

Diabetic nephropathy: Is it time yet for routine kidney biopsy?

Maria L Gonzalez Suarez, David B Thomas, Laura Barisoni, Alessia Fornoni

Maria L Gonzalez Suarez, Alessia Fornoni, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL 33136, United States

David B Thomas, Laura Barisoni, Department of Pathology, University of Miami Miller School of Medicine, Miami, FL 33136, United States

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Correspondence to: Alessia Fornoni, MD, PhD, Department of Medicine, University of Miami Miller School of Medicine, 1601 NW 12th Ave, Miami, FL 33136, United States. afornoni@med.miami.edu

Telephone: +1-305-2433583 Fax: +1-305-2434404

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Abstract

Diabetic nephropathy (DN) is one of the most important long-term complications of diabetes. Patients with diabetes and chronic kidney disease have an increased risk of all-cause mortality, cardiovascular mortality, and kidney failure. The clinical diagnosis of DN depends on the detection of microalbuminuria. This usually occurs after the first five years from the onset of diabetes, and predictors of DN development and progression are being studied but are not yet implemented into clinical practice. Diagnostic tests are useful tools to recognize onset, progression and response to therapeutic interventions. Microalbuminuria is an indicator of DN, and it is considered the only noninvasive marker of early onset. However, up to now there is no diagnostic tool that can predict which patients will develop DN before any damage is present. Pathological renal injury is hard to predict only with clinical and laboratory

findings. An accurate estimate of damage in DN can only be achieved by the histological analysis of tissue samples. At the present time, renal biopsy is indicated on patients with diabetes under the suspicion of the presence of nephropathies other than DN. Results from renal biopsies in patients with diabetes had made possible the classification of renal biopsies in three major groups associated with different prognostic features: diabetic nephropathy, non-diabetic renal disease (NDRD), and a superimposed non-diabetic condition on underlying diabetic nephropathy. In patients with type 2 diabetes with a higher degree of suspicion for NDRD, it is granted the need of a renal biopsy. It is important to identify and differentiate these pathologies at an early stage in order to prevent progression and potential complications. Therefore, a more extensive use of biopsy is advisable.

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Key words: Diabetic nephropathy; Kidney biopsy; Non-diabetic renal disease

Core tip: Diagnostic tests are useful to predict onset, progression and response to therapeutic interventions in diabetic nephropathy (DN). Renal biopsies help to classify renal diseases in three major groups associated with different prognostic features: diabetic nephropathy, non-diabetic nephropathy (NDRD), and a superimposed non-diabetic condition on underlying DN. Pathological renal damage is hard to predict only with clinical and laboratory findings. In patients with a higher degree of suspicion for NDRD, it is granted the need of a renal biopsy. For this reason, more studies are required to assess the routine use of kidney biopsies as a gold standard for diagnosis of diabetic nephropathy.

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem, and one of the major causes of mortality in the United States. It is characterized by kidney damage for more than 3 mo; defined by structural or functional abnormalities of the kidney, with or without decreased estimated glomerular filtration rate (GFR); or GFR < 60 mL/min per 1.73 m² for more than 3 mo, with or without kidney damage^[1]. Decreased GFR and albuminuria are indicators of major health outcomes of this condition, including end-stage renal disease (ESRD) and death^[2].

There is no definitive cure for this condition; and many of the patients may develop complications even before they are able to receive renal replacement therapies, including long term dialysis and kidney transplants. In 2010, more than 117000 patients started therapy for ESRD; the prevalent population reached 594000, from those a 74% (439560) required dialysis and 3% (17778) received kidney transplants^[3].

The most common cause of ESRD requiring dialysis is diabetes mellitus (DM). Up to 44% of patients with newly diagnosed ESRD cases also carry a diagnosis of diabetes^[3]. According to the World Health Organization (WHO) in 2012, 347 million people suffered from DM; this is about 5% of the total population. Individuals with diabetes and CKD have an increased risk of all-cause mortality, cardiovascular mortality, and kidney failure^[3-5]. WHO estimates that deaths related to diabetes will double from 2005 to 2030^[4].

