Brief overview on pathogenesis and treatment of diabetic nephropathy

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ABSTRACT
Diabetic nephropathy is a serious condition affecting the patients worldwide suffering from diabetes mellitus. Diabetic nephropathy is the leading cause of Chronic Kidney Disease (CKD) in diabetic patients. About 25–40% of patients with type 1 diabetes and 5–40% of patients with type 2 diabetes are more predisposed to develop diabetic kidney disease. The current review focuses on the current statistical scenario of diabetic nephropathy, its causes and the current treatment which is available for the treatment of this serious condition.

Keywords: Diabetic nephropathy, Treatment of diabetic nephropathy, Angiotensin Receptor blockers, ACE Inhibitors.

INTRODUCTION
Increasing burden of Diabetes mellitus is giving a wakeup call to all health care professionals and common people as well. Increasing prevalence of diabetes in nearly all countries is observed mainly because of increase in sedentary lifestyle, reduced physical activity and overconsumption of junk food. From 2010 to 2030 the overall total predicted increase in numbers of patients with diabetes is 54%, at an annual growth of 2.2%. In India and China alone absolute global increase of 154 million people is anticipated to happen. In this way diabetes is continuing to be an international health burden [1]. Type 1 Diabetes Mellitus (DM) is characterized by an extensive and selective loss of pancreatic β cells and a state of absolute insulin deficiency. In type 2 DM approximately (TTDM) 50% reduction in β-cell mass is observed resulting in a profound defect in first-phase insulin secretion and insulin resistance. [2] Diabetic nephropathy is the leading cause of Chronic Kidney Disease (CKD) in diabetic patients. It is estimated that 25–40% of patients with type 1 diabetes and 5–40% of patients with type 2 diabetes are more predisposed to develop diabetic kidney disease. [3]

About one-third of patients with diabetic kidney disease progress to End-Stage Renal Disease (ESRD) and contributes in making TTDM as the single leading cause of ESRD in the Western world as incidence of nephropathy caused due to type 1 diabetes is declining. [4]
Patients with TTDM undergoing maintenance dialysis have a significant share in financial resources than those with non-diabetic ESRD. In addition, type 2 diabetic patients show poor performance during dialysis, leading to an excess mortality. Diabetic nephropathy is also known as Kimmelstiel-Wilson syndrome or nodular diabetic glomerulosclerosis or intercapillary glomerulonephritis. British physician Clifford Wilson and American physician Paul Kimmelstiel were the first to describe diabetic nephropathy in 1936. Diabetic nephropathy (DN) is a clinical syndrome characterized by the occurrence of persistent microalbuminuria confirmed on at least two occasions 3-6 months apart, permanent and irreversible decrease in glomerular filtration rate (GFR) and arterial hypertension with the concomitant type 1 or type 2 DM. All patients with TTDM should be screened annually for CKD, starting at diagnosis. Urinary albumin excretion should be evaluated from the albumin-to-creatinine ratio in a random spot sample. As some patients with TTDM can have advanced stage nephropathy in the absence of albuminuria, evaluation of urinary albumin excretion alone is not sufficient to assess the presence and severity of CKD therefore serum GFR estimated from serum creatinine is also taken into consideration to decide the level of CKD.

**Table No. - 1 Stages of Diabetic Nephropathy.**

<table>
<thead>
<tr>
<th>Level/Stage of GFR</th>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increased and optimal</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>60-89</td>
</tr>
<tr>
<td>3a</td>
<td>Mild to moderate</td>
<td>45-59</td>
</tr>
<tr>
<td>3b</td>
<td>Moderate to severe</td>
<td>30-44</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albuminuria Stage</th>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Optimal and high normal</td>
<td>&lt;30</td>
</tr>
<tr>
<td>2</td>
<td>High</td>
<td>30-299</td>
</tr>
<tr>
<td>3</td>
<td>Very High</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

Diabetic nephropathy has been didactically categorized into stages based on the values of urinary albumin excretion (UAE): micro albuminuria and macro albuminuria. Micro albuminuria is defined as urinary albumin excretion greater than 30 mg/24 h (20 mg/min), and less than or equal to 300 mg/24 h (200 mg/min) irrespective of how the urine is collected. The natural course of DN is characterized by a mean rate of decline in GFR of 10-15 mL/min/year ranging from 0 to 25 mL/min/year. After the phase of micro albuminuria, there is a continued increase in urinary protein excretion with declining glomerular-filtration rate. This results in the development of Albustix-positive proteinuria and is known as overt nephropathy or macro proteinuria. If left untreated, uraemia will supervene and require referral to end-stage renal-failure programmes such as dialysis or transplantation.

