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Diabetic Nephropathy: Contemporary Insights into Risk Factors, Pathophysiology, and Emerging Therapeutic Frontiers

*Nievin A. Mahran[1] *, Helmy Gamal[1]*

[1] Biochemistry Department, Faculty of Dentistry, Sinai University, Kantara Campus, Ismailia, Egypt

**Corresponding author*

Correspondence:

Nievin A. Mahran
Email: nievin.mahran@su.edu.eg

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ABSTRACT

Diabetic nephropathy (DN) is one of the most serious complications of diabetes mellitus (DM). It often results in end-stage renal disease (ESRD). The global DM epidemic has made DN a public and clinical medical concern. It was shown that the age-standardized DN global prevalence was 15.48/1000 among men while 16.50/1000 among women. In Egypt, hypertension followed by DM are the primary causes of ESRD. Cross-sectional and longitudinal investigations revealed hyperglycemia, age, male gender, race, genetic susceptibility, hypertension, hyperfiltration, and smoking as DN risk factors. The earliest DN clinical evidence is microalbuminuria. Since structural damage could increase albumin excretion, there are several limitations to its diagnostic efficacy. Thus, specific and sensitive DN biomarkers are required. The pathogenesis of DN is complex and poorly understood; this resuls in poor treatment outcomes. The treatment of DN includes glycemic management, hypertension and hyperlipidemia treatment, protein restriction, and renal replacement therapy. Understanding the pathogenic mechanisms of DN is crucial for the development of new DN treatments. In this review, we aims to empower researchers with a comprehensive and contemporary understanding of DN, facilitating early risk stratification, timely diagnosis, and the development of more effective and targeted therapeutic interventions.

KEYWORDS: Diabetic nephropathy, Risk factors, Pathogenesis, Microalbuminuria, Treatment strategies.

1. Background

Diabetic nephropathy (DN) is a serious and common diabetes mellitus (DM) consequence that causes chronic renal failure [1, 2]. Diabetic patients are at a tenfold increased risk of developing end-stage renal disease (ESRD). Over 422 million individuals worldwide have DM, 40% of them are expected to develop ESRD [3]. Diabetics with DN have higher mortality and morbidity. Around one-third of diabetic patients develop DN after passivity periods that may last for several years [4]. While retinopathy is a common microvascular complication linked to DN, diagnosis can be complicated, as up to 40% of DN cases occur without retinopathy [5]. Nonproteinuric DN is more common in type 2 DM. The DN progression to ESRD was reported to be unaffected by standard treatment, which included blood pressure and sugar control [4]. New therapeutic treatments require better understanding of DN pathogenic mechanisms [6].

1.1. Definition

Classically, Hypertension, diabetic retinopathy, albuminuria (>300 mg/day or 30 mg/mmol or 300 mg/g of creatinine), and a progressive reduction of the glomerular filtration rate (GFR) are the clinical features of DN [7]. Nevertheless, it became evident that the course and clinical presentation of DN differ among type 1 DM (T1DM) and type 2 DM (T2DM) patients, and the absence of retinopathy among T2DM patients does not preclude DN

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incidence. Additionally, research has indicated that there are DN patients who exhibit non-classical clinical presentations besides the classical DN clinical presentation [8].

2. Risk Factors

Risk factors for DN were categorized as either modifiable or non-modifiable [2].

2.1. Modifiable Factors

2.1.1 Glycemic Level Management

The development and progression of ESRD and/or albuminuria (proteinuria) are independently predicted by inadequate glycemic control among DM patients with normoalbuminuric status [9]. Early precise blood glucose management in the course of DM has a long-lasting beneficial effect on DN risk, as reported in landmark trials among early-stage T1DM and T2DM patients. This "metabolic memory" or "legacy effect" suggests that early, precise glycemic control can inhibit irreversible damage associated with hyperglycemia, including epigenetic alterations [10]. Similar to conventional therapy, 10 years of accurate glycemic management (HbA1C: 7%) reduces microvascular sequelae, including DN, by 24% among newly diagnosed T2DM patients [11].

2.1.2. Hypertension

Several studies revealed that T2DM patients have 1.5-3 times greater risk for hypertension than age-matched non-T2DM patients. At least 56.9% of T2DM patients also had hypertension [12]. A meta-analysis and systematic review found that 80% of patients with hypertension and DM are expected to develop ESRD [13]. Studies in developing countries have demonstrated that hypertensive patients' decreased eGFR is a significant risk factor for DN development and that hypertension is an independent risk factor for DN among T2DM patients. [14].

