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Original Article

Aldosterone and blood pressure changes after rosuvastatin short term therapy: a gender-based study

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Received: 26 August 2025; **Revised:** 15 December 2025; **Accepted:** 17 December 2025

ABSTRACT

Statin can moderately reduce blood pressure in patients with hypertension, the suggested mechanisms are enhanced endothelial NO generation, anti-inflammatory and antioxidant effect. Previous studies also suggested involvement of angiotensin receptor blockade in statin mediated hypotension. The current aimed to examine the effect of acute rosuvastatin on aldosterone levels in relation to blood pressure reduction with special concern to male and female variation. Rosuvastatin was prescribed for 11 women and 15 men hypertensive patients with dyslipidemia. Evaluation of aldosterone, blood pressure, lipid profile, BMI, Na+, and K+ were conducted both before and after six weeks treatment. The pulse pressure (PP) and mean arterial pressure (MAP) was calculated to determine the vascular compliance and hemodynamic load. To evaluate the association factors, total male results were evaluated against female results using statistical t-test. A significant improvement in cholesterol and triglycerides was observed in all patients. SBP and aldosterone levels were significantly reduced. While Na^+ levels was slightly reduced, no significant change was observed with K^+ levels. Male patients showed significantly more reduction in aldosterone than female, suggesting a sex-specific differences. However, rosuvastatin lowered both pulse pressure and mean arterial pressure to a similar extent in both men and women. The results suggest that rosuvastatin have a wide-ranging effect on cardiovascular status. Sex variation might be important finding and deserve further research.

Keywords: Rosuvastatin, Aldosterone, Blood pressure, Total cholesterol, Gender differences

Introduction

Statin continue to be the cornerstone in decreasing low density lipoprotein and have been shown to decrease mortality in and cardiovascular health. Although their primary action is to reduce liver cholesterol synthesis via inhibition of 3-Hydroxy-3-methylglutaryl-CoA reductase enzyme with reduction in low density lipoprotein, an increasing findings indicate a wider range of beneficial effect collectively known as pleiotropic effects [1].

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Khalaf MM, Almukhtar HM, Alnori MKJ. Aldosterone and blood pressure changes after rosuvastatin short term therapy: a gender-based study. J Adv Pharm Educ Res. 2026;16(1):34-41. https://doi.org/10.51847/FxqbfcQBm1

These effects extend to enhanced endothelial cell function, dampened oxidative stress [2] and modulation of the renin–angiotensin–aldosterone system. Among the pleiotropic pathways, increasing interest has focused on the influence of statins—especially lipophilic statins—on blood pressure. Both clinical and laboratory investigations have consistently shown a small yet significant dip in systolic and diastolic pressure whether the subject is normotensive or already hypertensive. Improved endothelial release of nitric oxide and lowered systemic vascular resistance contribute to the overall picture, but new lines of inquiry are now assessing whether direct suppression of adrenal aldosterone secretion may also play a role [3].

Aldosterone, adrenal cortex derived hormone, is concerned with Na^+ and K^+ level, and thus regulation of blood pressure. Aldosterone overproduction causes adverse cardiovascular remodeling, alters cholesterol profile, disrupts endothelium with subsequent increase in blood pressure [4]. Previous study have shown that statins reduced aldosterone by mechanism not related

to cholesterol reduction [5]. The suggested mechanisms are either blocking cholesterol transport and/or downregulation of angiotensin receptors [6]. Nevertheless, little is known regarding reproducibility and clinical significance of aldosterone inhibition by statin. In addition, it remains unknown how the lipid profile and aldosterone level relate to changes in blood pressure in hypertensive patients.

According to previous evidence, biological sex significantly affects body response to pharmacological agents. differ in and cholesterol metabolism In addition to the variation in the cholesterol metabolism and the baseline regulation of blood pressure, there is also differential response to statin therapy between male and female patients [7]. Sex hormones, estrogen and progesterone, modulate vascular tone and cholesterol handling, they also affect steroidogenesis in the adrenal gland with resultant differences in aldosterone concentration and maintained of blood pressure [8]. Variations in pharmacokinetics of statin, absorption and hepatic transport and metabolism treatment between male and female further caused distinct therapeutic results [9]. Studying of statin pleiotropic effects necessitate attention for such sex-specific reactions. Rosuvastatin is relatively hydrophilic in nature if compared to other relatively lipophilic statins like atorvastatin and simvastatin and atorvastatin, it more potent in reducing LDL- cholesterol with prolonged duration of action, thus it is suitable for once daily dosing with extended effect even at low doses [10]. Thus, rosuvastatin is most commonly prescribed hypolipidemic agent in the clinical field because of its potency and lowered risk of muscle side effects [11]. The study investigated the acute effect of rosuvastatin treatment on aldosterone levels and blood pressure in hypertensive patients with hyperlipidemia, with special concern to the sex differences.

