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REVIEW

Evolving spectrum of diabetic nephropathy

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Abstract

Diabetes remains an important health issue as more patients with chronic and uncontrolled diabetes develop diabetic nephropathy (DN), which classically presents with proteinuria followed by a progressive decrease in renal function. However, an increasing proportion of DN patients have a decline in kidney function and vascular complications without proteinuria, known as non-proteinuric DN (NP-DN). Despite the increased incidence of NP-DN, few clinical or experimental studies have thoroughly investigated the pathophysiological mechanisms and targeted treatment for this form of DN. In this review, we will examine the differences between conventional DN and NP-DN and consider potential pathophysiological mechanisms, diagnostic markers, and treatment for both DN and NP-DN. The investigation of the pathophysiology of NP-DN should provide additional insight into the cardiovascular factors influencing renal function and disease and provide novel treatments for the vascular complications seen in diabetic patients.

Key words: Diabetic nephropathy; Non-proteinuric diabetic nephropathy; Diabetes; Kidney vascular complications

Core tip: Diabetes remains an important health issue as more patients with chronic and uncontrolled diabetes develop diabetic nephropathy (DN). In recent years, an increasing proportion of DN patients have a decline in kidney function and vascular complications without proteinuria, known as non-proteinuric DN (NP-DN). This manuscript advances this discussion by examining the potential pathophysiological mechanisms, diagnostic markers, and treatments relevant to NP-DN. Furthermore, it illustrates the significance of

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INTRODUCTION: PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

Diabetes remains an important health issue as an increasing number of patients with chronic and poorly controlled diabetes develop diabetic nephropathy (DN)[1-4]. The main risk factors associated with the development of DN include hypertension, poor glycemic control, smoking, and dyslipidemia[5]. Among several ethnicities, Native Americans have the highest incidence of DN followed by Asians, Hispanics,African-Americans, and Caucasians[6]. Several genetic polymorphisms are also associated with development of DN, including angiotensin type 2 receptor and angiotensin converting enzyme (ACE)[7-10]. In recent years, the number of patients seeking dialysis for kidney-related disorders has increased with the rise in DN[11]. Specifically, DN remains the leading cause of all excess mortality among type I and II diabetic patients with microalbuminuria, macroalbuminuria, or end-stage kidney disease[12,13]. Although kidney transplantation is an option, many DN patients have frequent post-operative complications associated with kidney transplant procedures, including cerebrovascular disease events and graft rejection[14,15]. As a result, clinical studies examining the pathophysiology and therapeutic interventions for DN remain an important public health concern for reducing DN-associated end-stage renal disease and mortality.

DN begins with glomerular hyperperfusion and renal hyperfiltration and then progresses to microalbuminuria and a lowered glomerular filtration rate (GFR). Current guidelines define DN using four main criteria: a decline in renal function, diabetic retinopathy, proteinuria, and a reduction in GFR[16]. Specifically, "Overt nephropathy is characterized by persistent proteinuria (> 500 mg/24 h) that usually precedes a fall in glomerular filtration rate (GFR) significant proteinuria has therefore long been regarded as the hallmark of DN"[17]. DN is diagnosed by urinalysis and confirmed, if necessary, by a kidney biopsy, and its progression is monitored through regular measurements of microalbuminuria, serum creatinine, and calculated GFR[1,18]. With advanced cases of DN, the kidney biopsy shows mesangial hypercellularity and expansion, thickening of the basement membranes, arteriolar hyalinosis, and interstitial fibrosis. In some cases, Kimmelstiel-Wilson lesion seen in DN kidney biopsies correlate with an increased risk of worsening renal function and retinopathy[19]. However, several studies have reported substantial variability in patients with DN that deviates from accepted guidelines, which has encouraged clinicians to incorporate routine biopsy of DN patients[20,21]. As a result, DN is now viewed as a spectrum of presentations with many authorities arguing for expanding the current pathological classification of DN to improve treatment strategies and outcomes[16,22,23].

