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Review Paper

A Concise Review Study on Diabetic Nephropathy: Risk Factors, Pathogenesis, and Treatment

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ABSTRACT:
Diabetes-related kidney disease is known as diabetic nephropathy (DN). It is also known as renal disease and manifests progressively over many years. It is assumed that DN will require therapy for about one in five diabetics. In developed countries, diabetic kidney disease is assumed as mainly responsible for end-stage kidney disease. It is suggested that about 40% of cases of diabetes are prone to diabetic kidney diseases. Thus, the incidence of increasing cases of this disease is linked to diabetic patients. Proteinuria is also an important indicator of diabetic kidney disease. However, the start and progression of kidney disease, as well as proteinuria, can vary widely from one person to another (Furuichi et al., 2018). Other pathological indicators include podocyte injury, structural changes in the glomerular filtration apparatus, reduction in glomerular filtration, and expansion of mesangium, etc. Although chronic albuminuria and a progressive loss in renal function are the hallmarks of the clinical illness. DN can also be treated to decrease its progression if identified early. This article will explain the clinical features of DN, epidemiology, risk factors, diagnosis, and treatment options.

Keywords: Diabetic nephropathy; Chronic Kidney Disease; Diabetic Kidney Disease; Podocyte injury; Glomerular filtration apparatus; Glomerular filtration rate

INTRODUCTION:

Urinary organs play an important role in our body. These organs comprise the kidney, ureter, urinary bladder, and urethra. These organs are involved in the filtration, processing, and transportation of urine. The kidney performs the filtration and processing of urine and these stages are termed as ultrafiltration, selective absorption, and selective secretion. During this processing essential metabolites, water, and electrolytes are conserved, and waste products are removed from the bold. The kidneys are bilateral organs that are located retroperitoneally in the upper left and right abdominal quadrants. Morphologically bean-shaped, the concave side has a hilum. Including the removal of metabolic waste and excess body fluid, the kidney also plays a key role in acid-base regulation, maintenance of blood pressure, and many other homeostatic parameters. Besides regulation of blood pressure and volume, kidneys also participate in the production of the active form of vitamin D (calcitriol), and the release of erythropoietin (Vaskovic, 2023).

Anatomically kidney comprises the cortex and medulla which contain nephrons, collecting ducts, and blood vessels. The nephrons are functional structures of the kidney that perform the processing of urine. Nephron has renal corpuscles (glomerulus, and Bowmans's capsule), convoluted tubules (PCT, DCT), straight tubules, and collecting tubules. The ultrafiltrate is generated in renal corpuscles and further processed in tubules. Finally, urinary filtrate enters the collecting duct via collecting tubules. Although in healthy kidneys, urine does not contain proteins, sugars, albumin, hemoglobin, and blood cells, but the presence of sugar, proteins, and RBCs represents kidney disorder. One of the main complications of diabetes mellitus (DM), DN leads to chronic renal failure. diabetes and hypertension, either in combination or separately leading to end-stage kidney failure. DN is found to be mainly responsible for kidney disease in patients starting renal replacement therapy (Gross et al., 2005).

This review article covers different aspects of DN; its association with diabetes, risk factors, and epidemiology. Including this, the pathogenesis of DN is discussed. Further, the role of structural changes in the glomerulus (podocyte, and basement membrane) and different other factors associated with DN are also discussed.

DIABETES AND DIABETIC KIDNEY DISEASE:

High blood glucose level is clinically termed hyperglycemia which is commonly developed due to insufficient production of insulin from the pancreas, or the body does not respond properly to insulin (Vaskovic, 2023). High blood glucose levels can harm the kidneys and cause renal disease. Diabetes is considered the most common cause of end-stage renal disease (ESRD) in the USA and causes more than 40% of patients to start renal replacement therapy every year. Gross et al., (2005) also suggested that DN affects about 40% of type 1 and type 2 diabetic individuals. However, it is also suggested that following early and rigorous blood glucose and blood pressure control, the development and progression of diabetic kidney disease may be slowed (Rabkin, 2003). Another study also suggested that about 40% of patients with diabetes have a chance to develop diabetic kidney disease (Qazi et al., 2022).

