Diabetic nephropathy (DN), KimmelStiel-Wilson syndrome, or Nodular diabetic glomerulosclerosis and intercapillary glomerulonephritis is a major complication of diabetes. DN is the main cause of end stage renal disease seriously affecting world population (Packham et al., 2012).

Diabetic kidney disease (DKD) traditionally has been referred to as diabetic nephropathy. However, the introduction of a new classification system for chronic kidney disease (CKD), irrespective of cause, and increasing awareness of the widening spectrum of CKD presentations in people with diabetes, beyond the traditional proteinuria-centered model, have promoted the use of the term DKD. Classifying patients with diabetic nephropathy should be reserved for those with persistent clinically detectable proteinuria that occurs with elevated blood pressure (BP) and decreased glomerular filtration rate (GFR). However, subclinical proteinuria, termed microalbuminuria, has been recognized as a definable early stage in the natural history of increasing albuminuria in DKD and sometimes is termed “incipient diabetic nephropathy.” (Richard et al., 2014).

The incidence of diabetes is increasing worldwide, mainly due to the dramatic increase in type 2 diabetes. The public health impact of this epidemic is vast because diabetes now is the leading cause of end-stage renal disease (ESRD) in Western countries. Diabetic nephropathy has been reported to occur in 25%-40% of people with type 1 or type 2 diabetes. People with DKD are not only at significant risk of progression to ESRD, there also is a concomitant increase in cardiovascular morbidity and mortality. Thus, it is of critical importance to identify people at greatest risk and initiate kidney- and cardiovascular-protective treatments as early as possible. (Groop et al., 2009)(Orchard et al., 2010).

The American Diabetes Association (ADA) proposed in its Clinical Practice Recommendations 2013 that all cases of albuminuria of 30 lg/mg Cr (=mg/g Cr) be defined as ‘increased urinary albumin excretion,’ thus abandoning the
division between micro- and macroalbuminuria. *(Summary of revisions for the 2013 clinical practice recommendations.)*

Again, while this concept was retained in the Clinical Practice Recommendations 2014, the ADA further proposed that microalbuminuria and macroalbuminuria be redefined as persistent albuminuria of 30–299 mg/24 h and ≥300 mg/24 h, respectively *(Summary of revisions to the 2014 Clinical Practice Recommendations.)*.

**Classification of DN:**

Long term exposure to diabetes induces renal complications and if untreated it leads to serious life threatening DN. Persons with long lasting diabetes will encounter histological and functional changes of the kidney before the onset of microalbuminuria *(Fioretto and Mauer, 2007).*

Histological features show that DN comprizes three major lesions, first of all thickening of glomerular and tubular basement membranes followed by mesangial expansion and finally hyalinizes with loss of afferent and efferent arterioles. According to the new classification, Class I consists of Thickening of the glomerular basement membrane (GBM). Class II Represents mild (IIA) to severe (IIB) mesangial expansion. Thickening of GBM and the accumulation of mesangial matrix are the first changes which usually occur between 2 and 5 years of diabetes. The extent of mesangial expansion inversely associates with capillary filtration area, which participates in the progression from hyperfiltration to reduced glomerular filtration rate (GFR). Class III represents nodular glomerulosclerosis. Finally, Class IV is categorized as advanced DN comprising more than 50% global glomerulosclerosis coupled with loss of podocyte *(Tervaert et al., 2010).*

Arteriolar hyalinosis, glomerular capillary subendothelial hyaline (hyaline caps), arteriosclerosis, and capsular Drops through out the epithelial parietal surface of the Bowman capsule (e.g., the exudative lesions of DN) may also be present *(Tervaert et al., 2010).* Interstitial fibrosis participates to the rate of Progression from moderate to severe reduction in GFR *(Adler et al., 1986).*
Data on urinary biomarkers in human also support that the Tubular injury plays a primary role in the development of early DN (Satirapoj et al., 2012).

Table (1) Classification of Diabetic Nephropathy 2014:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)</th>
<th>GFR (eGFR) (mL/min/1.73 m2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (pre nephropathy)</td>
<td>Normoalbuminuria (&lt;30)</td>
<td>≥30†</td>
</tr>
<tr>
<td>Stage 2 (incipient nephropathy)</td>
<td>Microalbuminuria (30–299)</td>
<td>≥30</td>
</tr>
<tr>
<td>Stage 3 (overt nephropathy)</td>
<td>Macroalbuminuria (≥300) or persistent proteinuria (≥0.5)</td>
<td>≥30</td>
</tr>
<tr>
<td>Stage 4 (kidney failure)</td>
<td>Any albuminuria/proteinuria status††</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Stage 5 (dialysis therapy)</td>
<td>Any status on continued dialysis</td>
<td></td>
</tr>
</tbody>
</table>

(Systematic research report from the Research Group of Diabetic Nephropathy, 2009-2012., 2012.)(Wada T et al., 2014)

(Diabetic nephropathy does not always progress from one stage to the next. The revised Classification takes into account findings on the prognosis of type 2 diabetic patients from a ‘historical cohort study’ carried out as part of the Ministry of Health, Labor and Welfare-subsidized Project on Kidney Disease, entitled ‘Diabetic Nephropathy Research, from the Ministry of Health, Labor and Welfare of Japan’. †Although a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m2 is consistent with the diagnosis of chronic kidney disease, underlying causes other than diabetic nephropathy might be involved in patients with a GFR below 60 mL/min/1.73 m2, thus calling for the differential diagnosis between diabetic nephropathy and any other potential non-diabetic kidney diseases. §Patients with microalbuminuria are to be diagnosed as incipient nephropathy after the differential diagnosis based on the criteria for an early diagnosis of diabetic nephropathy. ¶Precautions are required in patients with , in whom renal events (e.g., a decrease in estimated GFR [eGFR] to half its baseline value, the need for dialysis) have been shown to increase as the GFR decreases below 60 mL/min/1.73 m2. ††All patients with a GFR of less than 30 mL/min/1.73 m2 are classified as showing kidney failure, regardless of their urinary albumin/protein values. However, in those with normoalbuminuria and microalbuminuria, the differential diagnosis is required between diabetic
nephropathy and any other potential non-diabetic renal diseases. Key precautions in view of drug use: this table is intended, first and foremost, as a classification of diabetic nephropathy and not as a guide to drug use. All drugs, including antidiabetic drugs, particularly renally metabolized agents, are to be used in accordance with their prescribing information, with due consideration to relevant factors, such as GFR, in each patient.)

