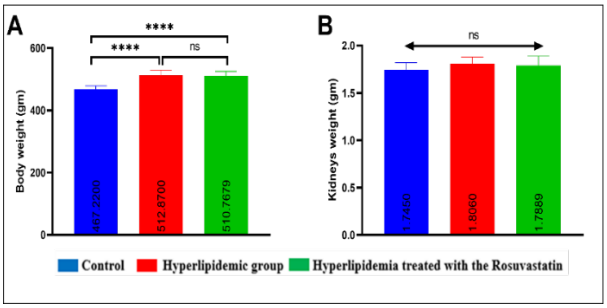

Figure 1: Impact of rosuvastatin on **A**) Body weight, and **B**) Kidney's weight in hyperlipidemic male rats. Values are shown as mean±SEM. *Significant difference ($p<0.05$). ns: not significant.

Kidney weight was slightly increased in the hyperlipidemic group compared to the control negative group, and rosuvastatin treatment resulted in a decrease in kidney weight compared to the hyperlipidemic group non-significantly (Figure 1B). The results of the study showed a highly significant increase ($p< 0.001$) in all inflammatory markers (IL-1, TNF-α, IL-6 and cystatin-C) in the hyperlipidemic group compared with the control group. In contrast, the group treated with rosuvastatin exhibited a significant decrease ($p< 0.001$) in inflammatory markers in male rats when

compared to the hyperlipidemic male rats, as illustrated in (Figure 2).

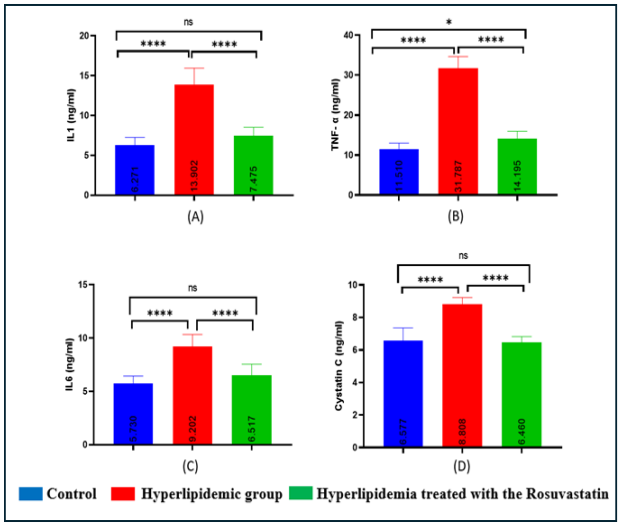

Figure 2: Impact of rosuvastatin on the inflammatory markers: **A**) IL1, **B**) TNF-α, **C**) IL6 and **D**) Cystatin C in hyperlipidemic male rats. Values are shown as mean±SEM. *Significant difference (p<0.05). ns: not significant.

Figure 3 shows the microscopic section of kidneys in different studied groups.

