https://www.scientificarchives.com/journal/archives-of-pharmacology-and-therapeutics

Archives of Pharmacology and Therapeutics Commentary

# Statins and the Diabetic Kidney

**Emad A. El-Bassiouni[1], Eman Elabd[2*]**

[1]Emeritus Professor, Pharmacology Department, Medical Research Institute, Alexandria University, Egypt

[2]Head of Radiation Sciences Department, Medical Research Institute, Alexandria University, Egypt

[*]Correspondence should be addressed to Eman Elabd; Iman.ElAbd@alexu.edu.eg

**Received date:** January 08, 2021, **Accepted date:** May 03, 2021



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, fluvastatin, 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. nephazodone, ketoconazole, and many antiviral drugs. Atorvastatin, lovastatin, and simvastatin may also be substrates for P-glycoprotein (P-gp) which functions as trance-membrane 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 diabetes, 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

1. Lotfy M, Adeghate J, Kalasz H, Singh J, Adeghate E. Chronic Complications of Diabetes Mellitus: A Mini Review. Curr Diabetes Rev 2017;13:3-10.

2. Keri KC, Samji NS, Blumenthal S. Diabetic nephropathy: newer therapeutic perspectives. J Community Hosp Intern Med Perspect 2018; 8:200-207.

3. Philips AO, Steadman R. Diabetic nephropathy: their central role of renal proximal tubular cells in tubulointerstitial injury. Histol Histopathol 2002; 17:247-252.

4. Toyama T, Shimizu M, Furuichi K, Kaneko S, Wada T. Treatment and impact of dyslipidemia in diabetic nephropathy. Clin Exp Nephrol 2014;18:201-205.

5. Clark LT. Treating dyslipidemia with statins: the risk-benefit profile. Am Heart J. 2003;145:387-396.

6. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol 2005;19:117-125.

7. McTaggart F, Buckett L, Davidson R, Holdgate G, McCormick A, Schneck D. Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Am J Cardiol. 2001;87:28-32.

8. Sirtori CR. The pharmacology of statins. Pharmacol Res. 2014;88:3-11.

9. Haslinger-Löffler B. Multiple effects of HMG-CoA reductase inhibitors (statins) besides their lipid lowering function. Kidney Inter. 2008:74(5):553-555.

10. Shen X, Zhang Z, Zhang X, Zhao J, Zhou X, Xu Q, et al. Efficacy of statins in patients with diabetic nephropathy: a meta-analysis of randomized controlled trials. Lipids Health Dis 2016;15:1-11.

11. Han E, Kim G, Lee JY, Lee YH, Kim BS, Lee BW, et al. Comparison between atorvastatin and rosuvastatin in renal function decline among patients with diabetes. Endocrinol Metab (Seoul) 2017;32:274-280.

12. Takazakura A, Sakurai M, Bando Y, Misu H, Takeshita Y, Kita Y, et al. Renoprotective effects of atorvastatin compared with pravastatin on progression of early diabetic nephropathy. J Diabetes Investigation. 2015;6:346-353.

13. Ballantyne CM, Corsini A, Davidson MH, Holdaas H, Jacobson TA, Leitersdorf E, et al. Risk for myopathy with statin therapy in high-risk patients. Arch Intern Med. 2003;163:553-564.

14. Alsheikh-Ali AA, Ambrose MS, Kuvin JT, Karas RH. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. Circulation. 2005;111:3051-3057.

15. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study.

BMJ. 2013;346:1-11.

16. Wang KL, Liu CJ, Chao TF, Huang CM, Wu CH, Chen SJ, et al. Statins, risk of diabetes, and implications on outcomes in the general population. J Am Coll Cardiol. 2012;60:1231-1238.

17. Bell DS, DiNicolantonio JJ, O'Keefe JH. Is statin-induced diabetes clinically relevant? A comprehensive review of the literature. Diabetes Obes Metab. 2014;16:689-694.

18. Egom EE, Hafeez H. Biochemistry of Statins. Adv Clin Chem. 2016;73:127-68.

19. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors, Am J Cardiol. 2004;94:1140-46.

20. Elsherbiny NM, Al-Gayyar MMH. The role of IL-18 in type 1 diabetic nephropathy: The problem and future treatment. Cytokine. 2016;81:15-22.

21. Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovas Ther. 2012;30:49-59.

22. Moreno JA, Gomez-Guerrero C, Mas S, Sanz AB, Lorenzo O, Ruiz-Ortega M, et al. Targeting inflammation in diabetic nephropathy: a tale of hope. Expert Opin Investig Drugs. 2018;27:917-930.

23. Rfaat R, Eldeeb A, Bakir M, El-Abd E, El-Bassiouni E. Differential renoprotective actions of simvastatin and rosuvastatin in streptozotocin- induced diabetes in Sprague-Dawley rat. Arch Pharm Sci ASU. 2020;4:104-112.

24. Maraqa AD. Effect of atorvastatin on interleukins and prostaglandin E2 in the kidney of type 1 diabetic rats. Eur Cytokine Netw. 2016;27:97-101.

25. McFarland AJ, Davey AK, Anoopkumar-Dukie S. Statins reduce lipopolysaccharide-induced cytokine and inflammatory mediator release in an *in vitro* model of microglial-like cells. Mediators Inflamm. 2017;2017:1-10.

