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An update on renoprotective and nephrotoxicity of statins

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Abstract

Statins are employed in the treatment of hyperlipidemia. Their main mechanism of action is inhibition of HMG-reductase, however, they have various other effects independent of their cholesterol lowering mechanism. These include anti-inflammatory and anti-oxidant properties. Statins can reduce acute phase reactant. They inhibit vascular micro-inflammation, enhancing endothelial cell function, inhibiting proliferation of vascular smooth muscle, reducing platelet activation and aggregation and increasing atherosclerotic plaque stability. Many of these effects are postulated to arise from disruption of small G-proteins. This is not clear whether statins are nephrotoxic or nephroprotective agents. There is not enough data about their effects on nephrons. Cardiologists and internists use statins widely in many conditions but there is evidences against their safety. Further studies are necessary to determine the biological mechanism of kidney injury in statin users.

Introduction

Statins are employed in the treatment of hyperlipidemia. Their main mechanism of action is inhibition of HMG-reductase, however, they have various other effects independent of their cholesterol lowering mechanism. These include anti-inflammatory and anti-oxidant properties. Statins can reduce acute phase reactant. They inhibit vascular micro-inflammation, enhancing endothelial cell function, inhibiting proliferation of vascular smooth muscle, reducing platelet activation and aggregation and increasing atherosclerotic plaque stability. Many of these effects are postulated to arise from disruption of small G-proteins (1). This review article investigates renal ameliorative effects of statins.

Core tip

There are various other effects independent of their cholesterol lowering mechanism for statins. These include anti-inflammatory and anti-oxidant properties. Statins can diminish acute phase reactant. They inhibit vascular micro-inflammation, enhancing endothelial cell function, inhibiting proliferation of vascular smooth muscle, reducing platelet activation and aggregation and increasing atherosclerotic plaque stability.

Materials and Methods

For this review, we used a variety of sources by searching through PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents; HMG-CoA reductase, statins, acute kidney injury, nephrotoxicity and renoprotection.

Mechanisms for statin actions

HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase) is a transmembrane protein and catalysis a key step in mevalonate pathway. Molecules like sterols, isoprenoids which are involved in inflammatory response and lipids are produced via this pathway. This means that statins as inhibitors of this enzyme, can reduce both cholesterol and isoprenoids (2). Both isoprenoid chains geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP) are products of mevalonate pathway. Non-lipid dependent effects of statins are exerted through inhibition of prenylation. Isoprenoid compounds become attached post-translationally to intra-cellular signaling proteins such as guanosine triphosphate (GTP). Prenylation or isoprenylation or lipidation is the addition of hydrophobic molecules to a protein or chemical compound. It is involved in post-translational modification to preparing molecules for their function in cells. Protein prenylation involves transfer of either a

farnesyl or a geranyl-geranyl to the target protein. Statins inhibit prenylation through prenylic substrate reduction. In fact HMG-CoA reductase inhibitors, arrest mevalonate synthesis and its products FPP and GGPP (3). Isoprenoid compounds become attached post-translationally to intracellular signaling proteins. These intracellular signaling molecules facilitate communication between growth factor receptors and the cellular cytoskeleton and influence cell biological pathways (4).

Statins and renoprotection

Statins probably have renoprotective effects. Analysis suggests that statin therapy reduces the risk of renal disease progression. Sandhu et al (5) showed the rate of glomerular filtration rate (GFR) reduction was 1.2 ml/min/year slower in statin recipients. Simvastatin prevents age induced GFR reduction in patient with coronary heart disease during 4.6 years (6).

Animal studies show dyslipidemia may damage mesangial cells, glomerular endothelial cells and podocytes. low-density lipoprotein cholesterol (LDL-C) can stimulate production of matrix protein, promote generation of pro-inflammatory cytokines (7). This can lead to glomerulosclerosis. Podocytes also can be damaged by triglycerides and cholesterol (8). Low plasma high-density lipoprotein cholesterol (HDL-C) and high triglyceride level have been associated with progression of renal disease (9). It has been proved that lipid disorders enhance the progression of renal injury (10). Reduced progression of renal disease may be caused by lipid lowering effect of statins. Among patients with mild and moderate renal failure the rate of kidney function loss was slower in whom treated with pravastatin than in patient with placebo (11). Another study on patients with hypertriglyceridemia and hypercholesterolemia showed reduction of the serum creatinine in the patients who received rosuvastatin for 3.8 years (12). G-proteins are involved in receptor mediated endocytosis, thus it is hypothesized that statins inhibit endocytosis of drugs and nephrotoxic agents. Statins represent a possible approach for the prevention of renal toxicity in man through blockade of uptake and accumulation of nephrotoxic drugs (13).

