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REVIEW

Insights into the Role of Renal Biopsy in Patients with T2DM: A Literature Review of Global Renal Biopsy Results

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ABSTRACT

Introduction: Renal biopsy performed in patients with type 2 diabetes mellitus (T2DM) for atypical or suspected diabetic kidney disease (DKD) reveals one of three possibilities: diabetic nephropathy (DN, pathological diagnosis of DKD), nondiabetic kidney disease (NDKD) and DN plus NDKD (mixed form). NDKD (including the mixed form) is increasingly being recognized worldwide. With the emerging concept of DKD and the complexity of routine application of renal biopsy, the identification of "clinical indicators" to differentiate DKD from NDKD has been an area of active research.

Methods: The PubMed database was searched for relevant articles mainly according to the keyword search method. We reviewed prevalence of the three types of DKD and different pathological lesions of NDKD. We also reviewed the clinical indicators used to identify DKD and NDKD.

Results: The literature search identified 40 studies (5304 data) worldwide between 1977 and 2019 that looked at global renal biopsy and pathological NDKD lesions. The overall prevalence rate of DN, NDKD and DN plus NDKD is reported to be 41.3, 40.6 and 18.1%, respectively. In Asia, Africa (specifically Morocco and Tunisia) and Europe, the most common isolated NDKD pathological type is membranous nephropathy, representing 24.1, 15.1 and 22.6% of cases, respectively. In contrast, focal segmental glomerulosclerosis is reported to be the primary pathological type in North America (specifically the USA) and Oceania (specifically New Zealand), representing 22% and 63.9% of cases, respectively. Tubulointerstitial disease accounts for a high rate in the mixed group (21.7%), with acute interstitial nephritis being the most prevalent (9.3%), followed by acute tubular necrosis (9.0%). Regarding clinical indicators to differentiate DKD from NDKD, a total of 14 indicators were identified included in 42 studies. Among these, the most commonly studied indicators included diabetic retinopathy, duration of diabetes, proteinuria and hematuria. Regrettably, indicators with high sensitivity and specificity have not yet been identified.

Conclusion: To date, renal biopsy is still the gold standard to diagnose diabetes complicated with renal disease, especially when T2DM patients present atypical DKD symptoms (e.g. absence of diabetic retinopathy, shorter duration of diabetes, microscopic hematuria, sub-

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nephrotic range proteinuria, lower glycated hemoglobin, lower fasting blood glucose). We conclude that renal biopsy as early as possible is of great significance to enable personalized treatment to T2DM patients.

Keywords: Type 2 diabetes mellitus; Renal biopsy; Diabetic kidney disease; Nondiabetic kidney disease; Clinical indicators

Key Summary Points

Renal biopsy for suspected or atypical diabetic kidney disease (DKD) classically reveals one of three possibilities: diabetic nephropathy (DN, pathological diagnosis of DKD), nondiabetic kidney disease (NDKD) and DN plus NDKD (mixed form). NDKD (including mixed form) manifests a wide spectrum of pathological lesions and variable prevalence across the world.

The emerging concept of DKD and the complexity of the routine application of renal biopsy has made the field of identifying DKD and NDKD from clinical indicators a hot topic.

The prevalence of these three types of DKD and pathological NDKD lesions in patients with type 2 diabetes mellitus (T2DM) are summarized and analyzed using data from 40 studies.

Clinical indicators for identifying DKD from NDKD are summarized, based on data from 42 studies. Regrettably, indicators with high sensitivity and specificity have not yet been identified.

Based these analyses, we conclude that, to date, renal biopsy is still the gold standard to diagnose diabetes complicated with renal disease, especially when T2DM patients present atypical DKD symptoms.

Future studies should place more focus on the identification indicators of DKD and NDKD.

