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## Are statins toxic or safe for kidney diseases? An updated mini-review study

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### ABSTRACT

Statins, as the most important cholesterol-lowering agents, inhibit the production of blood cholesterol by blocking an enzyme called the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statins have beneficial effects in some tissues during various injuries. Recent evidence suggests that unlike the beneficial effects of statins, administration of high doses of these drugs may increase renal impairment, although more research is needed in this regard. Therefore, this study aimed to evaluate the possible effect of different doses of statins on the morphology and function of the kidney tubular cells.

### *Implication for health policy/practice/research/medical education:*

The present study aimed to evaluate the possible effect of different doses of statins on the morphology and function of the kidney tubular cells. The results indicated that statins have beneficial effects on renal disorders. However, more attention should be paid to high-dose of statins in clinical conditions.

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### Introduction

Recently, cardiovascular diseases are considered as the first cause of mortality in industrialized societies and developing countries (1). One of the most effective prescription drugs lowering serum cholesterol levels are statins that were first introduced in 1976. These drugs inhibit the activity of a key enzyme named 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the pathway of cholesterol synthesis. Statins have a substantial influence on the primary and secondary prevention of cardiovascular disease, as well as in the treatment of ischemic cardiomyopathy. Therefore, it is widely recommended for people at risk of heart disease (2,3). Furthermore, one of the cardiovascular protective capacities of statins is the regulator of the vascular function by increasing the activation and expression of endothelial nitric oxide synthase (eNOS). The details of the mechanism are as follows: statins inhibit the Rho/

ROCK pathway through suppressing isoprenylation and translocation of Rho as a small GTPases. In fact, active forms of Rho and ROCK diminish phosphorylation and mRNA stability of eNOS and subsequently expression and activity of eNOS (4). Due to the efficacy and relative safety of HMG-CoA reductase inhibitors, prescription of statins remains unaffordable over the age of 50 years (5, 6). Recent studies have suggested that administration of high-dose statin to improve cardiovascular complications is more effective than that of low-dose. The consumption of this drug may be associated with severe side effects such as acute renal damage, diabetes, memory impairment, and rhabdomyolysis. Thus, more precise studies on the side effects of statins are required. Some studies have indicated that high-level statin therapy may increase the risk of acute kidney injury (AKI), while few studies have been conducted on this subject (7-9). Therefore, the present study aimed to investigate the possible effect of different

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doses of statins on the morphology and function of kidney tubular cells.

### Materials and Methods

For this study, we used various databases such as Web of Science, PubMed, Embase, Scopus and the directory of open access journals (DOAJ). Searching for articles was performed using keywords or their equivalents including cardiovascular diseases, statin, renal toxicity, statin doses, renal failure, and dyslipidemia.

### Protective role of statins in renal disorders

Dyslipidemia is considered as one of the known risk factors for the development of atherosclerosis as well as coronary artery disease, peripheral artery disease, and cerebrovascular diseases. Studies have shown that disruption in lipoproteins metabolism such as LDL, HDL, and triglyceride can accelerate renal dysfunction in people with chronic kidney disease (CKD), which indicates a positive relationship between dyslipidemia and kidney disease (10).

In fact, the accumulation of lipids in the renal arteries triggers the activation of mesenchymal cells and factors such as MCP-1 and M-CSF, which results in the use of monocytes and the conversion of macrophages into foam cells. Then, lipid oxidation can disrupt vascular function and expand kidney disorders (11).