Both absolute change and rate of change in albuminuria are linked strongly to the development and progression of reduced kidney function in diabetes. Despite this, the sensitivity and specificity of albuminuria as a marker of progressive DKD recently has been challenged, with more emphasis being placed on early changes in GFR. (Perkins and Krolewski, 2009).

There are several potential initiators and promoters of DKD, both irreversible and reversible. The main irreversible factors are age, sex, ethnicity, family history, and duration of diabetes. Genetic factors influence the development of DKD. Although risk for the development of DKD is influenced by familial and ethnic factors, sex also plays a role. In type 2 diabetes, males are more likely to follow an albuminuric pathway to decreased kidney function, whereas females are more likely to follow a nonalbuminuric pathway. Hyperglycemia is the key modifiable risk factor that promotes the development of DKD in both type 1 and type 2 diabetes. Hypertension classically is viewed as a promoter of DKD in type 1 diabetes, that is, it usually only develops after the onset of reduced kidney function. However, in type 2 diabetes, it most likely is an important initiator and promoter of DKD. Albuminuria, dyslipidemia, and smoking are other well-recognized modifiable initiators and promoters of DKD. (Retnakaran et al., 2006).

The mechanisms responsible for the development and progression of diabetic kidney disease remain poorly understood. However, it is known that progression of diabetic kidney disease correlates closely with level of hyperglycemia, and improving glycemic control decreases
the rate of progression of diabetic kidney disease and loss of kidney function. (Lewis et al., 1993).

Prolonged hyperglycemia leads to chronic metabolic and hemodynamic changes that modulate various intracellular signaling pathways, transcription factors, cytokines, chemokines, and growth factors. (Soldatos et al., 2008).

Chronic hyperglycemia results in structural changes in the kidney. Experimental evidence suggests that several molecular pathways may be implicated in the development of diabetic kidney disease. These pathways include increased oxidative stress, enhanced flux into the polyol and hexosamine pathways, activation of protein kinase C (PKC) and transforming growth factor b (TGFb)/Smad/mitogen-activated protein kinase (MAPK) signaling pathways and increased formation of advanced glycation end products (AGEs). Which in turn lead to increase formation of extracellular matrix (ECM) proteins, cellular hypertrophy, and apoptosis in the kidney. In addition, high glucose levels can activate the proinflammatory transcription factor nuclear factor-kB (NF-kB), resulting in increased inflammatory gene expression, in part through oxidative stress, AGEs, PKC, and MAPKs. (Schimd et al., 2006).
Figure (1): Mechanisms in DKD


Genetics and epigenetic:
Genetic and epigenetic factors may influence the development and progression of DKD. Although there is evidence for genetic susceptibility for the development of DKD, identification of causative genes has proved to be elusive. Diabetic siblings of patients with ESRD due to diabetes are known to be at 5-fold higher risk of ESRD compared
with those without a family history. (Freedman et al., 2007) (Thomas et al., 2012).

One recent study has shown that diabetic siblings of patients with ESRD due to diabetes have a high frequency of albuminuria (46%), suboptimal BP control (65%), suboptimal glycemic control (HbA1c ≥ 7.0%; 43%), smoking (26%), and failure to receive RAAS-modifying agents (42%).26 (Bleyer et al., 2008).

Candidate Genes Implicated in the Susceptibility for the Development of DKD

- Angiotensin-converting enzyme (ACE)
- Angiotensinogen
- Angiotensin II receptor (type 1)
- Aldose reductase
- Apolipoprotein E
- Atrial natriuretic peptide
- Heparin sulfate
- Intercellular adhesion molecule 1 (ICAM)
- Matrix metalloproteinase
- Methylene metalloproteinase 9 (MM-9)
- Na/H exchanger
- Nitric oxide synthase
- Plasminogen activator inhibitor 1 (PAI-1)
- Peroxisome proliferator-activated receptor (PPAR)
- Type 4 collagen
- 3-Adrenergic receptor
- Vascular endothelial growth factor (VEGF)
- Engulfment and cell motility 1 (ELMO1)

For patients with type 2 diabetes, reduced GFR has been linked with variants in the engulfment and cell mobility (ELMO1) gene. In type 1 diabetes, decreased GFR has been associated with variants in genes controlling matrix metalloproteinases and with endothelial nitric oxide (NO). (Pezzolesi et al., 2008).

The management of hyperglycemia in patients with kidney failure presents special challenges. Multifactorial alterations in glucose
homeostasis occur when kidney function declines. Abnormal insulin metabolism involves reduced renal insulin clearance, which usually occurs when CKD reaches stages 4 and 5. Reductions in pancreatic insulin secretion also may occur, perhaps related to hyperparathyroidism and vitamin D deficiency (Mak et al., 1992).

Figure (2). Overview of glucose/insulin homeostasis in chronic kidney disease. Disturbances of glucose metabolism include insulin resistance and glucose intolerance. Several factors contribute to hyperglycemia, which may coexist with hypoglycemia. Adapted with permission of the National Kidney Foundation from Kovesdy et al. (Kovesdy et al., 2008)
GLYCEMIC CONTROL: ITS VALUE AND ITS DETERMINATION IN CKD

Glycemic management in patients with diabetes (predominantly type 2) and CKD has become increasingly complex, in part reflecting controversies about safety/efficacy as applied to type 2 diabetes (Inzucchi et al., 2012).

Challenges cited in improving glycemic control in patients with advanced CKD include therapeutic inertia, monitoring difficulties, and complexity regarding the use of available treatments (O’Toole et al., 2012).

Hemoglobin A1c (HbA1c) is the standard measure for glucose monitoring in patients without kidney impairment. According to NKF-KDOQI guidelines, currently recommended HbA1c targets in the setting of CKD are no different from those for the general diabetic population; that is, <7.0%, although the seminal glycemic control trials in type 1 and type 2 diabetes have excluded patients with significantly decreased kidney function (National Kidney Foundation, 2007).

Although HbA1c combined with home glucose monitoring is the mainstay for assessing glycemic control, until recently, available evidence regarding the role of tight glycemic control on morbidity and mortality in patients with advanced CKD was sparse. HbA1c remains the most widely used index of glycemic control in the diabetic population. Superior glycemic control helps prevent diabetic CKD and other diabetic microvascular complications in individuals without CKD. Since the DCCT (Diabetes Control and Complications Trial) and UKPDS (Rohlfing et al., 2002).

