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Review

Statins in chronic kidney disease and kidney transplantation

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ABSTRACT

HMG-CoA reductase inhibitors (statins) have been shown to improve cardiovascular (CV) outcomes in the general population as well as in patients with cardiovascular disease (CVD). Statins' beneficial effects have been attributed to both cholesterol-lowering and cholesterol-independent "pleiotropic" properties. By their pleiotropic effects statins have been shown to reduce inflammation, alleviate oxidative stress, modify the immunologic responses, improve endothelial function and suppress platelet aggregation. Patients with chronic kidney disease (CKD) exhibit an enormous increase in CVD rates even from early CKD stages. As considerable differences exist in dyslipidemia characteristics and the pathogenesis of CVD in CKD, statins' CV benefits in CKD patients (including those with a kidney graft) should not be considered unequivocal. Indeed, accumulating clinical evidence suggests that statins exert diverse effects on dialysis and non-dialysis CKD patients. Therefore, it seems that statins improve CV outcomes in non-dialysis patients whereas exert little (if any) benefit in the dialysis population. It has also been proposed that dyslipidemia might play a causative role or even accelerate renal injury. Moreover, ample experimental evidence suggests that statins ameliorate renal damage. However, a high quality randomized controlled trial (RCT) and metaanalyses do not support a beneficial role of statins in renal outcomes in terms of proteinuria reduction or retardation of glomerular filtration rate (GFR) decline.

Contents

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Introduction

The use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) is the mainstay of treatment for the primary and secondary prevention of cardiovascular disease (CVD) [1,2]. Statins' beneficial effects are partly due to their lipid-lowering properties. Indeed, it is now well established that statins also exert a variety of cholesterol-independent "pleiotropic" effects that apart from the cardiovascular system also confer benefits in a wide range of pathophysiological processes [3]. Patients with chronic kidney disease (CKD) exhibit high rates of CVD even from early stages of CKD and these rates increase with increasing CKD stages [4–6]. Several explanations have been proposed for this observation including the substantially different dyslipidemia characteristics found in CKD [7], the presence of non-traditional cardiovascular (CV) risk factors [8] and the unique pathomechanisms involved in the development of CVD in CKD [9]. This diverse etiology of CVD in CKD sets a challenge for statins in meaningfully affecting the course of CVD in CKD.

It has also been suggested that dyslipidemia might accelerate natural renal function decline and may also accelerate CKD progression [10–12], mainly by increasing the oxidative stress and inflammation in the renal microenvironment [13,14]. Indeed, redundant preclinical evidence suggests that hypercholesterolemia is implicated in the induction of renal damage [15,16], and that treatment with a statin delays CKD progression or even reverses renal injury in terms of laboratory (proteinuria and glomerular filtration rate (eGFR)) and pathological indices improvement [17–19]. By extrapolation of preclinical evidence to human CKD one would expect that statins preserve renal function in CKD patients.

In this review we summarize the characteristics of dyslipidemia in CKD and its role in the pathogenesis of CVD in CKD patients. We also discuss preclinical evidence of the potentially beneficial pleiotropic effects of statins in CVD and renal injury in the CKD setting. Finally, we analyze available clinical data on the effects of statins on both CV and renal outcomes in CKD and kidney transplant patients.

CKD – definition and classification

CKD is defined as a reduction in kidney function (glomerular filtration rate (GFR) <60 ml/min/1.73 m^2) or the presence of kidney damage (structural or functional abnormalities other than decreased glomerular filtration rate (GFR)) for three or more months [20]. Decreased kidney function denotes a decreased GFR whereas kidney damage denotes the presence of urinary sediment abnormalities, urinary albumin excretion >30 mg/d, pathologic abnormalities (detected by a renal biopsy or imaging studies) or renal transplant status. The estimation of GFR (eGFR) is performed using several available equations that are based on serum creatinine with the most popular one being the Modification of Diet in Renal Disease (MDRD). Based on these assumptions the National Kidney Foundation (NKF) Kidney Disease Outcomes Initiative (KDOQI) introduced in 2002 a 5-stage classification system [20] (Table 1). By this classification patients with end stage renal disease (ESRD) or on any dialysis mode enlist in stage V whereas non-dialysis CKD patients enlist in stages I–IV. Although this classification is still widely used (and thus we will refer to this one in this review) in order to improve the stratification of CKD progression and its major complications a novel 18-stages classification system has been recently developed. In this classification the cause of CKD, subdivision of stage 3 and albuminuria stage have been added [21].

