Beyond the Lipid-lowering Effects Of Statins: Renal Effects

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ABSTRACT

Nowadays statins, 3-hydroxy-3-methylglutaryl Co A (HMG CoA) reductase enzyme inhibitors, are used in the treatment of hyperlipidemia. Statins have been shown to reduce cardiovascular mortality and morbidity in both coronary artery disease and peripheral arterial disease. Besides their lipid lowering effects, statins have pleiotropic effects such as improvement of endothelial dysfunction, atherosclerotic plaques stabilization, oxidative stress inhibition, anti-inflammatory and anti-thrombogenic effects. Some clinical trials have been revealed that statin therapy improved renal function; on the contrary it had been shown no beneficial effects in many studies. In this review, we aimed to evaluate the effects of statins on renal function.

Keywords: Statin, chronic renal disease, acute renal disease, contrast induced nephropathy

Statinlerin Lipit Düşürücü Etkilerinin Ötesi: Renal Etkileri

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ÖZET

Statin 3-hidroksi-3-metilglutaril CoA (HMG CoA) redüktaz enzim inhibitörü olarak günümüzde hiperlipidemi tedavisinde yaygın olarak kullanılmaktadır. Özellikle koroner arter hastalığı ve periferik arter hastalığında morbidite ve mortaliteyi azalttığı gösterilmiştir. Aynı zamanda aterosklerotik plak stabilizasyonu, endotel fonksiyonunu iyileştirme, oksidatif stress, inflamasyon ve tromboza yanıtın inhibisyonu gibi pleiotropic etkileri de bulunmaktadır. Statinin kanıtlanmış birçok yararlı etkisinin olmasının yanında, özellikle böbrek fonksiyonları üzerine etkisiyla ilgili çalışmalarda çelişkili sonuçlar bulunmaktadır. Bazı klinik çalışmalarda statinin böbrek fonksiyonları üzerine faydalı olduğu saptanmışken, birçok çalışmada da faydalı etkisinin olmadığı gösterilmiştir. Biz bu derlemede statin ile akut, kronik ve kontrasta bağlı nefropati ilişkilerini araştıran çalışmaları inceleyerek, statinin böbrek fonksiyonları üzerine etkisini değerlendirmeye çalıştık.

Anahtar Kelimeler: Statin, kronik böbrek yetersizliği, akut böbrek yetersizliği, kontrast nefropati

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Summary:

Nowadays statins, 3-hydroxy-3-methylglutaryl Co A (HMG CoA) reductase enzyme inhibitors, are used in the treatment of hyperlipidemia. Statins have been shown to reduce cardiovascular mortality and morbidity in both coronary artery disease and peripheral arterial disease. Besides their lipid lowering effects, statins have pleiotropic effects such as improvement of endothelial dysfunction, atherosclerotic plaques stabilization, oxidative stress inhibition, anti-inflammatory and anti-thrombogenic effects. Some clinical trials have been revealed that statin therapy improved renal function; on the contrary it had been shown no beneficial effects in many studies. In this review, we aimed to evaluate the effects of statins on renal function.

Introduction

In many randomized controlled trials significant beneficial effects of statins in cardiovascular disease have been shown as well as the various beneficial effects on other organ systems were reviled [1,2]. It is well known that statins inhibit of 3-hydroxy-3-methylglutaryl Co A (HMG CoA) reductase enzyme and show decreasing effect on cholesterol synthesis [3]. Beyond cholesterol-lowering effect of statins, there are other effects which are known as pleiotropic effects. These effects are explained by suppression of various molecules in cholesterol biosynthesis pathways. In addition to this, their properties are thought to arise by inhibiting the synthesis of isoprenoids intermediator [4]. These intermediators appear to play key roles on posttranslational modification of proteins to various intracellular, cell growth, and in signal transduction [5].