**The renin—angiotensin-aldosterone system in diabetes**

Renin—angiotensin-aldosterone system (RAAS) contributes significantly in pathogenesis of hypertension and diabetes related complications. The suppression of the systemic RAAS is mostly observed in DN. Renal haemodynamic factors are thought to be involved in the development and progression of diabetic kidney disease. Among these, high intraglomerular pressure and hyperfiltration coming under the influence of the RAAS system plays an important role. Angiotensin II formed by the cleavage of Angiotensin I is the main effector of the renin–angiotensin–aldosterone system (RAAS).
Angiotensin II leads to number of rapid effects including vasoconstriction (which reduces the capacity of the vascular tree), increased aldosterone secretion (which leads to salt retention), increased thirst and release of antidiuretic hormone (which leads to water conservation), increased myocardial contractility (which increases cardiac output), and increased activity of the sympathetic nervous system. As a consequence of a greater effect of angiotensin II on efferent than afferent arteriole, the glomerular capillary pressure increases. These changes in glomerular hemodynamics are responsible for injury to visceral epithelial and glomerular endothelial cells and mesangial expansion and these glomerular hemodynamic adaptations then finally consequent upon nephron loss ultimately proving to be maladaptive and results in damage to remaining nephrons, thereby establishing a vicious cycle of progressive nephron loss.

The shear stress and mechanical strain, resulting from altered glomerular hemodynamics and glomerular hypertension, cause the release of autocrine and/or paracrine cytokines and growth factors which in turn plays a role in genesis of glomerulosclerosis and interstitial fibrosis. The generation of advanced glycation proteins occurs as a result of chronic effects of glucose on tissues leading to tissue injury. AGE tends to accumulate in the kidney, particularly in people with diabetes or declining renal function, or both. Another glucose-dependent pathway, known as the polyol pathway has been shown to play role in the pathogenesis of diabetic nephropathy. Along with the range of renal functional abnormalities diabetic nephropathy involves pathological changes like extracellular matrix accumulation.

Glucose, AGE, and vasoactive hormones such as angiotensin II and endothelin stimulates the release of proinflammatory cytokine, transforming growth factor (TGF)-β in vitro which plays an important role in the development of diabetic nephropathy. TGF-β plays an important part in mediating the interaction between metabolic and haemodynamic factors leading to extracellular matrix accumulation in the diabetic kidney.

**Genetic factors involved in the development of diabetic nephropathy**

Genetic factors contribute significantly in the susceptibility to diabetic nephropathy. A family history of hypertension has also been associated with an increased risk of diabetic nephropathy. Association between red blood cell sodium-lithium counter-transport activity and hypertension is noted by some but not all investigators. Polymorphism of genes relevant to the renin-angiotensin system such as ACE and angiotensin type I receptor have been evaluated.

**Factors leading to diabetic nephropathy**

These changes are mostly caused by following factors
1. Hyperglycemia
2. Systemic hypertension
3. Glomerular hyper filtration early, with onset of diabetes late, with renal injury and nephron loss
4. Reduced nephron number
5. Genetic/racial
6. Proteinuria
7. AGEs
8. Anormalities of Renal RAS
9. Lipid abnormalities

The hyperglycemic state sensitizes the endothelium to injury from elevated blood pressure. Therefore a successful pancreas transplantation result in normal insulin regulation and normoglycemia is associated with a reversal of the lesions of diabetic nephropathy. Systolic and diastolic hypertension accelerates the progression of diabetic kidney disease. The ‘compensatory’ haemodynamic changes occurring due to hypertension were counterproductive, leading to mesangial cell stretch, extracellular matrix deposition and activation of various autocrine and paracrine factors associated with tissue injury and ultimately a decline in renal function.

The role of lipids in progression of nephropathy is not yet clear. It has been observed that with reduced nephron number, dietary-induced hypercholesterolemia worsens glomerular injury as well as administration of Cholesterol-lowering drugs to Zucker rats were associated with attenuation of glomerular lesions.
In diabetes and longstanding hyperglycemia, nonenzymatic modification of free amino groups of proteins by glucose and its metabolites leads to formation of Schiff bases that leads to the AGEs formation. Functional changes are produced in kidney by crosslinking of AGEs with the glomerular basement membrane and other vascular membranes. It activates cell signalling mechanisms which leads to increase in transforming growth factor b (TGF-b) and vascular endothelial growth factor (VEGF) expression, which contributes to diabetes complications. 

