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Breaking Down The Silent Killer: A Comprehensive Review Of Diabetic Nephropathy.

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ABSTRACT

Diabetic nephropathy (DN) is a chronic microvascular complication of diabetes mellitus (DM) that affects susceptible individuals after 15 to 25 years of DM. Globally, DN is the main cause to end-stage renal disease (ESRD) and is estimated to develop in one third of both types of DM. The pathophysiology of DN involves glomerular basement membrane (GBM) thickening and arteriosclerosis of small arterioles, induced by hyperglycemia, hyperfiltration, and increased blood viscosity. The hallmark of renal damage in DM is increased excretion of albumin in the urine. DN manifests as a clinical syndrome composed of albuminuria, progressively declining glomerular filtration rate (GFR), and increased risk for cardiovascular diseases (CVD). The alarming increase in the prevalence of DM, especially in developing countries like India, has an impact on the costs of management of DM and its complications, including DN. The care of DM and its complications presents a challenge for most healthcare professionals in developing countries. The cost of DN management in India is increasing, and patients with CKD spend more per hospitalization than patients without any complications. Therefore, early detection and management of DN are essential to reduce the burden of this chronic complication on healthcare systems and improve patient outcomes.
Keywords: Diabetic nephropathy, Diabetes mellitus, albuminuria, DM complications.

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INTRODUCTION

India has 15% of the global population. Even with a low prevalence rate, India's large population poses a major problem for diabetes mellitus (DM) patients. Many people may have undetected DM [1, 2]. DM is a metabolic disorder that causes chronic hyperglycemia, carbohydrate, fat, and protein metabolism disturbances, and insulin resistance or production at any age [3].

Scientists are still classifying and determining the prevalence of some DM variants. Type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational, and other types of DM are classified by the WHO and ADA based on aetiology [4, 5]. Ageing, rapid urbanisation, and obesogenic environments are responsible for T2DM's 90% rise. T1DM incidence is rising, contributing to diabetes prevalence [6-8].

This increase is unknown. Early detection, better management, and lower premature mortality in diabetics contribute to the increased prevalence [9]. Finally, as younger adults live longer, their T2DM prevalence has increased [6, 10]. DM's long-term "complications" have the greatest impact on health and the healthcare system [11]. Long-term, uncontrolled DM damages, dysfunctions, and fails organs, especially the eyes, kidneys, heart, neural tissue, and blood vessels, causing obesity, neuropathy, nephropathy, retinopathy, cardiopathy, osteoporosis, coma, and death [12, 13]. Microvascular complications are DM's most specific [14].

Diabetic Nephropathy

Diabetic nephropathy (DN) is a late chronic microvascular complication of T1DM and T2DM that develops in susceptible people after 15–25 years of DM [15, 16]. It causes most ESRD worldwide. [17] ESRD requires dialysis, which could become unaffordable even for developed countries [18]. One third of both main types of DM develop DN [19].

GBM thickening and small arteriole arteriosclerosis characterise nephropathy. Hyperglycemia, hyperfiltration-related glomerular pressure increase, and blood viscosity may cause glomerulosclerosis. [20-22] DM renal damage is marked by increased urine albumin excretion [23]. Most hemodialysis and renal transplant patients have DM, which can cause uremia [24].

In both developed and developing nations, DM is the most common cause of chronic kidney failure, and extrapolations suggest that the number will multiply in the future due to the fact that 1) DM, particularly T2DM, is increasing in prevalence; 2) DM patients now live longer; and 3) diabetic ESRD patients are now accepted for treatment in ESRD programmes [18, 20]. Family-based studies suggest that DN risk is genetic in 20-30% of DM patients [25]. DN is characterised by albuminuria, declining GFR, and increased cardiovascular disease risk (CVD) [18, 20].