2.1.3. Dyslipidemia

DM is frequently associated with dyslipidemia. Dyslipidemia has been proposed as a potential factor in the DN progression. Lipid-lowering therapies have been shown to have a protective effect on renal function in clinical studies. For instance, statins were recommended as a means of decreasing albuminuria among DN patients [15, 16].

2.1.4. Smoking

Independent of age, glycemic management, hypertension, and smoking was proposed as DN risk factor. Smoking accelerates DN progression in both T1DM and T2DM. According to the center of disease control (CDC), 21.8% of diabetic patients were smokers. [17].

2.2. Non-Modifiable Factors

2.2.1. Race

The prevalence of DM is higher among Blacks and South Asians compared to Whites. Among DN patients in England and Wales, the mortality rate is 3.5 times higher for Blacks and South Asians compared to Whites. Multiple studies have shown that diabetic Blacks and South Asians are more prone to DN and proceed faster to ESRD [18]. Studies found that Asians and Hispanics had higher ESRD and baseline albuminuria risk than White and Black people [19].

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2.2.2. Age

Age helps in the diagnosis of DM and determine disease progression and pathogenesis. Several DM-related cardiometabolic risk factors are identified by metabolic and immunological dysfunction severity. Although T1DM is most common in teenagers, over 50% of T1DM Korean incident patients are aged 30 years or above [20]. Western studies demonstrate that DM diagnosed before adolescence improves overall mortality and renal outcomes [21].

2.2.3. Sex

The frequency of T1DM and T2DM may be similar, but the burden appears to be gender specific. Type 1 and type 2 diabetic women have greater rates of DN risk factors, such as dyslipidemia, obesity, hyperglycemia, and hypertension, in addition to higher DM-related mortality and residual lifetime risk[25].

2.2.4. Gestation

Women with DN experience the worst pregnancy outcomes. Preeclampsia rates range from 7% among lupus nephritis women, 9-17% among DM women without nephropathy, to 35-64% among DN patients [22, 23]. Pregnancy does not accelerate DKD progression in DN patients with preserved renal function [24].

2.2.5. Genetic Variation Profile

The DN has been attributed to hereditary variants in genes including VEGF, HSPG2, FRMD3, EPO, eNOS, CPVL/CHN2, CARS, APOE, ALR2, UNC13B, GREM1, APOC1, ACE, CNDP1, CCR5, ELMO1, PPARγ, TGFβ1, PAI-1, and ADIPOQ [2].

3. Stages of Diabetic Nephropathy

The thickening of the glomerular basement membrane (GBM) initiates the initial DN phase. This stage generally has hypertension, albuminuria, and normal GFR for 5 years after GBM thickening. The following phase involves the development and expansion of mesangial tissue, which ranges from moderate to severe. After 2 years of GBM thickening and mesangial proliferation, GFR was normal, and no other symptoms were evident. Microalbuminuria (30–300 mg/day) and glomerular damage characterize the third stage. Nodular sclerosis begins 5-10 years after GBM development. Stage 4 DN involves advanced glomerulosclerosis with vascular and tubulointerstitial lesions. ESRD is defined when GFR is below 15 mL/min/1.73 m^2[2].

4. Pathogenesis

The pathogenesis and progression of DN involve multiple mediators and pathways, especially protein kinase C (PKC), reactive oxygen species (ROS), mitogen-activated protein kinases (MAPKs), activation of transforming growth factor-β1 (TGF-β1), connective tissue growth factor (CTGF), advanced glycation end product (AGE) formation, and the renin-angiotensin-aldosterone system (RAAS). Mediators and routes overlap because each pathway interacts with others or destroys cells. DN's molecular occurrence and pathogenic mechanism are unknown [4].

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5. Role of Oxidative Stress

Many DN pathogenic mechanisms, including hyperglycemia, produce oxidative stress [26]. Other pathogenic mechanisms can cause oxidative stress-induced damage. Hyperglycemia-induced-oxidative stress indirectly increases Ang-II, PKC, and TGF-β levels, causing extracellular matrix (ECM) remodeling and tubular interstitium fibrotic mechanisms [4, 28].

