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Diabetic Nephropathy and Management

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Abstract

Chronic kidney disease affects people worldwide. Approximately 1 out of 3 adults with diabetes have kidney disease. Among several etiological factors for CKD, diabetes mellitus (DM) and hypertension are the main factors. These factors not only cause CKD but are also responsible for several complications related to CKD. In this article, we have reviewed Diabetic Nephropathy (DN) in terms of etiology, pathophysiology, diagnosis, management, current guidelines for diabetic nephropathy management, and some of the research study findings. Diabetic nephropathy (DN) is the chief factor for end-stage renal disease (ESRD) development across the globe. The primary cause of DN is Diabetes Mellitus, which is an autoimmune lifestyle disorder having several etiological factors. Checking for urine albuminuria, estimated GFR (eGFR), and blood glucose are unswerving tests for DN diagnosis and subsequent monitoring. Controlling hyperglycemia, blood pressure, and proteinuria are critical in stopping the progression of DKD. Clinical practice and evidence-based medicine demonstrated that early diagnosis followed by treatment can prevent or halt DKD progression.

Keywords

Diabetic Kidney Disease, Diabetic Nephropathy, Chronic Kidney Disease, Cardiovascular Risk Management, Urine Albumin Creatinine Ratio, Renal Replacement Therapy, Chronic Kidney Disease Management

1. Introduction

[1] Chronic kidney disease and diabetic nephropathy have significant global prevalence and impact on public health and healthcare systems. CKD is a widespread health concern affecting people of all ages and backgrounds. According to the Global Burden of Disease Study 2017, globally CKD was considered as the 12th leading cause of death. CKD prevalence varies by region and population. In developed countries, the estimated prevalence of CKD stages 3 - 5 ranges from

5% to 15% of the adult population. Due to factors such as limited access to healthcare and high rates of diabetes and hypertension, CKD prevalence is higher in low and middle-income countries.

CKD and diabetic nephropathy impose a substantial economic burden on healthcare systems. Costs include treatments, medications, dialysis procedures, transplant surgeries, and management of associated complications. These conditions also lead to indirect costs due to lost productivity, decreased quality of life, and increased healthcare utilization. Therefore, it is crucial to address these medical conditions. CKD can progress to ESRD and requires kidney replacement therapy such as dialysis or transplantation. This poses a significant burden on healthcare systems and the quality of life for affected individuals. Patients with poorly controlled blood sugar levels are commonly prone to complications of DM. Especially as diabetes prevalence rises, the incidence of diabetic nephropathy is also expected to increase. Diabetic nephropathy is a leading cause of ESRD worldwide. It is significantly responsible for diabetes-related morbidity and mortality. It often requires intensive medical management, dialysis, or kidney transplantation to maintain kidney function.

Diabetes is considered an autoimmune, metabolic, lifestyle disorder. The exact cause of diabetes is difficult to detect; however, several factors can increase the propensity to get diabetes such as; genetic predisposition, hyperglycemia, autoimmune tendencies, stressful or unhealthy lifestyle, and dietary habits. Approximately 1 out of 3 diabetes patients develop diabetic nephropathy [2]. Diabetic Nephropathy (DN) is also called the kidney disease of diabetes or diabetic kidney disease, a major cause of end-stage renal disease (ESRD) across the world [3]. Chronic kidney disease is caused by systemic diseases such as increasing the duration of diabetes, hypertension, autoimmune disorders, malignancy, chronic infection, and genetic disorders. Therefore, early CKD screening is suggested in respective patients in addition to the patients who have a history of acute kidney injury, obesity, renal atrophy, recurrent urinary tract infections, kidney stones, reduced kidney mass, and certain medications such as certain antibiotics, laxatives, supplements, proton Pump Inhibitors (PPIs), NSAID, diuretics. DN is recognized as a microvascular complication characterized by persistent high glucose, increased albuminuria, and an ongoing decline in the glomerular filtration rate.