Diabetics require a lot of health care. Most doctors in developing nations like India struggle to treat diabetes and its complications. The alarming rise in diabetes prevalence affects the cost of diabetes management and complications in developing countries, especially India. CKD patients spent more per hospitalisation than non-CKD patients. Diabetics on hemodialysis cost four times more than pre-ESRD diabetics. Dialysis patients had a median cost of Rs. 61,170, compared to Rs. 12,664 for other CKD patients. Renal transplantation cost median Rs. 392,920 (range 50,800-527,000) [26].

Diabetes, hypertension, cardiac diseases, kidney or liver failure, mental illness, and cancer tertiary specialty care in India is changing. Due to diagnostic and treatment costs, low-income patients have trouble accessing health care. Even in public hospitals, patients had to pay out-of-pocket expenses (OOPE) that impoverished them. Khan A et al [27] found that ESRD patients spent Rs. 364,488.41 annually out of pocket. Dialysis and transplantation are included.

DN is caused by uncontrolled high blood glucose and characterised by increased urinary albumin excretion (UAE) greater than 300 mg in 24-hour collection, abnormal renal function, and no other renal diseases [20, 28]. Early DN is microalbuminuria. Microalbuminuria, a metabolic syndrome component, predicts CVD in both DM and non-DM patients [17].

Epidemiology Of DN

In 2000, DM caused almost 3 million deaths, 5% of global all-cause mortality [29]. DM patients are expected to rise to 10.2 percent (578 million) by 2030 and 10.9 percent (700 million) by 2045. [6]. DN, the leading cause of ESRD, has skyrocketed alongside DM [30].

DN causes 40% of ESRD worldwide [31]. ESRD and dialysis cost health, social, and financial resources. [29] 20-40% of T1DM and T2DM patients develop DN within 20-30 years of DM.[32]. African Americans, Asians, and Native Americans have more DN [33, 34]. African Brazilians are more likely to develop ESRD than European Brazilians, but micro- or macroalbuminuria is similar. Progressive kidney disease is more common in Caucasians with T1DM than T2DM, but because T2DM is more common, its prevalence in the DM population is higher [35].

Epidemiology studies of T2DM patients show DN prevalence ranging from 7.6 percent to 55 percent, while international registries show 11.5 percent in UK and 42.9 percent in Thailand. [16] In 1991–2001, DN doubled in US kidney replacement patients [33]. According to the 18-year Danish study and the European Diabetes (EURODIAB) Prospective Complications Study Group, microalbuminuria develops in 12.6 percent (after 7.3 years) and 33% of type 1 and type 2 DM patients, respectively [34]. Microalbuminuria in type 2 DM patients in Great Britain was 2% annually and 25% ten years after diagnosis, according to the UKPDS [36].

Six million six hundred thousand million of 30 million DM patients in India will develop DN. [28] DN causes 46% of CKD in the elderly. In the "Chennai Urban Rural Epidemiology Study," urban DM patients had 2.2 percent overt nephropathy and 26.9 percent microalbuminuria. [30] DN causes retinopathy, neuropathy, and other DM complications and is costly [20].

Classification Of Diabetic Nephropathy

Microalbuminuria, a "preclinical" stage of DN, was discovered in the early 1980s by independent researchers. Three stages of DN are taught. Table 1 shows the cut-off values for these stages [37, 35].

Table 1: Definitions of abnormal albumin excretion

	Urinary AER (mg/day)
Normal	<30
Microalbuminuria	30-300
Macroalbuminuria	>300

Since most T2DM patients have had hyperglycemia for years before diagnosis, microalbuminuria may be present at diagnosis. DM renal changes develop in stages [37]. The Ministry of Health, Labor, and Welfare-subsidized Project on Kidney Disease's "historical cohort study" on T2DM patients' prognoses was used to revise the classification. Microalbuminuria indicates incipient nephropathy. Regardless of urinary albumin/protein levels, patients with a GFR below 30 mL/min/1.73 m2 have kidney failure [38]. Although increased kidney size and Doppler indicators may be early morphological signs of DN, proteinuria and GFR are the best indicators of renal damage [37, 39, 40].

