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An update on renoprotective effects of atorvastatin

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Abstract

Statins such as atorvastatin, significantly reduce cholesterol synthesis via inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase and atorvastatin has antioxidant activity, so can increase blood antioxidant capacity. Diabetes mellitus is a major cause of chronic kidney disease (CKD). One of the most significant effect of atorvastatin is reduction of kidney injury especially in CKD. Also atorvastatin has beneficial effects in preventing contrast-induced acute kidney injury and in decreasing various factors, involved in type 2 diabetes mellitus and diabetic nephropathy. Ameliorative effects of atorvastatin have been studied by many researchers and this article attempts to review these studies including effectiveness of atorvastatin in patients with renal injury, type 2 diabetes mellitus and diabetic nephropathy. In most of studies, lower doses of atorvastatin were more effective than higher doses.

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Introduction

Atorvastatin (a statin drug) belongs to the group of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and has antioxidant activity (1). It has been shown that statins can reduce the expression of adhesion molecules, inhibit migration and proliferation of vascular smooth muscle cells (VSMCs), active the nitric oxide pathway in endothelial cells by augmenting the regulation of endothelial cell NO synthase (eNOS), induce anti-inflammatory responses and apoptosis (2,3). Nowadays, chronic diseases such as cardiovascular disease, diabetes mellitus, chronic respiratory disease, cancer and chronic kidney disease (CKD) are the major causes of death in the world (1-3). Several studies have revealed that atorvastatin can reduce intracellular reactive oxygen species. In 1985, atorvastatin was manufactured for the treatment of hyperlipidemia. Atorvastatin reduces cholesterol level via inhibiting the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (1). It is prescribed for hyperlipidemia and can reduce the complications of atherosclerosis (4).

Diabetes mellitus is a common endocrine disease and is determined by chronic hyperglycemia. Also type 2 diabetes accounts for more than 90% of diabetes and is resulting in impaired function in protein, carbohydrate and lipid metabolism. Statins are a first line lipid-altering therapy for patients with diabetes mellitus (5). Retinopathy, nephropathy, neuropathy and cardiovascular disease are the complications of uncontrolled diabetes. Atorvastatin has also been used for managing diabetic complications such as diabetic kidney disease (6). CKD is a public health problem in the world and is a global health burden especially for cardiovascular and cerebrovascular events. Statins have also lipid-independent benefits against kidney injury in CKD and in acute kidney injury (1). More recently, studies have emerged the findings about ameliorative effects of atorvastatin on various diseases such as renal dysfunction and diabetes mellitus and due to the increase of public awareness for expanding the use of this component, we try to explain some of these studies in this article.

Core tip

Atorvastatin has beneficial effects in preventing contrast-induced acute kidney injury and in decreasing various factors, involved in type 2 diabetes mellitus and diabetic nephropathy. Ameliorative effects of atorvastatin have been studied by many researchers and this article attempts to review these studies including effectiveness of atorvastatin in patients with renal injury, type 2 diabetes mellitus and diabetic nephropathy. In most of studies, lower doses of atorvastatin were more effective than higher doses.

Materials and Methods

For this review, we used a variety of sources by searching through PubMed, Web of science, Embase, Scopus, EBSCO and directory of open access journals (DOAJ). The search

was performed by using combinations of the following key words and or their equivalents; atorvastatin, antioxidant, oxidative stress, reactive oxygen species, diabetes mellitus, chronic kidney disease, contrast nephropathy and acute kidney injury. Manuscripts published in English as full-text articles and or as abstracts were included in the study.

Antioxidant effects of atorvastatin

It is well known that reactive oxygen species are responsible for several types of cell damages (7). These damages are including change in DNA, membrane peroxidation, oxidation of proteins and inactivation of enzymes (2). Numerous studies have revealed that statins may inhibit NADPH oxidase, so the generation of reactive oxygen species decreased. This effect is attributed to synergic property of statins with biological effects of antioxidants. Reactive oxygen species and insufficient antioxidant enzymes have been involved in the pathogenesis of hypercholesterolemia (3,4). In 2009, Nasar et al showed the antioxidant status of atorvastatin in hypercholesterolemic patients. This study conducted on three groups including control group (healthy subjects), hypercholesterolemic group and atorvastatin group (minimum dosage of atorvastatin was 10 mg/day). After 2 months of treatment, they revealed that the levels of oxidative stress were lower in the atorvastatin and control groups than in the hypercholesterolemic patients. Besides, the antioxidants levels were higher in the atorvastatin group in comparison to the hypercholesterolemic patients (4).

