Statins and the Diabetic Kidney

Emad A. El-Bassiouni¹, Eman Elabd²

¹Emeritus Professor, Pharmacology Department, Medical Research Institute, Alexandria University, Egypt
²Head of Radiation Sciences Department, Medical Research Institute, Alexandria University, Egypt

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Diabetes mellitus is one of the most common chronic diseases that affect people of all ages and races worldwide. Its prevalence is rapidly increasing, making it one of the most significant contributors to healthcare costs [1]. An important clinical feature of diabetes is its association with chronic tissue complications. Treatment in this case aims to either cure or delay the progress of tissue damage and preserve the function of the affected organ.

Diabetic nephropathy (DN) is a serious complication of diabetes mellitus, accounting for about 40% of end-stage renal disease (ESRD). It is responsible for significant morbidity and mortality, both directly by causing ESRD and indirectly by increasing cardiovascular risk [2]. The pathogenesis of DN appears to be multifactorial with dyslipidemia as a comorbidity, which may influence the development and progression of damage in the diabetic kidney [3]. Results from interventional studies revealed the possibility that antihyperlipidemic agents, such as statins, have a better effect on diabetic nephropathy through improvement of albuminuria and slowing down loss of renal function [4]. Current evidence points toward the need to prescribe statins in type-2 DM before a major decline in kidney function occurs. Statins have also been used for preventing and treating cardiovascular and cerebrovascular diseases, with relatively low incidence of adverse side effects as compared with other lipid-lowering drugs [5].

Although all statins share a common mechanism of action, they differ in terms of their chemical structures, pharmacokinetic profiles, and lipid-modifying efficacy. The chemical structures of statins govern their water solubility, which in turn influences their pharmacokinetic behaviour [6], where atorvastatin, fluvastatin, lovastatin and simvastatin are relatively lipophilic compounds, while pravastatin and rosuvastatin are more hydrophilic [7]. These differences are reflected in their relative efficacy and possibly in their parenchymal or muscular toxicities. The impact of the antagonism of statins on a crucial step of intermediary metabolism leads to a reduction of cholesterol biosynthesis as well as to additional pleiotropic effects [8]. Pleiotropic mechanisms of statins, including actions on cell proliferation/apoptosis and oxidative stress may exert beneficial effects independent of their lipid-modifying properties [9]. Although several studies have shown that statins suppress the progression of DN, few reports have directly compared the renoprotective effects among different statins [10-12]. On the other hand, administration of statins may have adverse side-effects, including myopathy [13], renal toxicity [14], and incident diabetes [15]. However, the cardiovascular benefits of statins outweigh their increased risk of new-onset diabetes [16,17].

The use of pravastatin, fluvasstatin, rosuvastatin, and pitavastatin may be preferred when concurrent therapy with a strong inhibitor of the liver isoenzyme cytochrome P450 3A4 (CYP3A4) cannot be avoided. Such inhibitors include clarithromycin, telithromycin, nefazodone, ketoconazole, and many antiviral drugs. Atorvastatin, lovastatin, and simvastatin may also be substrates for P-glycoprotein (P-gp) which functions as transmembrane efflux pump; therefore, drugs that inhibit P-gp, including cyclosporine and diltiazem, may increase levels of these statins [18,19]. Although most other lipid lowering agents can be used safely with statins in combination therapy in CKD patients, the fibrates (for example fenofibrate and gemfibrozil) require both adjustment in dose and careful monitoring because possible increased rise in rhabdomyolysis when combined with simvastatin or atorvastatin.

The inflammatory response has a pivotal role in the
pathophysiology of diabetic nephropathy, where pro-inflammatory mediators such as interleukin1-β (IL-1β) and tumour necrosis factor-α (TNF-α) are strongly correlated with the onset and progress of renal damage in diabetic subjects [20,21]. Thus, controlling excessive inflammation has therapeutic potential of inhibiting progressive kidney fibrosis. The role of IL-1β seems to be more specific than other cytokines in the inflammatory process and inhibitors of IL-1β are considered as promising therapeutic options to improve the renal outcome of patients with diabetic nephropathy [22].

In experimentally streptozotocin-induced diabetes in a rat model disturbances in the levels of inflammatory markers were observed. The mean level of IL-1β, was several times that of normal controls [23,24]. These high IL-1β levels were significantly attenuated, approximately, to the same levels, by treatment with either simvastatin or rosuvastatin suggesting their protective potential against diabetes-induced renal injury. Such results are in accordance with other studies, where both statins were found to exhibit similar anti-inflammatory activity within in vitro models of neuroinflammation [25,26]. The increase in the pro-inflammatory IL-1β was accompanied by a significant increase in renal levels of IL-10, which is a potent anti-inflammatory agent by virtue of its ability to suppress genes for pro-inflammatory cytokines [27]. It is probable that such increase represented a defense mechanism against the high levels of the pro-inflammatory mediators, in the diabetic kidney. The biological activities of IL-10, in modulating inflammation, have been proposed to be caused, in part, by down regulation of pro-inflammatory cytokines and their receptors and upregulation of cytokine inhibitors [28]. By shifting the pro/anti-inflammatory balance towards the normal state, statins promote the restoration of homeostasis through the resolution of inflammation [29].