**Pathological changes observed in diabetic nephropathy.**[36]

Unique changes in kidney structure are observed with diabetic nephropathy. Classic glomerulosclerosis is observed with increased glomerular basement membrane width, diffuse mesangial sclerosis, hyalinosis, microaneurysm, and hyaline arteriosclerosis. Tubular and interstitial changes are also seen. In 40–50% of patients developing proteinuria areas of extreme mesangial expansion called Kimmelstiel-Wilson nodules or nodular mesangial expansion are observed. Micro- and macro albuminuric patients with type 2 diabetes have more structural heterogeneity than patients with type 1 diabetes duration, degree of glycemic control, and genetic factors. There is an important overlap in mesangial expansion and glomerular basement membrane thickening among normo albuminuric, micro albuminuric, and proteinuric type 1 and type 2 diabetic patients with no clear cut off to distinguish the groups. 

**Treatment of diabetic nephropathy.**[2, 37-48]

The increased activity of the renin–angiotensin–aldosterone system (RAAS) plays an important role in pathogenesis of nephropathy in diabetic patients. Angiotensin II leads to vasoconstriction, increase of aldosterone secretion, growth, fibrosis, thrombosis, inflammation and oxidation. Therefore blockade of the RAAS will lead to beneficial effect on the development of diabetic nephropathy. Treatment of diabetic nephropathy involves mainly control of the glycaemic status and aggressive antihypertensive therapy, primarily with RAAS-blocking agents. RENAAL and IDNT trials demonstrated the successful use of Angiotensin receptor blockers in TTDM for prevention of diabetic nephropathy and independent decrease in blood pressure. ONTARGET investigates whether treatment with a combination of an ACEI and an ARB has a more potent beneficial effect on the nephropathy in type 2 diabetic patients as compared with separate treatment with the two agents. Following agents are widely used in the treatment of diabetic nephropathy.

**Angiotensin-converting enzyme inhibitors**

Angiotensin II is an important regulator of cardiovascular function. The ability to reduce levels of angiotensin II with orally effective inhibitors of angiotensin-converting enzyme (ACE) represents an important advance in the treatment of hypertension. Captopril (CAPOTEN) was the first such agent to be developed for the treatment of hypertension. Since then, enalapril (VASOTEC), lisinopril (PRINIVIL), quinapril (ACCUPRIL), ramipril (ALTACE), benazepril (LOTENSIN), moexipril (UNIVASC), fosinopril (MONOPRIL), trandolapril (MAVIK), and perindopril (ACEON) also have become available. These drugs have proven to be very useful for the treatment of hypertension because of their efficacy and their very favorable profile of adverse effects, which enhances patient adherence.

1. **Captopril (CAPOTEN)**

Captopril was the first ACE inhibitor to be marketed and is a potent ACE inhibitor with a $K_i$ of 1.7 nM. It is the only ACE inhibitor approved for use in the United States that contains a sulfhydryl moiety. Given orally, captopril is absorbed rapidly and has a bioavailability of about 75%. Peak concentrations in plasma occur within an hour, and the drug is cleared rapidly with a half-life of approximately 2 hours. Most of the drug is eliminated in urine, 40% to 50% as captopril and the rest as captopril disulfide dimers and captopril–cysteine disulfide. The oral dose of captopril ranges from 6.25 to 150 mg two to three times daily, with 6.25 mg three times daily or 25 mg twice daily being appropriate for the initiation of therapy for heart failure or hypertension, respectively. Most patients should not receive daily doses in excess of 150 mg. Since food reduces the
oral bioavailability of captopril by 25% to 30%, the drug should be given 1 hour before meals.