The influence of atorvastatin on production of reactive oxygen species, antioxidative enzymes and NADPH oxidase expression in VSMCs and spontaneously hypertensive rats (SHR) has been investigated. This research showed that atorvastatin had cellular antioxidant effects in cultured VSMCs and in the vasculature of SHR mediated by reduced expression of essential NAD(P)H oxidase subunits and by increase in catalase expression. Treating the rats with standard chow supplemented with atorvastatin for 30 days, decreased vascular mRNA expression of nox1 and p22phox. Western blot test revealed that membrane translocation of rac1 GTPase, which is needed for the activation of NADPH oxidase, was inhibited by 10 μmol/L of atorvastatin. Many antioxidative enzymes are involved in keeping the balance of ROS availability within vascular cells. After atorvastatin treatment, production of free radicals decreased in VSMCs, due to increase in expression of catalase, which led to the elimination of free radicals by the generation of oxygen and water but other antioxidative enzymes such as manganese superoxide dismutase (SOD), copper-zinc SOD, extracellular SOD, and glutathione peroxidase did not change by atorvastatin (3).

A number of studies compared the antioxidant effects of atorvastatin with other statins. The relationship between active metabolite of atorvastatin and membrane cholesterol domain formation has been investigated. In this study, the effect of atorvastatin active o-hydroxy metabolite on OS-induced cholesterol domain formation was compared with other statins including pravastatin, simvastatin and rosivastatin. Among the statins, just atorvastatin active o-hydroxy metabolite blocked membrane cholesterol domain formation as a function of oxidative stress. In other words, various concentrations of active o-hydroxy metabolite inhibited changes in membrane lipid organization and structure, including cholesterol domain formation, following oxidative stress. This activity of atorvastatin active o-hydroxy metabolite was attributed to antioxidant activity and the antioxidant effect was related to electron donation and proton consolidation mechanisms associated with its phenoxy group, which is located in the membrane hydrocarbon core (8). Another comparative study reported that a number of statins such as atorvastatin, fluvastatin, simvastatin and pravastatin as compared with uric acid and trolox (the water-soluble analogue of vitamin E) had significant antioxidant activity with both anti- peroxyl (ROO) and hydroxyl (HO) radical activity (2).

Atorvastatin and type 2 diabetes

In recent years, several studies have focused on effect of statins such as atorvastatin on various factors in type 2 diabetes mellitus patients (9). The first study of statin therapy (40 mg/day) for 2 months in hypertriglyceridemic patients with type 2 diabetes mellitus, demonstrated that atorvastatin improved lipid abnormalities by increasing the clearance of apoB lipoproteins and also by decreasing VLDL production (10). One study compared the effects of four statins on renal function in patients with type 2 diabetes over three years. They found atorvastatin improves the lipoprotein profile and oxidative status in individuals with type 2 diabetes. (11).

Dyslipidemia in diabetes mellitus

Diabetic dyslipidemia is characterized by elevated levels of triglyceride-rich lipoproteins (VLDLs), low levels of high-density lipoprotein cholesterol (HDL-C), postprandial lipemia and a high proportion of small dense low-density lipoprotein-cholesterol (LDL-C). Statins can decrease blood LDL cholesterol levels by inhibiting hepatic cholesterol synthesis and subsequent up-regulation of the receptors of hepatic LDL-C. In patients with diabetic dyslipidemia, treatment with statins significantly reduced secretion of apoB lipoproteins into plasma (5).

Several studies have revealed that atorvastatin improves diabetic dyslipidemia. Atorvastatin therapy (10 mg/d) on 110 type 2 diabetic dyslipidemia patients with LDL-C levels, improved oxidative status and lipoprotein profile (10-12). In 2004, Schneider et al, analyzed lipoprotein lipase activities and lipid profile in 61 patients with type 2 diabetic dyslipidemia. In this study, after 8 weeks treatment with 40 mg atorvastatin, lipoprotein lipase activity was increased by 25% and improved diabetic dyslipidemia (13). Triglyceride, serum creatinine, LDL-C, brain natriuretic peptide (BNP) and systolic and diastolic blood pressure significantly decreased in type 2 diabetic patients with dyslipidemia and hypertension by administration with a fixed combination tablet containing atorvastatin (10 mg) and amlodipine (5 mg) at 6 and 12 months. In contrast,

estimated glomerular filtration rate (eGFR) increased following 6 months drug usage. Also mean IMT and baPWV as markers of atherosclerosis, were importantly improved at 12 months. Malondialdehyde-modified LDL (MDA-LDL) promotes synthesis and secretion of cell adhesion molecules (CAMs), raises foam cell formation in atherosclerotic lesions, exerts cytotoxicity on endothelial cells, and increases monocyte adhesion and platelet association. The level of malondialdehyde-modified LDL was elevated in patients with diabetes and decreased after 6 and 12 months. Also, urinary albumin-creatinine ratio (ACR) was decreased at 12 months (13).

