



ROLE OF TELMISARTAN IN DIABETIC NEPHROPATHY A NOVEL TREATMENT AVENUE

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Globally, the prevalence of diabetes mellitus is continuously escalating. The complications of chronic diabetes mellitus include retinopathy, neuropathy, nephropathy, cardiomyopathy, and vasculopathy. Diabetes mellitus is the leading cause of renal failure and approximately 20-30% of all diabetic subjects develop evidence of diabetic nephropathy manifesting from microalbuminuria to macroalbuminuria and renal failure. Nephropathy is one of the major complications of uncontrolled diabetes mellitus. The renal pathologic alterations of diabetic nephropathy are associated with glomerular basement membrane thickening, mesangial cell expansion, glomerulosclerosis, interstitial fibrosis, podocyte loss, and tubular atrophy. These renal alterations during diabetic nephropathy could result in albuminuria, a decrease in glomerular filtration rate (GFR) and an increase in serum creatinine and urea nitrogen levels¹. The renin-angiotensin system (RAS) plays a pivotal role in the pathogenesis of diabetic nephropathy². The activation of the renin-angiotensin system, especially the angiotensin II type-1 receptor (AT1R) pathway, has been demonstrated to play a detrimental role in the progression of diabetic nephropathy³. Even though the etiology of diabetic nephropathy is poorly understood, chronic hyperglycemia and hypertension are considered major risk factors for diabetic nephropathy¹. Although various hyperglycemia-elicited metabolic derangements such as the increased formation of advanced glycation end-products (AGEs), protein kinase C (PKC) activation, and enhanced production of reactive oxygen species (ROS) have been proposed to contribute to the characteristic histopathological changes associated with diabetic nephropathy². Diabetic nephropathy is characterized by glomerular and tubular basement membrane thickening, extracellular matrix (ECM) expansion, microvascular damage, and fibrotic changes in the tubule-interstitium. Hypertension further increases the risk for onset of kidney disease and progression and cardiovascular (CV) morbidity and mortality. Multiple factors contribute to increases in blood pressure and hypertension in patients with diabetes and nephropathy. The major causes of hypertension in both diabetes type I as well as type II include volume expansion owing to increased renal sodium reabsorption and peripheral vasoconstriction as a result of dysregulation of factors that regulate peripheral vascular resistance. Excess sodium retention, activation of the sympathetic nervous system (SNS) and RAAS, endothelial cell dysfunction (ECD), and increased oxidative stress leads to hypertension in diabetic nephropathy⁴. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II type 1 (AT1) receptor blockers (ARBs) are often employed to treat diabetic nephropathy. Although new strategies for treating nephropathy are req

uired as current approaches are insufficient since most of the diabetic patients continue to show progressive renal damage. New studies indicate the therapeutic potential of Peroxisome proliferator-activated receptors (PPAR) ligands in the treatment of patients with diabetic nephropathy^{5,6}. PPARs are ligand-activated transcription factors of nuclear hormone receptor superfamily, which comprises of three members such as PPAR α , PPAR β and PPAR γ/δ . PPAR α plays an important role in the oxidation of fatty acids. Studies suggest that hyperlipidemia is an independent risk factor involved in the development of diabetic nephropathy⁷⁻⁹. The elevated levels of lipids are associated with the progression of renal dysfunction¹⁰. The increase in circulating lipids induces glomerulosclerosis and tubule-interstitial injury by accelerating the generation of reactive oxygen species (ROS) and stimulating the overexpression of transforming growth factor β (TGF- β) in the glomeruli and tubule-interstitium. It was suggested that circulating lipids are entrapped by extracellular matrix molecules where they undergo the process of lipid peroxidation and generate ROS to induce renal dysfunction¹⁰. Further evidence revealed that diabetes may mediate renal injury by increasing the expression of sterol regulatory element-binding protein-1 (SREBP-1), which are responsible for increasing the synthesis of triglycerides and cholesterol in the kidney, that is associated with the upregulation of TGF- β , vascular endothelial growth factor (VEGF) and extracellular matrix proteins, resulting in glomerulosclerosis and tubule-interstitial fibrosis to provoke diabetic nephropathy^{11,12}. Hence, reducing the circulating lipids in diabetic patients may provide a new therapeutic option in managing diabetic nephropathy. The agent like PPAR agonists has been suggested as a novel therapeutic intervention to manage diabetic nephropathy¹³.

Moreover, adiponectin, an adipose tissue-derived secreted cytokine, has been found to have insulin-sensitizing, anti-inflammatory, and vasculoprotective actions through binding to its receptors, AdipoR1 and AdipoR2. These two adiponectin receptors have been previously shown to mediate the increase in AMPK activities, as well as fatty acid oxidation and glucose uptake by adiponectin. There is a growing body of evidence demonstrating the renoprotective functions of adiponectin and its receptors, which protects against the development of albuminuria³. Thiazolidinediones, ligands for PPAR, have been employed for the treatment of type 2 diabetes mellitus, however, they have been found to increase the risk of myocardial infarction and heart failure. However, telmisartan has been suggested to be devoid of these undesirable effects. Thus, telmisartan could be a novel therapeutic choice to treat co-existing diabetes mellitus and hypertension-associated

progression of diabetic nephropathy¹.

