Title: The Spectrum of Renal Disease in Diabetes

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/nep.12288

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Abstract

The spectrum of renal disease in patients with diabetes encompasses both diabetic kidney disease (including albuminuric and non-albuminuric phenotypes) and non-diabetic kidney disease. Diabetic kidney disease can manifest as varying degrees of renal insufficiency and albuminuria, with heterogeneity in histology reported on renal biopsy. For patients with diabetes and proteinuria, the finding of non-diabetic kidney disease alone or superimposed on the changes of diabetic nephropathy is increasingly reported. It is important to identify non-diabetic kidney disease as some forms are treatable, sometimes leading to remission. Clinical indications for a heightened suspicion of non-diabetic kidney disease and hence consideration for renal biopsy in patients with diabetes and nephropathy include absence of diabetic retinopathy, short duration of diabetes, atypical chronology, presence of haematuria or other systemic disease, and the nephrotic syndrome.

Key words
Diabetic kidney disease, non-diabetic kidney disease, renal biopsy, AER, eGFR

Disclosure

The authors have no conflict of interest to declare.
Introduction

The global burden of diabetes is increasing, with the largest increase in prevalence estimated to occur in the Middle East, Sub-Saharan Africa and India\(^1\). This increase is principally attributable to a rapid rise in cases of type 2 diabetes (T2DM), driven by a combination of obesity, urbanisation and an ageing population. As such, the public health impact of diabetes-related complications is enormous, and is no better exemplified than by the rapid increase in chronic kidney disease (CKD) in people with diabetes. It is now well-documented that diabetes is the leading cause of end-stage renal disease (ESRD) in the world\(^2\).

The current clinical classification of CKD, regardless of aetiology, is based on estimated glomerular filtration rate (eGFR) and albumin excretion rate (AER)\(^3,4\), recognising the relationship between these two factors and adverse outcomes. This has resulted in a broadening spectrum of clinical presentations for diabetic kidney disease (DKD), with the phenotype of non-albuminuric CKD being increasingly recognised. The term “diabetic nephropathy” (DN) should therefore now only be reserved for patients with persistent clinically detectable proteinuria that is usually associated with an elevation in blood pressure and a decline in eGFR. However, the finding of subclinical proteinuria or microalbuminuria is sometimes referred to as “incipient DN”\(^5\).

There is also increasing awareness of the heterogeneity of renal biopsy findings in people with diabetes. Most patients with T1DM and reduced eGFR have classic glomerular changes of DN regardless of albuminuria status. Typical renal structural changes of DN are usually also observed in patients with T2DM, reduced eGFR and albuminuria. However, predominantly interstitial, tubular or vascular damage or near normal renal structure have
also been reported in biopsies obtained from patients with T2DM, regardless of eGFR or albuminuria status, in the absence of any other known cause for renal dysfunction. Despite the above, in people with diabetes and proteinuria, non-diabetic kidney disease (NDKD) alone or superimposed on DN changes is not an uncommon finding.

It is important that NDKD is diagnosed. Despite the attention to strict metabolic control and blockade of the renin-angiotensin-aldosterone system, proteinuric DKD is usually progressive, whereas NDKD is potentially treatable, depending on aetiology. Therefore, we have briefly reviewed the contemporary spectrum of DKD, the histology and clinical predictors of NDKD and present several clinical vignettes to illustrate the variability of renal disease in diabetic patients that have presented to one of our hospitals.

**Diabetic Kidney Disease (DKD)**

The earliest clinical evidence of classical DKD is the appearance of microalbuminuria (≥ 30 mg/day or 20 μg/min). Without specific interventions, up to 80% of T1DM patients with sustained microalbuminuria develop overt proteinuria (≥300 mg/day or ≥200 μg/min) over 10 to 15 years. ESRD develops in 50% of T1DM patients with overt proteinuria within 10 years and in >75% by 20 years. A higher proportion of T2DM individuals are found to have established proteinuria at the time of diagnosis of their diabetes due to the delay in the diagnosis of diabetes. Without specific interventions, up to 40% of T2DM patients with microalbuminuria progress to overt nephropathy, but by 20 years after onset of overt nephropathy, only approximately 20% will progress to ESRD.

The exact reasons why an individual with diabetes will progress to develop DKD and then subsequently develop ESRD still remain to be fully defined. Despite this, there is most likely a strong genetic determinant for the risk of developing DKD and ESRD. Indeed, recent
genomic-wide linkage studies have described the localisation of quantitative trait loci that influence GFR in diabetes\textsuperscript{11,12}. These findings may help to further elucidate the genetic susceptibility to the development of advanced DKD.