Statins modulate function of T lymphocytes. Expression of class II MHC molecule is essential for T cell mediated immune response regulation. They inhibit induction of MHC II (14) and inhibit the activation of Th1 cells and immune response, reduce the expression of adhesion molecules in monocyte in vivo and loss of adhesion of macrophage to endothelial cells in vitro (15). They inhibit expression of adhesion molecule on endothelium and reduce extravasation. Statins decrease levels of monocyte chemoattractant protein 1, interleukin-1B, TNFα, VCAM-1, hence they have anti-inflammatory and anti-proliferative effects (16). Statins cause upregulation and stabilization of endothelial nitric oxide synthase and increase nitric oxide (NO) production. NO has regulatory and modulatory role in inflammatory conditions, inhibiting platelet aggregation, neutrophil adhesion and slow cell proliferation after cytokine exposure (17).

Patients with glomerulonephritis shed podocytes that appear in urine (18). Reduction in podocyte loss was reported in patients with glomerulonephritis using cerivastatin (19). It was demonstrated that statins ameliorated podocyte damage and apoptosis in animal model so decreased glomerulosclerosis (20).

Lovastatin and pravastatin inhibit GTPase prenylation which is essential for progression from the G1 to S phase in cellular cycle (21). Therefore, statins can induce apoptosis, which play an important role for preventing glomerular hyper-cellularity and scarring following nephritis, while it is a critical mechanism governing glomerular remolding and normal cellularity after inflammatory injury it has beneficial effect in human glomerulonephritis (22). Simvastatin suppress mesangial cell proliferation, mesangial matrix expansion and, macrophage infiltration into the glomeruli in rat model of glomerulonephritis (23). These effects are potentially advantageous especially in inflammatory glomerular disease because they could inhibit cytokine activation network, proliferation, production of extracellular matrix and glomerular sclerosis.

Nephrotoxicity of statins

There are some data indicating administration of high potent statins is associated with increased risk of acute kidney injury compared with low potent statins. The hospitalization due to acute renal failure by statins was 34% more in group received high potency statin compared with the group received low potency statin. High potency statins include rosuvastatin, atorvastatin and simvastatin (24). How the statins develop kidney injury is not clear. Acute rhabdomyolysis induced by statins may cause renal failure however direct effect of statins on glomeruli and tubules begins before initiation of rhabdomyolysis.

Inhibition of protein geranylgeranylation induces apoptosis in human endothelial cells. It is widely known that the addition of statins to mammalian cell culture inhibits proliferation (25). Statins block the cell cycle in G1 phase and reduce DNA synthesis thus arresting progression from G1 to S phase (26). HMG-CoA reductase inhibitors, inhibit non-sterol mevalonate derived metabolites inducing compounds required for normal cellular growth (27). Fluvastatin has a pro-apoptotic effect on cultured VERO monkey renal cells (28). Apoptotic effect of statin appears to depend upon prenylation arrest. In fact, statins inhibit prenylation of Rho proteins which belongs to Ras superfamily (29). In physiologic conditions p21 rho is anchored to the cellular membrane through covalent binding with FFP and GGPP therefore in the presence of prenylation inhibition the rho protein remains in the cytoplasm thus induces apoptosis (30). Moreover, inhibition of prenylation of small G proteins interferes their biological effects; cell growth, cell differentiation, regulation and organization of actin cytoskeleton leading to increase in P53 protein synthesis and apoptosis (31).

Lovastatins inhibit c-jun, and c-fos expression in renal proximal tubular cells and impair function of activator

protein 1 (Ap-1) DNA binding activity. The Ap-1 is a transcription factor comprising c-fos and c-jun and regulates gene expression in response to variety of stimuli including growth factor and cytokines. Nuclear extracts from lovastatin treated tubular cells demonstrate functional impairment of AP-1 DNA binding activity (31). The inhibition of Ap-1 pathway by HMG-CoA reductase inhibitors is totally prevented by mevalonate. Analysis also shows lovastatin decreases ras p21 membrane. It has role in progression of G1 and S phase and function as a regulator in cell cycle.

Ras family proteins are small G proteins which are involved in transmitting signals within cells. Prenylation of small G proteins with farnesyl or geranylgeranyl groups is essential for their localization to cell membrane and their biological function (32). These results demonstrate that statins are anti-proliferative agents both in vivo and in vitro in epithelial tubular cells and this effect is exerted via inhibition of p21 activated and AP-1 dependent mitogen cascade (33).