Materials and Methods

Participants and study design

Twenty-six hypertensive patients with hyperlipidemia participated in this prospective observational study. They started rosuvastatin (20 mg/day) and the cases were followed for six weeks to examine the acute effects. Individuals between the ages of 18 and 75 who had elevated levels of triglycerides (≥ 150 mg/dL) and/or total cholesterol (≥ 240 mg/dL) were eligible. Primary aldosteronism, uncontrolled hypertension, endocrine disorders, and concurrent use of antihypertensive drugs that interfere with the renin-angiotensin-aldosterone pathway were the exclusion criteria.

Data collection and measurements

5-mls of venous blood were taken from each patients usually in duplicate, before starting rosuvastatin and at the end of study duration. Patients usually fast for at least 12hr overnight before blood collection [12]. Using conventional ELISA kits, the serum lipid profile, total cholesterol, and triglyceride (TG) concentrations were determined (Roche Cobas, Germany). The Maglumi Aldosterone Chemiluminescence Immunoassay (CLIA) Kit (Snibe Diagnostics, China) was used to assess the levels of serum aldosterone. In accordance with the manufacturer's instructions, the assay was carried out on an automated MAGLUMI analyzer [13]. In accordance with the manufacturer's instructions, flame photometry was used to measure the levels of (Na^+) and (K^+) [14]. In order to obtain further hemodynamic data, mean arterial pressure (MAP), to measure hemodynamic stress, and pulse pressure (PP), to measure tissue perfusion, were calculated from these observations to get additional hemodynamic data. PP (PP = SBP − DBP) was used to compute the difference between SBP and DBP. To estimate MAP, the conventional formula, MAP = DBP + ⅓ (SBP − DBP), was applied. According to this computation, diastole accounts for about two-thirds of the cardiac cycle and systole for one-third at normal heart [15].

Statistical analysis

Data were analyzed using paired t-test to examine the effect of rosuvastatin on blood pressure, aldosterone level and total cholesterol. Unpaired t-test to used compare sex differences, Correlation coefficients were determined using Pearson r-test. All analysis was conducted using Graphpad Prism 9.

Results and Discussion

Rosuvastatin clearly improved cholesterol and triglycerides levels within six weeks duration, similarly the was improvement in the blood pressure measurement, the systolic blood pressure reduced by about 5 mmHg while the diastolic pressure reduced 10 mmHg. Aldosterone hormone reduced significantly in both sexes, the reduction was higher in male (+5.00 ± 4.30) compared to female (+1.02 ± 4.32). Additionally, there was a significant decrease in serum Na^+ with no significant change in K^+ level.

Table 1. Comparison of Parameters Before and After Rosuvastatin Therapy

Parameter	Mean ± SD Before	Mean ± SD After	p value	Significance
BMI	28.64 ± 2.40	27.85 ± 2.17	0.0004	***
SBP	146.33 ± 7.73	136.17 ± 7.42	<0.0001	***
DBP	94.00 ± 7.56	89.33 ± 5.80	<0.0001	***
Aldosterone	37.03 ± 8.83	32.52 ± 7.80	0.0001	***
TC	254.21 ± 20.13	211.67 ± 23.89	<0.0001	***
TG	162.04 ± 21.19	145.00 ± 16.37	<0.0001	***
K	4.16 ± 0.39	4.19 ± 0.36	0.2846	ns
Na	141.52 ± 3.23	139.76 ± 2.44	<0.0001	***

The results are shown as means ± SDs. *P*-values are obtained using paired t-test. $p < 0.001$ = ***, ns = not significant

Figure 1 Represent values for each patient, before and after treatment using a chart bars. It is clearly that rosuvastatin

reduced total cholesterol (a), triglycerides (b), SBP (c) DBP (d) Na^+ level (e) K^+ level (f) BMI (g) aldosterone (h). The figure also shows the higher aldosterone reduction male compared to female gender (i) and lastly the higher reduction in systolic pressure compared to diastolic reduction by rosuvastatin treatment (j). Rosuvastatin significantly reduced pulse pressure (PP) and mean arterial pressure (MAP) in both sexes, **Table 2**.