An increase in the local production of renal prostaglandins (PGs) has been observed in clinical and experimental diabetic nephropathy and PG synthesis is augmented in the glomeruli of streptozotocin-induced diabetic rats [23,24,30]. The overproduction of PGE2 plays an important role in the end organ damage in diabetes [31]. It was suggested that IL-1β preferentially stimulates the production of prostaglandins and many of its biological activities are probably due to such increase in PGE2 production [27]. The decrease of IL-1β level, following treatment with simvastatin and rosuvastatin, was accompanied by a similar fall in PGE2 levels with no significant difference between the two drugs [23]. Similarly, pretreatment with either of the two drugs was able to significantly reduce lipopolysaccharide (LPS)-induced PGE2 production in microglial-like cells [25]. Fibrosis, in particular, is a prominent pathological hallmark of many forms of chronic kidney disease and is considered to be a central contributing factor for its progression towards end-stage renal disease [32]. Transforming growth factor-β (TGF-β) has been implicated as a major regulatory cytokine in CKD, especially in fibrosis development. Reduced TGF-β signaling activity has been shown to be associated with improved renal outcomes in experimental animal studies [33]. Serum TGF-β levels, in STZ-induced diabetic rats, were significantly increased compared with normal control rats [23]. Transforming growth factor-β signaling pathway has been shown to play a critical role in regulation of the extracellular matrix (ECM) accumulation of the kidney to promote the renal glomerulosclerosis [34] and inflammation in diabetic rat model [35]. Its levels and signaling are enhanced in renal cells during the progression of diabetic nephropathy [36]. The effective decrease, of serum TGF-β by both simvastatin and rosuvastatin is indicative of their potential antifibrotic and hence renoprotective effects [23]. This may be a pointer for possible attenuation of the progression of kidney damage.

Oxidative stress has the ability to act as a trigger, modulator, and link within the complex web of pathological events that occur in DN. In this respect various molecular events underlie and connect the metabolism, inflammation, and the oxidation [37]. Increased levels of inflammatory cytokines, like TGF-β, increase intracellular ROS production in mesangial and tubular epithelial cells [38]. Furthermore, there is increasing evidence that ROS, inflammation and fibrosis promote each other and are part of a vicious connection leading to development and progression of CVD and kidney disease in diabetes [39].

In animal experiments, oxidative stress was clearly shown in the diabetic kidney, by significantly decreased levels of reduced glutathione (GSH) and reduced/oxidised (GSH/GSSG) glutathione ratio. On the other hand, there were substantial increases in the levels of GSSG and MDA. However, the level of total glutathione was not modified either by induction of diabetes or by treatment with statins. This may indicate that the synthesis of glutathione was not affected by these manipulations and the problem lies with the reduction of GSSG. These changes were shifted toward the non-diabetic value following treatment with statins [23].

Excessive reactive oxygen species (ROS) production, in diabetics, can accelerate oxidative damage to macromolecules, including lipids and proteins, as well as to DNA. 8-Hydroxydeoxyguanosine (8-OHdG) a ROS-induced modification of a purine residue in DNA, is a sensitive index of oxidative DNA damage [40]. Previous studies demonstrated that urinary levels of 8-OHdG were significantly elevated in several models of diabetic nephropathy [41,42], and they correlate significantly with the severity of tubulointerstitial lesions [33]. However, the role of serum 8-OHdG, in the pathogenesis of diabetic nephropathy, has not been identified but was clearly
demonstrated, as a significantly higher serum levels of 8-OHdG, were observed in diabetic over normal control rats, and were effectively decreased by treatment with either simvastatin or rosuvastatin [23].

The antioxidant effect of both simvastatin and rosuvastatin was documented in experimental diabetic nephropathy [33,43,44]. Rosuvastatin seems to possess a more significant antioxidant effect, as indicated by improved GSH/GSSG ratio. While rosuvastatin had a more beneficial effect on reduced GSH levels, the antioxidant effect of simvastatin was more pronounced on serum 8-OHdG levels. These findings confirmed the renoprotective effect of treatment with either statin through attenuating oxidative stress damage in renal tissues of diabetic rats [23]. The levels of serum cystatin C, a glomerular filtration marker [45], were significantly elevated in diabetic rats as compared to normal non-diabetic controls [23]. The rate of progression from moderate to severe reductions in GFR is often proportional to the extent of interstitial fibrosis and tubular atrophy. Therefore, elevated serum cystatin C would be a strong predictor of diabetic nephropathy progression [45]. In experimental diabetes, both simvastatin and rosuvastatin significantly reduced serum cystatin C levels [23]. In patients with diabetic nephropathy, rosuvastatin was reported to effectively decrease serum cystatin C levels, independent of blood pressure and lipid levels [46,47]. Several statins were reported to delay the progression of diabetic nephropathy as indicated by their significant lowering of Cyst-C [12].

Apoptosis is frequently observed histologically in DN [48,49], where it contributes to nephropathy development. Increased oxidative stress and increased levels of inflammatory cytokines may also enhance the apoptosis levels in DN [50]. When the cell detects an apoptotic stimulus, such as DNA damage or metabolic stress, the intrinsic apoptotic pathway is triggered and mitochondrial cytochrome c is released into the cytosol [51]. Attenuation of the high levels of this parameter is therefore expected to be an indicator of improvement in renal function and slow progression of kidney disease.

Slowing renal function decline is one of the main areas of focus in diabetic nephropathy research, and effective strategies are urgently needed to prevent diabetic kidney disease progression.

References


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