Natural History

For over a decade, microalbuminuria has predicted progression to overt albuminuria in T1DM and T2DM. Clinicians should be alerted to prevent microalbuminuria from becoming proteinuria. Microalbuminuria is a sign of DN progression because research has shown that once proteinuria develops, renal function declines regardless of the type of DM at the same rate [37].

Albumin excretion is 10-15 mg/day in healthy people. However, unless albuminuria exceeds 300 mg/day, which is abnormal but cannot be detected by routine laboratory tests, these small amounts of albuminuria are not found. The first laboratory and clinical evidence of DN is microalbuminuria (30-300 mg/day), also known as incipient nephropathy [18, 20, 39]. It's 30% of T1DM patients [18]. 80 percent of T1DM patients with sustained microalbuminuria develop overt nephropathy or clinical albuminuria in 10–

15 years without treatment, with hypertension. Within 10 years, 50% of T1DM patients with overt nephropathy develop ESRD, and 75% do so within 20 years [20].

Since DM is present for years before diagnosis, a higher percentage of T2DM patients have microalbuminuria and overt nephropathy shortly after diagnosis. [20, 39] The onset of T2DM is unknown. Without treatment, 20–40% of T2DM patients with microalbuminuria develop proteinuria. After overt proteinuria develops, renal function declines and ESRD occurs within 7–10 years [18, 20].

Etiolgoy

From longitudinal and cross-sectional studies, race, genetic susceptibility, elevated blood pressure, increased blood sugar, hyperfiltration, smoking, and possibly male gender, dyslipidemia, and age are risk factors for DN [39]. Smoking, dyslipidemia, proteinuria, glomerular hyperfiltration, and diet protein and fat are other risk factors [40]. Age, race, and genetics are unchangeable, but others can and must be (hyperglycemia, hypertension, dyslipidemia, and GFR) [15].

Age

The risk of albuminuria in people with type 2 DM increases by age and the length of the disease. People with type 2 diabetes who were diagnosed before the age of 20 had a higher risk of developing terminal kidney failure, according to a population study of 1586 Pima Indians with the disease [15].

Race

The incidence and severity of DN are increased in African American, Mexican Americans, Asian Indian, Pima Indians, and Hispanics compared with Caucasians. Blacks are more likely to develop the disease and have more severe cases of it (3 to 6 times more than Caucasians).[15, 39] This observation in populations that are genetically incompatible points to the importance of socioeconomic factors, including poor nutrition and inadequate management of blood sugar, blood pressure, and body weight [15]. Even after adjusting for confounding factors such as lower socioeconomic status and increased incidence of hypertension in blacks, there is still a 4.8 times greater risk of ESRD in blacks compared to Caucasians [39].

Genetic Predisposition

Only 10%–40% of DM patients develop nephropathy, but epidemiological studies have shown that genetic predisposition is a major risk factor for both T1DM and T2DM [44]. Sibling, parent-offspring, and extended family studies have shown DN aggregation. DM siblings' risk of DN is 2-3 times higher. DN susceptibility may be caused by a few genes interacting with environmental factors. Some genes may contribute to proteinuria, GFR decline, or both. Knowing which gene(s) predisposes to DN will allow identification of high-risk patients and prevention [35].

Increased Blood Pressure (Hypertension)

Hypertension is 1.5 to 3 times higher in DM patients.[39] The most well-known risk factor for DN is arterial hypertension. UKPDS showed that every 10-mmHg reduction in systolic BP reduces microvascular complications by 13%, with the lowest risk in patients with systolic BP <120 mm Hg. DN causes hypertension in T1DM patients, which usually appears around microalbuminuria. One-third of T2DM patients have hypertension at diagnosis [15].

GFR

Increased GFR at diagnosis increases DN risk [15]. Intraglomerular hypertension and glomerular hyperfiltration are early abnormalities. DM's first renal sign is microalbuminuria [45]. One third of type 2 DM patients have elevated GFR, which could cause DN due to glomerular damage [16]. It causes endothelial wall damage, glomerular hyperfiltration, and hypertrophy [15].

