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BRIEF REPORT

Non Proteinuric Diabetic Kidney Disease: A Narrative Review

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Abstract

Albuminuria followed by a decline in glomerular filtration rate has been described to be the classical phenotype of diabetic kidney disease (DKD). A new phenotype, non albuminuric diabetic kidney disease (NADKD), has recently been observed in patients with decreased renal function and a urine albumin excretion rate < 30 mg in 24 hours or a urine albumin creatinine ratio of < 30 mg/g. The prevalence of this phenotype is rising, and more studies are needed to understand its pathophysiological mechanisms. In this review, the pathophysiological mechanisms, clinical characteristics, and prognosis of NADKD compared to albuminuric DKD are discussed.

Keywords

Albuminuria, Diabetic kidney disease, Phenotype, Pathophysiology

Introduction

Approximately 40% of all patients diagnosed with type 2 diabetes mellitus (T2DM) eventually develop diabetic kidney disease (DKD); this condition may lead to end-stage renal failure (ESRF), cardiovascular disease and premature death [1-10]. Albuminuria followed by a decline in glomerular filtration rate (GFR), has been long considered to be the pathognomonic sign of DKD [4-7,11]. However, this notion has been recently challenged, as it has been recognized that some patients with T2DM develop chronic kidney disease without albuminuria [1-7,11-26]. Non albuminuric diabetic kidney disease (NADKD) is a phenotypic variant of DKD that is diagnosed in patients with a urine albumin excretion rate (UAER) < 30 mg in 24 hours or a urine albumin creatinine ratio (UACR) of < 30 mg/g [4].

The prevalence of this phenotype is rising, ranging from 20 to 40% in patients with type 2 diabetes mellitus, but much is still yet to be understood about this phenotypic variant [1-26].

More studies are needed, to fully understand this phenotypic variant of DKD.

In this narrative review, emphasis is placed on describing potential pathophysiological mechanisms, clinical characteristics and prognosis of this variant when compared to albuminuric diabetic kidney disease.

Pathophysiology

Pathology

In diabetic patients with proteinuria, hyperglycaemia can lead to activation of inflammatory pathways and reactive oxygen species that cause inflammation, fibrosis, and vascular permeability [4,25].

As such, a podocytopathy ensues, resulting in albuminuria [4,25].

Albumin is a protein synthesized by the liver and is measured in both serum and urine [4,25].

Albuminuria, > 30 mg/day is a sign of kidney disease [4,25].

Morphological changes in the kidneys of patients with poorly-controlled diabetes include glomerular basement thickening, mesangial expansion, nodular sclerosis (Kimmelstiel-Wilson nodules) and hyalinosis characterized by exudative/insudative fibrin cap lesions [25].

Furthermore, nodular glomerular lesions have been

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described to be the characteristic pathognomonic finding on renal biopsy for albuminuric diabetic kidney disease [25].

Limited studies though, have investigated morphological features of NADKD [4].

In 1992 Lane, et al. [17], reported that patients with low creatinine clearance rates and albumin excretion exhibited more mesangial expansion and glomerular sclerosis compared to patients whose renal function was preserved [17].

Moreover, subsequent studies have shown patients with NADKD, have more advanced glomerular injury compared to patients with preserved renal functions without diabetes [4,25].

As reported by Deng, et al. in their review, patients with NADKD who underwent a renal biopsy, were found to have fewer glomerular lesions compared with patients who had albuminuric diabetic kidney disease [4].

In addition, Yamonouchi, et al. demonstrated that glomerular lesions were found on renal biopsy in 22% of patients with NADKD as opposed to 54% in patients with albuminuric diabetic kidney disease [25].

The main pathological findings identified on renal biopsy specimens from patients with NADKD are tubulointerstitial and vascular lesions [1-8,11-26].

In a study by Ekinci, et al., ⅜ (37.5%) patients with NADKD had disproportionately severe interstitial tubular lesions in comparison to 1/23 (4.3%) with albuminuric diabetic kidney disease [20].

What is more, it has been hypothesised that tubulointerstitial injury contributes to the development of NADKD through the actions of Liver fatty acid binding protein (L-FABP), a protein expressed in the proximal tubule [15].

How it achieves this, is still unknown [15]. In their study Elshair, et al., found increased levels of urinary L-FABP were associated with patients with NADKD [15].

Likewise, Nakamura, et al. showed elevated levels of L-FABP correlated with tubulointerstitial disease [18]. These findings suggest urinary L-FABP could be used as a biomarker of tubulointerstitial injury, but more studies are required [8,15].

Vascular lesions are predominant in patients with NADKD compared to patients with albuminuric diabetic kidney disease or preserved renal functions [1-8,11-26]. Previous observational studies that have compared NADKD patients with those with albuminuric diabetic kidney disease and normoalbuminuric kidney disease have shown that patients diagnosed with albuminuric DKD were at a higher risk of developing a cardiovascular event or renal function decline [5,11,12,14,18,25].