Hyperglycaemia causes disturbance in osmotic factors and leads to hyperfiltration, which is followed by metabolic, hormonal, haemodynamic, inflammatory, and epigenetic changes. Oxidative stress and hypoxia play a key role. These cause podocyte injury, mitochondrial distress, death of tissues, glomerulosclerosis, and interstitial fibrosis (Qazi et al., 2022).

STRUCTURAL CHANGES IN GLOMERULUS AND DN:

The changes in glomerular microvasculature are found linked with the development and progression of diabetic kidney disease.

Podocyte injury is assumed to contribute significantly to diabetic kidney disease, and loss of podocytes leads to proteinuria and progressive glomerulosclerosis (Ilatovskaya et al., 2015).

Podocytes are the important building blocks of kidneys. These cells are visceral cells of Bowman's Capsule and an important component of the glomerular filtration apparatus. The glomerular filtration barrier plays a key role in regulating renal function. Podocytes participate in maintaining the selectivity of the glomerular filtration barrier (GFB) and injury of the podocyte is associated with proteinuric glomerulopathies (Barutta et al., 2022). It has been demonstrated that podocyte injury is also a critical factor in the development of DKD.

Disturbances in podocyte function including hypertrophy, shedding, apoptosis, and reduced density affect the integrity of the glomerular filtration barrier, causing abnormal glomerular filtration rate, increased proteinuria, and increased creatinine levels (Li et al. 2023). It is also suggested that autophagy maintains lysosome homeostasis in podocytes under diabetic conditions and impairment in autophagy may be found associated with the pathogenesis of podocyte loss, causing severe proteinuria in DN (Yasuda-Yamahara et al., 2015).

Studies also revealed the role of endothelin-1 in the pathophysiology of DN. Endothelin-1 promotes podocyte injury through the activation of endothelin type A and B receptors. Further, endothelin receptor antagonists, (drugs like sparsentan and atrasentan) have shown nephroprotection in experimental models through decreasing podocyte injury and proteinuria (Empitu et al., 2024).

In the kidney, due to hyperglycaemia there will be non-enzymatic glycation of proteins of the basement membrane which results in increased glomeruli capillary pressure which further causes an increase in glomerular filtration rate. DN development takes years before the clinical manifestations, including microalbuminuria and reduction in the glomerular filtration rate (GFR).

In this duration, structural changes are established, like the thickening of the glomerular basement membrane (GBM), expansion of mesangium, and glomerulosclerosis (Marshall, 2016). The microalbuminuria (urinary albumin excretion of 30-300 mg/day, or 20-200 µg/min) is represented as the initial sign of vascular damage. It is also identified as a marker of general vascular dysfunction and used to predict worsening outcomes for heart and kidney patients (Koroshi, 2007).

The activation of RAAS, which results in efferent arteriolar vasoconstriction and afferent vasodilation and amplifies intraglomerular hypertension, is caused by hyperglycemia and SGLT2-assisted decreased distal sodium supply (Qazi et al., 2022). Systemic hypertension is made worse by RAAS activation. RAAS system is associated with the production of transforming growth factor (TGF-β), and plasminogen activator inhibitor that are further associated with matrix accumulation (Border and Noble, 1998).

When the oxygen supply cannot keep up with the demands of the kidneys, renal hypoxia occurs. While most of the demand is dependent on the metabolic activity in the tubules, this immediately correlates with the blood supply. There are numerous ways in which hyperglycemia can result in oxidative damage and hypoxia. Hyperglycaemia induces hyperfiltration and tubular hypertrophy, RAAS-mediated vasoconstriction produces ischemic damage, and over-activating SGLT2 channels leads the nephron to lose more adenosine triphosphate and oxygen, resulting in hypoxia.