Hypertension is not only a complication of diabetes nephropathy, but it is also considered to be a direct causative factor for diabetic nephropathy. Microalbuminuria is recognized as the product of vascular, endothelial dysfunction and the risk factor for cardiovascular disease [4]. It has been observed that high blood pressure and insulin resistance increase microalbuminuria and thereby increase cardiovascular and renal risk accompanied with or without metabolic syndrome. It has been shown that even with <30 mg/day microalbuminuria which is a higher normal limit, the cardiovascular and renal risk is increased; therefore, the treatment approach for DN is focused on early diagnosis, prevention, monitoring, and delaying the development of DN, microalbuminuria, and associated

complications including ESRD [5].

2. Epidemiology

Chronic kidney disease and diabetic nephropathy have significant global prevalence and impact on public health and healthcare systems. CKD is a widespread health concern affecting people of all ages and backgrounds. According to the Global Burden of Disease Study 2017, globally CKD was considered as the 12th leading cause of death. CKD prevalence varies by region and population. In developed countries, the estimated prevalence of CKD stages 3 - 5 ranges from 5% to 15% of the adult population. Due to factors such as limited access to healthcare and high rates of diabetes and hypertension, CKD prevalence is higher in low and middle-income countries. As diabetes prevalence rises, the incidence of diabetic nephropathy is also expected to increase. Diabetic nephropathy is a leading cause of ESRD worldwide. It is significantly responsible for diabetes-related morbidity and mortality. It often requires intensive medical management, dialysis, or kidney transplantation to maintain kidney function.

As reported by the World Health Organization in 2019, diabetes and related kidney diseases were responsible for 2 million deaths, and it includes approximately half of the population below 70 years of age. In 2021 according to the report of the International Diabetes Federation diabetes was the cause of 6.7 million deaths and affected almost 10% of the worldwide. The diabetes prevalence rate is forecasted to increase to 643 million and 783 million by 2030 and 2045 each. As per CDC report diabetes type I, and II are the most common causes of the development of DN, and it occurs in 20% to 50% of Diabetes patients. In the United States in 2023, about 26 million people were reported to have diabetes. Diabetes is responsible for more than 200,000 people, which is 44% of people with ESRD who are on chronic renal dialysis or had a kidney transplant. This number stands at 28% in the United Kingdom and 38% in Australia. Albuminuria could be seen at the diagnosis of T2 DM whereas for T1DM it may take up to 15 to 20 years to develop albuminuria after the initial diagnosis. The robust risk factors for developing diabetic nephropathy are longer duration of DM, uncontrolled glycemia, hypertension, genetic or family history of cardiovascular events, diabetes, and hypertension in immediate relatives. The lack of physical exercise, unhealthy dietary habits such as intake of fatty, fast food, lack of fruits, and vegetables, and chronic stress could increase diabetes risk. With the help of a healthy lifestyle and dietary choices, prediabetes is reversible. Prediabetes affects more than 38% of adults in the United States [6]. Diabetes gradually impacts the pathophysiology of the kidney resulting in proteinuria, reduction in GFR, and hypertension. As compared to DN patients with proteinuria, nonproteinuric diabetic kidney disease has superior blood pressure control, lesser pathophysiological changes in the kidneys, risk for disease progression, ESKD, and associated mortality; however, risk of major cardiovascular events and death still exist as compared to non-CKD status.

3. Pathophysiology

Uncontrolled blood glucose causes hyperfiltration, which can be seen as an adaptive response to cope with the increased glucose load, but over time, it can lead to maladaptive changes that worsen kidney function. Hyperfiltration can cause glomerular hypertrophy and increase the glomerular capillary pressure and permeability, allowing more protein and other molecules to leak into the urine. Hyperfiltration can also cause glomerulosclerosis, a scarring of the glomeruli due to inflammation and fibrosis. These changes can impact the optimum functionality of the kidney affecting the filtration of extra fluid and waste products from the blood [7].