Another mechanism is suppression of coenzyme Q10 a coenzyme with antioxidant properties. Ubiquinone or coenzyme Q10 (CoQ10) is an isoprenoid compound and fat soluble molecule. Q refers to the quinine chemical group and 10 refers to the number of isoprenyl chemical subunits, synthesized by HMG-CoA following mevalonate pathway (34). It has several biological functions in mitochondrial respiratory chain as an electron carrier, increase the efficacy of oxidative phosphorylation (35) and act as an antioxidant. It is a free radical scavenger, so it is a membrane stabilizer and plays a role in cell integrity (36). HMG CoA reductase inhibitors decrease CoQ10 in dose dependent manner and reduce overall rate of NADH and oxidized succinate (37). Circulating Q10 levels are dependent on endogenous synthesis and on dietary uptake. Simvastatin and pravastatin significantly lower CoQ10 plasma levels after a few weeks of treatment. In patients treated with these drugs a rise in hepatic and muscular enzyme indicate membrane damage (38). Renal tubular cells energy consumption is high because of high rate of active transportation of molecules between urine and blood. Thus, these cells can be hurt by low levels of CoQ10. Cell energy depletion promotes oxidation, damage and side effects.

Statins also can induce proteinuria. It is plausible that statins by interfering GTP binding protein impair receptor mediated endocytosis so impair protein absorption by proximal tubular cells and induce tubular proteinuria. That is consisted of proteins with lower molecular weight than albumin. Tubular cells reabsorb low molecular weight proteins normally filtered through intact glomerular barrier, by inhibiting of HMG CoA inhibitor, geranylgeranyl phosphate depleting and protein absorption through endocytosis stops (39). The inhibitory effect in a concentration dependent manner can be prevented by adding of mevalonate (40). Increased filtration of plasma proteins leads to upregulation of genes encoding inflammatory substrate leading inflammation in renal tissue induce fibrogenesis and scarring. Increase filtration of plasma proteins induce re-absorptive stress in proximal tubular epithelial cells. Almost all studies about statins agree about statin induced proteinuria do not have adverse effects on nephrons. Statins do not increase glomerular protein filtration and do not induce inflammation in glomeruli.

Data indicate that increased protein trafficking may contribute to tubule-interstitial disease (41).

A large cohort study of over 2 million patients reported statin use was associated with 50% more increase in risk of acute renal failure. In another study, use of high dose of rosuvastatin compared with placebo was associated with 35% more in risk of doubling of serum creatinine (24).

Statins induce apoptosis via interference with actin cytoskeleton. Actin disruption may activate DNase which is known to be responsible for internucleosomal DNA fragmentation in apoptosis of murine proximal tubular cells (35-41).

Statins can prevent drug induced nephrotoxicity

Many drugs have nephrotoxic effects. Mechanisms for renal cell injury are different and can be more than one pattern for each drug. The nephrotoxicity of gentamicin (GM) is through different mechanisms. It generates reactive oxygen species metabolite which cause cellular injury. In addition to oxidative stress, NF-κB is involved in nephrotoxicity caused by GM (42). Animal models show that the increase in serum creatinine and blood urea nitrogen (BUN) level induced by GM can be prevented by statins. Data suggest that statins have anti-inflammatory and anti-oxidant effects as well as NF-κB inhibitory properties. Additionally, selective uptake and accumulation of aminoglycosides into renal proximal tubular cells plays a key role in development of toxicity. Receptor mediated endocytosis requires GTP binding proteins which in turn are dependent upon C-terminal post-translational prenylation of G-proteins. Highly potent statins have been shown to inhibit proximal tubular uptake of molecules by inhibition of receptor mediated endocytosis (42).

Vancomycin is a glycopeptide antibiotic, used for treating gram positive infections, is associated with nephrotoxicity by oxidative effects on proximal tubular cells and by reducing antioxidant activity. It increases the production of reactive oxygen species and oxidative stress and induces tubular necrosis. Antioxidant activity of atorvastatin results in reduction of intracellular reactive oxygen species levels. It acts on the kidney as free radical scavenger and inhibits mitogen activated protein kinase and NF-κB signaling pathways which are activated by reactive oxygen species and prevent tubular cell apoptosis (43).

Statins also can attenuate the tubular and glomerular changes induced by other agents like cisplatin and intravenous contrast. Cisplatin is one of widely used cytotoxic agents in treatment of neoplasms. The nephrotoxicity by cisplatin is due to the release of free radicals. It induces sever degeneration in glomeruli, proximal and distal tubule resulting in elevation of serum urea and creatinine. Statins improve renal tissue damage induced by cisplatin in different animal models. They reverse oxidant-antioxidant imbalance and have good hydroxyl radical scaveng-

ing activity (44).