5.1. RAAS Role

Inhibiting the RAAS may hinder CKD progression, which is characterized by well-maintained renal function and reduced proteinuria, showing a significant role in kidney disease progression [4]. RAAS participation in DM has been associated with tubulointerstitium, glomerulus, and intraglomerular hemodynamic alterations [4, 29].

5.2. Angiotensin II Role

The important cytokine Ang-II affects the kidneys through renin angiotensin system (RAS) local activation and systemic consequences [30]. While oxidative stress is essential to cell damage, Ang-II may be the "master" molecule in renal injury. Many therapeutic studies on Ang-II and oxidative stress have yielded mixed outcomes [31].

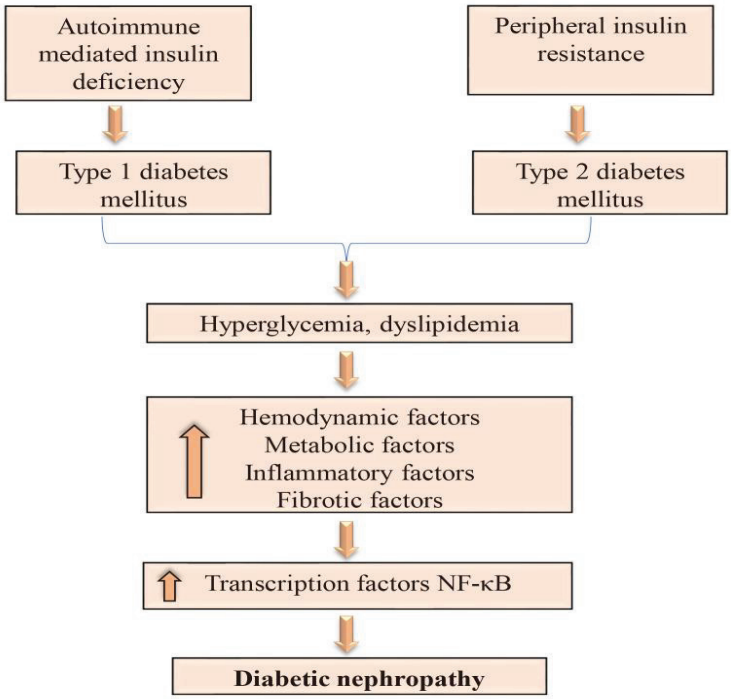

Fig. 1: Inflammatory mechanisms [2].

5.3. Local Intrarenal RAS Role

Renin, Ang-II, and angiotensin receptors can be locally synthesized by renal cells without the need for systemic RAS [32, 33]. Thus, kidneys maintain high intrarenal Ang-II levels. Interstitial renal Ang-II levels are 1000-fold higher than plasma; this suggests intrarenal RAS is most harmful [4]. High hyperglycemia increases Ang-II and renin production in mesangial cells (MCs) [34]. Intrarenal Ang-II promotes inflammation, renal cell hypertrophy and proliferation, ECM and cytokine synthesis, macrophage infiltration, along with glomerular

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capillary permeability (proteinuria) with pressure, which can lead to kidney injury [4]. Data suggests Ang-II blockage has many benefits beyond lowering blood pressure. RAS blockade can slow DN despite low systemic renin levels [4, 29].

6. Role of Inflammation

Inflammatory and immunological responses are critical in DN pathogenesis (Fig. 1) [35]. However, DN has not been historically considered inflammatory. Kidney inflammation appears to start DN progression and development. Several studies link DN to Interluckin- (IL) -1, -6, and 18 [36]. Monocytes, macrophages, and leukocytes were also implicated in DN occurrence [37]. Chronic renal tissue and circulatory system inflammation underlie DN. Hemodynamic, biochemical, and metabolic disorders in DN can cause inflammation [37]. Inflammatory markers including TGF-β1, IL-18, tumor necrosis factor (TNF-α), and IL-6 are elevated in the blood and contribute to DN occurrence and progression [38].