Statins are used as effective agents for the treatment of lipid disorders. The drug is capable to remove free radicals including reactive oxygen species (ROS) in the kidneys and also prevents the death of tubular cells by the inhibition of nuclear factor-kappa B (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK) signaling pathways (6, 12). Statins, in addition to the protective role against the rejection of cardiac transplantation, may be effective in the kidney and lung transplantation. One of the beneficial properties of statin is its pleiotropic effect in the treatment of chronic renal failure. It has been proven that statins in the kidney have an anti-inflammatory role and can affect various signaling pathways including inflammation, inhibition of neutrophil accumulation, cell death response and proliferative response (13). Statins also improve renal disease through potential mechanisms such as reducing vascular endothelial disorders and decreasing abnormal plasma proteins (14). Studies have demonstrated that there is a risk of heart disease in people with CKD and statins can be effective in reducing cardiac complications by reducing LDL (15-17). Simvastatin administration in CKD patients has been reported to decrease the severity of heart muscle damage (18). Hou et al found that statin injection in CKD patients undergoing dialysis could reduce the risk of cardiovascular disease (19). The evaluation of the effect of statin on the levels of

uric acid and estimated glomerular filtration rate (eGFR) and their relationship with patients of coronary heart disease and metabolic syndrome showed that long-term statin use can increase eGFR and decrease serum uric acid level (20). Proteinuria is one of the symptoms of kidney dysfunction and an important indicator of kidney disease. The result has revealed that statins may reduce proteinuria and glomerular damage in renal disorders, although some studies have found no relationship on this subject, which requires more research (21,22).

Renal ischemia-reperfusion (RIR) is one of the most important causes of acute renal injury. RIR can occur because of shock, infection, kidney transplantation, and vascular surgery (23).

Previous studies presented that statins possess a protective role against RIR injury. Recently, dos Santos et al investigated the efficacy of atorvastatin and ischemic postconditioning to inhibit RIR injury on 41 norvergic male rats. For this purpose, 3.4 mg/d of atorvastatin was used for 7 days. Their results suggested that both atorvastatin and ischemic postconditioning can alleviate renal tissue injury due to IR (24).

Lai et al performed a population-based study on the role of two types of statins including atorvastatin and rosuvastatin on renal function in type 2 diabetes patients. The results demonstrated no significant alteration in eGFR level between atorvastatin and rosuvastatin groups. However, eGFR level amended significantly in patients with CKD in stages 3 to 5 against stages 1 to 2 in both groups of high-potency statin consumers (25).

Recent developments regarding statins displayed their anti-neoplastic feature that can arrest cell cycle progression and inhibit tumor progression and metastasis in different cancers including prostate, colorectal, and breast. The findings presented that statin as an adjunct treatment may improve survival of patients with metastatic renal cell carcinoma, however, this supposition requires prospective assessment (26,27).

It has been proposed that statins can be lucrative to improve one of the sepsis complication including AKI (28). In this regard, the recent study of the literature designed on the effect of rosuvastatin on AKI due to sepsis-associated acute respiratory distress syndrome (ARDS) on 745 participants from 2010 to 2013. Their findings demonstrated that rosuvastatin therapy has no positive effect on de novo AKI or worsening of preexisting AKI in patients with ARDS and sepsis (29).

### The effects of different doses of statins on the kidney

It has been suggested that despite the beneficial effects of statins in reducing heart diseases, these drugs have different side effects. Rhabdomyolysis is one of the most important complications of statins, leading to lysis of

myocytes and the release of compounds such as creatine kinase and myoglobin into the plasma (30).

Rhabdomyolysis affects most organs of the body, including kidney and heart (cardiovascular disorders), pancreas (pancreatitis), damage to the respiratory system, and liver (hepatotoxicity) (31,32). In fact, renal disorders such as blockage of renal tubules, changing the levels of eGFR, and renal toxicity can be due to the myoglobin released during rhabdomyolysis (33). Additionally, statins alone or together with fibrates can cause myoglobinuria, kidney damage, or even death (34).

According to various evidence, the use of high-dose statin for the improvement of cardiovascular disease complications is more efficient than that of the low-dose of statin, while a new study showed that administration of high-power statins may cause damage to tubular cells and increase the risk of acute renal failure (35). The study conducted by Reddy et al on the effect of atorvastatin and garlic extract on 56 dyslipidemic rats illustrated that the combination of garlic extract and high-dose of atorvastatin in comparison with high-dose of garlic and low-dose of statin could endanger the health of the body. In fact, they concluded that the severity of kidney damage in rats receiving high-dose of atorvastatin alone or in combination with high levels of garlic is more than those of rats receiving low-dose of atorvastatin with high concentrations of garlic (36). In addition, Dormuth et al reviewed the health care records of patients over 40 years of age under statin therapy. They showed that the risk of acute renal damage in patients who received high levels of statin was more than those who received low-dose of statin (37).