Recent investigations suggest that statin therapy is associated with lower incidence of contrast induced nephrotoxicity. Although the exact mechanism of contrast induced nephrotoxicity is not known. However, oxidative injury, vasoconstriction injury from chemokines, tubular obstruction, mitochondrial injury and plasma membrane toxicity have been implicated (45).

To find the paradoxical impacts of atorvastatin on kidney tubular cells, we recently conducted an experimental investigation on 30 male Wistar rats which were designated into six equal groups for a 7-day period of intraperitoneal injections of gentamicin as a nephrotoxic agent and atorvastatin. In this study, group 1 received gentamicin, 80 mg/kg, while group 2 received phosphate buffer as the vehicle of atorvastatin. Additionally, rats in groups 3, 4, and 5 received gentamicin, 80 mg/kg/day, and then, after one hour interval, atorvastatin was injected intraperitoneally for 7 days as follow; group three, 10 mg/kg/day, group 4, 50 mg/kg/day and group 5, 150 mg/kg/day. Rats in group 6 received only 150 mg of atorvastatin. On the 8 day, blood samples were obtained for evaluation of creatinine (Cr) and BUN levels, and the animals' kidneys were removed for histopathological examinations. Morphological injuries to the tubular cells in groups 3 and 4 were less than those in groups 1 and 5. Injuries to the kidney tubular cells in the rats of group 5 (gentamicin + atorvastatin, 150 mg/kg/d) and in group 6 (atorvastatin 150 mg/kg/day alone) were more extensive than those in group 1. In this study, we concluded, the none-dose-dependent effect of atorvastatin to induce kidney tubular cell protection. Moreover, kidney tubular toxicity of atorvastatin in higher dose suggests that administration of low-dose atorvastatin in critical conditions will be associated with kidney tubular cell protection (46).

While, retrospective data suggests that high-potency statin therapy may increase the risk of acute renal damage, we intended to investigate the effect of the various doses of atorvastatin on kidney tubular cells, we conducted another experimental study. Our investigation was designed to test the kidney tubular cell effect of various doses of atorvastatin to find the possible aggravation of kidney function or morphology of the kidney. In this preclinical study 24 male Wistar rats were designated into four equal groups and treated as follows: Control group which received phosphate buffer as the vehicle of atorvastatin for 7 days. Groups 1, 2 and 2 received atorvastatin at a doses of 10, 50 and 150 mg/kg/day for 7 days, then on the 8 day, all rats were anesthetized using ketamine and the blood samples were gathered for test serum Cr and BUN levels and then all rats were sacrificed. The rats' kidneys were dissected out and histopathological examinations were conducted. This study showed that mean (±SD) of scores of damage to kidney tubular cells in control group was 4.2 ± 2.2 and in groups 1, 2 and 3 were 6.44 ± 4.9, 15.4 ± 8.5 and 25.8 ± 12.7 respectively. In group 3, which receive 150 mg/kg/day of atorvastatin had significant kidney injury in comparison to control group ($P < 0.001$). There was no significant difference of kidney damage score between control group with groups of 1 and 2. In this study, we found, atorvastatin with a dose of 150 mg/kg/day for 7 days had renal toxicity for rats. Whereas lower doses at 10 mg/kg/day or 50 mg/kg/day for 7 days was not accompanied by kidney damage. Hence, our findings revealed further attention to the administration of higher doses of atorvastatin in clinical situations (47).

Conclusion

Statins are employed in the treatment of hyperlipidemia. Their main mechanism of action is inhibition of HMG-reductase, however, they have various other effects independent of their cholesterol lowering mechanism. These include anti-inflammatory and anti-oxidant properties. Statins can diminish acute phase reactant. They inhibit vascular micro-inflammation, enhancing endothelial cell function, inhibiting proliferation of vascular smooth muscle, reducing platelet activation and aggregation and increasing atherosclerotic plaque stability. Many of these effects are postulated to arise from disruption of small G-proteins. This is not clear whether statins are nephrotoxic or nephroprotective. There is not enough data about their effects on nephrons. Cardiologists and internists use statins widely in many conditions but there is evidence against their safety. Further studies are necessary to determine the biological mechanism of kidney injury in statin users.

Authors' contribution

ZH and AB; data gathering, data interpretation, and manuscript preparation. MRK edited the final paper. All read and confirmed the final version.

Conflicts of interest

The authors 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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