Hyperglycemia/Glycemic control

Both in T1DM and in T2DM, hyperglycemia is a significant risk factor for the emergence of microalbuminuria. A 37% decrease in microvascular endpoints is correlated with a 1% decrease in HbA1c. Despite some studies showing a negative impact of high glucose levels on GFR, the role of metabolic control is less clear in the presence of micro- and macroalbuminuria. Furthermore, it was shown that renal damage in T1DM patients with mild to advanced DN lesions could be reversed by pancreas transplantation [16].

Overweight

Patients with DM who have a high body mass index (BMI) have a higher risk of developing CKD. Furthermore, these patients' kidney function and proteinuria are reduced by a proper diet and weight loss. It is unclear whether obesity plays a risk factor for DN (independent of diabetes and glycemic control) [15].

Smoking

Smoking might contribute the progression of DN. It is strongly advised to quit smoking in any phase of DN, also aiming to lower the associated cardiovascular and cancer risk, even though some studies did not support these observations [16].

Dyslipidemia

Elevated serum cholesterol in people with T2DM increases their risk of developing DN. Increased serum triglycerides, total cholesterol, and LDL cholesterol were linked to micro- and macroalbuminuria in T1DM patients. In macroalbuminuric T1DM patients, high serum cholesterol also appears to be a risk factor for GFR loss [16].

Proteinuria

Proteinuria itself may lead to the development of DN. A higher risk of ESRD is linked to proteinuria >2 g/24 h. Increased leakage of albumin may induce glomerular damage probably through activation of inflammatory cascades. This would be a reason to target decreased urinary albumin excretion in DN treatment [16].

Dietary factors

At least in T1DM patients, a higher dietary protein intake appears to be linked to higher urinary albumin excretion values. This association has not been proven in T2DM patients. The source of proteins in the diet also seems to be related to the presence of DN. A higher intake of fish protein is related to a lower risk of microalbuminuria in T1DM patients. The mechanisms involved in these findings are unknown but probably related to hemodynamic factors [16].

Pathophysiology

In diabetic patients, DN refers to a distinct set of structural and functional kidney abnormalities [39]. The pathogenesis of DN has been thoroughly studied, and the roles of various mechanisms have been determined [42]. DN is a complex condition caused by the interaction of hemodynamic and metabolic factors. Other factors thought to play a role in DN pathogenesis include inflammation, endothelial dysfunction, and oxidative stress. Early hemodynamic changes include glomerular hyperperfusion, hyperfiltration, and increased intraglomerular pressure, which is followed by proteinuria, systemic hypertension, and eventual renal function loss [37, 40, 41].

Albumin leakage from the glomerular capillaries is followed by structural changes such as GBM thickening, glomerular hypertrophy, nodular and diffuse glomerulosclerosis, tubular atrophy, interstitial fibrosis, mesangial cell expansion, and podocyte injury [32, 40].

Multiple factors have been identified as contributing to the development of hyperfiltration, despite the fact that the mechanism by which it occurs is not fully understood [15]. Blood glucose and blood pressure are the two most important factors in the onset and progression of nephropathy [37]. The pathogenesis of

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DN is aided by the fact that hyperglycemia stimulates both resident and non-resident renal cells, causing them to produce humoral mediators, cytokines, and growth factors that result in structural changes like increased extracellular matrix deposition and functional changes like increased GBM permeability [32].

Hyperglycemia appears to initiate nephropathy in a susceptible patient by increasing the generation of reactive oxygen species (ROS) and the formation of AGEs, upregulation of transforming growth factor-beta 1 (TGF-1), activation of protein kinase C (PKC), accumulation of polyol pathway via the aldose reductase pathway, and renin angiotensin system (RAS). ROS and AGEs both contribute to glomerular cell injury and the development of microalbuminuria, which may indicate systemic changes in endothelial function not only in systemic capillary beds but also in large vessels [41, 42].