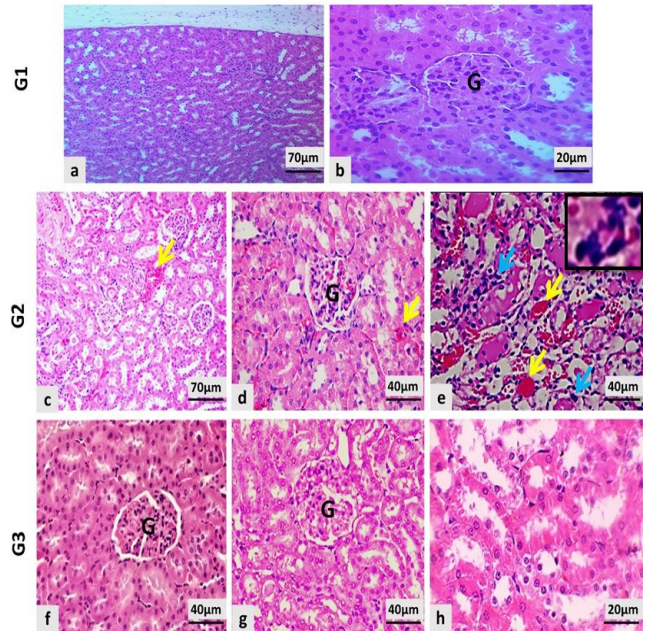

Figure 3: The microscopic section of kidneys in different studied groups showed **a** and **b**) Intact histologic structures of glomeruli (**G**), and renal tubules with vasculature in **G1**. **c-e**) Moderate swelling of glomeruli and hemorrhage, severe hydropic degeneration of renal tubules in section (**d**), and marked necrosis with interstitial hemorrhage (yellow arrows) in section e with few inflammatory reaction (blue arrows and inset: Note: inflammatory reaction is shown by that neutrophil appeared as irregular dark basophilic cells, but if necrotized they should either become pyknotic, karyorrhexis or karyolysis) in **G2**. **f-h**) Mild swelling of glomeruli, moderate cellular swelling of renal tubules in **G3**.

The tissue section of the kidney in the control group (G1) revealed normal cortex and medulla with intact glomeruli and renal tubules morphologic features with normal vasculature (Figure 3a and b), in comparison to the hyperlipidemia group, in which the kidney section showed moderate glomerular swelling with hemorrhage of glomerular tuft capillary, severe hydropic degeneration of proximal and distal convoluted tubules, and marked necrosis in some renal tubules that characterized by eosinophilic cytoplasm and pyknotic nuclear changes with interstitial hemorrhage and infiltration of few neutrophils (Figure 3c-e) compared to the treated group with rosuvastatin that showed attenuation of the pathological changes and revealed mild swelling of glomeruli, moderate cellular swelling of renal tubules in which had pale cytoplasm and narrow lumen (Figure 3f-h). Regarding the pathologic score, the peak was found in G2 vs. G3 (14 vs. 3), respectively, as shown in Table 2.

DISCUSSION

The current study discovered that feeding (atherogenic) a high-cholesterol diet to male rats for seven weeks resulted in hyperlipidemia, as demonstrated by significantly elevated levels of total cholesterol, LDL, and triglycerides (TG), with decreased levels of HDL compared with the control group. These results agree with studies achieved by Vinué *et al*. (2018), Kelle *et al*., and Sidorova *et al*. [25-27], which show that rats fed a high-cholesterol diet frequently have elevated levels of circulating low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL), contributing to elevated plasma lipid levels. Also, the level of triglycerides increases as the liver converts extra cholesterol to triglycerides, which are subsequently bundled into VLDL particles and discharged into the bloodstream. Furthermore, the level of HDL reduces, and its function impairs, resulting in decreased capacity for cholesterol clearance, which further contributes to hyperlipidemia. In addition, a study by Schell *et al*. found that a high-cholesterol diet can induce insulin resistance, impairing the normal regulation of lipid metabolism [28]. This resistance decreases the ability of insulin to suppress lipolysis (fat breakdown), leading to increased levels of free fatty acids in the blood, which are then re-esterified into triglycerides in the liver. Such re-esterification can contribute to hepatic steatosis. Moreover, Tan and Norhaizan demonstrated that a high-cholesterol diet can cause a chronic inflammatory state due to an increase in pro-inflammatory cytokine production [29]. A high-fat diet affects energy balance, leading to lipid accumulation in inappropriate locations and within cells, a phenomenon known as lipotoxicity [30,31]. Moreover, Ichimura *et al*. [32] found that an atherogenic diet reduces the expression of key liver genes involved in lipid metabolism, including the farnesoid X receptor (FXR), which regulates bile acid and cholesterol levels, and ABCG8, which aids in

cholesterol excretion into the bile. The decreased expression of these genes impairs the liver's ability to manage cholesterol and fats, potentially leading to the development of fatty liver disease.

Table 2: Impact of rosuvastatin on pathological scores on hyperlipidemic male rats.