26. Kata D, Földesi I, Feher LZ, Hackler L Jr, Puskas LG, Gulya K. Rosuvastatin enhances anti-inflammatory and inhibits pro-inflammatory functions in cultured microglial cells. Neuroscience. 2016;314:47-63.

27. Dinarello CA. Proinflammatory cytokines. Chest. 2000;118:503-8.

28. Glocker EO, Kotlarz D, Klein C, Shah N, Grimmbacher B. IL-10 receptor defects in humans. Ann NY Acad Sci. 2011;1246:102-7.

29. de Gaetano M, McEvoy C, Andrews D, Cacace A, Hunter J, Godson BE. Specialized pro-resolving lipid mediators: Modulation of diabetes-associated cardio-, reno-, and retino-vascular complications. Front Pharmacol. 2018;9:1488.

30. Like AA, Rossini AA. Streptozotocin-induced pancreatic insulitis: New model of diabetes mellitus. Science. 1976;193:415-417.

31. DeRobertis FR, Craven PA. Eicosanoids in the pathogenesis of the functional and structural alterations of the kidney in diabetes. Am J Kidney Dis. 1993;22:727-35.

32. Rockey DC, Bell PD, Hill JA. Fibrosis – a common pathway to organ injury and failure. N Engl J Med. 2015;372:1138-49.

33. Huynh P, Chai Z. Transforming growth factor β (TGFβ) and related molecules in chronic kidney disease (CKD). Clin Sci (Lond). 2019;133(2):287-313.

34. Isaka Y, Fujiwara Y, Ueda N, Kaneda Y, Kamada T, Imai E. Glomerulosclerosis induced by in vivo transfection of transforming growth factor-beta or platelet-derived growth factor gene into the rat kidney. J Clin Invest. 1993;92:2597-2601.

35. Chang AS, Hathaway CK, Smithies O, Kakoki M. Transforming growth factor-beta1 and diabetic nephropathy. Am J Physiol Renal Physiol. 2016;310:F689-696.

36. Kato M, Natarajan R. MicroRNA circuits in transforming growth factor-β actions and diabetic nephropathy. Semin Nephrol. 2012;32:253-60.

37. Tiwari BK, Pandey KB, Abidi AB, Rizvi SI. Markers of oxidative stress during diabetes mellitus. J Biomark. 2013;2013:1-8.

38. Chuang LY, Guh JY, Liu SF, Hung MY, Liao TN, Chiang TA. Regulation of type II transforming-growth-factor-beta receptors by protein kinase C iota. Biochem J. 2003;375:385.

39. Jha JC, Ho F, Dan C, Jandeleit-Dahm K. A causal link between oxidative stress and inflammation in cardiovascular and renal complications of diabetes. Clin Sci (Lond). 2018;132:1811-1836.

40. Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Clin Chim Acta. 2004;339:1-9.

41. Kaida Y, Fukami K, Matsui T, Higashimoto Y, Nishino Y, Obara N, et al. DNA aptamer raised against AGEs blocks

the progression of experimental diabetic nephropathy. Diabetes 2013;62:3241-50.

42. Varatharajan R, Abdul Sattar MZ, Chung I, Abdulla MA, Kassim NM, Abdullah NA. Antioxidant and pro-oxidant effects of oil palm (Elaeis guineensis) leaves extract in experimental diabetic nephropathy: a duration-dependent outcome. BMC Complement Altern Med. 2013;13:242.

43. Hussein MM, Mahfouz MK. Effect of resveratrol and rosuvastatin on experimental diabetic nephropathy in rats. Biomed Pharmacother. 2016;82:685-92.

44. Al-Rasheed NM, Bassiouni YA, Hasan IH, Al-Amin MA, Al-Ajmi HN, Mahmoud AM. Simvastatin ameliorates diabetic nephropathy by attenuating oxidative stress and apoptosis in a rat model of streptozotocin-induced type 1 diabetes. Biomed Pharmacother. 2018;105:290-298

45. Satirapoj B. Tubulointerstitial biomarkers for diabetic nephropathy. J Diabetes Res. 2018;2018:2852398.

46. Abe M, Maruyama N, Okada K, Matsumoto S, Matsumoto K, Soma M. Effects of lipid-lowering therapy with rosuvastatin on kidney function and oxidative stress in patients with diabetic nephropathy. J Atheroscler Thromb. 2011;18:1018-1028.

47. Abe M, Maruyama N, Yoshida Y, Ito M, Okada K, Soma M. Efficacy analysis of the lipid-lowering and renoprotective effects of rosuvastatin in patients with chronic kidney disease. Endocr J. 2011; 58:663-674.

48. Susztak K, Raff AC, Schiffer M, Bottinger EP. Glucose-induced reactive oxygen species cause apoptosis of podocytes and podocyte depletion at the onset of diabetic nephropathy. Diabetes. 2006;55:225-233.

49. Verzola D, Gandolfo MT, Ferrario F, Rastaldi MP, Villaggio B, Gianiorio F, et al. Apoptosis in the kidneys of patients with type II diabetic nephropathy. Kidney International 2007;72:1262-1272.

50. Sha J, Sui B, Su X, Meng Q, Zhang C. Alteration of oxidative stress and inflammatory cytokines induces apoptosis in diabetic nephropathy. Mol. Med Rep. 2017;16:7715-7723.

51. Kluck, RM., Bossy-Wetzel E, Green DR, Newmeyer DD. The release of cytochrome c from mitochondria: a primary site for Bcl 2 regulation of apoptosis. Science 1997;275:1132-1136.