Table 1
The five stages of CKD as defined by the National Kidney Foundation.

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or ↑GFR	≥90
2	Kidney damage with mildly ↓GFR	60–89
3	Moderately ↓GFR	30–59
4	Severely ↓GFR	15–29
5	Kidney failure	<15 or dialysis

From: National Kidney Foundation [20].

Dyslipidemia in CKD

In CKD a plethora of abnormalities (reviewed in [22]) is caused by a dysregulation of lipoprotein metabolism (Table 2). It should be noted that the lipid profile of CKD patients varies respective to CKD stage, the presence and amount of proteinuria and the dialysis modality [18]. Hypertriglyceridemia is present in 40–50 percent of CKD patients and is the hallmark of dyslipidemia in CKD. Moreover, in patients with stage 5 CKD total serum cholesterol and low-density lipoprotein (LDL) are normal or low, whereas high-density lipoprotein (HDL) is decreased [7,23]. However, non-dialysis patients might exhibit increased total cholesterol and LDL cholesterol whereas nephrotic and peritoneal dialysis patients usually exhibit a marked increase in total cholesterol and LDL due to protein losses in the urine or the peritoneal fluid effluent respectively [24,25]. These losses might result in the hepatic production of albumin and lipoproteins such as LDL and lipoprotein (a) (Lp(a)) (a modified highly atherogenic LDL) [26,27].

It is important to emphasize that CKD is also characterized by the accumulation of highly atherogenic lipoproteins and lipoprotein fragments such as chylomicron remnants, intermediate-density lipoproteins (IDL), oxidized LDL, small dense-LDL (sd-LDL) and Lp(a) [28]. The atherogenic potential of most of these lipoproteins is further increased by their oxidization. Moreover, LDL also undergoes protein carbamylation under uremic conditions. Carbamylated LDL possesses increased atherogenic properties by probably inducing smooth muscle cell proliferation [29]. sd-LDL-the predominate LDL fraction in CKD [30] – penetrates easier the endothelial barrier and binds to intimal proteoglycans [31], thus being longer retained in the arterial wall, a process that renders it more susceptible to oxidization by reactive oxygen species [32,33]. The effect of statins on sd-LDL levels remains misty, with one study reporting a decrease in sd-LDL in peritoneal dialysis but not in hemodialysis patients after statin commencement [34].

In the general population, Lp(a) is a CVD risk factor and exhibits a continuous association with coronary heart disease (CHD) risk [35,36]. Its levels are increased in patients with cerebrovascular disease [37] or premature CHD [38]. Lp(a) is the result of the covalent binding of apolipoprotein(a) to apolipoprotein B through disulfide linkage [39] and its structure is similar to that of the thrombogenic factor plasminogen [40]. Moreover, Lp(a) renders LDL more susceptible to oxidization [41], facilitates monocyte attachment to vascular endothelial cells [42] and promotes foam cell formation thus accelerating atherosclerosis [43]. Plasma levels of Lp(a) have been reported to increase in the CKD setting [44] (Table 2) and Lp(a) is now considered a CV morbidity and mortality risk factor in hemodialysis patients [45,46].

As discussed below most studies evaluating the role of statins in cardio- and nephroprotection in CKD patients do not assess these lipoproteins and this might be an explanation for the frequently reported negative results.

Cardiovascular risk factors in CKD-pathophysiology of CVD in CKD

It is well established that CV risk increases progressively with increasing stages of CKD with mortality rates of 25–34 years old