A key factor in the pathophysiology of DKD is inflammation. Through oxidative stress, ischemia, and damaged cells, diabetes activates multiple inflammatory pathways that lead to the production of inflammatory molecules. In DN, the kidneys

experience a wide range of alterations, including early renal hypertrophy, vasoconstriction, endothelial and tubular cell damage, and ultimately renal fibrosis.

Due to high metabolic demand, the renal tubules contain a significant number of mitochondria. Chronic hyperglycemia triggers the production of reactive oxygen species (ROS), which are involved in the activation of many pathways involved in associated with mitochondrial dysfunction, diabetic complications, as well as insulin resistance (Kaikini et al., 2017).

Unfortunately, all the aforementioned mechanisms combine and eventually lead to fibrosis and atrophic renal tissue. Renal function can also be predicted by the degree of tubulointerstitial fibrosis rather than glomerular abnormalities. This effect has been linked to local myofibroblasts, fibrocytes, and epithelial to mesenchymal transition in response to chemokines.

EPIDEMIOLOGY:

DN is the leading cause of chronic kidney disease in the United States and is a major cause of cardiovascular disease and death (Marshall, 2016). Although the percentage of diabetics who acquire chronic kidney disease (CKD) has decreased due to advancements in diabetes care, however, innovative treatments are required to treat, prevent, and reverse diabetic kidney disease (Thomas et al., 2015). According to studies, the prevalence of diabetes is expected to rise steadily worldwide, potentially impacting over 366 million people (Martínez-Castelao et al., 2015). Increasing the number of diabetic people will increase the number of patients with diabetic kidney disease. The World Health Organization's key facts about diabetes revealed that the number of diabetic people in the world has increased from 200 million (in 1990) to 830 million (in 2022). Furthermore, out of the total number of diabetic cases, type-2 diabetes contributes about 95% of cases (WHO, Diabetes Key Facts, 2024). One of the long-term complications of diabetes is diabetic kidney disease. At the global level, diabetic kidney disease is associated with the development of chronic kidney disease. In addition, Diabetic Kidney disease also causes high cardiovascular mortality and morbidity and reduces health-related quality of life (Hoogeveen, 2022). Thus, an increase in the number of diabetic cases is expected to increase the incidences of diabetic kidney diseases. Moreover, the type of diabetes, the technique of diagnosis, and the length of the disease all affect the prevalence of the condition (Koye et al., 2018). India and other developing nations are predicted to see the biggest rises. In a clinical study prevalence of DN was assessed in 200 patients diagnosed with type 2 diabetes patients. In this study, 13% prevalence of DN was found. Including this, 12% of patients were identified with microalbuminuria and 1% of patients were diagnosed with macroalbuminuria. (Ravindran et al., 2020). Mayo Clinic estimates that in the USA, about 1 out of 3 people having diabetes is affected with DN (Mayo Clinic, 2023).

RISK FACTORS:

Diabetic kidney disease is generally diagnosed in diabetic patients with prolonged diabetes with albuminuria and/or reduced estimated glomerular filtration rate. It is worthwhile to state that DN is one of the most important complications of diabetes.

People with type 1 and type 2 diabetes have similar risks of developing diabetic kidney disease. However, nephropathy will only develop in about 30–40% of individuals with either type (Tang et al., 2021). Including diabetes, there are many risk factors (Fig. 1) associated with DN such as; obesity, hyperglycemia, hypertension, high blood cholesterol, smoking, and a family history of diabetes and kidney disease (Mayo Clinic, 2023). It is suggested that chronic hyperglycemia and high blood pressure are the main risk factors associated with the development of DN (Samsu, 2021).