Collaborative studies on the administration of atorvastatin in diabetes mellitus

The collaborative atorvastatin diabetes study or CARDS as the first primary prevention study, focused to investigate the role of a statin in patients aged 40-75 years, who had type 2 diabetes. They did not have symptoms or signs of pre-existing vascular disease and just had average or below average cholesterol levels. One investigation showed the safety of atorvastatin therapy (10 mg/day) in 2838 patients with type 2 diabetes, without elevated LDL-C over a median follow-up period of 3.9 years. Similar results were achieved in patients with type 2 diabetes, in the CARDS which treated with atorvastatin (10 mg/day) for one year in LDL-C, non-HDL-C and apo B concentration (14).

Diabetic kidney disease

DM related kidney failure causes ailment outcomes, such as hypertension, fluid filtration deficits, angiopathy, edema, proteinuria and renal arteriosclerosis (15). Also DN is the major cause of end-stage kidney disease with a prevalence of 30% of all diabetic patients. The clinical application of atorvastatin is primarily used for preventing cardiovascular disease and decreasing blood cholesterol, related to the mechanism of inhibiting HMG-CoA reductase in kidney cells. Thus atorvastatin as a mediator of cholesterol-lowering, agent is potential method of anti-DN (16). Zhou et al (6), performed experimental investigations on streptozotocin (STZ)-diabetic rats and STZ-diabetic rats treated with atorvastatin (10, 20 mg/kg/d) for 8 weeks. Atorvastatin reduced significantly the blood glucose level, decreased serum concentrations of LDL-C and 24 hours urine protein content, increased the body weight of DN-rats, insulin and HDL-C levels in plasma. Furthermore, the TGF-β1 mRNA expression was down regulated in kidney tissue. STZ-induced DN-rats indicated low antioxidant ability and drastic lipotoxicity in kidney cells and atorvastatin reversed these conditions via increasing in SOD and glutathione peroxidase (GSH-Px) activity. In brief, atorvastatin showed protective effect against kidney injuries of STZ-diabetic rats (6). Patients with DN, who had a serum creatinine level of 0.9-1.5 mg/dl, were treated with 10 mg of atorvastatin and 10 mg pravastatin for 12 months. Atorvastatin group revealed a sharp decrease in LDL-C at 3 months. Cystatin C (CysC) is mainly used as a biomarker of kidney function. Atorvastatin inhibited the increase of CysC at 6 months and also 12 months in diabetic patients greater than pravastatin (17).

Atorvastatin and kidney

In recent years, there has been an increasing interest in studding the ameliorative effects of atorvastatin on kidney diseases. Atorvastatin as a mitogen-activated protein kinase and nuclear factor kappa B inhibitor and free radical scavenger, is able to act in the kidney (1-3). Gentamicin causes renal toxicity and induces apoptosis in renal tubular cells. Atorvastatin is able to inhibit signaling pathways activation by reactive oxygen species and prevent the tubule cell apoptosis. In 2015, we investigated the effect of different doses of atorvastatin on gentamicin-induced kidney injury. We chose 30 male Wistar rats and divided them into six groups. They were administered various doses of gentamicin (80 mg/kg/d) and atorvastatin (10, 50, 150 mg/kg/d) for 7 days. At the end of this research, we showed that protection of atorvastatin against kidney injury was not dose dependent. In this study, treatment with atorvastatin (10, 50 mg/kg) reduced the histopathological and biochemical changes of gentamicin-induced renal injury. In contrast, administration of 150 mg/kg of atorvastatin for 7 days aggravated tubular damage of gentamicin. Furthermore, administration of atorvastatin (150 mg/kg) alone had toxic effects on renal tubular cells (1). Injection of the atorvastatin with a dose of 150 mg/kg/day for 7 days also had nephrotoxic properties in rats. In this experimental study we used 24 male Wistar rats which were divided into 4 equal groups including groups one, two and three, which received 10, 50 and 150 mg/kg and control group that received phosphate buffer for 7 days. Administration of atorvastatin (10, 50 mg/kg/day) for 7 days was not accompanied by renal injury (18).

Researchers have studied the effect of atorvastatin on kidney function in 380 patients (between 18 and 85 years) with CKD. Sixty-four patients received 10 mg of atorvastatin and 68 patients received placebo. They showed 29% lower MDRD eGFR and 20% lower cockcroft-gault creatinine clearance (C–G CrCl) decline in atorvastatin-treated groups compared to placebo group (19). Previous studies have demonstrated increase of mortality and morbidity risk of cardiovascular complications in patients who had advanced CKD. One study examined the effect of atorvastatin on 341 patients with CKD who tolerated a major cardiovascular event compared with 561 patients with normal eGFR. Data showed that 10 and 80 mg of atorvastatin reduced the relative risk of major cardiovascular events by 32% in patients with CKD and 15% in patients with normal eGFR (20). Atorvastatin reduced epithelial sodium channels (u-ENaC), so atorvastatin may change sodium reabsorption in the nephron of patients with non-diabetic CKD stage II–III (21). One hundred seventeen patients with CKD, which had raised baseline plasma IL-6/8/10 and pentraxin-3, also serum creatinine >120 μmol/L, treated with 10 mg atorvastatin per day for a mean of 2.5 years. In this treatment group eGFR declined (22).