Hyperglycemia itself, which can increase oxidative stress and activate inflammatory pathways in the kidney cells [8]. AGEs and their receptors can induce cytokine production and leukocyte adhesion in the kidney cells and proteinuria can stimulate inflammatory responses in the tubular cells and interstitial tissues [9]. Infections, which can activate innate immunity and toll-like receptors in the kidney cells. Inflammation can contribute to kidney damage by causing endothelial dysfunction, vascular leakage, cell death, fibrosis, and tubular atrophy. Inflammation can also interact with hyperglycemia and hyperfiltration in a vicious cycle that amplifies renal injury. Therefore, hyperglycemia can cause both hyperfiltration and inflammation in the kidneys of people with diabetes. The timing and severity of hyperfiltration and inflammation may also depend on other factors such as genetic susceptibility, environmental exposure, comorbidities, and treatment interventions.

4. Histopathology

The histopathologic changes play important roles in the progression of the disease [10]. It includes inflammation, hypertrophy of glomerular and tubular basement membrane, endothelial and podocyte cell damage, Kimmelstiel-Wilson nodules and increase in mesangial matrix.

5. Management of Diabetic Nephropathy

Diagnosis

The criteria for DN diagnosis include:

- Persistent albuminuria > than 300 mg/g on two 3 - 6 months visits intervals.
- Persistent high blood pressure.
- Gradual decline in glomerular filtration rate.

Patients could be symptomless and DN could be an incidental finding during routine screening labs testing which indicates urine protein creatinine ratio 30 - 300 mg/g.

Or patients could present with signs and symptoms of feet edema due to nephrotic syndrome, hypoalbuminemia, foamy urine, fatigue, or other signs and symptoms of uncontrolled diabetes. Patients could have concomitant hypertension, coronary artery disease, diabetic retinopathy or peripheral vascular disease.

Urinalysis examination detects urea, protein and creatinine and urine microscopic examination rules out nephritic cause of kidney disease.

The patient is diagnosed with DN when early morning or random urine samples show urine protein creatinine ratio of 30 to 300 mg/g on repeated test performed on at least three-monthly intervals. Multiple myeloma can be ruled out with the help of Serum and urine electrophoresis test. Kidney ultrasound can be used for the diagnosis of CKD as it examines the morphology of kidney and rules out urinary obstruction [11]. The kidney biopsy is indicated if the cause is not clear, increased UACR, swift decline in GFR, presence of urinary cellular casts and dysmorphic red blood cells [11] [12] [13]. Kidney blood vessels status can be evaluated with the help of Magnetic resonance imaging and computed tomography scans.

DN typically do not any cause symptoms until 80% to 90% of kidneys get affected. Therefore, ADA and KDIGO guidelines suggested testing of kidney function test and albuminuria annually in diabetes type II patients and 5 years after the initial diagnosis in type I DM patients [14] [15].

Differential Diagnosis of DN

- Nephrotic Syndrome;
- Multiple Myeloma;
- Nephrosclerosis;
- Glomerulonephritis;
- primary glomerular disease;
- Renovascular Hypertension;
- Tubulointerstitial Nephritis;
- Renal Artery Stenosis;
- Renal Vein Thrombosis Imaging;
- Light-Chain Deposition Disease.

Sudden acute onset of albuminuria or nephrotic syndrome point out to primary glomerular disease rather than DN. Certain medical conditions can cause temporary rise in UACR such as uncontrolled hypertension or hyperglycemia, urinary tract infection, systemic infection or inflammation, heart failure, vigorous exercise etc. In T1DM patients DN is diagnosed when there is a moderate—severe ongoing albuminuria or > than equal to 5 mL/min/year reduction in EGFR. Patients with long long-term urinary catheters and ileal conduit it is difficult to construe UACR results in them.

6. Current Guidelines for Diabetic Nephropathy Management

Management of diabetic nephropathy is just like management of chronic kidney disease and it includes.

- Cardiovascular risk management, hyperlipidemia control with statin, blood pressure and albuminuria control with RASSi therapy (ACE and ARE inhibitors).
- Blood glucose control with the help of healthy life and dietary choices, oral or

subcutaneous hypoglycemic agents.

- Monitor kidney function test, urinalysis, urine albumin-creatinine ratio and Hemoglobin A1c level. Target HbA1 C value to be less than 7.5% in DM patients.
- In case of abnormal kidney function test mediate, treat the complications of chronic kidney disease followed by ongoing monitoring.
- Reduce protein consumption to 0.8 g/kg body, watch for wasting and nutritional deficiency.
- Avoid nephrotoxic agents and drugs.
- Healthy life choices such as renal compliance diet, exercise, weight reduction, avoidance of fatty or fast food, adding fruits and vegetables in the diet, smoking and alcohol cessation.
- Refer patients to see Nephrologist in case GFR is below 30 ml/min.

