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Research Article

Histophysiological Effect of Rosuvastatin on the Kidney in Male Albino Rats

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Abstract | The objective of the current study was to evaluate the physiological and histopathological effects of rosuvastatin in male albino rats. Thirty-two adult albino rats were used in the study. After acclimatization, the rats were randomly divided into four groups (8 rats in each group) as follows: The first control group was given normal saline solution, the second group 10 mg/kg rosuvastatin, the third group was given 20 mg/kg rosuvastatin, while the fourth group was given 40 mg/kg rosuvastatin. The dose was continued for 60 days in a once-daily dosing regimen. After the end of the experiment, chemical analyses were performed for kidney function, including cystatin C and vitamin D_3. Then, the rats were dissected, and kidney tissues were taken for histological study. Male rats treated with rosuvastatin showed an elevated cystatin C level and increased vitamin D_3. At the same time, the results of the microscopic examination showed significant histopathological changes in the kidneys of the groups treated with rosuvastatin compared to the control group, which included mild, moderate, and severe injuries: necrosis, congestion, hemorrhage, glomerular degeneration, fatty changes, cysts and vacuoles in the renal tubule cells and lymphocytic infiltration in the kidney tissue with gradual increase in rosuvastatin concentrations 10, 20 and 40 mg/kg, respectively. Conclusion: It was concluded in the current study that the use of rosuvastatin in high doses causes nephrotoxicity.

Keywords | Cystatin C, Cytotoxicity, Histopathology, Nephrotoxicity, Rosuvastatin, Statins, Vitamin D_3.

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INTRODUCTION

Man uses a variety of drugs to achieve desired therapeutic effects, but many of these drugs have undesirable or toxic side effects. The toxic effects of a medication are partially subordinate and can affect the entire body, including a specific organ like the kidney. The degree to which a man-made substance or a particular concoction of substances can harm a creature is its level of harmfulness. Age, weight, and general wellbeing also have an impact on the outcome (Kumar, 2021).

Statins are among the most widely used drugs in the world (Baigent et al., 2005). They are effective in reducing cholesterol levels in the blood, of which high levels cause hardening of the arteries and damage to the health of the heart and blood vessels, statins inhibit the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step of cholesterol synthesis in the kidney, the liver and other tissues, thus reducing hypercholesterolemia (Corsini et al., 1995).

Rosuvastatin is a synthetic statin that represents a development in pharmacological science, and is currently given to patients in abundance to lower total cholesterol and LDL cholesterol because it is one of the most powerful

LDL-lowering drugs and is used to prevent cardiovascular events (Law et al., 2003). But rosuvastatin may cause side effects like cardiac-valve sclerosis, nephrotoxicity, hepatotoxicity, type 2 diabetes, neurological effects, and others (Bitzur et al., 2013).

There is a direct correlation to renal toxicity with high doses of statins, as well as an indirect correlation by interactions with other factors, and this leads to an increase in the concentration of statins in the blood, rosuvastatin has several adverse effects on the kidneys, muscles, and liver (Almandoh et al., 2020). Statins including rosuvastatin cause changes in cell membrane permeability, decreased levels of coenzyme Q10, and reduced isoprenoids due to inhibiting cholesterol production that can lead to nephrotoxicity (Ahmadizar et al., 2023). Hematuria (blood in the urine) and proteinuria (protein in the urine) were diagnosed in 44% of kidney patients who were prescribed high doses of rosuvastatin, so it is recommended that no doses higher than 10 mg per day of rosuvastatin be taken (Shin et al., 2022).

Despite the challenges in defining statin toxicity, numerous international health organizations and institutions have determined that statin intolerance is of significant clinical importance and calls for additional research and studies (Mancini et al., 2013; Guyton et al., 2014; Stroes et al., 2015). Therefore, our study aimed to investigate the physiological and histopathological effects of rosuvastatin in male albino rats and to know the possibility of chronic nephrotoxicity at different concentrations of rosuvastatin in a specific period.

MATERIALS AND METHODS

Animal Grouping

In the current study, male albino rats were obtained from the Department of Biology - College of Sciences - University of Thi-Qar. Their ages ranged between (12-14) weeks, and weights (200-250) gm. A veterinarian examined the animals to ensure they were free from diseases, and then the animals were transferred to the animal house in the Department of Biology- College of Education and Pure Sciences, under controlled conditions at a temperature of 20-25 °C. The cabin air was changed continuously using a vacuum ventilation device with a fitted 12 hours light and 12 hours dark cycle.