Prospective Diabetes Study showed that HbA1c levels are strong predictors of the risk of microvascular complications in type 1 and type
2 diabetes, respectively, glycohemoglobin level has been the main focus of diabetes management. Strict glycemic control was found to reduce the risk of developing albuminuria, and in those with elevated baseline albumin-creatinine ratios, progression was found to be reduced with strict glycemic control. In a recent observational report from the Alberta Kidney Disease Network (Shurraw et al., 2011).

in patients with diabetes and non–dialysis dependent CKD stages 3-5, higher HbA1c levels were associated with markedly worse outcomes, including progression of kidney disease regardless of baseline estimated glomerular filtration rate (eGFR). The renoprotective effect associated with intensive control of glycemia in type 2 diabetes also was suggested by the recent ADOPT (A Diabetes Outcomes Prevention Trial) Study. (Lachin et al., 2011).

Greater durability of glycemic control in those treated with rosiglitazone (compared with metformin and glyburide) was associated with a smaller increase in albuminuria and with preservation of eGFR. The firm association between glycemic control and clinical outcomes hinges on the connection between hyperglycemia and elevated HbA1c levels. HbA1c makes up ~4% of total hemoglobin in normal adult erythrocytes. HbA1c level mirrors average blood glucose concentration over the preceding 3 months or so. (Dunn et al., 1979).

Patients with diabetes and progressively declining kidney function are at increased risk for hypoglycemia. Diabetes treatment options for patients with therefore may be limited due to safety and tolerability concerns. Because the risk of adverse events related to hypoglycemia may be greater in patients with reduced kidney function, attention increasingly is being given to the risks of hypoglycemia (glucose , 70 mg/dL) in patients with diabetes and CKD. In recent diabetes guidelines, there is greater concern than in the past about the dangers of hypoglycemia. (Inzucchi et al., 2012).
The American Diabetes Association (ADA) has recommended a target HbA1c level, 7.0% or as close to normal and as safely as possible without unacceptable hypoglycemia. American Diabetes Association. (2012). However, with increasing emphasis on tight glycemic control targets, hypoglycemia, often iatrogenic, is a growing concern with use of insulin secretagogues, missed meals, advanced age, duration of diabetes, and unawareness of hypoglycemia, factors that might increase the risk of hypoglycemia (Amiel et al., 2008). However, published reviews of glycemic control in patients with diabetic CKD typically mention hypoglycemia only in passing. The greatest risk of harm is in patients with both CKD and diabetes, especially the elderly (Munshi et al., 2011).

in whom hypoglycemic episodes may be difficult to diagnose. Partly as a result of mounting concerns about hypoglycemia, the ADA’s Standards of Medical Care in Diabetes, recommends less stringent HbA1c targets (ie, 7.5%- 8.0%) as appropriate for patients with advanced complications, extensive comorbid conditions, or severe hypoglycemia (Inzucchi et al., 2012).

The pathogenesis of hypoglycemia in patients with diabetic CKD is complex, particularly because there are other derangements in glucose metabolism in kidney failure. Consistent glycemic control is difficult to achieve in patients with ESRD due to altered glucose metabolism related to insulin resistance, impaired insulin secretion, and decreased insulin degradation, as well as effects on drug metabolism, adding further complexity to glycemic management. Diminished renal insulin clearance, as GFR decreases to 15-20 mL/min/1.73 m², prolongs the action of insulin. Aside from the liver, the kidneys represent the main site for insulin degradation, and as kidney function declines, so does the ability to remove insulin. Reductions in kidney mass and diminished kidney function lead to decreased renal gluconeogenesis, a major source of glucose production from precursor molecules during
starvation. Preliminary findings hint that the risk of hypoglycemia is particularly high in patients with diabetic ESRD who have more glycemic variability (Williams et al., 2009).

**RENALE PROTECTIVE THERAPIES TARGETING NEUROHORMONAL ACTIVATION:**

The renin–angiotensin–aldosterone system and angiotensin-converting enzyme 2 activation:

Animal models, mechanistic data and extensive clinical trials support a central role for intrarenal RAAS in the development and progression of diabetic nephropathy. Unfortunately, RAAS inhibitor trials have also produced some disappointing results, including the failure of primary prevention studies (The Renin Angiotensin System Study), and serious side-effects observed with dual RAAS blockade (Perez et al., 2015).

The lack of complete protection against the development of complications with traditional RAAS inhibitors underscores the need for new therapeutic strategies. Nevertheless, RAAS blockade continues to be of central importance for the management of diabetic nephropathy due to protective effects of traditional RAAS inhibitors, and because of recent advances in novel RAAS-related pathways. Over the last decade, new components of the RAAS have been identified, and our understanding of the processing and breakdown of angiotensins continues to evolve. In 2000, angiotensin-converting enzyme 2 (ACE2), a type 1 integral membrane protein, was identified (Donoghue et al., 2000). ACE2 has almost 40% homology with ACE and is especially abundant in the kidney (Mizuiri et al., 2015).

ACE2 cleaves the C-terminal amino acid of Ang II to generate the Ang 1–7 peptide, which subsequently acts via the Mas receptor to counteract the adverse effects of angiotensin (Ang) II and is thought to provide renoprotection by reducing oxidative stress, inflammation and lipotoxicity (Mizuiiri et al., 2015).
In contrast to ACE, ACE2 activity is not responsive to conventional ACE inhibition (Mizuiri et al., 2015).

Diabetic animal models are associated with Ang II overactivity (Marquez et al., 2015). and studies with downregulation of tubular ACE2 have been associated with accentuated albuminuria and tubular injury (Soler et al., 2007). In addition, ACE2-deficient mice demonstrate glomerulosclerosis (Oudit et al., 2006) and enhanced Ang II-induced renal oxidativestress with consequent renal injury (Zhong J et al., 2011). Consistent with these findings, animal models have also demonstrated that increased ACE2 activity at the podocytes can attenuate the development of diabetic nephropathy (Nadarajah et al., 2012). suggesting a potential mechanism to counteract diabetes-associated Ang II overactivity (Marquez et al., 2015). In fact, diabetic nephropathy is associated with reduced glomerular and tubular ACE2 expression (Reich et al., 2008). and ACE2 activity is associated with glycemic control and glomerular filtration rate in patients with diabetic nephropathy (Anguiano et al., 2015).

For these reasons, ACE2 has been investigated as a potential therapeutic target. In murine models, recombinant ACE2 lowers blood pressure and attenuates glomerular mesangial cell proliferation, oxidative stress, fibrosis and ultimately diminishes the progression of diabetic nephropathy(Liu CX et al., 2011)( Mizuiri et al., 2015).

The protective effect of recombinant ACE2 is likely due to a reduction in Ang II levels and increase in Ang 1–7 signaling, leading to reduced blood pressure, decreased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, as well as renal histological protective effects in experimental models (Shi Y et al., 5015).