**Histopathology of DKD**

The spectrum of histologic changes seen in DKD is variable. In 2010, a new pathological classification of DKD was proposed for patients with diabetes\textsuperscript{13}, based on glomerular features:

(i) Class I: Glomerular basement membrane thickening, diagnosed by transmission electron microscopy;
(ii) Class II: Mesangial expansion - A: mild, B: severe;
(iii) Class III: Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion);
(iv) Class IV: Advanced diabetic glomerulosclerosis (>50% global glomerulosclerosis).

The most characteristic lesion seen in patients with T1DM and DN is nodular glomerulosclerosis\textsuperscript{14}. Other typical lesions include hyalinosis of afferent and efferent arterioles, glomerular capsular drops, diffuse glomerular lesions with capillary wall thickening and mesangial matrix expansion (Case 1, Figure 1).

Renal histology in patients with T2DM is also markedly heterogeneous (Case 2, Figure 2). A study of T2DM patients with normal eGFR and microalbuminuria by Fioretto et al. categorised renal biopsy findings into three patterns:

(i) 29% had normal or near normal renal structure- Fioretto class 1 (C1);
(ii) 29% had typical DN with predominant glomerular changes- Fioretto Class 2 (C2);
(iii) 41% had atypical patterns with mild glomerular diabetic changes and disproportionately severe tubular, interstitial or vascular damage Fioretto Class 3 (C3). The reasons for different kidney reactions to glycaemic injury are unclear, although potential factors include degree and duration of metabolic control, co-existing hypertension, interlobar renal vascular changes and presence of diabetic retinopathy as a marker of microvascular damage.

**Normoalbuminuric DKD**

Recently, a new DKD phenotype has been described in diabetic patients with low GFR in the absence of microalbuminuria. Approximately 25% of patients with T1DM or T2DM have been reported to develop normoalbuminuric CKD. Distinct sets of risk factors have been described for the development of low eGFR or increased AER, suggesting that eGFR and AER are complementary rather than obligatory markers of DKD. Some studies that have attempted to document the natural history of normoalbuminuric DKD suggest a relatively benign course compared to albuminuric DKD, with lower rates of dialysis and mortality, whilst others have reported similar rates of decline in renal function.

Renal biopsies of normoalbuminuric T1DM patients with preserved eGFR showed that greater width of the glomerular basement membrane predicted progression of DKD. Moreover, normoalbuminuric T1DM patients with reduced eGFR had more advanced glomerular lesions compared to patients with preserved renal function. Similarly, in T2DM, patients with normoalbuminuric CKD (eGFR <60mL/min/1.73m²) were found to have more advanced glomerular, tubulointerstitial and vascular lesions compared to patients with normoalbuminuria and preserved eGFR. However, compared to patients with micro-
or macroalbuminuria and CKD, the typical glomerular changes of DKD were less common in patients with normoalbuminuric CKD\textsuperscript{25}.

The above suggests that renal structural changes are more heterogeneous in normoalbuminuric than in albuminuric CKD (Figure 3). In particular, for patients with T2DM and low eGFR, a recent biopsy study of 32 patients reported typical Fioretto C2 classification- typical DN changes for 22/23 micro- or macro-albuminuric patients with only 1/23 being classified as C3- atypical patterns of renal injury. For the patients with normoalbuminuria and low GFR, 2/8 had C1- near normal biopsy findings, 3/8 had C2- typical DN changes and 3/8 had C3- atypical patterns of renal damage. In contrast, as mentioned above, a similar proportion of C1, C2 and C3 changes have been reported in renal biopsies from patients with T2DM, microalbuminuria and preserved renal function\textsuperscript{15, 25}.

In summary, glomerular or non-glomerular renal structural changes in T2DM are more heterogenous in normoalbuminuric than in albuminuric renal insufficiency. This implies that age, blood pressure and intra-renal vascular disease may contribute to decreases in renal function independently of changes in albuminuria.