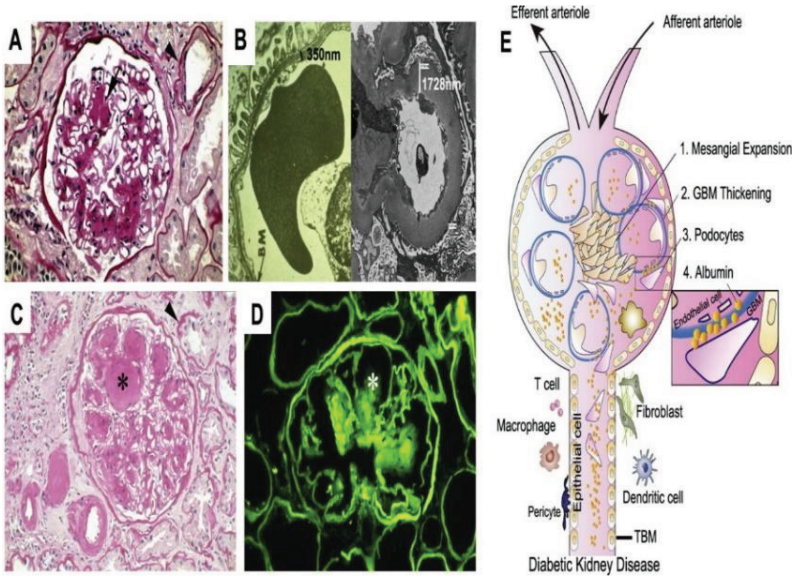

Fig. 2: Pathologic DKD lesions.

(A) Nonnodular DM-related glomerulosclerosis. The black arrow indicates ECM deposition. The thickening of the tubular basement membrane (TBM) is indicated by the arrowhead. (B) Electric microscopy indicates DN GBM thickness versus healthy control. (C) Nodular DM-related glomerulosclerosis, ECM accumulation, TBM thickening, and interstitial expansion in DN. The KW nodule is denoted by the black star. The thickening of the TBM is indicated by the arrowhead. (D) The immunofluorescence staining of immunoglobulin G in DN reveals a KW nodule (white star). (E) Formation of the DN microenvironment in. ECM: extracellular matrix [40].

7. Pathological Features

Following T2DM diagnosis, the glomerulus was first regarded as the first disease element (Fig. 2A). Pathological glomerular alterations in DKD are well known; they include GBM thickness, mesangial matrix progress, endothelium fenestration loss, and podocyte injury [39]. Cellular dysfunctions diminish the glomerular filtration barrier and alter microvascular permeability, leading to DKD clinical features including albuminuria or microalbuminuria. Early pathologic changes in DN include GBM thickening (Fig. 2B). The condition is caused by abnormal ECM turnover and alteration by podocytes and endothelial cells. In DN, GBM thickening indicates podocyte and endothelial activity as an early indicator of disease progression. DKD can cause podocytopathy, foot process effacement, podocyte loss, and

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cellular hypertrophy. Hyperglycemia also increases MC proliferation, which, in turn, increases ECM deposition and glomerulosclerosis [40]. Hyperglycemia may stimulate protein non-enzymatic glycosylation in the mesangial matrix. Pink hyaline Kimmelstiel-Wilson (KW) nodules are the most recognizable DN lesions caused by matrix non-enzymatic glycosylation. In affected glomeruli, capillary loops surround KWs, causing nodular glomerulosclerosis (Fig. 2 C, D). DN-sick glomeruli often develop microaneurysms [40].

8. Diagnosis

8.1. Diabetic Nephropathy Screening

The American Diabetes Association (ADA) recommends screening all T2DM patients for albuminuria and renal function upon diagnosis and annually thereafter, while T1DM screening begins five years after diagnosis [40]. As T1DM microalbuminuria incidence before five years can reach 18%, screening should begin one year after diagnosis. At diagnosis, 7% of T2DM patients exhibited microalbuminuria [40, 41]. It is recommended that the screening be creatinine levels are recommended for the evaluation of kidney function, while 24-hour urine or spot urine ACR measurements can be used to evaluate albuminuria [43].

8.2. Biomarkers

Despite the widespread use of micro-albuminuria as a DN indicator, its diagnostic efficacy is restricted by the possibility of structural injury that could accelerate albumin excretion [44]. Research have indicated that micro-albuminuria is not exclusive to DN, as it may also develop in NDKD patients [45]. Consequently, biomarkers that are both sensitive and specific were selected to predict the susceptibility of DN patients [42]. Significantly elevated serum and urinary biomarkers, as serum of osteopontin, VCAM-1, IL-6, IL-18, TNF-α, resistin, cystatin C, urinary of transferrin, retinol binding protein, NGAL, adiponectin, and plasma YKL-40 were observed among DN patients with marco- and micro-albuminuria. [42]. Other studies indicated that DM patients had significantly increased levels of biomarkers such asymmetric dimethyl arginine (ADMA) and 8-isoprostane before and after hemodialysis than normal controls. ADMA demonstrated superior efficacy in the diagnosis of DN in comparison to microalbumin [46].