Hyperlipidemia and hyperuricemia are two factors which

are related in progression of CKD (23). Atorvastatin can increase eGFR and inhibit urinary protein and can be used as a drug in the treatment of hyperlipidemia and hyperuricemia complications. Results of one study showed that atorvastatin had renal protective effect in stage III CKD patients with hyperlipidemia and hyperuricemia after 3 months. Furthermore, they showed a significant decrease in serum uric acid, triacylglycerol, LDL-C and total cholesterol levels after atorvastatin administration (24). In 2014, Azushima et al demonstrated that treatment with single pill-based combination of atorvastatin and amlodipine for 16 weeks significantly decreased systolic and diastolic blood pressure in 20 hypertensive CKD patients. Also, combination therapy with atorvastatin and amlodipine lowered LDL-C and total cholesterol levels, without important changes in parameters of inflammation and glucose metabolism (25). To evaluate, the impact of statins on renal outcomes in patients with CKD, Sanguankeo et al conducted a meta-analysis, consisting 142 full-text articles. They detected a significant difference in rate of eGFR change per year favoring statin. They found, high-intensity statins improve a decline in eGFR in patients with CKD not requiring dialysis compared with control subjects, however, moderate- and low-intensity statins were not. They also found that statins was not effective to decrease proteinuria in individuals with CKD (26).

Contrast-induced acute kidney injury (CIAKI) is an impaired renal function after administration of intravascular contrast agent within three days of contrast injection in the lack of another cause and also is one of the most common causes of AKI in hospitalized patients. It has been suggested that contrast-induced nephropathy is due to an alteration in renal blood flow accompanied with a decline in flow of the central part of the kidney and direct tubular epithelial toxicity. Statins have been shown effective by several researches in preventing contrast-induced nephropathy. Bidram et al, revealed the effect of short-term treatment (4 days) with high-dose of atorvastatin (80 mg) for prevention of contrast-induced nephropathy in computed tomography angiography candidates with normal kidney function. These results showed the protective effect of atorvastatin in alteration of serum creatinine after contrast material injection (27). In a study by Shehata et al, the effect of high dose of atorvastatin (80 mg/day for 48 hours) in prevention of contrast-induced nephropathy in 130 diabetic patients, who had mild to moderate CKD, undergoing elective percutaneous coronary intervention (PCI) was investigated. Results of this study indicated that serum creatinine level revealed a nonsignificant rising on the third day and afterwards decreased to baseline one level, on the 10th day. On the other hand, incidence of CIN was 20% in the placebo group and seven point 7% in atorvastatin group (28). Recent studies also have shown, the aggravation of renal function by oxidative stress and the ameliorative effects of statins in glomerulopathies too (29,30). Recently Cheungpasitporn at al (31) contacted a comprehensive literature review for randomized controlled trials of peri-procedural statin therapy for prevention of CIAKI. They selected, 13 prospective randomized controlled trials to include in their study. They observed, of 5803 individuals with contrast exposures, 304 patients had CIAKI. Individuals in the statin group had an overall lower incidence of CIAKI, in comparison to the control group. They detected a significant protective effect of peri-procedural statins on the incidence of CIAKI when compared to the control subjects. They concluded a statistically significant ameliorative effect of statin treatment during procedures with contrast media exposures. This finding propose the use of statins in addition to standard IV crystalloid hydration may be helpful in the prevention of CIAKI (31). Finally, in a more recent study by Johansen and Green, to investigate the use of statins in subjects older than 79 years without vascular disease, which take statins. They found, "many elderly Americans take statins without evidence of any benefit." Hence, the benefits and harms in elderly population with CKD, which is a current hot topic and requires further investigation (32).

Conclusion

Atorvastatin is a member of group 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). Statins are used to lower cholesterol levels by inhibiting the enzyme 3-hydroxy-3-methyl-glutaryl- CoA reductase. Furthermore, statins are a first line lipid-altering therapy for patients with diabetes mellitus. Findings of this review show that atorvastatin is a useful drug, which can improve hyperlipidemia, diabetic dyslipidemia, diabetic nephropathy, type 2 diabetic and renal injury in patients and also has antioxidant activity. In most of studies, lower doses of atorvastatin were more effective than higher doses. So we will need more in vivo and in vitro researches to examine different doses of atorvastatin on these diseases.

Author's contribution

MRK is the single author of the manuscript.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

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

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