Among the parameters used to identify DN patients, the presence of proteinuria represents an important prognostic factor reflecting damage to the glomerular filtration barrier[24]. However, several studies have described DN without significant proteinuria (> 500 mg/24 h) in over 50% of diabetic patients[25-32]. Among the 15773 Type 2 diabetic patients with varying severity of renal insufficiency examined in the Renal Insufficiency and Cardiovascular Events Italian Multicenter Study, 56.6% were normoalbuminuric, 30.8% were microalbuminuric (30 to 300 mg/24 h), and 12.6% were macroalbuminuric (> 300 mg/24 h)[33]. In some cases, the proteinuria vanishes with patients having normal albuminuria levels[34-36]. For example, a six-year longitudinal study conducted by the Joslin Clinic showed that 58 percent of the 386 patients who had microalbuminuria eventually had normal albuminuria levels[34].

Compared with patients with type II diabetes and DN, patients with type 1 diabetes and DN with normoalbuminuria had more of glomerular lesions, such as increased glomerular basement membrane thickness and more Kimmelstiel-Wilson nodules, and more frequent progression of DN[28]. As shown in Table 1, a new classification was created to characterize DN patients with a decline in kidney

function and vascular complications without proteinuria, known as non-proteinuric DN (NP-DN)[37,38]. Robles summarized these recent studies with this observation, "There have now been reports that in both type 1 and type 2 diabetes mellitus, a proportion of patients may have renal impairment without significant proteinuria or albuminuria, with a variable percentage of patients in these reports having advanced (stage 3–5) kidney disease. It could be interpreted as an accelerated kidney sclerosis due to the interaction of diabetes with other cardiovascular risk factors"[17]. Furthermore, a recent clinical study reported NP-DN is an increasing cause of chronic kidney disease globally[17]. At present, increasing age, repeated cardiovascular injury, such as hypertension, cardiovascular disease, and dyslipidemia, to the kidney, and an over-suppressed renal-angiotensin system have been proposed as potential mechanisms for NP-DN[17].

Despite the increased incidence of NP-DN, few clinical or experimental studies have thoroughly investigated the pathophysiological mechanisms and targeted treatment of NP-DN. As the nephrologist Jean Halimi summarized, "it is not clear why some patients develop the 'classical' deiabetic nephropathy with significant proteinuria, while others have impaired renal function associated with very low levels of proteinuria that sometimes persist as late as end-stage renal disease"[38]. Furthermore, a clinical review published by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative showed that "there is insufficient evidence to assume that interventions that prevent or reverse microalbuminuria will necessarily lead to improvement in clinical outcomes and conversely that failure to reduce microalbuminuria precludes a beneficial effect of treatment on diabetic kidney disease"[39]. In this review, we will discuss the differences between DN and NP-DN and consider potential pathophysiological mechanisms, diagnostic markers, and treatment for NP-DN.

POTENTIAL MECHANISMS OF NP-DN

Current research suggests that increased vascular resistance in renal interlobar arteries can damage glomerular and non-glomerular nephron structures and contribute to the onset and progression of NP-DN[37,40]. A recent study reported an elevation in arterial stiffness, measured using aortic and brachial-ankle pulse wave velocity, in NP-DN patients, which was strongly associated with increased atherosclerosis and cardiovascular morbidity and mortality and decreased renal function[40-47]. Thus, NP-DN patients likely have more atherosclerosis and increased vascular resistance which reduce glomerular function and damage glomerular-tubular structures.

Several studies examining NP-DN found elevated serum uric acid levels, which were strongly associated with the development of kidney disease[48-50]. Although an antioxidant in the blood, uric acid is also a potent pro-oxidant and damages mitochondria through the stimulation of NADPH oxidases[51]. Elevated uric acid levels could also damage vascular elements and induce endothelial dysfunction through various mechanisms, including activation of Toll-like receptor pathways[51,52]. Furthermore, uric acid induces renal inflammation, vascular smooth muscle cell proliferation, and activation of the renin-angiotensin system[53-56]. Prolonged elevation of uric acid levels in NP-DN patients can produce significant vascular changes that impair renal function leading to NP-DN[57]. Therefore, elevated uric acid levels in NP-DN patients can produce more vascular damage than in DN patients. In recent years, sodium-glucose 2 (SGLT2) inhibitors were shown to increas uric acid excretion through the proximal tubule transporter, SLC2A9 (GLUT9), which improved glycemia control, weight loss, and blood pressure control among DN patients[58-60]. Future clinical studies should include serial measurements of uric acid and uric excretion between DN and NP-DN patients prescribed SGLT2 inhibitors to investigate this mechanism.