**Non-diabetic Kidney Disease (NDKD)**

NDKD can either be independent of, or superimposed on, DN. Glomerular causes of NDKD include immunoglobulin A (IgA) nephropathy, membranous nephropathy, membrano-proliferative glomerulonephritis, acute interstitial nephritis (AIN), hypertensive renal disease, focal segmental glomerulosclerosis (FSGS) and crescentic glomerulonephritis due to ANCA-associated disease and anti-glomerular basement membrane (anti-GBM) glomerulonephritis (Cases 3-6, Figures 4-7).
The prevalence and type of NDKD in patients with diabetes reported in the literature is highly variable (Table 1). This disparity reflects different selection criteria and study design, reporting bias, threshold for biopsy, and geographical and ethnic differences. Mazzucco et al highlighted the impact of different biopsy criteria on reported prevalence of NDKD\textsuperscript{26}. They showed that although patients were recruited from an ethnically homogenous population belonging to the same geographic area, centres with unrestricted biopsy policies reported 50\% of patients having DKD alone, with the remainder having features of mixed DKD and NDKD; whereas centres with restricted biopsy policies had lower rates of DKD and the majority of NDKD was not associated with DKD.

Further complicating the diagnosis of NDKD in diabetic patients is the overlap in histology findings of mild glomerulonephritis with early DKD changes\textsuperscript{27}. Features of minimal change disease under light microscopy may appear similar to Class I DN. Hence, electron microscopy is important in renal biopsy assessment in diabetes.

**Clinical Predictors of NDKD**

Given the prevalence of NDKD and the potential for treatment, it is important to identify clinical predictive factors of NDKD in diabetic patients and perform a renal biopsy to confirm diagnosis. Recently, several retrospective studies have reported clinical parameters to differentiate DKD from NDKD.

The presence of diabetic retinopathy (DR) prior to renal biopsy is strongly associated with DKD\textsuperscript{28-32}. In one study analysing 110 renal biopsies of patients with T2DM, the presence of DR was highly predictive of DKD (sensitivity 84\%, specificity 63\%)\textsuperscript{30}. In contrast, up to
70% of diabetic patients without retinopathy, but with albuminuria may have DKD\textsuperscript{33}, suggesting that whilst the absence of DR is a strong predictor of NDKD, it cannot exclude DKD. A recent analysis of DCCT found DR and DKD to be risk factors for development and progression of the other, independent of other established microvascular risk factors, suggesting a shared aetiological basis\textsuperscript{34}. However, up to 25% of patients with T1DM had discordant DR progression and DN development, which would argue for a partly different pathological mechanism\textsuperscript{34}. Furthermore, an analysis of Asian patients with diabetes suggests that DR is only associated with albuminuric DKD, and not normoalbuminuric DKD\textsuperscript{35}.

Duration of diabetes is a significant predictive factor for NDKD. Given the natural history of DN, the onset of proteinuria less than five years from onset of T1DM would be suggestive of another disease process. Studies of T2DM patients have found that diabetes > 10 years duration was associated with a higher likelihood of DKD\textsuperscript{6, 30}. Conversely, Tone et al showed that duration of T2DM < 5 years was highly sensitive (75%) and specific (70%) for NDKD\textsuperscript{28}. Chang et al also reported a mean diabetes duration of 5.9 years in patients with NDKD versus 10.6 years in patients with DKD alone (p<0.001)\textsuperscript{36}. However in T2DM patients without DR, there appears to be no difference in duration of diabetes in those who developed DKD or NDKD\textsuperscript{33}.

A recent meta-analysis by Liang et al also identified absence of DR and shorter duration of diabetes as significant predictors of NDKD in patients with T2DM\textsuperscript{37}. Their results suggested lower HbA1C, lower blood pressure and the presence of haematuria to be potentially helpful in distinguishing NDKD, although heterogeneity between the studies prevented more definitive conclusions.
The relevance of microscopic haematuria in predicting NDKD remains controversial, partly due to varying definitions of haematuria. Some studies recognise the importance of microscopic haematuria in distinguishing NDKD (sensitivity 80%, specificity 57%)\[^{30}\]; others have found it less discriminative\[^{28,29}\]. Moreover, microscopic haematuria may be a feature of T2DM patients with biopsy-proven DKD and overt proteinuria\[^{38}\]. A study involving patients with biopsy-proven DKD and overt proteinuria, found an association between persistent haematuria and arteriolar hyalinosis, but this did not provide prognostic clinical significance\[^{39}\]. On the other hand, urinary acanthocytes are reported to have high specificity for glomerular NDKD (100%), but low sensitivity\[^{31,40}\]. The occurrence of acute renal failure also has high specificity (97%) but poor sensitivity (45%) in predicting NDKD\[^{30}\]. Although nephrotic-range proteinuria is common in DKD, nephrotic syndrome with gross oedema and low albumin levels is uncommon, and should prompt renal biopsy.