Recombinant ACE2 may provide further synergistic benefits in combination with conventional RAAS inhibition by preventing feedback escape and/or enhancing the generation of Ang 1–7, thereby
augmenting vascular protective effects associated with traditional RAAS inhibitors (Mizuiri et al., 2015).

Finally, enhanced ACE2 bioactivity can be achieved through increased endogenous expression. The two small-molecule ACE2 activators, xanthenone and diminazene aceturate (Jarajapu et al., 2013).

increased ACE2 activity and significantly decreased blood pressure in animal models (Hernandez Prada et al., 2008). Non peptide Mas-receptor agonists are also under investigation to determine if activation of Ang (1–7)-Mas pathways produce cardio-renal protective effects in experimental models of diabetes (Singh et al., 2012). Despite the strong mechanistic rationale for ACE2 renal protection based on animal models, very little is currently known about this emerging class in humans (Singh et al., 2012).

Neprilysin inhibition:

Another neurohormonal system strongly related to RAAS is the natriuretic peptide system. Natriuretic peptides are a family of three neurohormonal peptides: atrial, brain and c-type natriuretic peptides (Judge et al., 2015). Neprilysin is a widespread enzyme responsible for degradation of natriuretic peptides, and a range of other vasoactive peptides including bradykinin, substance P, Ang II and endothelin. However (Judge et al., 2015), chronic-isolated NEPi does not translate into clinically meaningful blood pressure reductions as the vascular effects of NEPi are often negated by upregulation of the RAAS and increased sympathetic nervous system activity (Mangiafico et al., 2013). Accordingly, the beneficial renal effects of NEPi are enhanced when combined with traditional RAAS, which has led to the development of combined NEPi/RAASi agents. Although no large-scale human trials have to date been conducted with NEPi or NEPi/RAASi in a chronic kidney disease (CKD) cohort, animal models have shown promising results. For instance, in a 5/6 nephrectomy model (an
experimental model for CKD), AVE7688, a vasopeptidase-blocking ACE and NEP led to increased renal synthesis of nitric oxide and decreased synthesis of endothelin-1, resulting in a significant reduction in proteinuria, glomerulosclerosis and tubulointerstitial fibrosis (Benigni et al., 2004). Similar findings have also been observed in diabetic and hypertension murine models (Cao Z et al., 2001)(Anand et al., 2003). In another 5/6 nephrectomy model, omapatrilat (combined NEPi/ACEi) was associated with a reduction in blood pressure, intraglomerular pressure, proteinuria and delayed progression of renal disease compared with ACEi alone (Taal et al., 2001), and similar protective effects have been demonstrated by others (Cheng et al., 2005).

RENEAL PROTECTIVE THERAPIES TARGETING TUBULOGLOMERULAR FEEDBACK MECHANISMS:

Sodium-glucose cotransporter-2 inhibitors:

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are glucose-lowering agents, which are known to decrease blood pressure, weight and improve arterial stiffness (Stanton RC. Sodium glucose transport 2 (SGLT2) inhibition decreases glomerular hyperfiltration: is there a role for SGLT2 inhibitors in diabetic kidney disease. (Skrtic et al., 2015). A more novel potential role of SGLT2i is renal protection, which is thought to be mediated by effects on the tubuloglomerular feedback mechanism (Cherney et al., 2014) (Skrtic et al., 2015). Increased filtered glucose load at the proximal tubule during hyperglycemia results in about 36% overexpression of SGLT2 in diabetes (Skrtic et al., 2015). Consequently, increased reabsorption of sodium at the proximal tubule leads to decreased distal sodium delivery to the macula densa, which is incorrectly sensed as a reduction in effective circulating volume by the juxtaglomerular apparatus leading to downregulation of the tubuloglomerular feedback mechanism, vasodilation of the afferent
renal arterioles and thus, hyperfiltration characteristic of diabetes mellitus (Skrtic et al., 2015). The sodium transport into macula densa cells is thought to be an energy-dependent process, and thus the SGLT2-mediated decrease in sodium leads to decreased ATP breakdown to adenosine – a vasoconstrictor at the afferent renal arteriole (Vallon et al., 2009), leading to reduced hyperfiltration, albuminuria and inflammation in diabetic mouse models (Vallon et al., 2014)(Panchapakesan et al., 2013)(Tahara et al., 2014).

Incretin-based therapies:

Incretin-based therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 inhibitors (DPP-4i), are another class of glucose-lowering agents that are gaining considerable interest as emerging renal protective agents. Endogenous GLP-1 lowers glucose by increasing pancreatic b-cell insulin secretion and inhibiting glucagon secretion. GLP-1 is rapidly degraded at the N-terminal by DPP-4 at the brush border of proximal tubules and glomerular podocytes (Tonneijck et al., 2015). Higher expression and activity of DPP-4 and lower GLP-1 receptor expression were observed in diabetic animal studies (Tonneijck et al., 2015). In patients with T2D, DPP-4 activity is increased (Mannucci et al., 2005). and correlates with higher HbA1c (Ryskjaer et al., 2006). and albuminuria (Sun AL et al., 2012). Consequently, GLP-1 and DPP-4i were shown to inhibit the Na⁺-H⁺ exchanger in the proximal tubule, which increases sodium excretion and triggers the tubuloglomerular feedback mechanism described above (Crajoinas et al., 2011). In addition to effects on tubuloglomerular feedback, GLP-1R agonists and DPP-4i decrease oxidative stress, the local inflammatory response, counteract the action of Ang II and reduce albuminuria and glomerular sclerosis in diabetic animal models (Tonneijck et al., 2015). Limited clinical data are available on the renal protective effects of incretin-based therapy. In
T2D patients, DPP-4i treatment appears to limit the development and progression of microalbuminuria (Groop et al., 2013).

**Metformin:**

Metformin elicits its therapeutic effects through many mechanisms including activation of AMPK pathway. The beneficial effects of metformin in patients with DN are partly mediated through AMPK activation. Metformin-mediated AMPK activation leads to inhibition of mTOR. Metformin inhibits podocyte apoptosis induced by hyperglycemia. This effect is mediated by activation of AMPK and inhibition of mTOR signaling. (Regazzetti et al., 2011).