Furthermore, an association with metabolic syndrome as well as other macrovascular complications have been described [3,4,5,16]. Additionally, a diagnosis of NADKD was not associated with classic pathologies, for example retinopathy or the long-term impact of glycaemic exposure [6-10,16-26]. Consequently, these findings have put forward the notion that NADKD is primarily linked with macro opposed to microangiopathy [8-10, 20-26].

Proposed Pathophysiological Mechanisms

Vascular mechanisms and inflammation

The pathophysiology of NADKD remains incompletely understood [4,11,18,22,26]. Multifactorial pathophysiological mechanisms have been proposed, though no clear mechanism has been identified [4,11,18,22,26]. Increased vascular resistance in the renal interlobar arteries can damage the nephrons [7]. Diabetic patients with a GFR of less than 60 mls/min have a higher renal artery resistive Index and greater degree of intrarenal vascular disease, measured by the intrarenal resistive index than patients with preserved GFR, independent of UAER [21]. As such, increased elevation in arterial stiffness measuring aortic and brachial pulse wave velocity, has been shown to have a strong association with increased atherosclerosis, cardiovascular mortality and morbidity and decreased renal function [4,7,18].

Moreover, damage to vascular elements may induce endothelial dysfunction, leading to to activation of inflammatory pathways, Toll like receptor pathways that further augment renal inflammation; leading to vascular smooth muscle proliferation and activation of the renin aldosterone angiotensin system (RAAS) pathway, causing vascular changes [7] other inflammatory mediators such as serum tumour necrotic factor alpha (TNFa) also play a role in activating inflammation in the kidneys [7,21]. Increased levels of TNFa are involved in the development of NADKD [7,21].

Furthermore, TNFa is reported to a play role in the evolution of acute kidney injury (AKI), regulation of blood pressure, blood flow, inflammation of the renal blood vessels and apoptosis [7,21].

Similarly, raised levels of uric acid have been noted in patients with NADKD damaging vascular elements and causing endothelial dysfunction [7,21].

Acute kidney injury

Repeated episodes of AKI may result in damage to glomerular and tubular structures resulting in interstitial fibrosis [4,21]. It is known, diabetic patients have an inherent susceptibility in developing episodes of AKI [4]. Onuigbo, et al. proposed that once AKI occurs in diabetic patients, renal function decline is more likely, and this is independent of albuminuria [9]. Furthermore,

single, or recurrent AKI is a risk factor for chronic kidney disease (CKD), independent of albuminuria in diabetes [23].

Use of renoprotective agents

Renoprotective agents including RAAS inhibitors, lipid reducing therapies and sodium glucose transporter inhibitors (SGLT2i) help reduce albuminuria [4,8-10,16,21-26]. It has been speculated that early use of RAAS inhibitors along with SGLT2 inhibitors partially contribute to the development of NADKD [6].

Clinical characteristics

NADKD is more commonly diagnosed in females than males [1-8,11-26]. It is also associated with an older population group, non-smokers and those who have had a shorter duration of diabetes [1-8,11-26]. Likewise, patients with NADKD have been reported to have lower levels of systolic blood pressure, diastolic blood pressure and normal levels of HbA1C, total cholesterol, low density lipoprotein (LDL) and raised levels high density lipoprotein (HDL) [4-21].

With respect to prognosis, patients with NADKD exhibit lower mortality and reduced risk of developing cardiovascular disease or ESRF compared with those diagnosed with albuminuria [1-26]. Recently it was demonstrated in a multi-centre prospective cohort study, that patients with NADKD in comparison to patients with no DKD, had a high risk of all-cause mortality, hospitalisation for heart failure and risk of CKD progression [6].

Surprisingly, risk of cardiovascular disease was not significantly greater [6]. What is more, Yokoyama, et al. identified the risk of death or cardiovascular disease. In NADKD patients without prior cardiovascular disease, was like those in non diabetic patients without cardiovascular disease [26].

However, the risk in NADKD with prior cardiovascular disease as well as other DKD phenotypes: Albuminuric diabetic kidney disease was higher [26]. Most importantly, Yokoyama, et al., have suggested the presence of macrovascular complications are thought to be the main prognostic determinant rather than renal manifestations [26].

Conclusions

NADKD is a distinctive phenotypic variant of DKD, that typically presents with macrovascular complications, rather than microvascular complications [1-8,11-26]. The underlying pathology of NADKD is different from the classical phenotype of DKD. Patients with NADKD also have a better prognosis compared with patients with albuminuric diabetic kidney disease. The prevalence of NADKD is rising and more studies investigating the pathophysiological mechanisms are needed to allow for treatment options.

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