Thirty-two adult males albino rats were divided randomly into four equal groups; each group included 8 males and gavage for 60 consecutive days according to the method of Mohammed and Hossain (2022) as follows:

1. Control group: all rats were given an equivalent volume of normal saline.
2. Group 10 mg: all rats were given 10 mg/kg/day of rosuvastatin.
3. Group 20 mg: all rats were given 20 mg/kg/day of rosuvastatin.
4. Group 40 mg: all rats were given 40 mg/kg/day of rosuvastatin.

All groups were treated with oral gavage for 60 days.

Preparation Of Drug

Rosuvastatin is obtained in the form of commercial rosuvastatin (Crestor) in film-coated tablet form and concentrations (10-20-40) mg produced by Pharma Science Incorporated- Montreal/ Canada), approved in the United States since 2003. Rosuvastatin tablets were mashed with a sterile pestle/mortar and then dissolved in (0.9%) sodium chloride solution to obtain rosuvastatin solution as a compound, after which albino rats were orally gavaged according to the animal's body weight (Nair and Jacob, 2016; Kamel and Al-Owaidy, 2022). Then, the fully dissolved suspension was stored at 4 °C until use.

Sample Collection And Biochemical Examination

After the end of the gavage period, animals were anesthetized by inhaled chloroform 1% (0.05 ml/ liter of container volume) (Aledani et al., 2020), and blood was drawn directly from the heart by cardiac puncture using 5 mL medical syringes, and placed in a gel tube were collected to coagulating, then centrifuged at 3000 rpm for 10 min to get the serum, and then samples of serum were kept in a freezer at –20 ºC till use (Hassan and Sharhan, 2014). For renal function, cystatin C was measured based on the method of Newman (2002) for calculating the concentration of cystatin C in serum and vitamin D_3 concentration based on the method of Holick (2007) for calculating the concentration of vitamin D_3 in serum.

The animals were dissected for all groups, kidneys were removed, and the histological sections were prepared according to the method of Muhammad-Azam et al. (2019). Starting with the fixation of the tissue organ with formalin 10 %, followed by tissue processing, as follows: it which included several steps, it included dehydration by ethanol at concentrations (70% - 90% - 95% - 100%), then clearing by xylene, and finally infiltration by paraffin wax, then followed by the process of embedding and the process of trimming the wax molds containing the sample, then pasted on the wooden mold for a Rotary microtome, it was cut with a thickness of (4-5) mm. Finally, for histological evaluation of the kidney, the sections were placed on plain glass slides and stained with hematoxylin and eosin stains (H & E) according to the method of Sharhan et al. (2020). H & E-stained sections were observed for abnormalities of histological features under a light microscope at 40×, 100×

and 400×. The histological sections was photographed using Sony a7riv camera attached to Krüss stereomicroscope, then digital images were montaged using software (Helicon Focus™ 8.1.0).

Kidney Histopathology Scoring

The degree of kidney injury was scored based on the grading system done by the previous study (Al Asmari et al., 2017). Briefly, the extent of tissue injury was graded from 0 to 4 based on the microscopical findings, including degeneration in the epithelial cells, glomerulus damage, hemorrhage, necrosis, cysts in the renal tubules, fatty changes, lymphocytic infiltration, and the presence of vacuoles. As shown in Table (1).

Statistical Analysis

The statistical analysis of the results was conducted by ANOVA and significant differences were determined according to Duncan's multiple range test and the level of significance (P≤0.05) by SPSS program (Bryman and Cramer, 2012).

RESULTS

Effect Of Rosuvastatin On The Kidney Function

Kidney function parameters, such as cystatin C and vitamin D_3 serum, were measured in the experimental groups by biochemical analysis to investigate the effects of rosuvastatin on kidney function (Table 1).

Table 1: kidney injury scoring system.

Description	Score
Normal - no change in the tubules	0
Mild - < 25% of tubular injury	1
Moderate - 25% to 50% of tubular involvement	2
Severe - 50% to 75% of tubules showing the characteristic change	3
Very severe - more than 75% of tubular damage	4

Effect Of Rosuvastatin On Cystatin C Serum Levels

The statistical analysis in Figure (1) and Table (2) showed a significant increase (P≤0.05) in the concentration of cystatin C in the groups treated with rosuvastatin compared with the control group. The results also showed a significant increase (P≤0.05) in the 40 mg group compared to the 20 mg and 10 mg groups. There was also a significant increase (P≤0.05) in the 20 mg group compared to the 10 mg group.