**Thiazolidinediones:**

The effects of the thiazolidinedione, pioglitazone hydrochloride, on urinary podocalyxin and MCP-1 excretion were studied in T2DM to explore its possible renoprotective mechanisms. Aside the significant decline in both systolic and diastolic BP, both UAE and urinary podocalyxin excretion decreased significantly after 12 weeks of pioglitazone. These results highlight a podocyte protective capacity of pioglitazone that was partly attributed to its effective suppression of diabetes induced local renal inflammation. The declines in GFR below baseline measurements at stages 3 and 4 of CKD were significantly slower for T2DM treated with losartan and pioglitazone compared with those treated with losartan alone. (Pan., 2007).

**Hypolipidemic treatment:**

Treatment of all DN patients with statins is recommended (Sharaf El Din et al., 2016). Statins decrease the risk of atherosclerotic cardiovascular disease in CKD patients. However, they have a minimal effect on CKD progression (Wanner., 2015).
Review of literature

Chapter 2

Quitting smoking:

A recent study of 3613 T1DM patients showed that the 12-year cumulative risks of microalbuminuria, overt proteinuria and ESRD were significantly higher in current and ex-smokers compared to non-smokers and the risk increases with increasing the dose of smoking (Feodoroff et al., 2016). Quitting smoking is mandatory not only in T1DM but also in T2DM. Smoking is one of the important factors responsible for DN progression in T2DM (Gambaro et al., 2001).

Diet control:

Dietary salt restriction to less than 5–6 g (100 m mol)/day significantly reduces BP in T1DM and T2DM. It seems that salt restriction should be advised very early in the course of diabetes mellitus. This reduction in salt intake leads to fall in BP and UAE in individuals with diet-controlled T2DM or impaired glucose tolerance. Salt intake is an independent factor that affects the annual creatinine clearance decline in T2DM in stage 4 CKD (Kanauchi et al., 2015). The association between dietary sodium intake and clinical outcome is more complicated in T1DM. Patients with the highest, as well as the lowest, daily urinary sodium excretion, had reduced survival. Patients with the lowest urinary sodium excretion had the highest risk of ESRD (Thomas et al., 2011). Decreased salt intake can lead to exaggeration of glomerular hyperfiltration in hyperglycemic state. This salt paradox was explained in T1DM. Although the tubuloglomerular feedback has not been well evaluated in T2DM, clinical observations support that the tubuloglomerular feedback is also true in T2DM. There is controversy regarding the impact of protein restriction on CKD progression in DN. The most recent meta-analysis reported a significant impact only in T1DM (Rughooputh et al., 2015). For CKD stages 1 and 2, a protein intake of 0.8 g/kg is recommended, while in stages 3 and 4 the allowance should be 0.6–0.8 g/kg (National Kidney Foundation., 2012). In spite of the established cardiovascular favorable effects of
polyunsaturated fatty acids’ consumption in diabetic patients, they do not seem to attenuate glomerular dysfunction in DN patients (Shapiro et al., 2011).

Treatment of hyperuricemia:

Three years treatment of T2DM patients suffering DN with allopurinol significantly decreased UAE and serum creatinine and significantly increased GFR (Chen et al., 2015). In addition, treatment of asymptomatic hyperuricemic stage 3–4 CKD patients (44% of them had T2DM) with febuxostat for 6 months significantly slowed the decline of GFR compared to placebo (Sircar et al., 2015). A recent meta-analysis of 19 randomized controlled trials enrolling 992 participants showed a significant favorable effect of allopurinol on the rate of GFR decline (Kanji et al., 2015).

Phosphate handling:

Hyperphosphatemia is suggested as a potential risk factor for the rapid decline in renal function in CKD patients (Barsotti et al., 1984). Combining dietary phosphate restriction and sevelamer in non-dialysis CKD patients (24% of them were diabetic) led to a significant decrease of overall mortality and progression to dialysis (Russo et al., 2015).

Control of chronic metabolic acidosis:

Low serum bicarbonate level is an independent risk factor for CKD progression. Sodium bicarbonate supplementation in stage 4 CKD patients (27.5% of them were diabetic) succeeded to significantly slow the rate of decline of renal function and to improve nutritional status (Jeong et al., 2014).
Sarpogrelate:

Sarpogrelate is a 5-hydroxy tryptamine receptor antagonist. It is used as an anti-platelet agent as it inhibits thromboxane A2 production. Sarpogrelate treatment causes a significant decrease of UAE and MCP1 in serum and urine of DN patients (Ogawa et al., 2008).

Vitamin D receptor agonists:

Paricalcitol in a dose of 2 lg /day showed a significant effect on UAE in T2DM patients with overt nephropathy (de Zeeuw et al., 2010).

Potential therapeutic modalities:

Sulodexide:

In a recent multicenter double-blind placebo controlled study in T2DM with incipient nephropathy, sulodexide failed to decrease UAE (Lewis et al., 2011).

Endothelin receptor antagonists:

In spite of the favorable effect of endothelin receptor antagonists on UAE in DN patients, a meta-analysis of five randomized controlled studies that included 2034 patients disclosed that their use is complicated by serious adverse events in comparison to placebo. These findings necessitate further trials of larger sample size and of longer duration for proper evaluation. An ongoing hard outcome trial, the SONAR, in T2DM patients with DN to evaluate atrasentan might settle this issue (Schievink et al., 2016).

Aldose reductase inhibitors:

Advances were achieved on the potential role of aldose reductase inhibitors in the treatment and management of the major complications of diabetes like cataract, retinopathy, neuropathy, nephropathy and cardiovascular disease. However, their use in DN is limited to early stage (Grewal et al., 2016).
Interleukin 17:

Treatment of diabetic mice with low doses of IL-17A reversed DN in these mice. Treatment with low doses of IL-17A significantly decreased UAE, kidney size, mesangial matrix expansion, interstitial fibrosis, urine MCP1, IP10, TNFa, IL-6, and serum urea level in comparison to control animals (Mohamed et al., 2016).

Exogenous klotho:

Klotho is an anti-senescence protein that favors epithelial regeneration and inhibits fibroblast phenotype transformation during EMT (Hu MC et al., 2010). In high glucose cultured renal interstitial fibroblasts, exogenous klotho attenuated TGF-b bioactivity, type II TGF-b receptor protein expression, TGF-b Smad2/3 signaling, and fibronectin expression induced by high glucose (Huang et al., 2014). When intravenously delivered to diabetic rats, klotho gene was able to prevent the progression of renal hypertrophy and fibrosis (Deng et al., 2015).