Patients with NP-DN have elevated concentrations of serum tumor necrosis factor alpha (TNFα) and Fas-pathways[61]. TNFα is a key mediator of inflammation through the induction of chemokines, IFN-γ inducible protein-10, intercellular adhesion molecule-1, and vascular adhesion molecule-1, which increase glomerular vasoconstriction and albumin permeability[61]. Furthermore, TNFα is involved in the acute kidney injury, regulation of blood pressure, blood flow, and inflammation within the renal vasculature[62-64]. TNFα and Fas also have important roles in apoptosis[61]. The FasL-Fas system regulates renal cell apoptosis during immune and inflammatory responses through the activation of renal cell Fas receptors[65]. In addition, murine models that block the FasL-Fas system prevent renal and tubular cell injury during ischemia-reperfusion experiments[65]. Thus, increased levels of TNFα

Table 1 Pathophysiology of diabetic nephropathy and non-proteinuric diabetic nephropathy

Clinical parameter	Diabetic nephropathy	Non-proteinuric diabetic nephropathy
Proteinuria	Present	Absent
Regression of proteinuria	Present	Absent
Histology	Abnormal	Normal or abnormal
Glomerular filtration rate	Decreased	Decreased
Increased risk of chronic kidney disease	Present	Present

and Fas in NP-DN can alter renal vasculature and damage the kidney.

NP-DN patients also have elevated levels of osteoprotegerin and vascular endothelial growth factor (VEGF), which function in inflammation and angiogenesis, respectively[66]. Interestingly, VEGF levels are inversely related to proteinuria levels in DN patients[67]. In the presence of TGF-β, VEGF signaling leads to apoptosis and potentially cause glomerular vascular atrophy[68]. Elevated serum VEGF levels in murine models initiate a feedback inhibition of VEGF production by podocytes leading to glomerular injury[69]. In addition, osteoprotegrin is associated with chronic kidney disease in diabetic patients, leading to calcification of vascular tissue, glomerular damage, and proteinuria[70,71].

In summary, the pathogenesis of NP-DN appears to involve vascular and soluble elements circulating in the blood, as shown in Figure 1. Comparisons between DN and NP-DN patients should provide insight into the functions of these receptors and other inflammatory responses occurring within the kidney. Furthermore, additional studies investigating non-enzymatic glycation of proteins, metabolic stress, hypertension, N-terminal fragment of pro brain natriuretic peptide and glomerular vascular injury can provide additional insight into the pathogenesis of NP-DN[72]. This information may provide unique insights and possibilities for developing novel treatment for DN and NP-DN.

DIAGNOSTIC MARKERS FOR NP-DN

Given the recent identification of NP-DN, current guidelines should be expanded to include NP-DN and other forms of DN. Kidney biopsies are readily available and provide a detailed analysis of a patient's renal disease. However, complications, such as infection, bleeding, and other vascular injuries, limit its wider use by physicians[73]. Furthermore, kidney biopsies may not fully detect the vascular changes occurring in NP-DN and DN patients. As a result, the development of safer and accessible diagnostic markers is critical for improving early diagnosis and treatment of conventional DN and NP-DN patients.

Ultrasound technology is one alternative which has provided opportunities for diagnosing and monitoring the progression of DN. Unlike renal biopsies, ultrasound represents an inexpensive and non-invasive method for examining and grading the progression of DN and other related renal pathologies, such as renal cysts or stones[74]. Ultrasound technology can provide measurements on renal anatomy and function associated with DN, acute renal failure, and cirrhosis[75]. Recent studies using ultrasound have provided an additional method for evaluating renal function in DN patients at various stages of the disease[75-79]. Specifically, an increase in the Renal Resistive Index (RRI), which measures renal vascular resistance, has been shown to reliably detect and monitor the progression of DN and NP-DN[75,80,81]. For example, a study in diabetic patients showed that RRI values were elevated in diabetic patients without overt proteinuria or renal atherosclerosis[82]. Therefore, ultrasound sonography provides an effective method to screen, identify, and monitor hemodynamic and morphologic changes in DN patients[82]. Furthermore, diabetic patients identified as high risk for DN could qualify for preventative pharmacologic treatment, which might prevent the onset of DN before the appearance of proteinuria[83]. Recent reports with ultrasound technology and DN strongly suggest that this technology could be used to differentiate DN and NP-DN for diagnostic and screening purposes[82]. In addition, only a few studies have systematically compared the renal function, prognosis, and various blood and urine components in conventional DN and NP-DN patients. More studies examining changes in the levels of TNFα, TGF-β, endothelin, and other interleukins in the blood and urine of DN and NP-DN might provide additional diagnostic criteria and potential insight into the pathophysiological mechanisms of NP-DN. More analysis comparing both groups