Table 2. Blood pressure parameters (PP) and (MAP) before and after statin treatment

Parameter	Mean ± SD Before	Mean ± SD After	p value	Significance
SBP (mmHg)	146.60 ± 8.00	136.40 ± 7.00	< 0.0001	***
DBP (mmHg)	94.60 ± 7.49	90.20 ± 5.68	< 0.001	***
PP (mmHg)	52.00 ± 7.07	46.20 ± 6.50	< 0.001	***
MAP (mmHg)	111.93 ± 6.90	105.60 ± 5.33	< 0.0001	***

The values are presented as the means ± SDs. *P*-values are based on unpaired t-test. Significance codes: $p < 0.001$ = ***

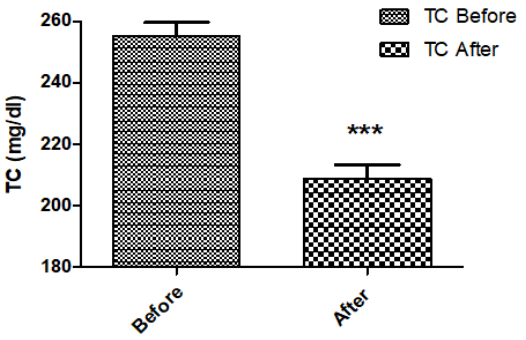
Table 3 shows the results of additional study that showed sex-related variations in the response to rosuvastatin medication, with a focus on aldosterone levels. Aldosterone levels varied considerably between males and females (p = 0.04), despite the fact that most metrics did not differ significantly in terms of mean change (Δ). In particular, there was a significant sex-specific response to therapy, as males had a larger mean decrease in aldosterone (5.00 ± 4.30 ng/L) than females (1.02 ± 4.32 ng/L) ($p < 0.01$), with a substantial effect size (Cohen's d = 0.93).

Table 3. Gender-based comparison of parameters before and after rosuvastatin therapy

Parameter	Mean Δ Males	Mean Δ Females	p value	Significance
BMI	+0.70 ± 1.02	+0.68 ± 0.67	0.95	ns
SBP	+9.38 ± 5.15	+10.00 ± 4.08	0.65	ns
DBP	+4.69 ± 3.60	+3.64 ± 2.93	0.42	ns
Aldosterone	+5.00 ± 4.30	+1.02 ± 4.32	0.04	* (significant)
TC	+46.56 ± 27.59	+37.27 ± 21.89	0.29	ns
TG	+13.75 ± 8.18	+17.09 ± 13.33	0.52	ns
K	−0.01 ± 0.31	−0.09 ± 0.24	0.36	ns
Na	+3.31 ± 4.18	+2.09 ± 1.92	0.14	ns

The values are presented as the means ± SDs. *P*-values are based on unpaired t-test. Significance codes: $p < 0.05$ = *, ns = not significant

No statistically significant relationships were found when correlations between variations in SBP and several biochemical markers were analyzed. There was a weak positive correlation between SBP change and Na^+ change **(Figure 2c)**, with Pearson's r = 0.303 (p = 0.125). Similarly, the relationships between SBP change and total TC **(Figure 2b)** and between TC and aldosterone **(Figure 2d)** were negligible, with Pearson's correlation coefficients (r = 0.035, p = 0.860) and (r = -0.01981, p = 0.7580), respectively. Pearson's analysis indicated a moderate negative correlation between SBP change and aldosterone change (r = –0.380, p = 0.057) **(Figure 2a)**. This inverse trend implies that the extent of blood pressure reduction was not directly proportional to aldosterone suppression.