2. **Enalapril (VASOTEC)**
   Enalapril maleate, the second ACE inhibitor approved in the United States, is a prodrug that is hydrolyzed by esterases in the liver to produce the active dicarboxylic acid, enalaprilat. Enalaprilat is a highly potent inhibitor of ACE with a $K_i$ of 0.2 nM. Although it also contains a "proline surrogate," enalaprilat differs from captopril in that it is an analogue of a tripeptide rather than of a dipeptide. Enalapril is absorbed rapidly when given orally and has an oral bioavailability of about 60% (not reduced by food). Although peak concentrations of enalapril in plasma occur within an hour, enalaprilat concentrations peak only after 3 to 4 hours. Enalapril has a half-life of only 1.3 hours, but enalaprilat, because of tight binding to ACE, has a plasma half-life of about 11 hours. Nearly all the drug is eliminated by the kidneys as either intact enalapril or enalaprilat. The oral dosage of enalapril ranges from 2.5 to 40 mg daily (single or divided dosage), with 2.5 and 5 mg daily being appropriate for the initiation of therapy for heart failure and hypertension, respectively. The initial dose for hypertensive patients who are taking diuretics, are water- or Na⁺-depleted, or have heart failure is 2.5 mg daily.

3. **Lisinopril (PRINIVIL, ZESTRIL)**
   Lisinopril, the third ACE inhibitor approved for use in the United States, is the lysine analogue of enalaprilat; unlike enalapril, lisinopril itself is active. In vitro, lisinopril is a slightly more potent ACE inhibitor than is enalaprilat. Lisinopril is absorbed slowly, variably, and incompletely (about 30%) after oral administration (not reduced by food); peak concentrations in plasma are achieved in about 7 hours. It is cleared as the intact compound by the kidney, and its half-life in plasma is about 12 hours. Lisinopril does not accumulate in tissues. The oral dosage of lisinopril ranges from 5 to 40 mg daily (single or divided dosage), with 5 and 10 mg daily being appropriate for the initiation of therapy for heart failure and hypertension, respectively. A daily dose of 2.5 mg is recommended for patients with heart failure who are hyponatremic or have renal impairment.

4. **Fosinopril (MONOPRIL)**
   Fosinopril is the only ACE inhibitor approved for use in the United States that contains a phosphinate group that binds to the active site of ACE. Cleavage of the ester moiety by hepatic esterases transforms fosinopril, a prodrug, into fosinoprilat, an ACE inhibitor that in vitro is more potent than captopril yet less potent than enalaprilat. Fosinopril is absorbed slowly and incompletely (36%) after oral administration (rate but not extent reduced by food). Fosinopril is largely metabolized to fosinoprilat (75%) and to the glucuronide conjugate of fosinoprilat. These are excreted in both the urine and bile; peak concentrations of fosinoprilat in plasma are achieved in about 3 hours. Fosinoprilat has an effective half-life in plasma of about 11.5 hours, and its clearance is not significantly altered by renal impairment. The oral dosage of fosinopril ranges from 10 to 80 mg daily (single or divided dosage). The dose is reduced to 5 mg daily in patients with Na⁺ or water depletion or renal failure.

5. **Ramipril (ALTACE)**
   Cleavage of the ester moiety by hepatic esterases transforms ramipril into ramiprilat, an ACE inhibitor that in vitro is about as potent as benazeprilat and quinaprilat. Ramipril is absorbed rapidly (peak concentrations of ramipril achieved in 1 hour), and the rate but not extent of its oral absorption (50% to 60%) is reduced by food. Ramipril is metabolized to ramiprilat and to inactive metabolites (glucuronides of ramipril and ramiprilat and the diketopiperazine ester and acid) that are excreted predominantly by the kidneys. Peak concentrations of ramiprilat in plasma are achieved in about 3 hours. Ramiprilat displays triphasic elimination kinetics with half-lives of 2 to 4 hours, 9 to 18 hours, and greater than 50 hours. This triphasic elimination is due to extensive distribution to all tissues (initial half-life), clearance of free ramiprilat from plasma (intermediate half-life), and dissociation of ramiprilat from tissue ACE (terminal half-life). The oral dosage of ramipril ranges from 1.25 to 20 mg daily (single or divided dosage).
Angiotensin antagonists (Angiotensin receptor blockers)

Over the past 2 decades, several nonpeptide orally active AT_1 receptor antagonists have been developed as alternative to ACE inhibitors. These include losartan, candesartan, valsartan, telmisartan, irbesartan, etc. Oral bioavailability of ARBs generally is low (<50%, except for irbesartan, with 70% available), and protein binding is high (>90%).

1. Candesartan Cilexetil (ATACAND)
Candesartan cilexetil is an inactive ester prodrug that is completely hydrolyzed to the active form, candesartan, during absorption from the gastrointestinal tract. Peak plasma levels are obtained 3 to 4 hours after oral administration, and the plasma half-life is about 9 hours. Plasma clearance of candesartan is due to renal elimination (33%) and biliary excretion (67%). The plasma clearance of candesartan is affected by renal insufficiency but not by mild to moderate hepatic insufficiency. Candesartan cilexetil should be administered orally once or twice daily for a total daily dosage of 4 to 32 mg.