DEFINITION OF DIABETIC NEPHROPATHY AND WORLDWIDE IMPACT

Diabetic nephropathy (DN) is one of the most important long-term complications of diabetes. It is characterized by the development of proteinuria with a subsequent decline in glomerular filtration rate, which progresses over a long period of time, often for 10-20 years^[3,6,7].

Over the past 20 years, the prevalence of DN in the United States has increased in direct proportion to the prevalence of diabetes^[6]. Although DN cases vary largely among countries; in average it develops in 30% to 40% of patients with diabetes^[7]. The clinical diagnosis of DN usually depends on the detection of microalbuminuria (albumin excretion of more than 30 mg/g of creatinine in 2 out of 3 random urine samples collected in within a six month period)^[8]. A subset of patients with microalbuminuria will develop advanced DN; referred as overt nephropathy, clinical nephropathy, proteinuria, or macroalbuminuria^[9]. However, progression to microal-

Table 1 Diabetic nephropathy stages

Stage 1 Early hyperfunction and hypertrophy	ACR < 30 mg/g creatinine
Stage 2 Morphologic lesions without signs of clinical disease	ACR > 30 and < 300 mg/g creatinine
Stage 3 Microalbuminuria	ACR > 300 mg/g creatinine and/or persistent proteinuria with serum concentration of creatinine 2.0 mg/dL
Stage 4 Overt nephropathy	Serum concentration of creatinine 2.0 mg/dL with proteinuria
Stage 5 End-stage renal disease with uremia	On dialysis

ACR: Albumin to creatinine ratio.

buminuria usually occurs after five years from the onset of diabetes. Pathogenesis of the disease is multifactorial, *e.g.*, smoking, hyperglycemia, hypertension, male, genetic predisposition, advance age, retinopathy, macrovascular disease were the risk factors of diabetic nephropathy; and it involves genetic and environmental factors that affect multiple metabolic pathways not necessarily activated by hyperglycemia^[10].

STAGES OF DIABETIC NEPHROPATHY

Progression of the diabetic nephropathy is divided in clinical stages depending on the duration of the disease^[11-13] (Table 1). The first stage starts prior to any renal damage. It is characterized by renal vasodilation and hyperfiltration that occur early in the onset of diabetes. Several factors may lead to this hyperfiltration: including hyperglycemia, prostaglandins secretion and increased sodium/glucose reabsorption in the proximal tubule^[14]. It has also been associated to increased urinary albumin excretion related to physical activity^[15].

During the second stage, morphologic lesions develop without signs of clinical disease. The earliest structural abnormality in diabetes is glomerular basement membrane (GBM) thickening. The kidney with early diabetes suffers significant hypertrophy; characterized by enlargement of the organ with a combination of hyperplasia and hypertrophy^[16]. This occurs in nearly all patients 1.5 to 2.5 years after the onset of type 1 DM (T1DM). Nonspecific vascular or interstitial changes are prevalent in these patients. Mesangial expansion and occlusion of glomerular capillaries lead to a loss of available surface area for filtration and to a decline in function^[14].

Third stage is characterized by small amounts of albumin in the urine, not usually detected by conventional methods. This stage is also named incipient nephropathy^[9]. A slow and gradual increase of albuminuria over the years is a prominent feature in this stage. According to the DCCT/EDIC Study, persistent microalbuminuria develops most frequently during the second decade after diagnosis of diabetes^[6]. It reflects the existence of endothelial damage in the absence of specific renal lesions; and it is also associated with the beginning of advanced

renal pathology^[7]. Microalbuminuria could also represent podocytes loss; as podocyte number in patients with type 2 DM (T2DM) correlates with the change of albuminuria over time^[17].

Although microalbuminuria has been considered a risk factor for macroalbuminuria, not all patients progress to this stage; some of them stay or even may regress to normoalbuminuria^[18]. Microalbuminuria is considered to be predictive of progression to nephropathy in T2DM. However, that may not be the case in T1DM^[14]. Normoalbuminuric patients with diabetes are extremely heterogeneous in renal function and structure^[19]. Both, microalbuminuric and normoalbuminuric patients benefit from optimal glycemic control^[20]; since it has been shown that about one third of the normoalbuminuric subjects develop diabetic nephropathy within few years after onset of diabetes^[19,21-23]. The cause of albuminuria in patients without diabetic glomerulopathy is unclear. It might be related to early and very mild ultrastructural changes^[24].