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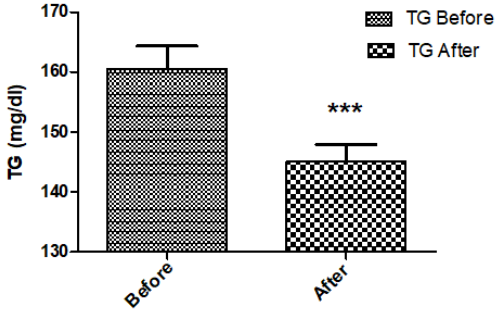

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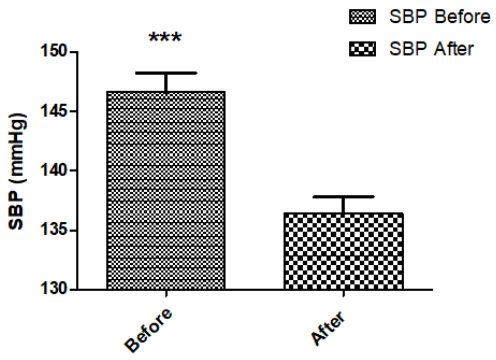

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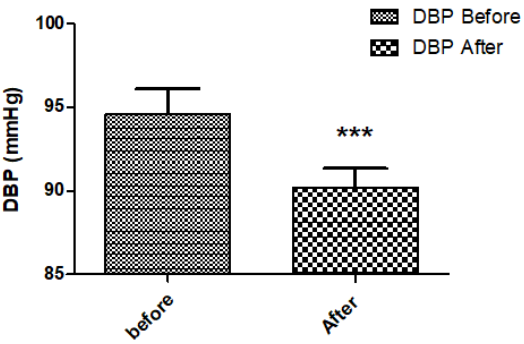

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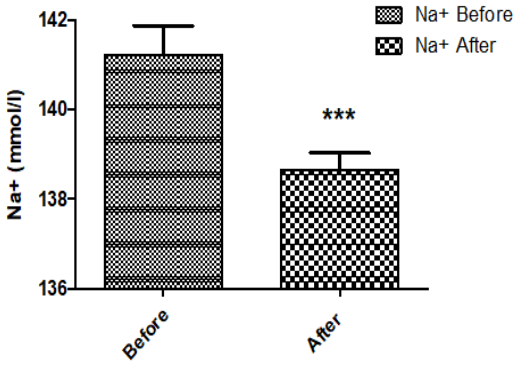

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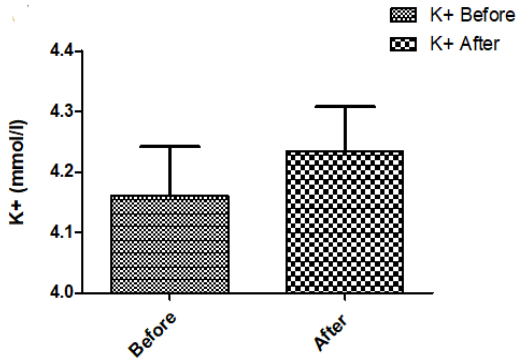

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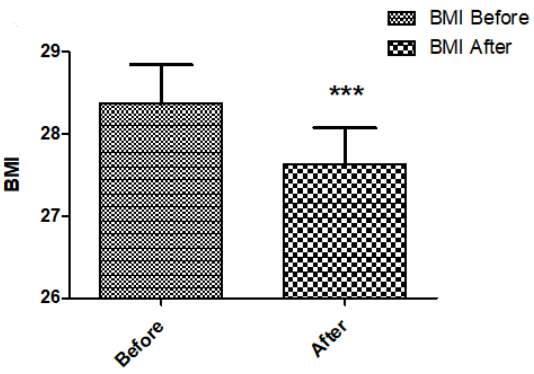

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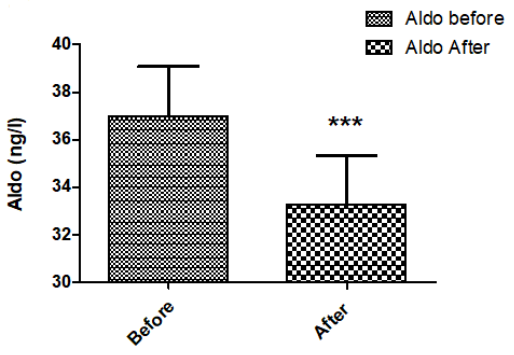