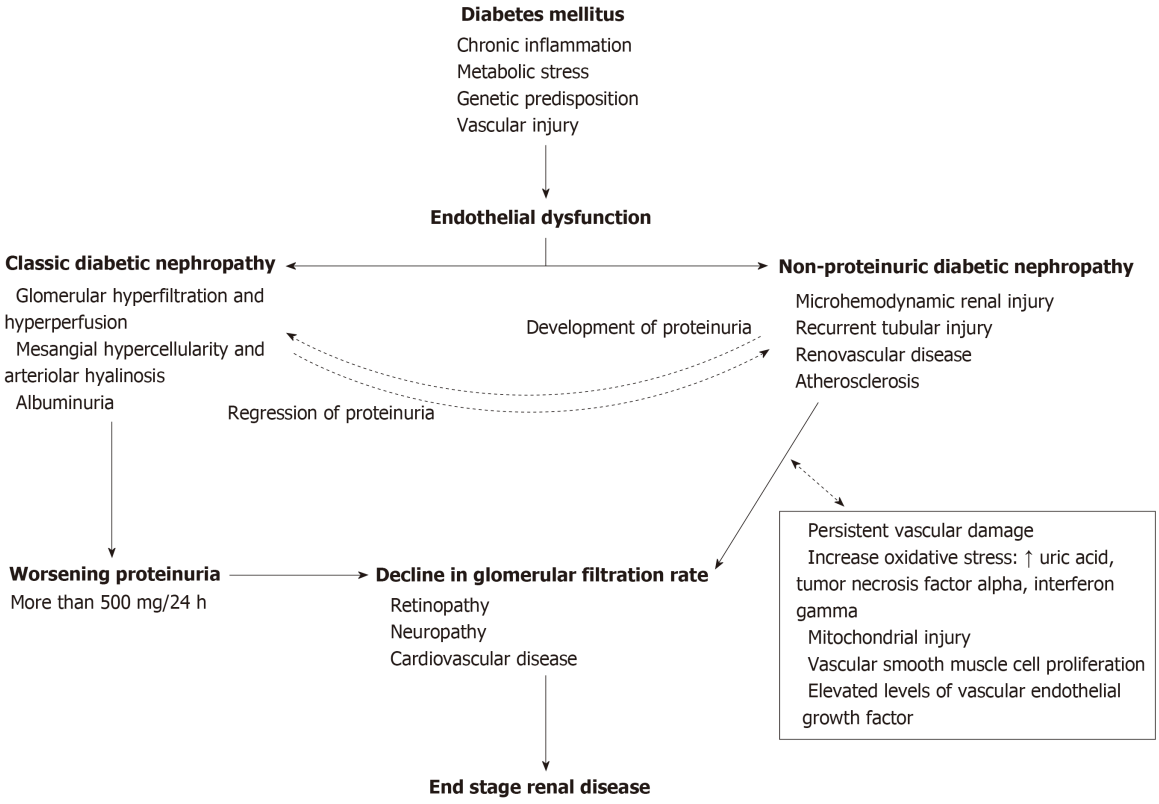

Figure 1 Pathophysiology of diabetic nephropathy and non-proteinuric diabetic nephropathy.

should help clarify distinct pathological and diagnostic criteria for DN and NP-DN.