Overt nephropathy is characterized by persistent albuminuria (UAE > 300 mg/d or > 500 mg/d urinary protein excretion) that usually accompanies a decrease in GFR^[25]. Macroalbuminuria has been associated to the presence of proliferative retinopathy, coronary heart disease, and foot ulcers^[14]. The prevalence of hypertension increases with higher levels of albuminuria^[15]. Other risk factors to develop overt nephropathy include uncontrolled diabetes, smoking, advanced age and high lipids levels^[26,27]. ESRD is defined by the presence of signs and symptoms of kidney failure requiring replacement therapy, regardless of the GFR level^[1]. It has been described as an important independent predictor of hospitalization and death in adults with heart failure. The deterioration rate from one stage to the next one is 2% to 3% per year^[28].

DIAGNOSTIC TOOLS FOR DIABETIC NEPHROPATHY

One of the main goals concerning the timely diagnosis of DN is to delay and if possible interrupt the natural course of this disease; from the progression of renal damage to ESRD in patients with diabetes. Diagnostic tests are useful tools to determine onset, progression and to predict response to therapeutic interventions.

Current screening recommendations

Although not all patients with early renal involvement, such as microalbuminuria progress to macroalbuminuria and ESRD; the risk is higher among these patients. Some of them stay or even may regress to normoalbuminuria^[18]. Ideally, it would be very useful to be able to predict which patients are at higher risk to develop ESRD, even before onset of DN. Unfortunately, at the present time, there is a lack of precise diagnostic tools that could definitively identify such patients^[29].

The National Kidney Foundation (NKF) and the American Diabetes Association (ADA) recommend that

patients with CKD and diabetes should be screened every year for DN. Screening should start 5 years after diagnosis in T1DM patients, and at the time of diagnosis in T2DM patients. This is done by measuring the urinary albumin/creatinine ratio in spot urine, serum creatinine and GFR^[1]. Although UAE is routinely used to diagnose DN; in some cases, patients with diabetes have a decrease GFR with normal UAE. Both GFR and UAE, correlate with the severity of glomerular lesions, duration of diabetes, glycaemic control and genetic factors^[30,31].

Currently, microalbuminuria is considered the earlier noninvasive marker^[32-34]. Patients with both elevated albuminuria and reduced GFR are at higher risk for a cardiovascular event^[35]. This emphasizes the importance to detect microalbuminuria and a close follow up of especially in young patients with diabetes.

Renal biopsy

Once the presence of albumin in the urine is confirmed, patients should undergo complete evaluation; including work-up for other etiologies. Renal diseases other than DN have been reported in patients with diabetes. DN usually develops 10 years after onset of T1DM^[18]; however, in T2DM this is variable^[23].

An accurate estimate of damage in DN can only be achieved by the histological analysis of tissue samples^[7]. Therefore, the kidney biopsy in patients with diabetes could represent a valuable procedure to establish the stage of the renal disease^[36]. The relevance of this diagnostic tool is supported by the observation that when a renal biopsy is performed in patients with DM, results may vary from primary and secondary renal disease with changes unrelated to diabetes to changes of underlying DM^[23].

Some of the earliest lesions are characterized by the thickening of the GMB visualized under electron microscopy, but with no findings under light microscopy. The morphologic lesions in T1DM predominantly affect the glomeruli, with thickening of the GBM and mesangial expansion; although the podocytes, renal tubules, interstitium, and arterioles also undergo substantial changes, especially at later stages of disease^[37,38].