INTRODUCTION

The number of persons with diabetes mellitus (DM) is increasing globally, especially type 2 DM (T2DM) [1]. In the USA, 23 million adults were diagnosed with diabetes in 2016, of whom 90.9% had T2DM and only 5.8% had type 1 diabetes (T1DM) [2]. Diabetes can lead to many microvascular complications. Diabetic kidney disease (DKD) [3, 4] is a long-term and major complication of DM that occurs in approximately 30% of patients with T1DM and approximately 40% of those with T2DM. It is the leading cause of end-stage renal disease (ESRD) worldwide and is associated with the occurrence of and death due to cardiovascular diseases, especially in T2DM patients [5–8]. In high-risk groups, such as middle-aged African Americans, native Americans and Hispanics, the incidence of ESRD caused by DKD continues to rise [9]. The various complications and comorbidities associated with DKD and ESRD places a heavy economic burden on healthcare systems [9, 10].

Over the past decades, renal biopsy in T2DM patients suspected of having DKD has shown that many patients actually suffer from nondiabetic kidney disease (NDKD) or diabetic nephropathy (DN) plus NDKD, with both conditions mistakenly identified as DKD. This translates into a difference in approach to treatment and overall prognosis: to date, controlling the incidence of DKD and improving prognosis of DKD are mainly attributed to the improvement of diabetes care. Innovative strategies to prevent, treat and reverse DKD are still unmet and need to be further explored [10, 11]. Unlike DKD, most of the glomerular and tubulointerstitial diseases caused by NDKD usually benefit from personalized treatments, such as immunosuppressive therapy, and can be alleviated or even cured if identified in a timely manner [12]. That is to say, early identification and treatment of NDKD is of great significance to reduce global ESRD prevalence and its various complications, such as cardiovascular complications. However, due to the limitation of renal biopsy applications, a confirmed diagnosis of DKD that at the same time excludes NDKD with

certainty in clinical practice is challenging. The introduction of the DKD concept in 2007 [3] encouraged many researchers to search for indicators that can be used to distinguish NDKD from DKD on clinical grounds. However, to date, there has been lack of large published studies that can be considered to be representative, including those with a large amount of data. In addition, it is generally believed that the incidence of NDKD in patients with T1DM is comparatively rare; consequently, data in this area are particularly scarce [13]. Compared with T1DM, T2DM often occurs in middle-aged and elderly people on a background of kidney degenerative lesions. Hypertension, hyperlipidemia, high uric acid level and other metabolic syndromes together may also cause damage to the kidney. In terms of pathology, structural changes in patients with T2DM are more heterogeneous than those in T1DM patients and they correlate less with clinical manifestations, which are also highly heterogeneous [1, 14]. Given this context, studying T2DM patients may have more clinical significance.

Based on the above, the aim of this article is to review the pathological findings of renal biopsy in T2DM patients worldwide and review the clinical indicators used to distinguish DKD from NDKD, in order to help clinicians evaluate patients with T2DM and chronic kidney disease (CKD) and possibly deliver more effective medical management to patients.

METHODS

We conducted a literature review using the PubMed literature database covering the time period between 1977 and 2019. The following keywords (and their combination) were used: "type 2 diabetes," "diabetic kidney disease," "renal biopsy," "nondiabetic kidney disease," "pathological lesions" and "clinical indicators." Relevant published papers listed on the web page of the "similar articles" section of PubMed/ automatically recommended were also included. Studies with a small number of cases and those failing to list the pathological NDKD lesions were excluded. All articles on renal biopsy results and pathological NDKD lesions in T2DM patients (40 articles in total) were included (summarized in Table 1, with studies describing pathological NDKD lesions listed as the top three). Additionally, articles on relevant clinical indicators to differentiate DKD from NDKD (42 articles in total) were included (summarized in Table 3).