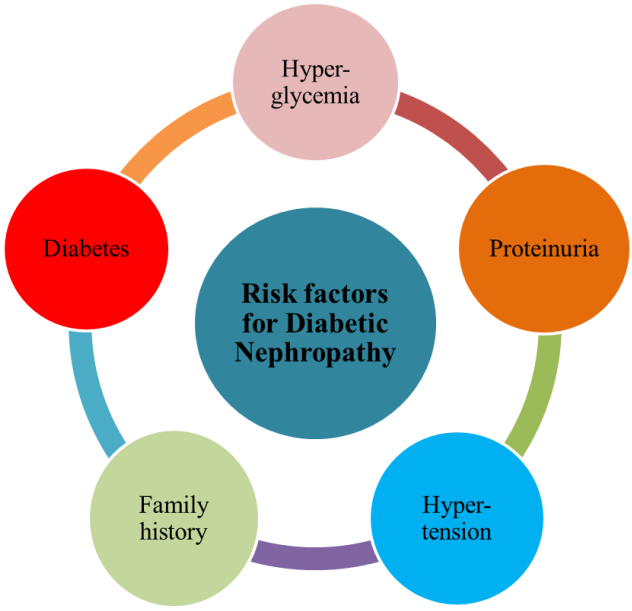

Fig.1: Risk factors for diabetic nephropathy

Natesan and Kim (2021) classified risk factors into groups; modifiable (hypertension, glycemic level management, and dyslipidemia) and non-modifiable factors (race, gender, age, gestation, and genetic profile). Proteinuria is also an important hallmark of diabetic kidney disease and independent risk factor for both cardiovascular disease and renal disease progression (Jefferson et al., 2008).

PATHOGENESIS OF DN:

DN is one of the major causes of microvascular conditions (Park, 2014). DN develops in patients having a history of diabetes and renal failure (Nazar, 2014). DN and DKD are mainly considered responsible for end-stage kidney disease in the United States and many other developed countries. In the USA, diabetes is associated with 30% to 50% of the cases of end-stage kidney disease (Umanath and Lewis, 2018). There are varieties of treatment options available for DN but no permanent cure.

Diabetic kidney disease is represented by the accumulation of extracellular matrix proteins in the kidney, which results in tubulointerstitial fibrosis, thickening of the GBM, mesangial hypertrophy and enlargement, and infiltration of macrophages and monocytes causing inflammation. These factors further cause loss of kidney functions and lead to progressive chronic kidney disease and failure of the kidney (Tang et al., 2021).

The pathogenesis of DN is complex. Numerous pathways and mediators are involved in the intricate pathophysiology of DN, which aids in the onset and advancement of the condition. Abnormal homeostasis, which includes hemodynamic and metabolic abnormalities as well as hormone production like angiotensin II (Ang-II) is usually the cause of DN. Reactive oxygen species (ROS), protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), transforming growth factor-β1 (TGF-β1), connective tissue growth factor (CTGF), renin-angiotensin-aldosterone system (RAAS), and advanced glycation end products (AGEs) are important pathways linked to the progression of DN (Samsu, 2021).

Because many pathways play overlapping functions, the precise pathogenic process is still unknown. Growth, hemodynamic, metabolic, and proinflammatory or fibrotic factors produce lesions in kidney compartments. Further involvement of enzymes, molecules, and transcription factors results in glomerulosclerosis, interstitial fibrosis, tubular atrophy, ECM enlargement, and end-stage renal disease (Agarwal, 2021).

METHODS TO DIAGNOSE DN:

DN is generally diagnosed during the regular testing of diabetes patients. Routine screening tests for DN may be Urinary albumin test, Albumin/creatinine ratio, and Glomerular filtration rate (GFR). Including this, other diagnostic methods associated with the diagnosis of DN are X-Ray, Ultrasonography, CT, MRI, and kidney biopsy (Mayo Clinic, 2023).

The diagnosis to check the presence of microalbuminuria, macroalbuminuria, and high plasma creatinine also plays an important role in the diagnosis of nephropathy. Adler et al., (2003) used the many stages of nephropathy: No nephropathy, Microalbuminuria, Macroalbuminuria, and Elevated plasma creatinine or renal replacement therapy.