Table 2: Shows the impact of rosuvastatin on the serum levels of cystatin C (CYS) and Vitamin D3 in the study groups (Mean ± SD) at (P≤0.05).
*a-d Different letters within column indicate significant differences between groups

Group/Parameters	CYS C MG/L Mean ± SD	Vitamin D_3 NG/ML Mean ± SD
Control group	0.12±0.008[a]	12.30±0.17[a]
Group 10 mg/kg	0.24±0.012[b]	12.46±0.37[a]
Group 20 mg/kg	0.33±0.11[c]	13.06±0.40[a]
Group 40 mg/kg	0.39±0.008[d]	17.20±2.98[b]

Effect Of Rosuvastatin On Vitamin D_3 Serum Levels

The results of the current study showed in Figure (2) and Table (2) that there was a gradual increase in the vitamin D_3 level in the groups treated with rosuvastatin compared with the control group. The results showed a significant increase (P≤0.05) in the 40 mg group compared to the 20 gm and 10 mg groups, while a non-significant increase appeared in the 20 group compared to the 10 mg group.

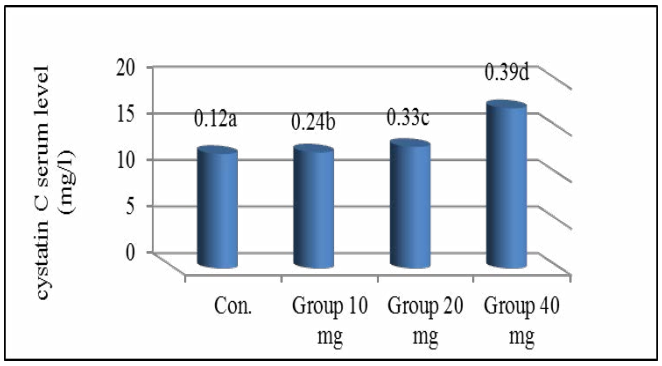

Figure 1: The mean (n=8) serum cystatin C level (mg/l) in the study groups.
[a-d] Different letters indicate standard deviation at (P≤0.05).

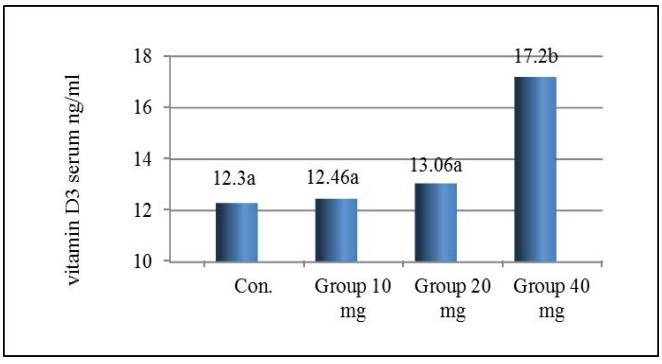

Figure 2: The mean (n=8) serum vitamin D_3 level (ng/ml) in the study groups.
[a-d] Different letters indicate standard deviation (P≤0.05).

Histological Changes Of Rosuvastatin On Kidney

According to used scoring system, the histopathological findings of the severity of kidney tissue injury in the rats of the study groups are summarized in the following Table (3).

Table 3: Scoring of kidney histopathological injury percentage and score of the study groups.

Group	Kidney injury %	Score
Control group	0 %	0
Group 10 mg/kg	20%	1
Group 20 mg/kg	40 %	2
Group 40 mg/kg	62 %	3

The results of the histological study of the kidneys of the control group animals showed normal architecture in the glomerulus and normal epithelial cells. According to the scoring system, the severity of injury showed a zero degree of damage (Figure 3). The results of the histological study of the kidneys of the 10 mg group showed mild injury (score = 1): degeneration of the epithelial cells, irregularity in the normal form of the renal glomerulus, and hemorrhage in the renal tubules (Figure 4A, B). While the histological study of the kidneys of the 20 mg group showed moderate injury (score = 2): damage to the glomerulus, necrosis and hemorrhage, congestion in the renal tubules, cysts in the renal tubules, fatty changes, lymphocytic infiltration, dilation of the renal tubules and the presence of vacuoles and narrowing of the renal tubules and dilation of some of them (Figure 5A, B).

The histological study of the kidneys of the 40 mg group showed severe injury (score = 3): abnormal architecture, severe hemorrhage, sever glomerular degeneration, fatty changes and destruction of the renal epithelial cells lining the renal tubules, cysts and vacuoles in the renal tubule cells (Figure 6A and B).