8.3. Clinical Diagnosis

The current guidelines for the DN detection are based on four primary criteria: a decrease in kidney function, proteinuria, DM-related retinopathy, and a reduction in GFR [47]. Nevertheless, the definitive DN characteristics include the absence of other renal disease symptoms, concomitant retinopathy, and constant albuminuria. Among DM patients, DN is characterized by persistent albuminuria (>200 μg/min or >300 mg/day) at 2 out of 3 examinations within 3-6 months, hypertension, and a declining GFR [40, 43]. The natural development of DN varies based on albuminuria (30 - 300 mg/day) and the type of DM. DN is infrequently detected within the first ten years of T1DM after diagnosis; however, the DN prevalence ratio is approximately 3% per year between the ages of 10 and 20 [48]. DN prevalence declines after 20 years. Therefore, people with normal urine albumin excretion and renal function after 30 years of T1DM have a lower risk of DN. Thus, DN risk varies by patient and is determined by T1DM duration and other factors [40, 43].

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9. Diabetic Nephropathy Treatment Advances

9.1. RAAS Blockade

Renoprotective effects and reduced albuminuria have been demonstrated in patients with heart and renal disorders taking ACE inhibitors and angiotensin receptor blockers (ARBs). ARBs and ACE inhibitors are the mainstay of DN treatment [49]. The conversion of angiotensin I to angiotensin II by ACE has several consequences, including increased aldosterone secretion and arteriolar vasoconstriction, increased tubular chloride and sodium absorption, increased sympathetic activity, and pro-fibrotic and pro-inflammatory actions [50]. Captopril was effective in preventing renal function decline among T1DM patients (proteinuria ≥500 mg/day and creatinine ≤2.5 mg/dL), regardless of blood pressure management, according to a trial that compared captopril with placebo [51]. Another trial found that losartan (an angiotensin II antagonist) reduced ESRD risk by 28% and creatinine doubling risk by 25% [52].

9.2. Sodium Glucose Transport Protein 2 (SGLT2) Inhibitors

Previous investigations found that SGLT2 inhibitors increased urine glucose excretion among T2DM patients [53, 54]. These medicines provide renal and cardiovascular advantages in addition to their glucosuric impact. Glomerular hypertension is one of the maladaptive mechanisms that contribute to the development of DN. Inhibiting SGLT2 is still the most used renal protective method [49]. SGLT2 inhibitors block SGLT2 in the proximal tubule, causing tubulo-glomerular feedback and afferent arteriole vasoconstriction, reducing glomerular hyperfiltration [55]. Reduced hyperfiltration, like RAAS inhibitors, prevents DN [49]. Furthermore, reports have indicated that SGLT2 inhibitors have the potential to improve anti-inflammatory and antioxidant signaling pathways, which could potentially reverse ECM turnover, inflammation-related molecular mechanisms, and fibrosis [56].

Another hypothesis proposes that SGLT2 inhibitors can induce a decreased ketotic state by enhancing the production of ketone bodies and decreasing their excretion in the urine. This theory (thrifty substrate) proposes that ketones can be oxidized more frequently than unbound fatty acids, which greatly benefits the kidneys and heart by reducing oxidative stress [49].

9.3. Glucagon-Like Peptide-1 (GLP-1) Agonists

Glucagon-like peptide-1 (GLP-1) are incretin hormones that are generated by the lower intestine L cells in response to increased plasma glucose and food intake. GLP-1 has been reported to possess a variety of renal protective effects, such as the inhibition of Ang-II inflammatory effects [57], the inhibition of albuminuria and oxidative stress [58], and the capacity to reduce mesangial matrix expansion, glomerular hypertrophy, glomerular hyperfiltration, and albuminuria within animal models [49]. They are a prospective alternative for early use in DN patients, as recent studies have demonstrated kidney and cardiovascular advantages, in addition to their weight loss features [49].