POTENTIAL TARGETED THERAPIES FOR NP-DN

Uncontrolled hypertension produces hemodynamic stress that causes fibrinoid necrosis of small blood vessels leading to acute renal failure. The current pharmacological treatment for hypertensive disorders and glomerular vascular syndromes includes thiazide diuretics, beta blockers, ACE inhibitors, angiotensin II receptor blockers, calcium antagonists, and α_1 blockers. However, these anti-hypertensive drugs fail to prevent progressive declines in GFR and renal disease[84]. As a result, the development of new pharmaceutical regimens for managing DN and NP-DN are needed[85,86]. Several studies have found ACE-inhibitors lisinopril and enalapril and the angiotensin II receptor antagonist losartan were effective in treating patients with normoalbuminuric type II diabetes through reductions in albuminuria excretion, blood pressure, creatine clearance[87-89]. In recent years, pharmacological alternatives for DN, such as heparin and antibody therapy, have been proposed for treating glomerular vascular syndromes.

Heparin is a potent glycosaminoglycan and anticoagulant used to treat and prevent deep vein thrombosis, pulmonary embolism, and arterial thromboembolism. Patients with diabetes have abnormal metabolism and catabolism of glycosaminoglycans[90]. Diabetic mouse models treated with heparin sulfate and glycosaminoglycan had significant improvement in morphological and functional renal abnormalities[90]. Unlike antihypertensive drugs, heparin reduces proteinuria and improves GFR without interacting with the renin-angiotensin-aldosterone system[91]. Similarly, sulodexide, a heparin derivative, reduced proteinuria and improved renal function in murine models when given orally, intramuscularly, or intravenously[92,93]. Clinical trials with long-term low-dose sulodexide have reported reduced proteinuria and renoprotective properties in DN, chronic kidney disease, hypertensive nephropathy, and primary glomerulonephritis[93,94]. Thus, heparin could provide an effective additive for reducing proteinuria and GFR in conventional DN and NP-DN patients on conventional antihypertensive therapy.

Given the inflammatory activities associated with diabetes, some anti-inflammatory drugs, such as pentoxifylline, have been studied in the treatment of DN[95,96]. Pentoxifylline is a methylxanthine derivative and a non-specific phosphodiesterase

inhibitor of TNF-α. Several studies with pentoxifylline have shown a decrease or stabilization in the progression of DN with additional reno-protective effects, such as decreased C-reactive protein, TNF-α, and risk for long-term dialysis[97-100]. In addition, pentoxifylline attenuates the progression of glomerular crescents, sclerosis, mesangial expansion, and interstitial fibrosis seen in DN patients[101]. Patients with NP-DN have elevated levels of TNF-α and other cytokines and could respond to pentoxifylline with improvement in renal vasculature and glomerular structures. Additional studies investigating other anti-inflammatory drugs in DN and NP-DN patients would provide an alternative first-line treatment in conjunction with current anti-hypertensive therapy. Table 2 shows the summary of NP-DN literature.

In summary, inflammation remains a central factor involved in the onset and pathogenesis of diabetes and diabetes-related complications. With the increase in NP-DN cases, new treatment and diagnostic markers are needed to understand the pathogenesis of both DN and NP-DN. New therapies beyond current anti-hypertensive therapy regimens hold promise in providing an effective measure for the prevention and treatment of DN and NP-DN. More clinical studies are needed to examine the differences between DN and NP-DN in pathogenesis, diagnosis, and treatment. Specifically, additional studies examining the use of allopurinol to reduce uric acid levels among NP-DN patients would provide a readily accessible treatment for both clinicians and patients. Furthermore, studies examining RRI can yield additional anatomical and pathophysiological data distinguishing NP-DN and DN. Despite these challenges, investigation of the pathophysiology of NP-DN requires further analysis into the cardiovascular factors influencing renal function and disease and identify novel treatment for the vascular complications seen in diabetic patients.

Table 2 Summary of non-proteinuric diabetic nephropathy literature

Field	Summary of non-proteinuric diabetic nephropathy literature
Prevalence	57% of diabetic nephropathy patients
Pathogenesis	Vascular and soluble elements, such as uric acid, TNFα, and VEGF, affecting renal microhemodynamics
Diagnosis	(1) Increased renal resistive index; (2) Alterations in TNFα, TGF-β, endothelin, and other interleukins
Treatment	(1) Enalapril; (2) Losartan; (3) Heparin; (4) Pentoxifylline

TNFα: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor; TGF: Transforming growth factor.

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