Nephropathy in patients with T2DM is associated with two distinctive patterns of glomerular pathology (nodular and non-nodular)^[39]. Nodular type glomerulosclerosis (Kimmelstiel-Wilson nodules) was reported in 1936 by light microscopy. This lesion was initially identified as the only specific feature of DN^[40]. It consists of nodular lesions containing areas of marked mesangial expansion forming large round fibrillar mesangial zones with palisading of mesangial nuclei around the periphery of the nodule and compression of the associated glomerular capillaries. Later on, diffuse type glomerulosclerosis was described as a different type of diabetic glomerular lesion^[41]. All these diabetic glomerular changes are related to advanced or late DN associated to heavy proteinuria and/or decreased renal function. Arteriosclerosis is also frequently associated to diabetic glomerulopathy^[42].

It has been shown that there is not substantial difference in the injury caused in patients with T1DM in comparison to T2DM; and damages are considered basically similar in both types^[29]. For this reason, there is a consensus classification combining type 1 and type 2 DN. It is divided into four classes of glomerular lesions. Class I: GMB thickening, composed of isolated GMB thickening and only mild, nonspecific changes by light microscopy that do not meet the criteria of classes II through IV. Class II: mesangial expansion; mild (IIa) or severe (IIb), without nodular sclerosis or global glomerulosclerosis in more than 50% of glomeruli. Class III: nodular sclerosis (Kimmelstiel-Wilson lesions); at least one glomerulus with nodular increase in mesangial matrix (Kimmelstiel-Wilson) without changes described in class IV. Class IV: advanced diabetic glomerulosclerosis, more than 50% global glomerulosclerosis with other clinical or pathologic evidence that sclerosis is caused by diabetic nephropathy^[42,43] (Figure 1).

Podocyte injury is also an important feature of DN^[16,44-49], and podocyte loss (podocytopenia) is considered an independent predictor of DN progression in patients with T2DM^[17].

Indications for kidney biopsy

There are no standardized criteria for kidney biopsy in patients with DM; therefore, currently the decision to perform one is made by the primary physician^[50,51]. Nowadays, up to 25% of all renal biopsies are done in patients with DM^[51].

Rapid onset of proteinuria (regardless of the progression from microalbuminuria to macroalbuminuria), absence of retinopathy, presence of hematuria, active urinary sediment, rapid decrease of renal function, and suspicion of other nephropathies secondary to systemic disease, are some of the indications for renal biopsy^[50,52], e.g., Nephrotic syndrome, Urinary abnormalities, Isolated hematuria, Nephritic syndrome, Rapid onset of renal insufficiency, Unexplained renal failure at presentation, and No retinopathy are major indications for kidney biopsy. Some authors had considered retinopathy as a highly specific indicator for DN^[53,54]. On the other hand, other studies have shown to be a poor predictor of DN in T2DM^[55,56]. For this reason, kidney biopsy may have an opportunity to be proven as a gold standard for diagnosis of DN^[57].

Biopsy findings in patients with diabetes

Results from renal biopsies in patients with diabetes have made possible the classification of renal biopsies in three major groups associated with different prognostic features: DN, non-diabetic renal disease (NDRD), and a superimposed non-diabetic condition on underlying DN. There has been described a more rapid deterioration of renal function on patients with DN than with NDRD^[53]. Patients with non-diabetic nephropathies, including extracapillary glomerulonephritis, minimal change glomerulopathy, cryoglobulinemic nephritis, non-diabetic

membranous glomerulopathy, focal glomerulosclerosis, and IgA nephropathy, among others, might be modified by therapy; and for this reason, it results important the detection of such histological patterns following an appropriate therapeutic management; as this could promote a better outcome in those patients^[23]. The most common non-diabetic glomerulopathy found across reports in literature is IgA nephropathy^[60-72].

Clinical presentation varies among age groups. It is known that chronic nephritic syndrome is usually more common in young patients, and nephrotic syndrome and CKD in the elderly^[50]. The average time of onset of nephropathy in patients with diabetes is about 7-10 years^[18].