Established Classes for FDA approved antidiabetic medications:

Types of Insulin, Sodium-Glucose Cotransporter Type 2 Inhibitors, Sulfonylureas (SU), Meglitinides, Incretin-Dependent Therapies (GLP1 Receptor Agonists and DPP4 Inhibitors), Biguanides, Thiazolidinediones, Alpha-Glucosidase Inhibitors.

In progressive kidney failure diabetic medications require frequent monitoring and dose adjustment as the medications may stay in the body for extended time due to reduced renal clearance leading to hypoglycemia. Hypoglycemic agent Metformin is prohibited if GFR < than 30 mL/min/1.73m^2 as it can cause lactic acidosis.

Nephrotoxic medications: NSAID, intravenous contrast requires nephrology consultation due acute kidney injury risk among DN patients. NSAID is also not recommended for CKD patients who are on ACE/ARB [16]. For CKD patients Eight joint National Committee and Kidney Disease guidelines suggested a goal of < than 140/90 mm Hg systolic and diastolic blood pressure [11] [17] and a goal of < than 130/80 mm Hg systolic and diastolic blood pressure for patients who has UACR > 30 mg per 24 hours [11] [18]. Simultaneous intake of two different RAASi therapies can cause adverse events such as hyperkalemia and acute kidney injury [19] [20] therefore it should not be prescribed together.

Due to the risk of hyperkalemia RAASi therapy is contradicted or restricted in some patients and it may require frequent dose adjustments. In such patientss sodium zirconium cyclosilicate and patiromer can be used to manage hyperkalemia [21] [22].

There were several emerging or experimental treatments being explored for diabetic nephropathy. SGLT2 Inhibitors reduce glucose reabsorption by kidneys and increase excretion. Recent studies have shown that SGLT2 inhibitors might also have beneficial effects on kidney function and can slow the progression of diabetic nephropathy. Empagliflozin, canagliflozin, and dapagliflozin are examples of SGLT2 inhibitors. GLP-1 Receptor Agonists improve blood sugar control by stimulating the release of insulin and suppressing glucagon, such as liraglutide and semaglutide. These agents have shown potential in the reduction of

CKD progression in patients with diabetes. Chronic inflammation plays a major role in the development and progression of DN. Researchers have been investigating various anti-inflammatory agents, including certain monoclonal antibodies and small molecules, to target inflammatory pathways and potentially slow down kidney damage. Researchers are exploring new ways to modulate the renin-angiotensin aldosterone system to improve kidney health. For instance, dual-acting angiotensin and neprilysin inhibitors (ARNIs) are being studied for their potential benefits in diabetic nephropathy. Endothelin is a peptide that contributes to blood vessel constriction and plays a role in kidney damage. Endothelin receptor antagonists, such as avosentan, were being investigated to block the effects of endothelin and potentially slow the progression of kidney disease. Atrasentan is an investigational drug that targets the endothelin system. It's being studied for its potential to reduce proteinuria and slow the progression of diabetic nephropathy. Regenerative medicine approaches, such as stem cell therapy, are being explored to promote kidney tissue regeneration and repair. Research is ongoing to identify specific genes and molecular pathways that contribute to diabetic nephropathy. Targeting these pathways through genetic or molecular interventions could provide new treatment avenues [22].

7. Renal Replacement

ESRD patients with GFR 10 - 15 ml/min peritoneal dialysis, hemodialysis, renal transplant, conservative treatment are suggested. The appropriate treatment options should be discussed and evaluated with the patients; patients' thoughts and decisions be considered.