Inhibitors of renal leukocyte recruitment:

Therapeutic interventions targeting the membrane receptors on the surface of leukocytes can interrupt their renal recruitment. MCP-1 (CCL2) is a pro-inflammatory chemokine that is able to play an important role in leukocytes renal recruitment in DN. Using non-natural nucleotides, a mirror image (Spiegelmer) of MCP-1 was in vitro built-up. Emapticap Pegol binds and neutralizes MCP-1. In a phase IIa study, intravenous Emapticap Pegol administration for 12 weeks significantly reduced UAE in T2DM patients with DN (Menne et al., 2016). Another CCR2 antagonist (CCX140-B) was tried in DN T2DM patients. Oral CCX140-B in a dose 5 mg/day on top of the standard of care treatment caused a significant reduction of UAE. This was associated with improvement in rate of GFR decline. However, phase 3 study of CCX140-B did not support the significant impact on GFR but confirmed
the anti-proteinuric outcome reported in the earlier study (deZeeuw et al., 2015).

**Anti-inflammatory drugs as therapeutics:**

Diabetic nephropathy involves activation of chronic inflammatory cascade and enhanced immune response (Imig et al., 2013). Development of diabetic nephropathy is associated with significant inflammatory cells infiltration along with an increase in plasma levels of C-reactive protein (CRP) and proinflammatory cytokines such as vascular cell adhesion molecule-1 (VCAM-1), interleukins (IL-1, IL-6, and IL-18) and tumor necrosis factor-α (TNF-α) (Sanchez et al., 2009). Transcription factors such as NF-κB, upstream stimulatory factor (USF) 1 and 2, against diabetic nephropathy nuclear factor of activated T-cells (NFAT), stimulating protein 1 (Sp1) and cAMP-response-element-binding protein (CREB) are stimulated by hyperglycemic environments (Sanchez et al., 2011). NF-κB plays a prominent role in the pathogenesis and progression of diabetic nephropathy and is stimulated by many types of stimuli such as reactive oxygen species or oxygen free radical, cytokines and viral products (Wada et al., 2013). Intracellular adhesion molecule-1 (ICAM-1) and VCAM-1 are synthesized by glomerulus endothelial cells, mesangial cells and renal tubular epithelial cells and known to be elevated during diabetic nephropathy (Duran-Salgado et al., 2014)(Li T et al., 2015). Clausen et al. (2000) found elevated plasma concentrations of soluble vascular adhesion molecule (sVCAM)-1 and soluble intercellular adhesion molecule (sICAM)-1 in patients suffering from Type 1 diabetes mellitus with microalbuminuria and nephropathy. AGEs are another key factor that binds to a receptor of RAGE and high expression of AGE/RAGE interactions have been reported in the progression of diabetic nephropathy (Mima et al., 2013). Now, the question arises, whether anti-inflammatory drugs may protect the kidney against diabetes or not? However, this question is not new, the renoprotective effects of
non-steroidal anti-inflammatory drugs (NSAIDs) were assessed in diabetic patients more than 30 years ago itself. Findings from the study suggest that indomethacin treatment significantly decreased serum creatinine and chronic dialysis in patients suffering from diabetic nephropathy (Heerspink et al., 2016).

**Cyclooxygenase (COX) and xanthine oxidase (XO) inhibitors in diabetic nephropathy:**

COX is a key enzyme involved in prostaglandin (PG) synthesis from arachidonic acid in the body (Tessaro et al., 2015). Various types of cells present in different parts of kidney express high levels of COX enzymes. Both the subclasses, COX-1 and COX-2 are known to be expressed with the predominance of COX-2 in tissues such as macula densa and thick ascending limb (Quadri et al., 2015). All renal cells can synthesize PGE2, with highest production rates seen in the collecting ducts and glomeruli; this leads to activation of renin release, glomerular filtration and activation of prostanoid (EP) receptors (Cherney et al., 2008). By acting on four classes of EP receptors PGE2 is reported to be involved in regulation of various processes in progression of kidney diseases. Researchers have evaluated effect of PGE2 in regulating diabetic nephropathy in various pre-clinical models. (Makino et al., 2002) used selective antagonist of the PGE receptor EP1, ONO-8713 and compared its effect with non-selective PGE synthase inhibitor, aspirin in streptozotocin (STZ)-induced diabetic rat model. Findings from this study suggests that both the selective and non-selective inhibitors attenuate mesangial expansion but glomerular hypertrophy and proteinuria were inhibited only by treatment with selective inhibitor of PGE receptor (Makino et al., 2002). These findings suggest that, PGE2 along with COX can provide us with promising targets for kidney diseases owing to their effect on various parameters associated with diabetic nephropathy such as hyperglycemia, hypertension, inflammation and oxidative stress (Nasrallah et al., 2014).
Development and progression of diabetic nephropathy is associated with an increase in the COX-2 expression in podocyte cells of kidney (Wang et al., 2008). Non-specific COX inhibitors such as aspirin and specific COX-2 inhibitors reduce glomerular injury, pro-fibrotic cytokines, proteinuria and increase renal hemodynamics in preclinical models of diabetes (Cheng et al., 2011). Pre-clinical studies have reported that XO and COX-2 play a significant role in the pathogenesis of diabetic nephropathy and can be treated by XO inhibitors. In one pre-clinical study; type 2 diabetes was developed in Zucker obese rats and these animals were treated for 18 weeks with Febuxostat. XO inhibitors normalized serum uric acid and attenuated renal structure change, albuminuria, renal protein expression collagen 4, TGF-β, connective tissue growth factor more efficiently (Omori et al., 2012). In addition to this, XO inhibitors also known to enhance the action of other drugs such as ACE inhibitors (Komers et al., 2016).

**Monocyte-chemoattractant protein-1 (MCP-1) inhibitors :**

MCP-1 promotes monocyte and macrophages activation and infiltration into glomeruli which in turn is linked to increased expression of adhesion molecules, and other proinflammatory cytokines and glomerular injury (Lim et al., 2012). MCP-1 is produced by various types of renal cells, including podocytes, mesangial cells, tubular cells and monocyte-macrophages (Gnudi L ., 2015). Moreover, patients suffering from type-II diabetes and nephropathy excrete high levels of MCP-1 in urine (Amann et al., 2003). Recently, MCP-1 inhibitors such as breviscapine, triptolide, and other anti-diabetic drugs found to protect against DN by blocking MCP-1 receptor in animal models. Breviscapine treatment significantly attenuated nephropathy by inhibiting MCP-1 and PKC activities, and attenuating oxidative stress, TGFb1, and renal fibrosis via phosphorylation of p38, Akt, JNK1/2 and PKC β II (Xu X et al., 2013). Triptolide is another MCP-1 inhibitor which was found to be beneficial in a pre-clinical model of type-II diabetes. Triptolide
attenuated diabetic nephropathy by decreasing inflammation and podocyte injury in rat model of diabetic nephropathy (Jiang et al., 2015). Triptolide was found to regulate the proportion of Th1/Th2 cells, reduced MCP-1 expression, macrophage infiltration as well as expression of related inflammatory factors in the kidney (Ma et al., 2013). These preclinical findings suggest that MCP-1 inhibitors holds a potential for the treatment of diabetic nephropathy and needs to be further explored.