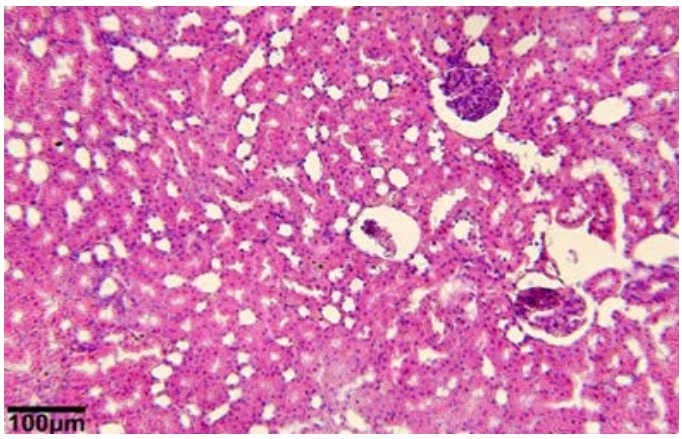

Figure 3: Photomicrograph of rat kidney of the control group showing: kidney normal histology, stained with H&E, Scale bar=100 µm.

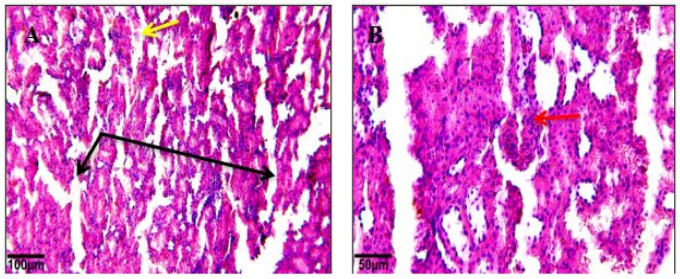

Figure 4 and B: Photomicrograph of rat kidney of 10 gm group showing, (A): hemorrhage (yellow arrow), degeneration in the epithelial cells (black arrow), (B): irregularity in the normal form of the renal glomerulus (red arrow), stained with H&E, (A) Scale bar=100 µm, (B) Scale bar=50 µm.

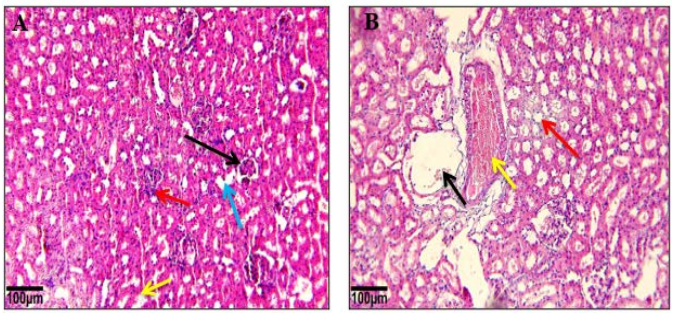

Figure 5A, B: Photomicrograph of rat kidney of 20 gm group showing, (A): glomerulus damage (black arrow), necrosis (blue arrow), dilation of the renal tubules (yellow arrow), lymphocytic infiltration (red arrow), (B): congestion (yellow arrow), hemorrhage (black arrow), fatty changes (red arrow) stained with H&E, Scale bar=100 µm.

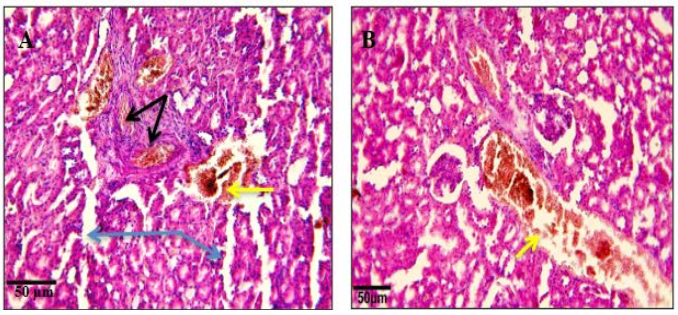

Figure 6A, B: Photomicrograph of rat kidney of 40 gm group showing: sever congestion (black arrow), sever hemorrhage (yellow arrow), sever glomerular degeneration (blue arrow), stained with H&E, Scale bar=50 µm.