It is important to emphasize that among patients with diabetes; especially in those with T2DM, renal complications may be frequently due to heterogeneous non-diabetic lesions. Reported NDRD varies in the literature from a range of 14%-82.9% (Table 2), regardless of geographic region or ethnicity. The wide range in these highly variable results could be explained by the heterogeneity of the populations in the studies done around the world. Nzerue *et al*^[61], reported a prevalence of NDRD among African-Americans with T2DM based on renal biopsy. They found DN alone in 42%, while NDRD was seen in 19%; the rest of the patients had a superimposed NDRD with DN^[62]. Similar results were reported in two different studies in Japan^[68,73]. On the other hand; Wong *et al*^[53], reported different results in the Chinese population which showed a predominance of NDRD. As the population sample used in some of these studies was larger (*i.e.*, studies with population sample of more than 70 patients), the proportion of DN vs NDRD become more homogeneous; resulting in 30% prevalence for each of these groups. Although there is a male predominance for DN in general, this is not statistically significant among the studies^[58,62,71,74].

Pathological renal damage is hard to predict only with clinical and laboratory findings^[23,52,54]. In patients with T2DM with a higher degree of suspicion for NDRD, it is granted the need of a renal biopsy^[53]. Therefore, a more extensive use of biopsy is advisable. There are other cases where is not routinely performed; for example in patients with T2DM and ESRD, especially in those who present with criteria for clinical diagnosis^[57].

Complications of kidney biopsy

Kidneys are highly vascular organs; therefore the most common complications associated to kidney biopsies are those related to bleeding, including hematomas and gross hematuria^[87]. Iversen and Brun, in 1951 reported the first large series of needle biopsies in kidneys^[88]. Later on, Parrish *et al*^[89] also engaged in the labor of performing renal biopsies. Initially, the position of the kidney was determined by abdominal X-ray. Later on, sonography became available. They reported the common complications encountered in a period of 37 years (1951-1988). Complications occurred in 7% of the total