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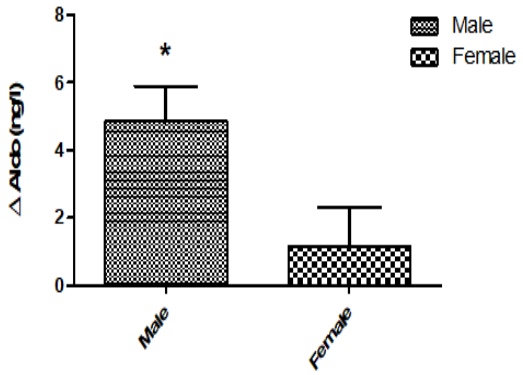

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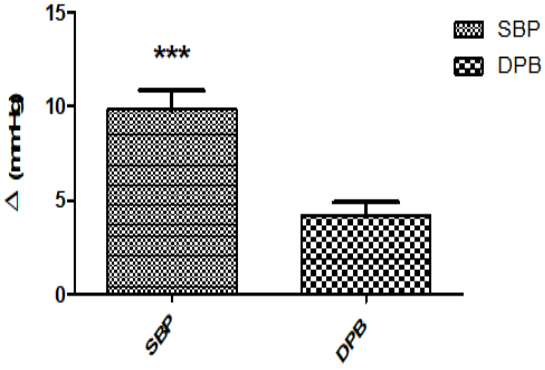
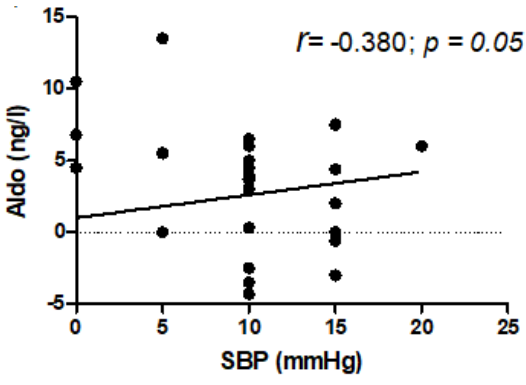


j)

Figure 1. shows how clinical and biochemical indicators are affected after six weeks of rosuvastatin medication. Before and after therapy, the values are shown as means ± standard deviations (SDs). Serum potassium (K^+) levels stayed constant without appreciable alterations (f), although there were notable decreases in (a) TC, (b) TG, (c) SBP, (d) DBP, (e) serum sodium (Na^+), (g) BMI, and (h) aldosterone. Males had a higher mean decrease in aldosterone than females, according to paired analysis (i). Furthermore, the drop in SBP was noticeably bigger than the drop in DBP (j).
Significance codes: $p < 0.05$ = *, $p < 0.01$ = **, $p < 0.001$ = ***.



a)