Abnormalities	Control	Hyperlipidemic rats	Hyperlipidemic rats treated with rosuvastatin	*p*-value
Glomeruli Swelling	0.000	2.925±0.104	1.203±0.133	
Glomerular hemorrhage	0.000	3.344±0.1528	0.507±0.1667	
Tubular degeneration/or necrosis	0.000	3.805±0.135	1.814±0.129	0.001
Interstitial hemorrhage	0.000	2.711±0.14	0.218±0.131	
Inflammatory reaction	0.000	1.203 ± 0.128	0.116±0.097	

In this study, the result showed that feeding a high-cholesterol (atherogenic) diet for seven weeks significantly increases body weight compared to the control group. The current finding was in tune with those reported by Bortolin *et al*., Choi *et al*., and Picklo *et al*. [33-35], which have demonstrated that high-fat diets alter the composition and permeability of the intestinal microbiota that contribute to increased endotoxemia, body adiposity, insulin resistance, steatosis, leptin production, and inflammation, all of which promote weight gain. These metabolic disturbances indicate that diet is a major contributor to the obesity epidemic. Rosuvastatin treatment found a decrease in body weight compared with the hyperlipidemic group, but the difference was not significant. This may be due to the short duration of administration (four weeks), during which the drug did not have a significant effect on total body weight. The slight weight increase suggests that rosuvastatin, as an HMG-CoA reductase inhibitor, affects cholesterol biosynthesis by catalyzing the conversion of HMG-CoA to mevalonate, a precursor in cholesterol synthesis. This leads to a compensatory increase in LDL receptors on hepatocytes, enhancing the uptake of LDL cholesterol from the bloodstream for degradation [17]. By reducing LDL cholesterol and triglycerides, improving insulin sensitivity, and exerting anti-inflammatory effects, rosuvastatin supports better overall metabolic health. These mechanisms collectively contribute to its role in weight management. This is supported by the study of Gaudette *et al*. (2015) [36], which found that statins decrease the risk of obesity—a major risk factor for type II diabetes, ischemic heart disease, ischemic stroke, hypertension, osteoarthritis, and several cancers. Our data observed a slight increase in kidney weight in the hyperlipidemic group compared to the control group, though the difference was not statistically significant. To the best of our knowledge, there are limited studies on the relationship between kidney weight and hyperlipidemia. However, this slight increase in kidney weight may be attributed to increased renal fat accumulation and inflammation. A similar result was reported by Wicks *et al*. (2016) [37], who explained that atherogenic diets lead to excessive lipid accumulation in the kidneys, resulting in glomerular damage, glomerulosclerosis, and tubulointerstitial injury, which can cause renal hypertrophy. This finding contrasts with the results of Watson *et al*. (2020) [24], who demonstrated a decrease in kidney weight in mice fed a high-fat diet, potentially due to chronic kidney injury caused by prolonged exposure to high cholesterol, leading to fibrosis and a reduction in functional renal mass. Rosuvastatin treatment resulted in a non-significant increase in kidney weight; this also may be due to the short duration of administration (four weeks), during which the drug did not have a significant effect on kidney weight, and this slight increase in kidney weight is possibly due to the drug's role in reducing inflammation and lipid accumulation in the kidneys associated with hyperlipidemia and related inflammatory processes [17,18]. The current study discovered a significant rise in inflammatory markers (IL1, IL6, TNF-alpha, and cystatin-C) in the hyperlipidemic group versus the control group. This is in agreement with the results of Muller *et al*. (2019) [1], who observed a substantial correlation between increased levels of pro-inflammatory markers and fat accumulation, which is the major factor in mediating the harmful alterations in renal function. In the current study, rosuvastatin was found to significantly decrease these inflammatory markers, which is in agreement with Dicken *et al*. (2022) [38], who found that rosuvastatin decreased the inflammatory state and oxidative stress induced by renal mass reduction. This was demonstrated by reducing the kidney's DNA damage, phox flavocytochrome and p22phox expression, and NF-κB activity. However, Iacovelli *et al*. (2024) [39] found that rosuvastatin is a desirable target for the management of endothelial dysfunction in chronic kidney disease. Some pleiotropic benefits can be linked to a reduction in oxidative stress, cytokines, and adhesion molecules by improving flow-mediated dilation (FMD). On the other hand, Laufs and Isermann (2020) [40] found no evidence linking rosuvastatin to improved renal function [41]. Ramachandran *et al*. (2024) discovered that the rise in pro-inflammatory markers resulted from the stimulation of the NLRP3 inflammasome, a protein complex in immune cells triggered by different stress signals, such as high lipid levels [42]. After being switched on, this inflammasome stimulates the generation of IL-1, which then sparks the generation of other cytokines like IL-6 and TNF-α. The result of the study observed a significant increase in cystatin C levels in the hyperlipidemic rats, which is consistent with results reported in earlier studies involving mice and rats with hyperlipidemia [43,44]. Although cystatin C is