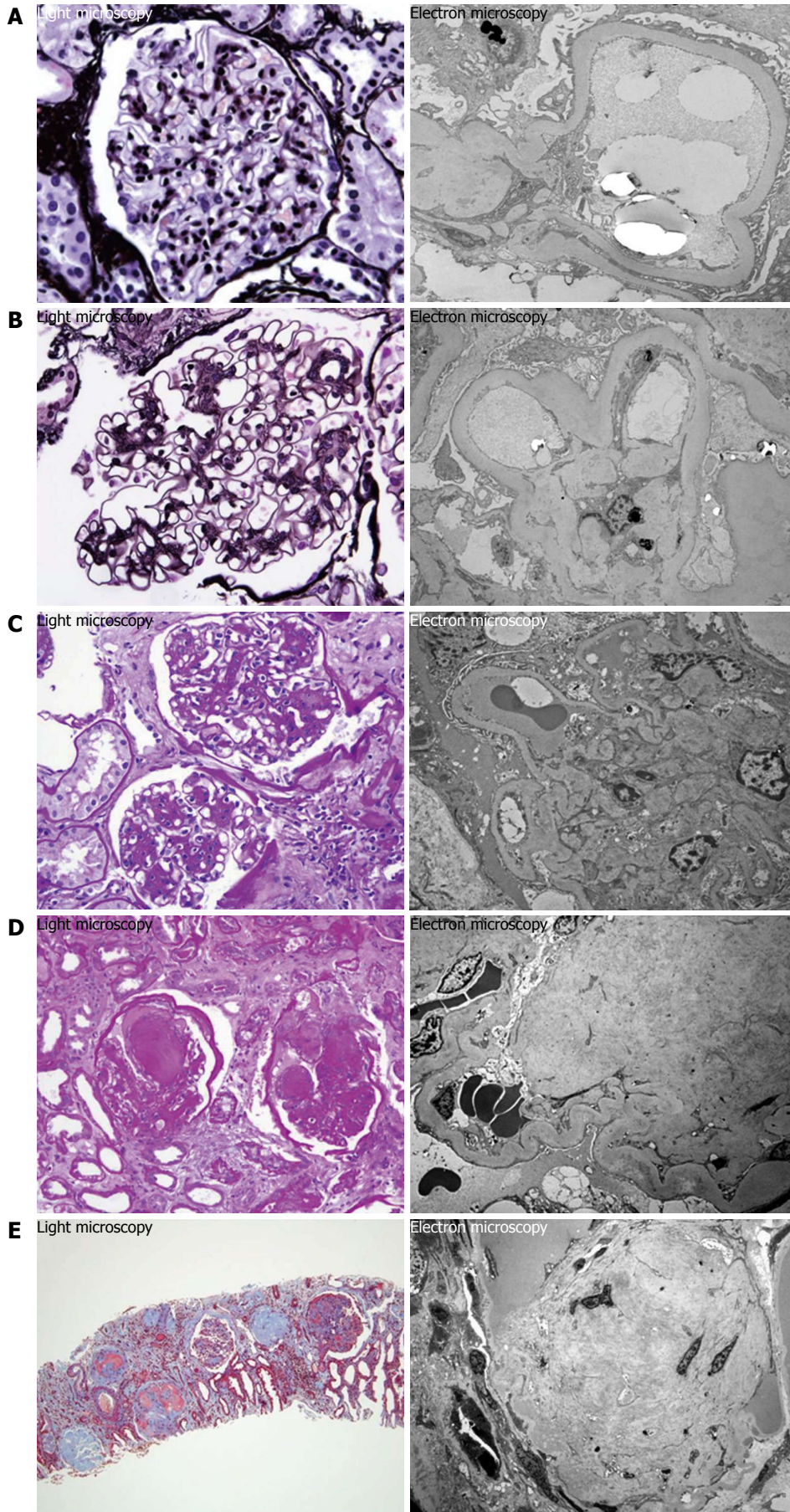


Figure 1 Diabetic nephropathy class. A: Glomerular basement membrane thickening; B: Mild mesangial expansion; C: Severe mesangial expansion; D: Nodular sclerosis (Kimmelstiel-Wilson lesions); E: Advanced diabetic glomerulosclerosis.

Table 2 Comparison of diabetic nephropathy and non-diabetic renal disease prevalence reported in the literature

Ref.	Country	Population	Type 1 or 2 DM	% DN	% NDRD	% Mixed
Mazzucco <i>et al</i> ^[22]	Italy	393	2	39.7	43	17.3
Christensen <i>et al</i> ^[24]	Denmark	51	2	68.6	13.8	NR
Zhang <i>et al</i> ^[37]	China	130	2	73.9	26.1	NR
Zhuo <i>et al</i> ^[50]	China/Japan	216	2	6.5	82.9	10.7
Sharma <i>et al</i> ^[51]	United States	620	2	37	36	27
Hironaka <i>et al</i> ^[52]	Japan	35	1 and 2	71.4	14.3	14.3
Wong <i>et al</i> ^[53]	China	68	2	35	46	19
Prakash <i>et al</i> ^[55]	India	23	2	56.5	30.5	13
Mak <i>et al</i> ^[56]	China	51	2	67	16	17
Biensebach <i>et al</i> ^[57]	Austria	84	2	78.5	21.5	NR
Richards <i>et al</i> ^[58]	United Kingdom	68	1 and 2	61	32	3
Parving <i>et al</i> ^[59]	Denmark	35	2	77.1	20	2.9
Cordonnier <i>et al</i> ^[60]	United Kingdom	26	2	85	15	NR
Nzerue <i>et al</i> ^[61]	United States	31	2	41.9	19.4	38.7
Lee <i>et al</i> ^[62]	South Korea	22	2	36.4	50	13.6
Izzedine <i>et al</i> ^[63]	France	21	1 and 2	62	38	NR
Castellano <i>et al</i> ^[64]	Spain	20	2	45	55	NR
Serra <i>et al</i> ^[65]	Spain	35	2	74.3	17.2	8.5
Premalatha <i>et al</i> ^[66]	India	18	2	50	50	NR
Rychlík <i>et al</i> ^[67]	Czech Republic	163	2	42.4	47.5	10.1
Tone <i>et al</i> ^[68]	Japan	97	2	36	16.5	47.5
Moger <i>et al</i> ^[69]	India	26	2	34.6	23.1	42.3
Soni <i>et al</i> ^[70]	India	160	2	42.5	27.5	30
Pham <i>et al</i> ^[71]	United States	233	2	27.5	53.2	19.3
Kharrat <i>et al</i> ^[72]	Tunisia	72	2	34.1	69.5	NR
Akimoto <i>et al</i> ^[73]	Japan	50	2	68	26	6
Huang <i>et al</i> ^[74]	China	52	2	55.7	38.5	5.8
Lin <i>et al</i> ^[75]	Taiwan, China	50	2	48	22	30
Ghani <i>et al</i> ^[76]	Kuwait	31	2	54.8	NR	45.2
Arif <i>et al</i> ^[77]	Pakistan	73	2	27.3	49.3	NR
Hashim Al-Saedi <i>et al</i> ^[78]	Iraq	80	1 and 2	NR	NR	100
Mou <i>et al</i> ^[79]	China	69	2	47.8	52.2	NR
Haider <i>et al</i> ^[80]	Austria	567	1 and 2	68	17.4	NR
Chang <i>et al</i> ^[81]	South Korea	119	2	36.2	53.8	10
Bi <i>et al</i> ^[82]	China	220	2	54.5	NR	45.5
Chong <i>et al</i> ^[83]	Malaysia	110	2	62.7	18.2	19.1
Harada <i>et al</i> ^[84]	Japan	55	2	54.5	34.5	10.9
Oh <i>et al</i> ^[85]	South Korea	126	2	39.7	51.6	8.7
Yaqub <i>et al</i> ^[86]	Pakistan	68	2	31	52	17