**Tumor necrosis factor-α (TNF-α) inhibitors:**

TNF-α is an inflammatory cytokine synthesized primarily by monocytes, macrophages and T-cells. Intrinsic renal cells such as tubular epithelial cells, mesangial cells, glomerulus and endothelial cells are also able to synthesize it (Ji et al., 2016). TNF-α plays a key role in the pathogenesis and progression of renal damage in diabetic nephropathy. Multiple actions of TNF-α are mediated by specific cell surface receptors such as a myeloid cell type receptor (p75) and epithelial cell-type receptor (p55) (Navarro-González et al., 2009). TNF-α induces a number of signal transcription pathways which in turn starts expression of a variety of transcription factors, cell adhesion molecules, acute phase proteins, major histocompatibility complex proteins, cytokines, growth factor receptors and mediators of inflammatory processes (Navarro et al., 2006). In vitro studies reveals the presence of a significantly increased concentration of TNF-α in the supernatant of isolated glomeruli culture from many renal diseases such as nephrotoxic serum nephritis, rapidly progressive glomerulonephritis and experimental focal and segmental glomerulosclerosis (Lentz et al., 2010). TNF-α inhibitor SKF86002 significantly decrease glomerulus TNF-a production and improves renal function in diabetic nephropathy (Prichett et al., 1994). Pan et al. (1996) also suggests that pretreatment of animals with the cytokine inhibitor SKF86002 prevented drop in renal blood flow.
However, it did not affect glomerular synthesis of vasoconstrictor eicosanoids (Pan et al., 1996).

Pentoxifylline also leads to decreases in mRNA expression of TNF-α in the glomerulus and epithelial kidney cells of diabetics (Garcia et al., 2014). The combination of pentoxifylline with angiotensin converting enzyme inhibitors, AT1 receptor blockers reported to significantly decreases urinary albumin excretion in diabetic nephropathy (Navarro-González et al., 2014).

Pentoxifylline added to maximized RAS blockade had a significant positive impact on renal disease progression in T2DM patients in stage 4 DN. The dose of Pentoxifylline in this trial was 1200 mg/- day. Pentoxifylline was associated with a slower rate of GFR loss and a significant reduction in UAE (Navarro-González et al., 2015).

Pentoxifylline a derivative of methylxanthine phosphodiesterase inhibitor with anti-inflammatory properties, significantly inhibits TNF-α gene transcription, reduces expression levels of mRNA encoded TNF-α and may play important role in renoprotection in patients with diabetic nephropathy. Prospective, multicenter and a randomized double-blind clinical study were conducted in 174 patients (103 males, 71 females) with diabetes having albumin to creatinine ratio of (albuminuria; >30 mg/g of creatinine). Patients in the pentoxifylline group received 1200 mg of pentoxifylline daily (400 mg dosage three times in a day; n = 87) for 6 months, whereas the placebo group (n = 87) received equal starch tablets on the same schedule. Pentoxifylline treated group was found to have percentage decrease of 23% (proteinuria) as compared to baseline and placebo group. In addition other effects of pentoxifylline such as reductions in glycosylated hemoglobin, fasting plasma glucose and renal function was significantly improved in comparison to placebo group (Han et al., 2015).
Nuclear factor-kappa b (NF-κβ) signaling in diabetic nephropathy:

NF-κβ is induced by a wide variety of cellular response to stimuli including hyperglycemia, obesity, growth factor, increase plasma free fatty acid, cellular ligands, hypertension, cytokines and bacteria that plays an important role in the development of diabetic nephropathy (Lopez-Parra et al., 2012). Increased expression of NF-κβ is observed in proximal tubular cells, glomerular endothelial cells and podocytes in the kidney of the diabetic patients (Szeto et al., 2016). Various types of receptors present on cell surface such as toll-like receptors (TLRs), respond to extracellular signals like hyperglycemia, oxidative stress, and inflammatory mediators (Luo et al., 2015). These upon stimulation by extracellular signals activate iKB kinase which in turn lead to phosphorylation of NF-κβ present in complex inactive form with iKBa. Upon phosphorylation, this complex dissociates to make active form of NF-κβ along with degradation of phosphorylated iKBa. Activated NF-κβ enters the nucleus and activates pro-inflammatory genes and cytokines such as MCP-1, IL-6 and leads to renal apoptosis (Karin ., 1999). NF-κβ also leads to mesangial cell fibrosis by activating cell adhesion molecules such as ICAM, VCAM (Patel et al., 2009). Inhibitors of NF-κβ have been used for amelioration of diabetic nephropathy, improvement of kidney function and reduced renal injury by inflammation (Navarro-Gonzalez et al., 2008). Other inhibitors of NF-κβ such as an ellagic acid (2, 3, 7, 8-tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione) that is present in many fruits and plant extracts also known to improve kidney function (Ayhanci et al., 2015). Thus, drugs targeting NF-κβ selectively holds a potential for the treatment of diabetic nephropathy and other kidney disorders.
Role of protein kinase C (PKC) in diabetic:

Protein Kinase C (PKC) is a group of serine or threonine kinase enzyme consisting of 12 isoforms which has been reported to be associated in the progression and pathogenesis of diabetic nephropathy (Yang et al., 2015).

PKC plays an important role in several cellular functions and signals transduction pathways as shown in Fig. 3. Based on their regulatory domains these isoforms are classified into three subgroups as conventional (PKC isoforms a, b I/II and c), a novel (PKC isoforms d, e, g and h) and atypical (PKC isoforms f and i/k). These conventional, novels and atypical isoforms are regulated by calcium + Diacylglycerol (DAG), DAG alone and non-calcium /non-DAG mechanisms respectively (Geraldes et al., 2010)( Meier et al., 2007).

PKC activation is known to be associated with progression and pathogenesis of diabetic nephropathy. Hyperglycemia leads to PKC activation along with other stimuli such as including reactive oxygen species, AGE receptors, advanced glycation end products (AGEs) and angiotensin-II in diabetic nephropathy condition (Budhiraja et al., 2008).