2. Eprosartan (TEVETEN)
Peak plasma levels are obtained approximately 1 to 2 hours after oral administration, and the plasma half-life ranges from 5 to 9 hours. Eprosartan is metabolized in part to the glucuronide conjugate, and the parent compound and its glucuronide conjugate are cleared by renal elimination and biliary excretion. The plasma clearance of eprosartan is affected by both renal insufficiency and hepatic insufficiency. The recommended dosage of eprosartan is 400 to 800 mg/day in one or two doses.

3. Irbesartan (AVAPRO)
Peak plasma levels are obtained approximately 1.5 to 2 hours after oral administration, and the plasma half-life ranges from 11 to 15 hours. Irbesartan is metabolized in part to the glucuronide conjugate, and the parent compound and its glucuronide conjugate are cleared by renal elimination (20%) and biliary excretion (80%). The plasma clearance of irbesartan is unaffected by either renal or mild to moderate hepatic insufficiency. The oral dosage of irbesartan is 150 to 300 mg once daily.

4. Losartan (COZAAR)
Approximately 14% of an oral dose of losartan is converted to the 5-carboxylic acid metabolite EXP 3174, which is more potent than losartan as an AT_1-receptor antagonist. The metabolism of losartan to EXP 3174 and to inactive metabolites is mediated by CYP2C9 and CYP3A4. Peak plasma levels of losartan and EXP 3174 occur approximately 1 to 3 hours after oral administration, respectively, and the plasma half-lives are 2.5 and 6 to 9 hours, respectively. The plasma clearances of losartan and EXP 3174 (600 and 50 ml/min, respectively) are due to renal clearance (75 and 25 ml/min, respectively) and hepatic clearance (metabolism and biliary excretion). The plasma clearance of losartan and EXP 3174 is affected by hepatic but not renal insufficiency. Losartan should be administered orally once or twice daily for a total daily dose of 25 to 100 mg. In addition to being an ARB, losartan is a competitive antagonist of the thromboxane A_2 receptor and attenuates platelet aggregation (Levy et al., 2000). Also, EXP3179, an active metabolite of losartan, reduces COX-2 mRNA up-regulation and COX-dependent prostaglandin generation (Krämer et al., 2002).

5. Olmesartan Medoxomil (BENICAR)
Olmesartan medoxomil is an inactive ester prodrug that is completely hydrolyzed to the active form, olmesartan, during absorption from the gastrointestinal tract. Peak plasma levels are obtained 1.4 to 2.8 hours after oral administration, and the plasma half-life is between 10 and 15 hours. Plasma clearance of olmesartan is due to both renal elimination and biliary excretion. Although renal impairment and hepatic disease decrease the plasma clearance of olmesartan, no dose adjustment is required in patients with mild to moderate renal or hepatic impairment. The oral dosage of olmesartan medoxomil is 20 to 40 mg once daily.

6. Telmisartan (MICARDIS)
Peak plasma levels are obtained approximately 0.5 to 1 hour after oral administration, and the plasma half-
life is about 24 hours. Telmisartan is cleared from the circulation mainly by biliary secretion of intact drug. The plasma clearance of telmisartan is affected by hepatic but not renal insufficiency. The recommended oral dosage of telmisartan is 40 to 80 mg once daily.

7. Valsartan (DIOVAN)
Peak plasma levels occur approximately 2 to 4 hours after oral administration, and the plasma half-life is about 9 hours. Food markedly decreases absorption. Valsartan is cleared from the circulation by the liver (about 70% of total clearance). The plasma clearance of valsartan is affected by hepatic but not renal insufficiency. The oral dosage of valsartan is 80 to 320 mg once daily.

CONCLUSION
Increasing cases of Diabetic Nephropathy due to consistently high TTDM patients has led to various treatment complications and it has become alarmingly difficult for the doctors to treat such patients. There is a scope of development of more advanced medicines for the treatment of diabetic nephropathy. Continuous monitoring of the renal performance and micro and macro albuminuria is also necessary. Patients also need to take care of their dietary habits to control the complications related to diabetic nephropathy. Thus diabetic nephropathy is a serious condition related to TTDM and needs a lot of attention to be taken care of.

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