DN: Diabetic nephropathy; NDRD: Non-diabetic renal disease; DM: Diabetes mellitus.

biopsies performed (> 1800), consisting mainly of gross hematuria lasting for more than 12 h and pain.

With the introduction of the ultrasound, renal biopsy has become easier and safer. Ultrasound-guided biopsy is the standard method to obtain kidney tissue for diagnosis^[90]. Currently, complications are usually minor^[37]. A recent meta-analysis that included more than 9400 renal biopsies showed a small risk of macroscopic hematuria of 3%, only requiring blood transfusion in 0.9% of the cases^[91]. However, these events are not considered to represent serious medical problems; as they resolve within few hours after the procedure. Bleeding risks are also reduced by using smaller needle gauge, in order to obtain less tissue; but with adequate number of glomeruli per biopsy specimen for pathological diagnosis^[90].

Major complications, such as embolization of the renal artery, surgical intervention or death are relatively low. Patients with higher serum creatinine levels, especially women, have shown higher complication rates^[87,91].

Biopsy should be avoided in patients with bleeding

problems, uncontrolled hypertension, or those unable to cooperate; as these cases have been associated with an increased risk for complications after renal biopsy^[92].

Relative contraindications include: severe azotemia, anatomic abnormalities of the kidney such as arterial aneurysm, anticoagulant use, pregnancy, and urinary tract infection^[93].

Ongoing development of minimally invasive diagnostic tools

Some useful clinical indicators for DN are the presence of diabetic retinopathy and longer duration of diabetes. In contrast; for NDRD, signs include the presence of acute renal failure and microscopic hematuria^[83]. However, these clinical markers are not completely accurate and therefore, efforts have been directed to develop more modern technology in non-invasive diagnosis of DN to help clinicians to decide when a kidney biopsy should be warranted. These include the use of imaging techniques as well as the identification of serum and urinary bio-

markers.

Nowadays, diagnostic imaging technology has evolved to help clinicians on their daily decision making regarding which patients to biopsy in order to confirm DN. Insalaco *et al.*^[94] had reported the use of eco-colour-Doppler sampling of interlobular renal arteries and determination of their intrarenal resistance indices (RI) to differentiate DN from NDRD.

RI helps to measure hemodynamic changes in the renal arteries. These are usually seen in patients with DN, due to alterations in the compliance of the vessels affecting the blood flow. Therefore, early changes in blood flow are detected by renal Doppler and they may reflect the progression of DN^[95]. RI higher than 0.70 is a strong predictor of disease progression to renal failure, as well as RI lower than 0.70 is associated to a slow progression of renal disease^[96]. Also, it has been shown that RI in patients with DN is significantly higher than those with NDRD. RI evaluation could help determine prognosis and guide therapy; as this could potentially help to predict which patients with diabetes presenting with proteinuria should undergo renal biopsy; consequently reducing the indications for this procedure.