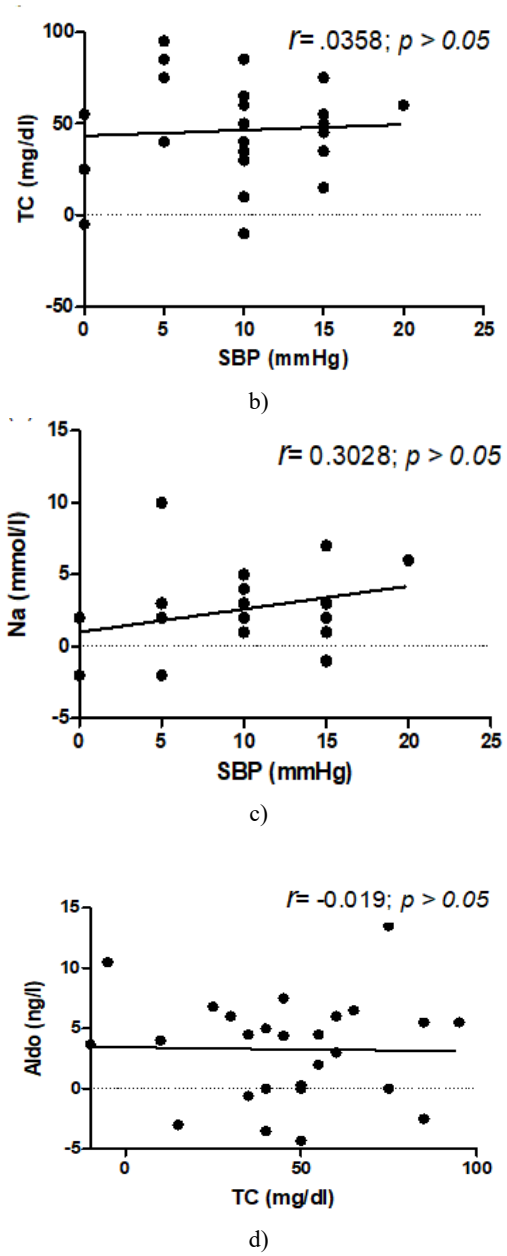


Figure 2. Scatter plots show the relationship between changes in important biochemical markers and changes in systolic blood pressure (SBP) following treatment. The panels show (a) SBP vs. aldosterone, (b) SBP vs. triglycerides (TGs), (c) SBP vs. sodium (Na^+), and (d) aldosterone vs. total cholesterol (TC). Each plot includes the corresponding Pearson correlation coefficient (r) and p-value. None of the examined pairs demonstrated a statistically significant association,

Aldosterone is traditionally recognized for controlling blood pressure and electrolyte balance, but new research indicates that it may also have an impact on lipid metabolic pathways and adipocyte differentiation through the mineralocorticoid receptor. On the other hand, increased triglyceride production and dyslipidemia have been linked to elevated aldosterone levels, especially in obese or metabolic syndrome patients [16].

The data revealed a significant decrease in aldosterone levels after rosuvastatin treatment [17-19]. Subtle but directionally consistent reduction in serum sodium (−2.6 mmol/L) with a concurrent rise in potassium (+0.07 mmol/L) over a six-week period. Aldosterone encourages potassium excretion and sodium retention. Thus, aldosterone inhibition consequently promotes potassium conservation and natriuresis [20]. Although there is currently little information available on hydrophilic statins such as rosuvastatin, such hormonal effects have been shown in the past with lipophilic statins such as atorvastatin and simvastatin. Earlier research showed that statins can lower aldosterone levels within two weeks of starting therapy; however, the effect varies depending on the statin type and dosage [21].

Interestingly, previous data have linked statin use to hormonal modulation by demonstrating that better lipid profiles can reduce oxidative stress in the adrenal cortex [22]. There is increasing evidence that statins may have indirect endocrine effects through pathways related to their primary lipid-lowering action, specifically on adrenal steroidogenesis. A reduced availability of cholesterol can directly restrict the production of aldosterone because it is the necessary substrate for aldosterone synthesis [23]. Moreover, increased ACTH responsiveness and the stimulation of intracellular signaling cascades such as ERK/MAPK and oxidative stress—particularly through NADPH oxidase and reactive oxygen species (ROS)—can increase the synthesis of aldosterone [24]. This pro-aldosterone signaling milieu may be dampened by statins by lowering tissue-specific and systemic oxidative stress [3].

Crucially, the data show that drops in aldosterone levels after statin medication do not exactly correspond to drops in triglycerides or total cholesterol. This partial independence suggests that, in addition to their lipid-lowering actions, statins may have direct or indirect impacts on aldosterone production or signaling [25].

Blood pressure reduction

In line with earlier meta-analyses showing that statins moderately lower blood pressure, especially in hypertensive or metabolically impaired individuals, the current study revealed a mean reduction in blood pressure [26]. The current data suggest a preferential effect on systolic pressure, even though direct comparison studies on the differential effects of aldosterone on systolic and diastolic blood pressure are still scarce. Aldosterone affects systolic pressure mainly by causing arterial stiffening and vascular remodeling, especially in large elastic arteries such as the aorta. Diastolic pressure, on the other hand, is more strongly linked to peripheral resistance, which is also influenced by aldosterone but to a lesser extent through vasoconstriction and endothelial dysfunction [27].