Clinical findings of systemic illness are useful in predicting NDKD. Purpura and arthralgia may suggest Henoch-Schonlein purpura often associated with IgA nephropathy, whereas precedent infection is a strong indicator of acute post-streptococcal glomerulonephritis.

In terms of serologic abnormalities, positive ANA titres were not helpful in differentiating between DKD and NDKD\[^{6,31}\]. Some studies have found positive ANCA titres highly specific for pauci-immune glomerulonephritis\[^{31}\]; others found no difference in ANCA positivity between DKD and NDKD\[^{6}\].

The absence of peripheral neuropathy is not useful in predicting NDKD. One study found that neuropathy occurred in < 10% of diabetic patients with renal impairment, although the absence of neuropathy may have impacted on the initial decision for renal biopsy\[^{29}\].
Clinical Indications for Renal Biopsy

The routine presumption that DKD is the cause of renal impairment in diabetic patients may be inaccurate; however the threshold for renal biopsy varies amongst nephrologists.

Biesenbach et al argued that for T2DM patients fulfilling the clinical criteria for DKD (proteinuria, normal urinary sediment, normal kidney size and diabetes duration > 10 years), and vascular nephropathy (normal urine status, normal or near normal protein excretion, shrinkage of kidney, renal artery stenosis on ultrasonography), routine renal biopsy is not required. Others advocate more extensive use of renal biopsies, given that NDKD is not easily predictable based on clinical and laboratory findings. Even in the presence of diabetic retinopathy, prediction of DKD based on clinical course of disease and laboratory findings had only 65% sensitivity and 76% specificity.

We suggest that renal biopsy be considered in diabetic patients with CKD (eGFR < 60mL/min/1.73m$^2$) and the following features:

- Absence of DR
- Short duration of diabetes (<5 years)
- Absence of typical chronology e.g. acute onset of proteinuria, progressive decline in renal function
- Presence of haematuria
- Presence of other systemic disease
- Nephrotic syndrome
Summary

There is significant heterogeneity in the spectrum of renal disease seen in patients with diabetes. Although DKD is a common cause of chronic kidney disease in patients with diabetes, exclusion of NDKD is important because many forms of NDKD are potentially treatable and reversible. Renal biopsy should be considered in a carefully selected population where the disease course is atypical and clinical suspicion of NDKD is high. Absence of retinopathy and short duration of diabetes are the strongest predictors of NDKD.
### Clinical Case Vignettes

#### Case 1. DKD in T1DM
A 47 year-old man was diagnosed with T1DM since childhood, with multiple complications including proliferative retinopathy, peripheral neuropathy and cerebrovascular disease. Other medical history included obesity and hypertension; there was no family history of renal disease. He presented with worsening nephrotic-range proteinuria (24-hour urinary protein 6.5g) and rapid deterioration in renal function; HbA1C was 9.8%. Renal biopsy confirmed Class IV DN (Figure 1).

#### Case 2. DKD in T2DM
A 38 year-old obese woman presented with rapid weight gain (12kg in one week) associated with bilateral oedema to her upper thighs. She had significant proteinuria (urinary protein/creatinine ratio 378mg/mol) with impaired renal function (serum creatinine 122µmol/L). Past history was notable for gestational diabetes. She was diagnosed with T2DM (HbA1c 13.4%) and renal biopsy confirmed Class III DN with nodular glomerulosclerosis (Figure 2).

#### Case 3. FSGS causing nephrotic syndrome
A 43 year-old obese woman with 11-year history of T2DM, presented with nephrotic syndrome (gross peripheral oedema, urinary protein/creatinine 913mg/mol, serum albumin 26g/L) and preserved renal function (eGFR 77ml/min). Her HbA1c was 7% with no known diabetic complications. Renal biopsy demonstrated FSGS with mild chronic tubulointerstitial damage (Figure 4).

#### Case 4. Hypertensive kidney disease
A 74 year-old man with T2DM for 7 years was referred with gradually worsening renal impairment (eGFR 21ml/min). His HbA1C was 6.3% on oral agents with no vascular
complications. Other medical history included hypertension and obstructive sleep apnoea. Urine sediment did not show any proteinuria; kidneys were small-sized on ultrasonography. Renal biopsy revealed hypertensive nephrosclerosis (Figure 5).