mainly known as a marker for kidney function, it also indicates the presence of inflammation. Increased levels of cystatin-C indicate kidney problems caused by tubulointerstitial fibrosis and glomerulosclerosis. Rosuvastatin treatment at 10 mg/kg per day for four weeks showed a significant reduction in inflammatory biomarkers. Along with its strong cholesterol-lowering abilities, the drug is recognized for its anti-inflammatory and antioxidant effects. The results are supported by the study of Hu *et al*. (2020) [45], which found rosuvastatin hinders the activation of NF-κB, an important transcription factor that controls the expression of different pro-inflammatory genes. Other studies done by Winzer *et al*. (2016) and Laufs and Isermann (2020) [46,41] reported that rosuvastatin enhances the activity of endothelial nitric oxide synthase (eNOS), resulting in elevated production of NO. NO can reduce inflammation and prevent inflammatory cells from sticking to the vascular endothelium. In our results, we observed that the mechanisms of enhanced kidney injury in the hyperlipidemic group are probably associated with both glomerular and vascular injury, which is represented by glomerulomegaly, which leads to glomerular hyperfiltration/hyperperfusion and causes proteinuria and hematuria. Our findings revealed increased injury in the kidney's corpuscle, tubules, and interstitial tissue. This is consistent with the histological evidence of severe tubular damage [47]. Significant hemorrhage and congestion were observed in the glomeruli and interstitial tissue in the current investigation. A related study demonstrated that the renal vascular bed in hyperlipidemic mice responded more favorably to norepinephrine, vasopressin, serotonin, and angiotensin II [48]. Undoubtedly, a number of these mediators, particularly the renin-angiotensin system, have been demonstrated to be crucial in the renal changes that result in edema, which is consistent with the current finding [49]. Our explanation is based on the fact that rosuvastatin attenuated renal damage and decreased the lesion score by raising antioxidant levels. This was accompanied by a drop in serum nitrite/nitrate, a downregulation of renal SOD, and a reduction in glutathione activity, all of which were indicative of high oxidative stress and impaired antioxidant defenses, as demonstrated by earlier research [19]. Since previous research has shown that a lack of NO results in excessive ROS generation, ongoing oxidative stress, and decreased renal antioxidant defense by inhibiting antioxidant enzymes [9,30]. Our findings imply that inflammation plays a significant role in renal damage in this paradigm by linking leukocyte infiltration and elevated production of many proinflammatory cytokines to hyperlipidemia-induced kidney injury. Moreover, rosuvastatin significantly reduced leukocyte infiltration, kidney damage, and cytokine expression levels. The renal inflammatory response and the significant vascular and glomerular damage brought on by hyperlipidemia are visible, according to the earlier study [41].

Conclusion

The current study demonstrated that rosuvastatin treatment modulates the impact of hyperlipidemia on the kidneys of male rats, resulting in a decrease of the proinflammatory markers (IL-1, IL-6, cystatin-C, and TNF-α) and reduced pathological changes of the kidney, such as glomeruli swelling, glomerular hemorrhage, tubular degeneration/or necrosis, interstitial hemorrhage, and inflammatory reaction.

Conflict of interests

The authors declared no conflict of interest.

Funding source

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Data sharing statement

Supplementary data can be provided by the corresponding author based on reasonable request.

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