There is not a clear mechanism to explain of renoprotective effects of statins, but different pathophysiological mechanisms have been proposed. It was shown in a study, the decline of renal function may have been related with dyslipidemia. Statins reduce hypertension related renal damage and proteinuria, independently of cholesterol or blood pressure values in a experimental study [6]. Some studies have demonstrated the role of lipids decrease of renal function with glomerulosclerosis [7,8]. Statins have a protective effect on renal function by reducing lipid related

glomerulosclerosis [9]. Another mechanism the early increase in creatinine clearance is related to an effect of statin treatment on endothelial related vasodilatation by improving endothelial function, leading to increased renal perfusion [6].

Pleitropic effects of statins:

Statins are used primarily for lipid lowering effects in cardiovascular diseases. At the same time, there are pleiotropic effects of statins (Table 1) such as corrective endothelial function, stabilizing atherosclerotic plaques and inhibiting of oxidative stress, inflammation and thrombogenic responses [10].

One of the important features of statins is the anti-inflammatory effect that its pathophysiology is unknown but are tried to explain by several mechanisms. Some of these mechanisms are that statins reduce inflammatory responses by binding to specific regulatory regions such as β2 integrin and leukocyte function antigen-1 [11] and connected to the statin treatment proinflemmatuv cytokines (IL-1β and TNF-α) and the C-reactive protein (hs-CRP) which is produced in response to proinflammatory cytokines is decreasing [12,13].

Immunomodulatory effects of statins bring about ways that interferon-δ-induced expressions of MHC Class II decrease, increase the inhibition of leukocyte function antigen-1, decrease T cell activation and decrease activation of monocytes[14-16]. Also studies so far have shown that by several mechanisms statins inhibit the formation of oxygen free radicals and reduce oxidative stress [17].

Statins show the healing effects of endothelial function by increasing nitric oxide (NO) release and reducing endothelin-1 synthesis [18]. Also, it is reported that statins accelerate endothelialization by increasing the number of circulating endothelial progenitor cells, increasing the residence time in circulation and increasing movement of endothelial progenitor cells from bone marrow [19]. Another possible mechanism of statins is the positive antioxidant effect on endothelial function [20].

Statins increase angiogenesis. But are also known to create inhibitory action on angiogenesis in high doses of these drugs. Additionally, statins cause significant reduction in thrombotic events including major cerebral ischemia and stroke risk with increased fibrinolytic extracellular activity; decrease expression of tissue factor and reduce platelet activation [21,22].

Beyond their lipid-lowering effects of statins are also known to lead to down-regulation in the angiotensin receptors, decrease endothelin synthesis and cause vasodilation. Statins are also known to correct the endothelial dysfunction by rapidly increasing the nitric oxide level. Statins are known to have a rapid onset of anti-oxidant efficacy after the initiation of treatment and reduce inflammation by inhibiting the synthesis of the pro-inflammatory mediators. They decrease the reactive oxygen radicals and may be beneficial in nephropathy. Given all these physiological effects of statins may have beneficial effects in preventing nephropathy [23].

Effects of statins in normal renal function:

It has been shown in studies that there is a protective effect of statins on renal function not only in patients with kidney disease but also in individuals with normal renal function. In the study by *Greek Atorvastatin and Coronary Heart Evaluation* (GREACE), patients with coronary artery disease and normal creatinine levels found that atorvastatin use significantly increases creatinine clearance compared to untreated dyslipidaemia group. In this study, patients with dyslipidemia and coronary heart disease (CHD) who have normal baseline renal function show a decline in creatinine clearance over time. Long term statin treatment significantly increases creatinine clearance. This beneficial effects are related by improve endothelial related vasodilation and reduce lipid related glomerulosclerosis [6].

In the followıng studies, it was revealed that statins have no protective effects on renal function: Baigent C. et al on simvastatin[24], Asselberg FW. et al on provastatinin [25], Lemas PA. et al on fluvastatin [26] , and Ridker PM. et al. on rosuvastatin (secondary analysıs of the JUPITER study)[27]. Also, Atthobari J. et al, using data from the Prevention of Renal and Vascular End-stage

Disease Intervention trial (PREVEND-IT) and the PREVEND, have shown that pravastatin has no effect on albuminuria, and GFR [28] . Additionally, Collins R. et al, found negative effects from simvastatin on renal function in theır study of simvastatin's effects on heart protection [29].