Oxidative stress depletes nitric oxide, preventing flow-mediated dilation of blood vessels and injuring the endothelium. This causes the production of cytokines, the acceleration of inflammation, and the worsening of blood vessel rigidity as a result of atherosclerosis [41]. It is distinguished by an abnormally large, gradual, and progressive deposition of extracellular matrix in the kidney. Pathological changes in mesangial and vascular cells occur with renal damage, leading to glomerular mesangial expansion, GBM, nodular and diffuse glomerulosclerosis, and tubulointerstitial fibrosis [37, 39, 43].

These changes cause a variety of cellular responses, the expression of secretory factors, and the formation of extracellular matrices, all of which contribute to the development of DN. [42] Figure 1 depicts a schematic illustration of the interaction between hemodynamic and metabolic factors in the pathophysiology of DN.

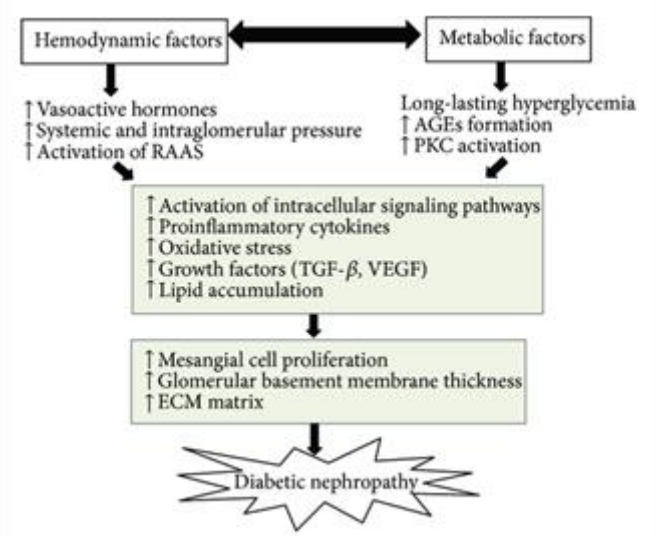

Figure 1: Schematic illustration of the interaction between hemodynamic and metabolic factors in the pathophysiology of DN. [44]

The passage of macromolecules through the basement membrane may also activate inflammatory pathways, which may contribute to secondary damage [45]. Later, extensive tubule-interstitial lesions and the development of mesangial nodules represent the hallmark lesions of Kimmelstel-Wilson nephropathy [37].

Heparanase Expression

Increasing albumin permeability of the glomerular filtration membrane is caused by a change in the negative charge of the glycocalyx caused by a decrease in heparin sulphate on the surface of endothelial cells, which is a critical step in the pathogenesis of DN [15].

Prorenin

The levels of serum have increased. Prorenin contributes to the DN development in kids and teenagers. The signal pathway of mitogen-activated protein kinases (MAPK) is activated when prorenin binds to a particular tissue receptor, accelerating the development of kidney damage [15].

Role of GAGs

Albuminuria is known to be exacerbated by increased intraglomerular pressure, the loss of negatively charged glycosaminoglycans in the basement membrane, and, later in the course of the disease, increased basement membrane pore size. The primary glycosaminoglycan component of glomerular basement membranes, heparan sulphate proteoglycan, is lost when an anionic charge is lost [37].

Screening For Albuminuria

Controlling blood glucose, blood pressure, and lipid levels, quitting smoking, and taking antiplatelet agents can delay DM complications. To detect nephropathy, serum creatinine and urine albumin should be tested annually. There is no way to predict which patients who develop complications will progress to end points like ESRD beyond screening and treatment recommendations [43].

T2DM patients should be tested for microalbumin at diagnosis. After 5 years of T1DM, screening for microalbuminuria should begin. Due to the difficulty of dating the onset of T2DM, screening should begin at diagnosis. After the initial screening, a microalbumin test should be done annually in the absence of microalbuminuria. Microalbuminuria screening can be done three ways [20].