Telmisartan is a long-lasting, non-competitive/insurmountable, non-peptide ARB with the strongest receptor binding affinity having potent anti-hypertensive action. Telmisartan chemically is 2-(4-{{[4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl] methyl} phenyl} benzoic acid. It is orally active and possesses good oral absorption and tolerability. The oral clearance was associated with age and dose. The oral clearance was noted to be decreased with advanced age. The volume of distribution for the central compartment was noted to be related to age and dose, and the volume of distribution for the peripheral compartment was noted to be related to body weight and gender. The absolute bioavailability of telmisartan is dose-dependent, and food may slightly reduce its bioavailability. It is a lipophilic compound widely distributed to tissue and is highly bound to plasma proteins up to 99.5%. Telmisartan 1-O-acylglucuronide is the principal metabolite of telmisartan in humans. Biliary fecal excretion is a primary elimination route of telmisartan and its metabolite. Being an ARB, telmisartan reduces high blood pressure by antagonizing the aforementioned actions of angiotensin-II. Because of its long half-life, a once-daily dose of telmisartan has been found to be effective in minimizing the elevated blood pressure. Interestingly, telmisartan has the additional property of activating PPAR γ partially, which could make it a unique agent in preventing cardiovascular and renal complications. Telmisartan induces PPAR γ activity independently to its AT1 receptor blocking action. Patients with uncontrolled type 2 diabetes mellitus are prone to hypertension and persistent proteinuria ranging from microalbuminuria to macroalbuminuria. RAAS over activation plays a central role in the pathogenesis of diabetic nephropathy. Telmisartan has renoprotective effects that are mediated by its long-acting AT1 receptor blocking action and PPAR γ partial agonistic action, both of which could be beneficial in affording renal vasodilation, preventing renal inflammation, inhibiting renal oxidative stress and halting renal injury in patients with diabetic nephropathy.

The groundbreaking 'Diabetics Exposed to Telmisartan And enalapril (DETAIL)' trial addressed the long-term (5 years) effects of telmisartan versus enalapril on renoprotection in patients with hypertension and early type 2 diabetic nephropathy. This study suggested that telmisartan was not inferior to enalapril in reducing the decline in glomerular filtration rate. The long-term treatment with telmisartan afforded renoprotective efficacy comparable to enalapril in patients of early-type 2 diabetic nephropathies with greater tolerability¹⁴.

THE INCIPIENT TO OVERT:

Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study determined whether telmisartan could provide clinical benefits in normotensive patients with diabetes mellitus and diabetic nephropathy. The patients treated with telmisartan showed a reduction in the transition rate from microalbuminuria to overt nephropathy as compared to the placebo group. Moreover, a significant number of patients in the telmisartan group was reverted to normoalbuminuria. This clinical trial strongly suggested that telmisartan could prevent the progression of microalbuminuria, and also induce remission of albuminuria in normotensive Japanese patients with type 2 diabetes mellitus.

A comparison of telmisartan versus losartan in hypertensive type 2 Diabetic patients with Overt nephropathy (AMADEO) study compared the efficacy of telmisartan with losartan for reducing urinary protein-to-creatinine (UPC) ratio from baseline after 52 weeks of therapy in hypertensive patients

with type 2 diabetes mellitus and overt nephropathy. This clinical trial reported that telmisartan-based regimen in these patients showed a greater anti-proteinuric effect than a losartan-based regimen at similarly achieved blood pressure lowering effects^{1,15}. Further, the long term renoprotective potential of telmisartan with effects of "standard" (80 mg once daily) versus "high" (80 mg twice daily) doses of telmisartan in hypertensive patients without diabetes with biopsy-proven chronic proteinuric nephropathies was carried out by Aranda et al.¹⁶. The study was carried out in 78 patients. At the end of the study, blood pressure control did not differ between groups. In the group administered telmisartan, 80 mg once daily, serum creatinine level increased from 1.6 ± 0.6 to 2.7 ± 0.9 mg/dL (141 ± 52 to 239 ± 80 μ mol/L), and estimated creatinine clearance declined from 68 ± 30 to 50 ± 34 mL/min (1.13 ± 0.50 to 0.83 ± 0.57 mL/s), whereas in that administered 80 mg twice daily, serum creatinine (1.6 ± 0.7 to 1.6 ± 0.8 mg/dL [141 ± 62 to 141 ± 71 μ mol/L]) and estimated creatinine clearance values (67 ± 38 to 74 ± 38 mL/min [1.12 ± 0.63 to 1.23 ± 0.63 mL/s]) did not change during the study. The decrease in proteinuria was more pronounced ($P < 0.01$) in patients administered the high dose of telmisartan compared with those treated with the standard dose. It was concluded that long-term administration of high doses of telmisartan seems to improve the efficacy of the drug to decrease proteinuria and slow the progression to end-stage renal failure in nondiabetic hypertensive renal disease¹⁶.

Attenuation of the renal damage of diabetic nephropathy through the inhibition of AT1R-AdipoR1 heterodimerization and alleviation of downstream inflammatory responses and cell apoptosis by telmisartan has also been proposed to be another mechanism of renoprotective action of telmisartan³. Simultaneously, the Telmisartan versus Ramipril in renal Endothelium Dysfunction (TRENDY[®]) study showed that treatment with telmisartan or ramipril for 9 weeks significantly improved ($p < 0.001$) the response of the renal vasculature to nitric oxide, an indicator of basal nitric oxide activity and thereby of endothelial function of the renal vasculature. The magnitude of the effect of telmisartan appeared somewhat greater than that of ramipril¹⁷.

CONCLUSION

An essential component of the management of diabetic patients, especially those with other risk factors such as nephropathy, is the control of blood pressure to prevent cardiovascular events and premature death. Blood pressure targets are in most cases not being met and further complicating the disease state. Telmisartan seems to be an ideal drug for such a situation. Telmisartan possesses dual action of cardioprotection along with underlying long term renoprotective action by virtue of inhibiting AT II and induces PPAR γ activity. Thus, it seems logical to adopt telmisartan in therapy for the better management of diabetes complicated with hypertension and diabetic nephropathy.

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