Some studies indicated that there is a relationship between nephrotoxicity and the use of statin, while this issue is not completely clear and it might be due to an abnormality in metabolic function such as the activation and fluidity of the membrane chloride channel, and the impairment of renal mitochondrial function (38). The data were obtained from the evaluation of the dose-dependent effects of atorvastatin on rat kidneys for 17 days illustrated that there was no significant difference in serum BUN and creatinine level in rats treated with doses of 5 mg/kg and 10 mg/kg of atorvastatin and no abnormality in kidney function and nephrotoxicity was observed, although doses more than 20 mg/kg increased serum levels of BUN and creatinine (39). Statins may cause proteinuria and hematuria in individuals treated with 80 mg/kg dose of rosuvastatin (40, 41). Therefore, to determine the details of the dose-dependent effect of statin, it is necessary to conduct studies on a large population with the possibility of determining the different dosages of the drug.

Contrast-induced nephropathy (CIN) is recognized as the third most prevalent reason for acute renal failure

that related to intravascular administration of iodinated contrast in cardiovascular patients. Commonly, the disturbance caused by contrast agents is defined as a promotion of serum creatinine more than 25% or  $\geq 0.5$  mg/dL from basal levels within 2-3 days after the use of contrast agents (42).

CIN pathogenesis may occur via the induction of oxidative stress, the production of ROS, and nephrotoxicity due to contrast agents. Additionally, one of the properties of statins is antioxidant activity that can reduce ROS during the intracellular process (43).

A study was performed on 130 patients undergoing angiography including 53 women and 77 men with an average age of  $54 \pm 10$  years to evaluate the effect of high-dose of atorvastatin in the prevention of CIN in the short-term. The results showed that high-dose of atorvastatin has a beneficial effect on the prevention of CIN in the short-time. It has been indicated that inflammatory processes and oxidative stress play a role in the development of CIN, statins can reduce inflammation by improving endothelial function and increasing the bioavailability of nitric oxide (44,45).

Additionally, the study on diabetic patients with mild-to-moderate CKD performed to measure the role of atorvastatin in the improvement of CIN undergoing elective percutaneous coronary intervention (PCI). In this prospective study, patients randomly and double-blind received 80 mg/d of atorvastatin for 48 hours and then 72 hours and 10 days afterward, GFR and serum creatinine surveyed preintervention. The finding revealed that 80 mg/d dose of atorvastatin declined CIN in diabetic patients with CKD undergoing PCI (46).

Zahr et al surveyed the protective effect of atorvastatin on a murine model of sickle cell nephropathy by urine and flow analysis, assessment of renal histology, GFR estimation and the evaluation of cysteine, glutathione disulfide, cystine, and glutathione levels in kidney and gene expression of NOX4, CYBB, and EDN1 for the determination of the oxidative stress level in renal tissue. Their results revealed that treatment of humanized sickle cell mice with 10 mg/kg/d dose of atorvastatin at 8-10 weeks diminished albuminuria and also ameliorated urine concentrating ability, GFR, glomerular tuft area, oxidative stress, and kidney injury (47).

## Conclusion

The results of various studies indicate that statins, in addition to the cholesterol-lowering effect, have beneficial effects in renal disorders. However, taking this drug with high-dose can have a deleterious effect on the kidneys, and more attention should be paid to high-dose of statins in clinical conditions. Therefore, due to the side effects of statins, the use of these drugs in patients with various risk

factors should be done with caution.

### Authors' contribution

BY conducted the searches and gathered the related articles and prepared the draft. SB edited the final manuscript. All authors read and signed the final paper.

### Conflicts of interest

None.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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