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Prevalence and Pathological Types

Analysis of the results of the 40 studies on renal biopsy results and pathological NDKD lesions in T2DM patients (Table 1) showed that the prevalence rate of DN alone ranges from 8.2 to 62.7%, with an average of 41.3%, which is similar to the T2DM rate of about 40% reported by Alicic et al. [1]. The overall prevalence of NDKD (including the mixed form) is 58.7%, which is consistent with the reported prevalence of NDKD in T2DM patients ranging from 8 to 93.5% [55]. The prevalence of isolated NDKD ranges from 0 to 68.6%, with an average of 40.6%, and the prevalence of DN plus NDKD ranges from 0 to 45.5%, with an average of 18.1%. As shown in Table 1, the prevalence and pathological types of isolated NDKD or DN plus NDKD are quite variable, which can be explained by the following:

1) Kidney biopsy criteria. Kidney biopsy is essential for identifying renal damage caused by DN, NDKD or DN plus NDKD [12]. Dong et al. [56] suggested that patients with type 2 diabetes complicated with renal damage should actively undergo renal biopsy for five reasons: high significance of the correct DKD diagnosis; limitations in diagnosing DKD diagnosis; necessity of biopsy-proven pathological diagnosis; indications of renal biopsy; safety of renal biopsy. However, there is no uniform standard for performing kidney biopsy worldwide, which may result in a selection bias.

Table 1 Renal biopsy results and pathological types of renal disease in patients with type 2 diabetes mellitus

Country	Study population (*n*)	Number of cases diagnosed by pathology (%)			NDKD characteristics (%)	Mixed characteristics (%)
		DN	NDKD	Mixed		
Asia						
China [15]	207	51 (24.6)	142 (68.6)	14 (6.8)	MN (34.5), IgAN (19.7)	MN (35.7), TIL (28.6), IgAN (21.4)
China [16]	505	302 (59.8)	174 (34.5)	29 (5.7)	MN (32.2), IgAN (21.8), MCD (16.7)	IgAN (37.9), MN (34.5), MCD/FSGS/MPGN (6.9), LN (3.4)
China [17]	244	20 (8.2)	205 (84.0)	19 (7.8)	—	IgAN (52.6), TIL (21.1), MPGN (15.8), MN (10.5)
China [18]	220	120 (54.5)	—	100 (45.5)	—	IgAN (34.0), MN (22.0), MPGN (14.0)
China [19]	273	68 (24.9)	175 (64.1)	30 (11.0)	MN (29.7), IgAN (22.8), MPGN (8.0)	HRD (63.3), MN (20.0),I gAN/IN (3.3)
Taiwan [20]	50	24(48.0)	11 (22.0)	15 (30.0)	IgAN (11.5), MN/CIN (7.7)	AIN (42.3), MN (11.5)
Hong Kong [21]	68	24 (32.3)	31 (45.6)	13 (19.1)	IgAN (32.3), HRD (22.6), MN (16.1)	IgAN (23.1), MN (23.1), HRD (15.4)
Korea [22]	110	41 (37.3)	59 (53.6)	10 (9.1)	IgAN (43.5), MN (14.5), RPGN (7.2),T IL (4.3)	IgAN (60.0), MCD/RPGN (10.0)
Korea [23]	220	114 (51.8)	86 (39.1)	20 (9.1)	Mild-to-moderate proteinuria: IgAN (27.3), AIN (12.7), RPGN (10.9), ATN (9.0); Heavy proteinuria: MN (35.5), IgAN/MCD (12.9), MPGN (9.7)	Mild-to-moderate proteinuria: MN/ATN (33.3) Heavy proteinuria: MN (52.9), IgAN (17.6)
Korea [24]	119	43 (36.1)	64 (53.8)	12 (10.1)	MN (29.7), MCD (18.8), FSGS/IgAN (12.5)	MN (50.0), FSGS/IgAN (8.3), AIN/MPGN (8.3)
Korea [25]	126	50 (39.7)	65 (51.6)	11 (8.7)	MN (20), IgAN (13.8), FSGS (12.3)	IgAN (63.6), FSGS/MN (18.2)