However, it should be pointed out that the studies done to date have not been sufficient to reach a definite conclusion because of 1: homogenization of patients has not been maintained in these studies and 2: the results obtained in different studies have yet to be analyzed retrospectively.

There is as yet no full clarification of the renal protective effects of statins, as a number of different factors are involved in the development of nephropathy and different pathophysiological mechanisms coexist.

Effects of statins in chronic renal failure:

Chronic renal disease (CKD) is associated with cardiovascular risk factors. The prevalence of dyslipidemia in patients with CKD are more than the general population and is associated with the deterioration of renal function [30]. Albuminuria is one of the most important early indicators of renal damage and is an indicator of endothelial dysfunction [31] . It is clear that progress in proteinuria and permanent renal damage is corrected by early treatment of albuminuria patients [32]. There are numerous studies that examine the relationship between albuminuria and use of statin [30,33-35] .

Studies by Inoue T. et.al showed the antioxidant effect of fluvastatin to reduce urinary albumin excretion [30]. Various studies have shown that statins corrects albuminuria and provides renoprotection by multiple mechanisms such as increased NO release, corrected endothelial function, reduced oxidative stress, and protected from oxidative damage and the effect of lipid-lowering [26,36]. Proteinuria is one of the indicators of renal disease. When proteinuria increases, chronic kidney damage increases and more rapid decline in GFR is observed [37]. Additionally, when proteinuria decreases, the progression of CKD is shown to slow down [38]. In the Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease-I

(PLANET-I) and PLANET-II studies, the effect on renal function and urinary protein excretion of atorvastatin 80 mg and rosuvastatin 10 and 40 mg was evaluated. In the PLANET-I it was shown that while atorvastatin significantly reduces proteinuria, rosuvastatin showed no significant effect on proteinuria. In the PLANET-II it was also shown that atorvastatin significantly reduces proteinuria [37] . At the same time Sandhu S. et al in a meta-analysis of 39,704 participants, the treatment of cholesterol-lowering with different statins reduced the effect of proteinuria and protected kidney function was shown [39]. An other meta-analysis found a significant reduction in 24 hour urinary protein excretion (g/24 h) in chronic kidney disease (pre-dialysis) patients receiving different statins compared with placebo [40]. In the light of these results, we have concluded that due to the effects of statins reducing proteinuria may show a protective effect on kidney function.

Studies of patients with chronic renal disease have been shown to increase evidence of oxidative stress and inflammation compared to healthy subjects [41]. Statins anti-oxidant and anti-inflammatory effect can contribute to improvement in renal function. In a study by Inoue T. et al, it was shown that fluvastatin decreases glomerular and tubular damage by anti-oxidant effect [30].

Dyslipidemia may cause deterioration in renal function with changes to vascular structures as well as direct damage glomeruli and tubulointersititial areas [42] . Although the underlying pathophysiological mechanism is not fully understood, there ıs increased data showıng that lipid-induced oxidative stress on the glomeruli and tubulointersititial areas could contribute to the damages [38,43]. Furthermore it is also shown in animal studies that lipid accumulation occurs in the glomerulus and proximal tubules; intracellular lipid accumulation causes renal injury; hypercholesterolemia and hypertriglyceridemia are associated with severe podocyte injury which secondarily leads to mesangial sclerosis. The renoprotective effects of statins seem to provide both lipid-lowering and pleiotropic effects.

The effects of statins on creatinine and GFR were also examined by the studies. The results of 27 randomized trials, (a total of 39,704 cases), were shown to inhibit a reduction (approximately 1.2 ml/min) in renal dysfunctions for each year mentioned [36].

Available data from post-hoc analyses of statin trials provide evidence for the beneficial effects of statin therapy on cardıovascular dısease outcomes in patients with stages 2 and 3 chronic kidney disease. The Pravastatin Pooling Project (PPP) included 19 737 subjects with a median follow-up of 64 months. 191 The benefit was most marked in subjects with both chronic kidney disease and diabetes. Notably there was also a significant reduction in the risk of all-cause mortality [(44)].