TREATMENT:

Diabetic Kidney Disease is heterogeneous in nature due to its histopathology, clinical manifestations, and progression rate. Specific treatment of patients with DN can focus on 4 major areas: glycemic control, control of blood pressure, risk reduction of cardiovascular diseases, and controlling the renin-angiotensin system (Umanath and Lewis, 2018).

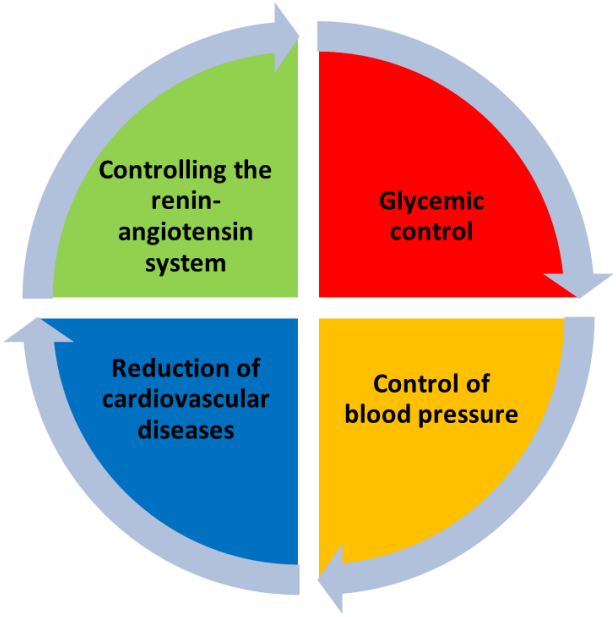

Fig. 2: Approaches to control the diabetic nephropathy

Mayo Clinic has suggested multiple therapeutic options for DN. These medicines are used to control Blood pressure (use angiotensin 2 receptor blockers and ACE inhibitors), blood sugar (use of insulin, metformin, glucagon-like peptide 1 receptor agonists and SGLT2 inhibitors), high cholesterol, and kidney scarring (Finerenone/Kerendia) (Mayo Clinic, 2023). Research has shown that medicines might lower the risk of kidney failure.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are specifically recommended for blood pressure control since these RAAS inhibitors have shown renoprotective effects in addition to lowering blood pressure. It is recommended to target a haemoglobin A_{1c} concentration < 7%, blood pressure < 140/90 mm Hg with therapy using a RAS-blocking agent (Umanath and Lewis, 2018).

Despite the glycaemic control and blood pressure management, renin-angiotensin-aldosterone system (RAAS) blockade, the current therapeutic approaches are not completely controlling the progression of DKD to ESKD in some patients. Including this, two categories of antidiabetic drugs, glucagon-like peptide-1 (GLP-1) receptor agonists, and inhibitors of sodium-glucose cotransporter 2 (SGLT2), demonstrated renoprotection demonstrated kidney protection (Sugahara et al., 2021).

CONCLUSION:

Diabetes mellitus patients who have DN, sometimes referred to as diabetic kidney disease, experience a continuous loss of kidney function. The most common cause of end-stage renal disease and chronic kidney disease is DN. Many types of CKD have the triad of protein leakage into the urine (proteinuria or albuminuria), escalating blood pressure with hypertension, and finally declining renal function. Proteinuria is considered as the main sign of DN. This develops slowly, starting out as sporadic microalbuminuria, then progressing to constant proteinuria and sporadically nephrotic syndrome.

The understanding of the risk factors and processes of DN, the stages of renal involvement in diabetes, and the therapy approaches to stop or slow the course of DN have all advanced significantly in recent years. For treatment, there are many suggested approaches such as maintenance of blood sugar level, blood pressure, and lipids with medication, change in lifestyle (exercise, healthy diet, and quitting smoking etc), and use of proper medications. Despite the advancement in care, the number of patients suffering from diabetic kidney disease and end-stage renal disease is increasing. This reflects that current management strategies are not sufficient (Park, 2014).

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