However, there is still no general agreement for the routine use of Doppler ultrasonography in patients with DN. Results may vary due to other factors that also modify renal vascular resistance; such as age, vascular compliance, high blood pressure, elevated heart rate, and the use of ACE-Inhibitors^[97].

Several serum circulating biomarkers may also help to identify patients that will develop DN in patients with diabetes and/or to identify those patients at risk to progress to ESRD in those with DN. Among them: uric acid^[98], vitamin D^[99], FGF23^[100] and TNFR1 and TNFR2^[101,102] are promising biomarkers.

Elevated serum concentrations of TNFR1 and TNFR2 are strongly associated with early renal function loss in patients with T1DM and T2DM^[101,102]. In contrast, low complement levels (C3 and/or C4) and M-spike have been associated with NDRD (alone or with coexistent DN) in kidney biopsies^[51]. Whether any of this biomarker could be causative of the disease initiation and progression remains to be proven through either experimental studies or through intervention studies. It would also be interesting to know if and how these biomarkers correlate to any given histological finding.

MicroRNA profiling has also been studied as a promising tool in the diagnosis of DN. Studies have been reported using this approach to determine different stages of diabetic nephropathy by analyzing urinary microRNA. This includes the potential benefit to distinguish early indicators of DN and to provide a tool for personalized medical therapy^[103].

Metabolomics is an evolving field dedicated to identify new metabolites predicting DN in patients with diabetes^[104]. Similarly, analysis of urinary proteomics and urinary exosomes have yield promising results^[105]. More recently, we have reported that a cell based assay where

normal human podocytes are cultured in the presence of the sera of patients with diabetes may help predict the progression to CKD^[106].

Finally, it would be interesting to have an integrative approach, where clinical phenotype combines to findings on kidney biopsies. This biologic application would likely represent a very powerful individualized diagnostic and prognostic tool in DN^[107].

CONCLUSION

Unfortunately, patients with NDRD are often designated as having DN because of the overlapping features of glomerulopathies^[70]. It is important to identify and differentiate these pathologies at an early stage in order to prevent progression and potential complications.

There is an overwhelming number of cases where these diagnoses would lead to changes in treatment, ranging from the use of immunosuppression to titration of renin-angiotensin-aldosterone system blockade^[108].

Common clinical practice is to biopsy patients with diabetes with a low pre-test probability for DN, such as patients presenting with AKI, low complements, and hematuria suggesting an increased likelihood of finding NDRD on biopsy^[51]. Nevertheless, as loss of renal function correlates with increased mortality. Therefore, any intervention that would help to delay progression to ESRD should significantly increase survival. In view of the fact that histology is necessary to characterize different glomerular diseases originating several nonspecific clinical presentations, kidney biopsy would help to direct a better management^[109].

Routine use of renal biopsy should be implemented, especially in those with atypical features^[83], for several reasons: (1) it helps to characterize the epidemiological features of renal diseases in diabetic patients^[110,111]; (2) it provides the opportunity to determine how histological and high-throughput profiling correlate with the clinical phenotype^[111]; and (3) it set the basis for personalized management strategies^[23,112].

The ability to differentiate between renal pathologies other than DN (that could be reversed with a specific treatment) and DN would be of extreme importance. We strongly support the recommendation that kidney biopsy should become a routine tool in specific patients at high risk of developing CKD, especially in those cases where this practice helps to reverse and/or prevent further kidney damage as it will help to direct assertive and aggressive treatment to many of the non-diabetic nephropathies to prevent or delay poor outcomes^[81,108].

There is lack of studies in the literature regarding the universal use of kidney biopsy on patients with diabetes. As new studies have become available to demonstrate how quantitative histological features may predict the disease course earlier than albuminuria^[113], our level of confidence to perform routine kidney biopsies in patients with diabetes should increase. New research studies are required, longitudinal observational clinical trials

as well as interventional trials, where the implementation of routine kidney biopsy is evaluated for patients with diabetes at time of diagnosis to evidence improvement in outcomes. These findings on kidney biopsies may help select the population of patients at highest risk of disease progression and may offer a new hard outcome measure to study DN.

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