Some important studies evaluating the effects of statins on kidneys are summarized in Table 3.

Effects of statins in acute renal failure:

Although studies have shown that statin lead to acute renal failure, it can have a preventive effect on the renal function if it is used post-operative and in intravenous administration of contrast agents. The study by Dormuth CR. et al showed that high-potency statins (at least 10 mg rosuvastatin, at least 20 mg of atorvastatin, and at least 40 mg of simvastatin) more than low-potency statins caused acute kidney damage [(43)]. In the study by Corrao G. et al, within 6 months after the start of treatment, administration of high-potency statins (at least 10 mg rosuvastatin, at least 20 mg of atorvastatin, and at least 40 mg of simvastatin) patients were shown to develop acute kidney damage more than patıents being given low-potency statins [(45)]. In a analysis rosuvastatin was significantly more likely to be associated with the composite end point of rhabdomyolysis, proteinuria, nephropathy, or renal failure [(46)] . Otherwise in the JUPITER study, compared to a placebo, there were no significant differences renal ınjury. Total numbers of reported serious adverse events were similar in the 20 mg rosuvastatin and placebo [(47)].

High-potency statins are more at risk of developing rhabdomyolysis. Therefore, the high-potency statin group has a greater risk of developing acute kidney damage. Another mechanism put forward shows that statins inhibit the production of co-enzyme Q-10. As shown in study by Corrao G. et al, 28 days of co-enzyme Q use improves renal function [(45)].

Although studies have shown the relationship between high-potency statins and acute kidney injury, there has been no evidence that high-potency statins are implicated in the onset of chronic kidney injury. When the clear benefits of statins are considered, a low dose should be used where possible to avoid renal injury which may develop in the early stage and in cases where a high dose is necessary, there must be close monitoring. Rosuvastatin, which has higher potency compared to other statins but entails a greater risk of renal damage [46] should not be the first preference. It can be recommended that a low dose is started with close monitoring or in patients with a high lipid level, the combination of statin+ezetimib can be considered

In the study by Molnar et al, statin use in major elective surgery have been decreased the incidence of acute renal failure. And, this decrease has been more noticeable of low-potency statins [48]. The use of statins after major abdominal, cardiac, thoracic and vascular surgery have been shown to decrease the development of acute kidney damage [43].

Protective effects of statins against contrast-induced nephropathy:

Contrast induced nephropathy (CIN) increased serum creatinine more than 0.5 mg/dl (or 25%) within 24-48 hours after administration of the contrast agent [23]. There are two main mechanisms in the pathogenesis of CIN: 1) the direct cytotoxic effect of the contrast agent and 2) renal medullary hypoxia resulting in vasoconstriction (Table 2). According to this hypothesis; various mediators are released after exposure to contrast agents. Developing vasoconstriction of renals, impairment of vasodilation and reductıon of medullary blood flow is due to the reduction of NO production and the effect of these mediators (angiotensin, vasopressin, endothelin). Additionally, free oxygen radicals, proinflammatory cytokines and dependent complement activity cause tubule damage. When protein precipitate exists, it accumulates in the tubules and they become obstructed [49].

The lipid lowering effect of statins also causes down regulation of angiotensin receptors in the endothelium and reduction in the synthesis of endothelin, causing vasodilatation [50]. Statins

rapidly increase NO levels and bioavailability and show an improvement on endothelial dysfunction [51]. In addition, statins prevent the occurrence of contrast nephropathy by anti-oxidant and anti-inflammatory effects [52]. An antioxidant effect is known to occur within 24 hours after initiation of statin therapy [53]. Statins inhibit the formation of pro-inflammatory cytokines and reduce inflammation [54]. In addition, statins reduce the production of reactive oxygen radicals [55]. The physiological effects of statins in achieving and maintaining adequate renal perfusion occur by enabling the formation of contrast nephropathy and is thought to exert inhibitory effects.