The initial drop in SBP is probably more volume-based and hemodynamic, potentially associated with the natriuretic effects resulting from aldosterone suppression. Systolic pressure continues to decrease as arterial stiffness improves over time, whereas diastolic pressure, which is caused mostly by peripheral resistance, can plateau sooner [28]. Crucially, the decrease in PP points to an improvement in arterial compliance, suggesting that statins may lessen vascular stiffness, which is a significant factor in cardiovascular risk that goes beyond blood pressure readings. A decrease in total hemodynamic stress is also indicated by the observed decrease in MAP, which could improve end-organ perfusion and lessen chronic vascular damage. Together, these

results strengthen the idea that statins have pleiotropic effects in the treatment of cardiovascular disease by having vasculoprotective effects that go beyond decreasing cholesterol. Because aldosterone enhances vasoconstriction and inhibits natriuresis, rosuvastatin can quickly lower peripheral vascular resistance and, consequently, blood pressure, frequently in hours or days. However, remodeling of the vascular wall appears more gradually, usually over the course of weeks to months. Similarly, following 12 weeks of eplerenone treatment for hyperaldosteronism, a substantial decrease in pulse wave velocity was noted [29].

Correlation analyses revealed no significant direct connections between aldosterone, salt, cholesterol, and systolic blood pressure, although these variables were observed to decrease after statin therapy . This lends credence to the idea that statins may work not only through lipid-lowering or sodium-handling pathways but also through pleiotropic mechanisms, such as increased endothelial function, decreased oxidative stress in the adrenal cortex, or calcium channel modulation, to produce antihypertensive and hormonal effects [30, 31]

Sex differences in the aldosterone response to rosuvastatin

Following rosuvastatin treatment, male participants in our sample presented a noticeably greater decrease in serum aldosterone levels than female participants did. This result is consistent with previous data that point to sex-specific variations in the endocrine effects of statins [32]. The pharmacokinetic differences between males and females could be one reason. Statins are generally better absorbed and metabolized by the liver in males, which may improve the capacity of the medication to inhibit intracellular cholesterol synthesis in steroidogenic tissues such as the adrenal cortex [9]. Because aldosterone biosynthesis depends on cholesterol, male aldosterone production may be more inhibited when there is less substrate available. Additionally, estrogen in females may provide protective effects by upregulating compensatory pathways such as LDL receptor expression or alternative lipid uptake mechanisms, whereas testosterone may increase adrenal sensitivity to cholesterol depletion [33].

According to regression to the mean, the males in our study also tended to have higher baseline aldosterone levels, which might have contributed to a greater absolute reduction after treatment. Male participants may be more susceptible to the renin–angiotensin–aldosterone system (RAAS)-modulating effects of statins due to greater RAAS activation in men, which is frequently linked to higher baseline blood pressure and visceral obesity [34].

According to animal models, sex hormones alter the amount of lipids in the adrenal glands; in males, testosterone increases the amount of cholesterol pools, whereas in females, estradiol decreases it. Only male SHR rats presented increased aldosterone synthesis in response to dietary hypercholesterolemia in hypertensive rats [35]. These results, along with the sex-specific pharmacokinetics of rosuvastatin, point to a potential mechanism for increased aldosterone suppression in male individuals. All of these results lend credence to the theory that biological sex may influence how rosuvastatin affects adrenal steroidogenesis, which may have consequences for managing cardiovascular and metabolic risk in relation to sex.

Conclusion

This study shows that statin medication has an impact on both lipid profiles and aldosterone levels, which have no associations with lipid profiles and blood pressure metrics. Our results are especially intriguing, in spite of its decreased lipophilicity, rosuvastatin still seemed to somewhat lower aldosterone levels, suggesting that its effects might be mediated more via systemic or metabolic processes than by direct action on the adrenal cortex. Our findings proposed another pleiotropic effect of rosuvastatin especially in patients with hyperlipidemia and hypertension, the results also highlight a sex differences with relation to rosuvastatin response.

Limitations

Despite the novelty of our results, the study has certain limitation like the small number of patients selected, in addition the study didn't measure renin and angiotensin system so we cannot determine whether the effect is primarily on aldosterone or secondary to angiotensin inhibition.

Acknowledgments: The authors are thankful to the University of Mosul/ Department of pharmacology (https://uomosul.edu.iq/en/pharmacy/department-of-pharmacology-and-toxicology/) for their help to complete our research.

Conflict of interest: None

Financial support: None

Ethics statement: Ethical approval was obtained from the College of pharmacy (project code: CCMRE phA-22-12). The research aim and method was fully explained to all patients, they all signed a special consent form before starting the experiment.

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