8. Research Studies Findings

CKD Prognosis Consortium conducted a meta-analysis which showed CKD patients with DM has higher risk of outcome such as ESKD, mortality, cardiovascular mortality as compared to those without diabetes, the risks of these outcomes are similar with the abnormal values of eGFR and UACR. This conclusion led to the suggestion that one of the agents of RASSi therapy in combination with direct renin inhibitors, may provide additional benefit by greatly reducing albuminuria. Several studies showed ideal blood pressure control and HbA1C control at 7% reduces the risk of cardiovascular mortality and microvascular complications, including nephropathy [23].

Research Studies showed the benefits of glycemic control in reducing proteinuria and microalbuminuria in T2DM and T1DM [24]. Clinical practice and evidence based medicine demonstrated the effectiveness of RASSI therapy in controlling hypertension, albuminuria, delaying microvascular complications, cardiovascular events, neuropathy, nephropathy, retinopathy, progression of kidney disease and death [25] [26].

Research studies documented that in DN patients' albuminuria has been reduced in 90 days after the addition of third-generation mineralocorticoid receptor antagonist, finerenone and RASSi therapy. The secondary outcome of Car-

diovascular studies showed the beneficial effect of SGLT2 inhibitors in the reduction of DN progression, cardiovascular mortality, and albuminuria [27] [28].

Many research studies are in the process of finding the beneficial effect of these medicines in the progression of CKD.

9. New Insights, Methodologies, or Perspectives

Researchers have been working on identifying biomarkers and genetic markers that can predict DN development and its development at an earlier stage. This allows for more targeted interventions and personalized treatment approaches. Advances in genetics and personalized medicine have led to a growing interest in tailoring treatments for diabetic nephropathy based on an individual's genetic makeup, metabolic profile, and other specific factors. Emerging research has suggested a potential link between the gut microbiome and kidney health. Alterations in the gut microbiota composition could influence the development and progression of diabetic nephropathy. Understanding this connection might lead to novel therapeutic strategies. New imaging technologies, such as advanced MRI techniques, allow for a more accurate assessment of kidney structure and function. These techniques can provide insights into early changes in the kidneys before significant damage occurs. Analysis of data from a large number of patient populations by using AI and machine learning can identify disease patterns and predict disease progression more accurately. Research targets the specific molecular pathways that are responsible for the development of diabetic nephropathy. These therapies aim to slow down or halt the progression of the disease. Some researchers are exploring regenerative medicine approaches, including stem cell therapy, to promote the regeneration of damaged kidney tissue and restore proper function. Lifestyle factors like healthy diet and exercise play a significant role in managing diabetes and its complications. New insights into the optimal dietary patterns, exercise regimens, and other lifestyle modifications could have emerged. Instead of relying solely on one treatment approach, combining multiple therapies such as pharmacological, lifestyle, etc. might yield more effective results in managing diabetic nephropathy. A shift toward more patient-centered care involves considering individual patient preferences, values, and circumstances when making treatment decisions [29].

10. Conclusions

Diabetic nephropathy is the primary cause of chronic renal disease and the outcome of ESRD. It increases the risk for Cardiovascular mortality and risk for all-cause mortality 15 - 30 times higher than patients without Diabetic nephropathy. The best strategy to prevent diabetic nephropathy is; early diagnosis, control of hyperglycemia, hyperlipidemia, microalbuminuria, hypertension, appropriate treatment approaches, timely checking screening labs, implementation of healthy life choices such as weight reduction, balanced diet, smoking cessation, exercise, and controlled protein intake.

Diabetic nephropathy often develops gradually, and early detection allows for interventions that can slow or even halt its progression, reducing risk for DN related complications and improving the quality of life of patients. Preventing or delaying kidney failure reduces the need for subsequent expensive interventions. Ongoing research aims to develop innovative therapies targeting specific molecular pathways involved in diabetic nephropathy. These treatments could offer more effective ways to slow or reverse the progression of the disease. Research efforts are focused on identifying biomarkers that can predict DN development and progression at an early stage.

In summarize, early diagnosis allows for timely intervention, effective management strategies can slow disease progression and reduce complications, and ongoing research efforts drive innovation in treatment approaches. The collaboration between healthcare providers, researchers, and individuals with diabetes is essential to combat diabetic nephropathy and improve the lives of those affected by this condition.

Conflicts of Interest

The author has no conflict of interest.

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