In animal studies, the effects of statins in preventing the development of CIN have been shown to improve endothelial function and prevent ischemic nephropathy by antioxidant effects [56]. Renal hypo-perfusion occurs when contrast exposure causes angiotensin receptor down regulation and decreased levels of endothelin-1[57]. The study by Al-Otaibi KE et al. proved that simvastatin sorts oxidative stress; pro-inflammatory myeloperoxidase and NO. Cao S. et al. found that atorvastatin prevents the development of oxidative stress which leads to the prevention of CIN [58,59]. Also, Han Y. et al have shown that rosuvastitin prevents the development of CIN in patients with diabetes and chronic kidney disease [59]. Current studies have provided additional data on atorvastatin. The study by Kaya A. et al proved that atorvastatin 80 mg and rosuvastatin 40 mg have a similar effect in preventing CIN [23] .

The implementation of high-dose statin before diagnostic catheterization has been shown to reduce the incidence of CIN and should be considered as an additional preventive measure in patients without contraindications [60].

Conclusion:

Many studies have shown the substantial benefits of statin therapy in patients with cardiovascular disease. Although it has been said in several investigations that rosuvastatin could cause renal damage, there are other studies and meta-analyses that have reported that statins did not increase renal damage and some, particularly atorvastatin, could even be beneficial in renal damage. We

believe that this assumption should be confirmed or refuted by randomized and prospective studies with large patient groups.

Conflıct of Interest:

None declared

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Table 1: Pleitropic effects of statins

1- Anti-inflammatory effect
2- Antioxidant effect
3- Inhibiting of thrombogenic responses
4- Immunomodulatory effects
5- Healing effects of endothelial function
6- Stabilizing atherosclerotic plaques

Table 2: Mechanisms in the pathogenesis of contrast-induced nephropathy

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1) The direct cytotoxic effect of the contrast agent
2) Renal medullary hypoxia resulting in vasoconstriction:
-***Impairment of vasodilation and reductıon of medullary blood flow***: The reduction of NO production and the effect of angiotensin, vasopressin, endothelin
-***Tubule damage***: Free oxygen radicals, proinflammatory cytokines and dependent complement activity
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Table 3. The effects of statins on the kidneys

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Study	Intervention (statin), Dose (mg/day)	Follow up(month)	Patient population	Outcomes	Overview of renal outcomes
GREACE - Subgroup analysis [19]	Atorvastatin10–80 mg / day or usual medical care	36	1,600 patients with dyslipidemia and CAD	Rate of kidney function decline	CrCl had a 12% increase in atorvastatin group (p<0.001) CrCl had a 5.2% decrease in patients not treated with statins (p<0.001) CrCl had a 4.9% increase in the usual care group on various statins
Baigent C - Subgroup analysis [20]	Patients were randomly assigned to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo.	48-108	Randomised double-blind trial included 9270 patients with chronic kidney disease (3023 on dialysis and 6247 not) with no known history of myocardial infarction or coronary revascularisation.	The key prespecified outcome was first major atherosclerotic event.	Statins have no protective effects on renal function
Asselbergs FW – Subgroup analysis [21]	Pravastatin 40 mg/daily	48	864 patient were randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo	Primary end point was cardiovascular mortality and hospitalization for cardiovascular morbidity	Pravastatin did not reduce urinary albumin excretion, and subjects treated with pravastatin showed a 13% lower incidence of the primary end point than subjects in the placebo group (0.87 [0.49 to 1.57], P=0.649, log-rank).
Lemas PA [22]	Fluvastatin 80 mg/daily	36-48	Complete data for creatinine clearance calculation were available for 1,558	Patients were randomized to fluvastatin or placebo after	The benefit of fluvastatin was unrelated to any effect on renal