Table 1 continued

Country	Study population (*n*)	Number of cases diagnosed by pathology (%)			NDKD characteristics (%)	Mixed characteristics (%)
		DN	NDKD	Mixed		
Thailand [26]	101	52 (51.5)	20 (19.8)	29 (28.7)	IgAN (35.0), MN (25.0), LN (20.0)	ATN (38.9), AIN (33.3), RPGN (8.3)
Pakistan [27]	68	23 (33.8)	34 (50.0)	11 (16.2)	AIN (32.0), DPGN (17.0), MN/RPGN (12.0)	AIN (63.6), FSGS (27.2), MPGN (9.0)
India [28]	75	27 (36.0)	45 (60.0)	3 (4.0)	MCD (13.3), MN/RPGN (11.1)	PIGN/IgAN (33.3), CIN (33.3)
India [29]	160	44 (27.5)	68 (42.5)	48 (30.0)	MN (19.2), FSGS (11.8), AIN/MCD (7.3)	PIGN/AIN (33.3), RPGN (6.3)
India [30]	26	9 (34.6)	6 (23.1)	11 (42.3)	RPGN (11.5), AIN (8.0)	DPGN (27.0), AIN (15.3)
Malaysia [31]	110	69 (62.7)	20 (18.2)	21 (19.1)	AIN (45.0), MCD (15.0), IgAN (10.0), HRD (10.0)	AIN (52.4), HRD (38.1), CPN (9.5)
Japan [32]	55	30 (54.6)	19 (34.5)	6 (10.9)	Non-DN: IgAN (23.6), FSGS (5.5), arteriosclerosis (5.5)	
Japan [33]	109	80 (73.4)	0 (0.0)	29 (26.6)	—	IgAN (44.8), PIGN (37.9), MN (6.9)
Kuwait [34]	31	17 (54.8)	0 (0.0)	14 (45.2)	—	RPGN (21.4), AIN (14.3), HRD (14.3)
Saudi Arabia [35]	16	8 (50.0)	1 (6.2)	7 (43.8)	MN (100.0)	MN/IN (28.6), IgAN/PIGN/MPGN (14.3)
Turkey [36]	115	36 (31.3)	46 (40.0)	33 (28.7)	MN/FSGS (13.0), TIL(10.9)	TIL (42.4), ANCA-/pauci-immune (6.1)
Turkey [37]	71	34 (47.9)	37 (52.1)	0 (0.0)	FSGS (18.9), CTIN (16.2), MN (13.5), ATN (10.8)	—
Turkey [38]	48	20 (41.7)	24 (50.0)	4 (8.3)	MN (29.2),TIN (20.8),IgAN/FSGS/MCD (12.5)	TIN (50.0), MN/FSGS (25.0)
Iran [39]	46	16 (34.8)	20 (43.5)	10 (21.7)	MN (45.0), FSGS (30.0)	AIN (60.0), IgAN (20.0), MN (10.0)

Table 1 continued

Country	Study population (*n*)	Number of cases diagnosed by pathology (%)			NDKD characteristics (%)	Mixed characteristics (%)
		DN	NDKD	Mixed		
North America						
USA [40]	233	64 (27.5)	124 (53.2)	45 (19.3)	FSGS (21.0), MCD (15.3), MN (13.3), Pauci (12.9)	IgAN (15.6), MN (13.3), arteriosclerosis (13.3)
USA [41]	611	227 (37.2)	220 (36.0)	164 (26.8)	FSGS (21.8), HRD (17.7), ATN (17.3), IgAN (10.5), MN (8.2)	ATN (43.3), HRD (18.9), FSGS (12.8), IgAN (7.3)
USA [42]	31	13 (41.9)	6 (19.4)	12 (38.7)	FSGS (50.0), MN (33.3), MCD (16.7)	Immune-complex GN(50.0), FSGS (25.0), RPGN (16.7)
Africa						
Morocco [43]	40	24 (60.0)	14 (35.0)	2 (5.0)	MN (18.8), HSP (12.5), PIGN (12.5), LN (12.5)	HSP (6.3), myeloma-cast nephropathy (6.3)
Morocco [44]	16	10 (62.5)	6 (37.5)	0 (0.0)	IgAN (19.0), myeloma-cast nephropathy (6.0)	_
Tunisia [45]	75	18 (24.0)	33 (44.0)	24 (32.0)	FSGS (21.2), MN (15.2), IgAN/RPGN/PIGN (12.1)	MN (25.0), FSGS (20.8), CTIN/PIGN (16.7)
Europe						
Croatia [46]	80	37 (46.3)	29 (36.2)	14 (17.5)	MN (24.1), IgAN/FSGS (17.2), MCD (6.9)	HRD (28.6), FSGS (21.4), IgAN (21.4), MN (14.3)
Bosnia and Herzegovina [47]	28	8 (28.6)	17 (60.7)	3 (10.7)	MN (17.6), HRD (11.8), FSGS (5.9)	HRD (66.7), LN (33.3)
Poland [48]	76	27 (35.5)	38 (50.0)	11 (14.5)	FSGS (34.2), MN (21.1), IgAN (15.8), RPGN (13.2)	_
Italy [49]	393	216 (55.0)	109 (27.7)	68 (17.3)	MN (28.4), IgAN (22.0), MCD/FSGS (20.2)	PIGN (38.2), IgAN (17.6), CGGN (16.2), MN (14.7)
Denmark [50]	51	35 (68.6)	16 (31.4)	—	IgAN (18.6), MPGN (6.3)	_