DISCUSSION

In the current study, cystatin C was measured, which is filtered by the renal glomeruli and completely reabsorbed by the proximal renal tubule and has a higher molecular size than creatinine (Suzuki et al., 2012), thus, cystatin C is more predictive of events that occur in the kidneys than creatinine or GFR (Vigil et al., 2014). Luaibi et al. (2020),

Dabbi and Hussain (2021) also confirmed that there is a significant correlation between serum cystatin C, urea and creatinine.

The current study showed significant changes in kidney function among the four study groups, including cystatin C, where a significant increase in its level was observed in the three pre-treated groups of rosuvastatin compared with the control group, these results are consistent with Wijesurendra et al. (2023), who found an increase in cystatin C level while administering rosuvastatin to patients. In increased level of cystatin C indicates decreased kidney function, these levels increase due to the kidneys being unable to properly filter the blood regularly, causing it to build up in the blood (Pasala and Carmody, 2017).

As for the relationship between vitamin D_3 levels and statins is still unclear, so studies need to be done on it (Bhattacharyya et al., 2012). The results of the current study showed a gradual increase in the level of vitamin D_3 for all groups treated with rosuvastatin, especially the 40 mg group, compared to the control group, and this result was consistent with Orces et al. (2020), which found that there an effect on the level of vitamin D_3 when taking doses of statins, which was observed even in the beginning of treatment. Elevated 25(OH)D concentrations were also observed in 18 individuals with familial hypercholesterolemia who were given statins, suggesting that some statin treatments raise vitamin D levels (Wilczek et al., 1989; Wilczek et al., 1994). Moreover, it has been hypothesized that the multidirectional effects of statins may be mediated by vitamin D (Grimes, 2006).

Guryev et al. (2003) was reported that rosuvastatin raises vitamin D levels by HMG-CoA reductase action, which has a role in cholesterol biosynthesis. (Pérez-Castrillón et al., 2007) also confirmed that an increase in vitamin D concentration led to increased enzymatic inhibition, working synergistically with statins in lowering cholesterol.

The histological effects in the current study were based on the microscopic examination of the kidneys of rats of four experimental groups, the results of the current study showed the presence of nephrotoxicity. The control group had a normal histological architecture with undamaged proximal and distal renal tubules. While the groups treated with rosuvastatin showed a significant injury to the kidney tissues compared to the control group, degeneration was diagnosed in the renal tubules, necrosis, congestion, hemorrhage, vacuoles and narrowing of the renal tubules and infiltration of lymphocytes, and these results are consistent with Al-Khafaji (2021) who found degeneration and necrosis in the cells lining the renal tubules, congestion, thickening of the basement membrane and lymphocyte infiltration when rosuvastatin was taken. These findings are in agreement with other studies as well (Dodiya et al., 2011; Hsu et al., 2018), indicating that acute nephrotoxicity is associated with high-potency statins (Dormuth et al., 2013). Ward et al. (2016) reported a case of renal tubular toxicity due to the initiation of rosuvastatin at a dose of 40 mg in a patient without prior evidence of disease. Van Zyl-Smit et al. (2004) also reported a case of direct renal tubular toxicity, which was positively associated with an increase in the patient's dose of rosuvastatin to 80 mg daily and inhibited nephrotoxicity after discontinuation of the drug.

CONCLUSIONS AND RECOMMENDATIONS

In the current study, it was concluded that high doses of rosuvastatin lead to kidney injury. Moreover, infection was confirmed by high cystatin C level and decreased vitamin D_3 level, in addition to histopathological changes that revealed renal tissue injury. We recommend that many future studies be conducted on the effect of the drug on patients, especially since it is available in the market from different companies and a comparison between them.

ACKNOWLEDGMENTS

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LIST OF ABBREVIATIONS

ANOVA, Analysis of Variance; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; SPSS, Statistical Package for Social Sciences.

CONFLICT OF INTEREST

The authors have not declared any conflict of interests.

NOVELTY STATEMENT

The present study presents the effect of widely used statins, especially rosuvastatin, on the kidneys and their level of nephrotoxicity with increasing doses. Some medications may have negative side effects for patients. Therefore, the aim of this study was to evaluate the effect of rosuvastatin on some biochemical properties and histological changes in the kidneys of male albino rats.

AUTHOR'S CONTRIBUTION

All authors contributed equally.

ETHICAL APPROVAL

Following the guidelines of the Animal Welfare Committee, the experimental procedures were approved by the Ethics Committee of the College of Education for Pure Sciences/ University of Thi-Qar (According to No. 126 dated 16/10/2022).

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