Case 5. IgA nephropathy
A 50 year-old man presented with significant proteinuria, 5 years post-diagnosis of T2DM. His medical history included obesity, hypertension and hyperlipidaemia. Urinary protein excretion was 11g/day, with normal eGFR and active urinary sediment. HbA1C was 8%. Renal biopsy showed features of mesangial proliferative IgA nephropathy with chronic tubulointerstitial damage and nephrosclerosis (Figure 6).

Case 6. Membranous nephropathy and anti-GBM disease
A 22 year-old male with T1DM presented with nephrotic syndrome (urinary protein excretion 14g/day, serum albumin 23g/L), acute kidney injury (serum creatinine 387μmol/L) and active urinary sediment (>1000 x 10⁶/L dysmorphic erythrocytes). Renal biopsy showed focal segmental necrotising glomerulonephritis on a background of moderate nodular mesangial expansion and hypercellularity with several showing Kimmelstiel-Wilson nodules (Figure 7). Immunofluorescence showed strong linear GBM staining for IgG. Electron microscopy showed Stage 1 membranous nephropathy with small subepithelial electron dense “immune-type” deposits with GBM membrane spike formation.
<table>
<thead>
<tr>
<th>Country (Hunan)</th>
<th>Type of diabetes</th>
<th>Number of cases</th>
<th>Duration of study (years)</th>
<th>NDKD prevalence*</th>
<th>Most common NDKD</th>
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<td>China (Shanghai)</td>
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<td>52.2%</td>
<td>FSGS</td>
<td>Mou et al^{47}</td>
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<td>NA</td>
<td>50%</td>
<td>Membranous nephropathy</td>
<td>Premalatha et al^{48}</td>
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<td>Soni et al^{59}</td>
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<td>16</td>
<td>30%</td>
<td>Membranous nephropathy</td>
<td>Akimoto et al^{38}</td>
</tr>
<tr>
<td>Japan</td>
<td>T2DM</td>
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<td>63.9%</td>
<td>IgA nephropathy</td>
<td>Tone et al^{28}</td>
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<td>4</td>
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<td>AIN</td>
<td>Yaqub et al^{51}</td>
</tr>
</tbody>
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Table 1. Prevalence and type of NDKD in some studies from the Asia-Pacific region reported in the literature. *including mixed DN and NDKD
NA = not available
Figures

**Figure 1.** Case 1: Class IV DN. (A) >50% of glomeruli are globally sclerosed. (B) Preserved glomeruli show severe mesangial expansion.

**Figure 2.** Case 2: Class III DN. (A) This glomerulus shows severe mesangial expansion with Kimmelstiel-Wilson nodule (arrow). (B) Both afferent and efferent arterioles show marked arteriolar hyalinosis (asterisks).

**Figure 3.** Histological spectrum of renal biopsy findings seen in patients with low eGFR and normoalbuminuria. (A) Normal glomerulus and arteries, (B) Advanced diabetic glomerulosclerosis and arteriosclerosis (inset), (C) Minimal glomerular mesangial expansion and severe arteriosclerosis (inset). All images periodic acid–Schiff stain, original magnification X 200 (Reproduced with permission from Ekinci et al.²⁵).

**Figure 4.** Case 3: FSGS. Glomerulus with segmental sclerosis (arrow). Other glomeruli showed no evidence of DN.

**Figure 5.** Case 4: Hypertensive nephrosclerosis. Of 3 glomeruli, one is sclerosed, one shows ischemic change (arrow) and the other no evidence of DN.

**Figure 6.** Case 5: IgA nephropathy. (A) Glomerulus with mild mesangial hypercellularity but no evidence of DN. (B) Immunoperoxidase stain shows strong granular mesangial staining for IgA.
Figure 7. Case 6: Membranous nephropathy and anti-GBM disease. (A) Glomerulus with segmental necrosis (arrow) and cellular crescent (asterisk). (B) Glomerulus with class III DN with Kimmelstiel-Wilson nodule (arrow). (C) Strong linear GBM staining for IgG characteristic of anti-GBM GN. Inset shows dual pattern of GBM staining, both granular and linear, on confocal microscopy. (D) Electron microscopy shows GBM thickening and small subepithelial electron dense deposits characteristic of early membranous nephropathy.
References


Case 3

nep_12288_f4
Case 6

nep_12288_f7 A & B
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Title:
Spectrum of renal disease in diabetes

Date:
2014-09-01

Citation:

Persistent Link:
http://hdl.handle.net/11343/44025

File Description:
Accepted version