- Random spot collection of albumin-to-creatinine ratio [20]. To screen for microalbuminuria, all DM patients should have an annual urinary albumin-to-creatinine ratio (ACR). Repeat the test if the ACR is 3.0–70 mg/mmol. If the initial ACR is 70 mg/mmol or higher, a repeat sample is not needed to confirm microalbuminuria [41].
- Twenty four hour collection with creatinine to measure creatinine clearance [20] and
- Timed (e.g., 4-hour or overnight) collection: 30 mg/24 h urinary albumin excretion indicates microalbuminuria. Exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can temporarily increase urinary albumin excretion [20].
- Caution should be taken to exclude a urinary tract infection (UTI) prior to processing the urine sample, as the presence of a UTI can cause false positive results [41].

Treatment

DM is most common in India, and avoidable complications and early death are common. Appropriate community-based primary health care interventions can reduce many of these complications [29]. DN is best prevented. Early detection of microalbuminuria in DM patients allows for effective treatment. ACE inhibitors or Angiotensin receptor blockers (ARBs), dyslipidemia treatment, strict glycemic control, blood pressure control, and protein restriction slow the progression from microalbuminuria to nephropathy. Renal replacement therapy is needed for ESRD patients [39, 45].

Strict Glycemic Control

Improved glycemic control can delay microalbuminuria in T1DM and T2DM, but its effect on renal disease progression in the presence of overt nephropathy is unclear.[30] In advanced renal insufficiency, sulfonylureas and metformin are contraindicated, but the kidney degrades insulin, lowering insulin needs [45]. Tight insulin control during microalbuminuria prevents diabetic nephropathy [37].

Strict Blood Pressure Control

In patients with T1DM or T2DM, hypertension is common and strict blood pressure control is important in preventing progression of DN and other complications [45]. A reduction in systolic blood pressure by 10 mmHg can decrease the risk of developing DM complications by 12%, with target blood pressure recommended to be below 130/80 mm Hg according to current guidelines [30].

Inhibition of RAS

In DM patients, RAS inhibition with ACE inhibitors or ARBs reduces overt nephropathy, microalbuminuria, and CVD risk. If ACE inhibitors or ARBs are not available, non-dihydropyridine calcium channel blockers may slow GFR decline, but their efficacy is unproven. After 2–3 months, proteinuria should

be measured and the drug dose adjusted to optimise results while monitoring for hyperkalemia or renal insufficiency [45].

Plasma lipid reduction

DN increases the risk of dyslipidemia in diabetics. Reducing plasma lipids aggressively reduces cardiovascular risk and DN progression. Statins slow DN progression, and fenofibrate, which activates nuclear peroxisome proliferator-activated receptors alpha, reduces albuminuria in DM patients. DM and DN patients, including those with microalbuminuria, should have intensive glycemic control, RAS inhibitor-controlled blood pressure, and statin or fenofibrate-controlled serum lipids [30].

Other Factors

TGF-beta inhibition prevents DN development and progression in experiments. Diltiazem slows most morphological changes in DN, but monotherapy increases tubule-interstitial fibrosis and global glomerulosclerosis, which can be reversed with ACE inhibitors. Tiazolidinedones, PPAR gamma agonists, reduce fibrosis, mesangial proliferation, inflammation, albuminuria, and blood pressure. PPARs are involved in the development of DN. More randomised clinical trials are needed to confirm their reno-protective effects in DN patients [15].

New Treatment Strategies

Current treatment doesn't always work. Thus, new treatments are being investigated. In animal models, high doses of thiamine and benfotiamine may slow microalbuminuria by reducing PKC activation, protein glycation, and oxidative stress. In animals, the AGEs metabolizer ALT-711 reduced blood pressure and kidney damage. In animals, PKC-beta inhibitor ruboxistaurin improves kidney function and reduces albuminuria. Despite conflicting clinical trials, pimagedin, a second-generation AGE inhibitor, reduces albuminuria and GFR decline in T1DM patients with proteinuria. Modified heparin glycosaminoglycan prevented albuminuria and extracellular matrix protein accumulation in an induced glomerulosclerosis model. Novel treatments need large randomised clinical trials [15, 46].

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