9.4. Mineralocorticoid Receptor Antagonists

In addition to the antagonistic effect of mineralocorticoid receptor (MR) on epithelial sodium channels (ENaC) [59], the activation of these receptors has been noted to induce inflammation and generate ROS [60], and MR overexpression has been related to renal hypertrophy [61]. Meta-analyses have demonstrated that mineralocorticoid receptor antagonists (MRAs), including eplerenone, spironolactone, and the non-steroidal finerenone,

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can mitigate proteinuria and defend against oxidative stress among patients who are already receiving RAAS antagonist treatment [62]. Finerenone, the most notable non-steroidal MRA, offered great promise for proteinuria and cardiovascular health [49]. Several noteworthy published studies demonstrate the therapeutic potential of finerenone for DN [63, 64].

9.5. Endothelin Antagonists

Endothelin receptors are present in the kidney, and there is evidence indicating their excessive expression in DM[49]. It has been hypothesized that the renal endothelin system has an essential part in the initiation and progression of DN, as well as the development of glomerular nephritis and hypertension, in the context of normal renal function [65]. Endothelin receptor antagonism may improve renal microcirculation and minimize protein excretion [66]. Studies have been conducted to evaluate the efficacy of endothelin antagonists in the DN therapy, in considering these advantages[67].

9.6. MicroRNA as DN therapeutic Targets

MicroRNAs (miRNAs) have the ability to target signaling pathways that are specifically implicated in the pathophysiology of DN. This demonstrates that the use of specific miRNA antagonists in vivo to silence the appropriate mRNA could be a promising DN treatment strategy [68]. Researchers revealed that miR-192 that targets E-box repressors is elevated in DN and enhances collagen production in mesangial cells (including Zeb1 and Zeb2) [69]. MiR-21 has been identified as one of the primary upregulated miRNAs in the kidneys of DN patients through overall expression profiling. In the mouse model of Alport disease, it was proposed that the pharmacological silencing of miR-21 can effectively accelerate the progression of DN by stimulating metabolic pathway [70]. Other studies subsequently utilized a locked nucleic acid that targeted miR-21 to treat DN, and inflamed symptoms, interstitial fibrosis, and proteinuria were significantly ameliorated. Consequently, the pharmacological silencing of miRNAs could serve as an innovative therapeutic strategy for treating DN in the future [68].

9.7. Additional prospective future therapeutic options

Early research suggests that dipeptidyl peptidase-4 (DDP-4) inhibitors may be advantageous for DN patients along with GLP-1 agonists. Studies have indicated that albuminuria may decrease in patients who are administered DPP-4 inhibitors [71].

Given the documented role of numerous inflammatory pathways in the progression of DN, researchers have mostly focused on pharmacological interventions that target these pathways as potential treatment strategies [49]. One intriguing approach is the suppression of JAK1/JAK2 by baricitinib. Even though it has been discovered to reduce albuminuria, the impact on the progression of DN is still unknown [72]. Antifibrotic therapy with pentoxifyolline or pirfenidone [5], chemokine cytokine inhibition [73], and Nox1/4 inhibition [74] are additional potential targets. Each patient may be provided with a treatment protocol that is tailored to their genetic and biomarker profile in the future of DN management [75].

10. Summary and Recommendation

Globally and in developing countries, including Egypt, DN continues to be a major contributor to ESRD. Risk factors for DN include modifiable factors (hypertension, poor glycemic index, dyslipidemia, and tobacco smoking) and non-modifiable factors (age, race, genetic profile, and sex). The pathogenesis of DN is multifactorial, involving several mediators

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and pathways, such as ROS, MAPKs, PKC, CTGF, TGF-β1, AGE formation, and RAAS. While microalbuminuria is commonly utilized as a DN indicator, its diagnostic efficiency has limitations, necessitating the identification of specific and sensitive biomarkers.

Recent therapeutic advances have improved the DN treatment and management, including RAAS blockade, ACE and SGLT2 inhibitors, GLP-1 agonists, MRAs, endothelin antagonists, and miRNA-based therapies. A multifactorial approach targeting accurate blood glucose, pressure, and lipid control is recommended and desirable among proteinuric patients. Additionally, it is recommended that community-based, low-cost initiatives be supported to encourage good lifestyle choices and enhance physical activity.

CONFLICT OF INTEREST

There was no conflict of interests.

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