			patients	successful completion of a first PCR.	function.
JUPITER-secondary analysis [23]	Rosuvastatin 20 mg/daily	Median follow-up was 22.8 month	among those with moderate chronic kidney disease at study entry (n = 3,267) with those with baseline eGFR >or=60 ml/min/1.73 m(2) (n = 14,528).	Performed a secondary analysis comparing cardiovascular and mortality outcomes	Median eGFR at 12 months was marginally improved among those allocated to rosuvastatin as compared with placebo.
PREVEN- IT [24]	Pravastatin 40 mg/daily	48	consisted of 864 participants and 839 survivors	the primary end point determined by the combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity was registered in several national databases and electronic hospital systems.	Subjects originally assigned to pravastatin had no overall risk reduction in the primary end point (P = .99).
Fluvastatin Renal Evaluation Trial (FRET)[26]	Fluvastatin 10 mg/daily, 20 mg/daily or 30 mg/daily	3	In 43 dyslipidemic patients with chronic kidney disease	-	Fluvastatin reduces both UAE and the urinary L-FABP level, and thus, has renoprotective effects, independent of its lipid lowering effects in dyslipidemic patients with chronic kidney disease
Sandhu et al.[32] Metaanalysis	Different statins	-	27 studies (21 with data for GFR), 39,704 participants	Change in GFR	Statins slowed the loss of GFR by a mean of 1.22 mL/min/year; 95% CI: 0.44–2.00 In studies of CVD, patients were slower than controls

					(0.93 mL/min/year, 95% CI: 0.10–1.76), with statistical significance
PLANET I [30] Randomized double blind, multicenter trial	Rosuvastatin 10 mg/day or rosuvastatin 40 mg/day versus atorvastatin 80 mg/day	12	325 patients with diabetes who had proteinuria and hypercholesterolemia	Change in urinary protein excretion (urinary protein/creatinine ratio)	Atorvastatin significantly reduced proteinuria by about 15% rosuvastatin had no significant effect on proteinuria Patients on atorvastatin lost 1 to 2 mL/min per 1.73 m2, those on rosuvastatin 10 mg/day lost 4 mL/min per 1.73 m2, and those on rosuvastatin 40 mg/day lost 8 mL/min per 1.73 m2 over 52 weeks
PLANET II[30] Randomized double blind, multicenter trial	Rosuvastatin 10 mg/day or rosuvastatin 40 mg/day versus atorvastatin 80 mg/day	12	220 patients without diabetes who had proteinuria and hypercholesterolemia	Change in urinary protein excretion (urinary protein/creatinine ratio)	Atorvastatin reduced proteinuria by 23.8% ( ) Significant decline in GFR with rosuvastatin No significant difference in the amount of lipid lowering was reported among the treatment groups
ALLIANCE[61] Post hoc subgroup analysis	Atorvastatin 10–80 mg/day or usual medical care	48	2,442 patients with dyslipidemia	Rate of kidney function decline	CrCl did not change in the atorvastatin group versus baseline CrCl declined by 4.4% in the usual care group (versus baseline

CARE[62] Post hoc subgroup analysis	Pravastatin 40 mg/day versus placebo	48	3,384 individuals of whom 690 (20.4%) had GFR < 60 mL/min per 1.73 m2	Change in GFR	The decline in the pravastatin group versus placebo was nonsignificant In patients with GFR < 40 mL/min per 1.73 m2, the rate of change in the pravastatin versus placebo group was 2.5 mL/min per 1.73 m2/year slower (95% CI: 1.4–3.6;)
SHARP [63]Randomized double blind, multicenter trial	Ezetimibe 10 mg/day + simvastatin 20 mg/day versus placebo versus simvastatin 20 mg/day	58.8	9,270 participants, including 3000 receiving hemodialysis	ESRD, major atherosclerotic events	17% reduction in major atherosclerotic events No difference of progression to ESRD

GREACE: Greek Atorvastatin and Coronary Heart Disease Evaluation; ALLIANCE: Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; CARE: Cholesterol And Recurrent Events; SHARP: Study of Heart and Renal Protection; PLANET: Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients; CAD: coronary artery disease; CrCl: creatinine clearance; GFR: glomerular filtration rate; ESRD: end-stage renal disease; CVD: cardiovascular disease; CKD: chronic kidney disease; PCR: percutaneous coronary revascularization;UAE: urinary albumin excretion, L-FABP: Urinary liver-type fatty acid binding protein; PREVEND IT: Long-term effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria:Ten years of follow-up of Prevention of Renal and Vascular End-stage Disease Intervention Trial.