The pathway initiates with the conversion of glucose to DAG which activates PKC kinase which in turn increases TNF-b1 mRNA expression, activation of NADPH oxidase and altered vasomotor tone (PGE2/PGI2 or NO) (Zhu et al., 2015). TNF-b1 leads to increases in tissue fibrosis (mesangial expansion), basement membrane thickening, hemodynamic alterations and increase reactive oxygen species; all these factors leads to renal injury and diabetic nephropathy (Thallas-Bonke et al., 2013).

Thus, PKC inhibitors have the potential for treatment of diabetic nephropathy but owing to their non-selective action, it may lead to
potential toxicity. Therefore, selective PKC inhibitors are preferred over non-selective ones. A randomized, double blind, clinical trials study was conducted to evaluate the effectiveness of ruboxistaurin in diabetic nephropathy patients. The study involves 123 diabetic subjects with persistent albuminuria and compared ruboxistaurin (32 mg/day) with placebo (Mochly-Rosen et al., 2012).

After one year, estimation of key parameters of diabetic nephropathy such as albumin/creatinine ratio and glomerulus filtration rate (GFR) was done. Patients receiving ruboxistaurin showed reduction of albumin to creatinine ratio up to 24 ± 9% which was much higher than placebo groups (9 ± 11%). Study concluded that decrease in albumin to creatinine ratio and glomerulus filtration rate was significant in active drug group (61 patients) and placebo group (63 patients) respectively but didn’t find any statistically significant difference between intergroups (placebo and ruboxistaurin) (Budhiraja et al., 2008).

In an another study, JTT-010 was found to ameliorate the symptoms associated with diabetic neuropathy (Sasase et al., 2005)( Geraldes et al., 2010).
Figure(3): Role of protein kinase C in hyperglycemia-induced diabetic nephropathy. Hyperglycemia leads to activation of protein kinase C by inducing AGEs, ROS, angiotensin–II and diacylglycerol (DAG). These pathways alters the normal physiology of kidney and results in diabetic nephropathy. AGEs: Advanced glycation end products; DAG: Diacylglycerol; ROS: Reactive oxygen species; TGF-b: Transforming growth factor-b; CTGF: Connective tissue growth factor; VEGF: Vascular endothelial growth factor; PGE2/PGI2: Prostaglandins E2/I2; NO: Nitric oxide; NADPH: Nicotinamide adenine dinucleotide phosphate oxidase.
Novel molecular targets in diabetic nephropathy:

From last few decades conventional targets and mechanisms were utilized for management and treatment of diabetic nephropathy but recent advances in molecular biology techniques and genetic tools have helped in identifying more potent and specific targets (Muhonen et al., 2009).

Recently, several enzymes, microRNAs (miRNAs), and epigenetic targets have been explored as potential therapy against diabetic nephropathy (Badal et al., 2014).

MicroRNAs and diabetic nephropathy:

miRNAs are a novel class of non-coding RNAs discovered by Ambros and co-workers, in 1993. This discovery has led to the deep understanding of gene regulation. These are expressed in all human tissues and play an important role in various disease conditions including diabetes (Moura et al., 2014).

Micro-RNAs (miRNAs) are evolving as important regulators of kidney cell gene expression under diabetic conditions. In diabetes, many types of miRNAs are dysregulated in the kidney (Schena et al., 2013).

Dysregulated miRNAs bind with the 3’UPR of renoprotective genes and decrease their expressions. As a result, dysregulated miRNAs leads to progression of diabetic nephropathy (Wu et al., 2014). In Table 1 we have discussed the different miRNA and their role and mechanism in diabetic nephropathy. There are multiple mechanisms by which different microRNA’s may mediate renal injury under diabetic condition. It has been reported that miR-192 and miR-200 leads to the activation of TGF-β1 and fibrosis which may ultimately lead to kidney damage (Kato et al., 2011).
Moreover, TGF-β also leads to acetylation of chromatin to restore repression of miR-192 in diabetic nephropathy. The induction of miR-192 by TGF-β involves Smad transcription factors which is followed by sustained expression promoted by acetylation of the histone H3 (Kato et al., 2013).

Under hyperglycemic conditions, miR-21 also contributes to renal cell hypertrophy and matrix expansion by affecting phosphatase and tensin homolog (PTEN) tumor suppression gene activity. Overexpression of miR-21 leads to decrease in PTEN levels and increase in Akt phosphorylation and causes pathologic features of diabetic nephropathy (Dey et al., 2011).

Fiorentino et al. (2013) also reported that, in a mice model of type 1 diabetes, miR-21 were significantly upregulated, which led to downregulation of tissue inhibitors of metalloproteinase 3 (TIMP3) (Fiorentino et al., 2013). Recently, TIMP3 deficiency has shown to play a significant role in diabetic nephropathy (Basu et al., 2012), which indicates that miR-21 is a potential inducer of diabetic nephropathy. Thus, modulation of miRNA may prevent diabetic nephropathy by regulating various biological switches. Induction of kidney protective miRNAs and silencing of inducing miRNAs are some of the ways to restore renal function in patients suffering from diabetic nephropathy (Kato et al., 2015).
Diabetic Nephropathy in Renal Transplants:

Historically, the majority of diabetic transplant recipients have developed histologic changes of RDN, in some cases within 1 year after transplantation. However, the incidence of diabetic nephropathy as a cause of graft failure is thought to be rare (Owda et al., 2004).

In patients with pre-transplantation diabetes mellitus, RDN occurs in the transplanted kidney after w5.9 years (Bhalla et al., 2033).

Traditionally, the typical histologic finding are accompanied by significant proteinuria (mean, 5.3 g/d; range, 1.1e12.0 g/d) and renal filtration dysfunction (mean serum creatinine level, 2.8 mg/dL). It is also thought that the development of diabetic nephropathy is associated with a higher rate of graft failure (Hariharan et al., 1996).

Despite the extensive data on the pathways that lead to diabetic nephropathy in the native kidney, very little is still known about RDN. Mechanisms implicated in RDN include an initial injury of podocytes, which later leads to the progression of the classic changes of diabetic nodular glomerular sclerosis and interstitial fibrosis (Fiorina et al., 2014)( Fraenkel et al., 2008).

The management of RDN requires a multifaceted approach, given that this condition affects multiple organs other than the allograft itself. Regarding the patients who develop diabetic nephropathy de novo after renal transplantation, strict glycemia control (Barbosa et al., 1994).

in addition to angiotensin inhibitors and statins remains strongly recommended. Our study showed the potential benefit of these drugs to prevent RDN. In transplant patients, other than the aforementioned measures extrapolated from the general population, the benefit of decreasing steroids should be carefully weighed against the risk of provoking arejection in the allograft (Pascual et al., 2010).