Table 1 continued

Country	Study population (*n*)	Number of cases diagnosed by pathology (%)			NDKD characteristics (%)	Mixed characteristics (%)
		DN	NDKD	Mixed		
Spain [51]	20	9 (45.0)	11 (55.0)	0 (0.0)	MN (55.0), vasculitis (27.3), IgAN (9.0)	_
Czech Republic [52]	163	69 (42.3)	77 (47.3)	17 (10.4)	IgAN (17.5), MN/HRD (11.1), NV (9.5)	_
UK [53]	51	16 (31.4)	31 (60.8)	4 (7.8)	IN (20.0), RPGN(14.3), MN/FSGS (11.4)	–
Oceania						
New Zealand [54]	263	94 (35.7)	72 (27.4)	97 (36.9)	FSGS (63.9), AIN (8.3)	AIN (35.1), FSGS (33.0)

AIN Acute interstitial nephritis, *ATN* acute tubular necrosis, *CGGN* cryoglobulinemic glomerulonephritis,*CIN* chronic interstitial nephritis, *CPN* chronic pyelonephritis,*CTIN* chronic tubulointerstitial nephritis, *DPGN* diffuse proliferative glomerulonephritis, *DN* diabetic nephropathy, *FSGS* focal-segmental glomerulosclerosis, *HSP* Henoch-Schönlein purpura, *HRD* hypertensive renal disease, *IgAN* immunoglobulin A nephropathy, *immune-complex GN* immune-complex glomerulonephritis, *IN* interstitial nephritis, *LN* lupus nephritis, *MCD* minimal change disease, *Mixed* DN plus NDKD, *MPGN* membrane proliferative glomerulonephritis, *MN* Membranous nephropathy, *NDKD* nondiabetic kidney disease, *NV* necrotizing vasculitis, *Pauci* NCA + pauci-immune, *PIGN* post-infectious glomerulonephritis, *RPGN* rapidly progressive glomerulonephritis, *TIL* tubulointerstitial lesions, *TIN* tubulointerstitial nephritis, *TMA* thrombotic microangiopathy

The criteria for renal biopsy in each region, in each country even in each nephrologist's practice are not identical, which is one of the main reasons for the great variability in the reported prevalence of the pathological types [57]. Furthermore, even if renal biopsy is strongly recommended based on clinical factors, patient compliance is also a factor, leading again to great variability.

2) Geographical regions and heterogeneity of populations worldwide. The prevalence of DN, NDKD or DN plus NDKD differ according to geographical regions and populations, as indicated by two different studies carried out in India. Prakash et al. [58] reported the prevalence of NDKD in North India to be 12.3%, while John et al. [59] reported a higher prevalence of NDKD in South India, especially the proliferative glomerulonephritis type, which was as high as 21.5% among the patients studied. Data from studies conducted in the USA [40–42] show a high prevalence of focal segmental glomerulosclerosis (FSGS) in isolated NDKD (22%), which may be associated with the increased incidence of FSGS in Americans, especially in black individuals. Distribution of the pathological type DN plus NDKD appears to be relatively average [40–42], but glomerulonephritis is dominant overall [60]. However, in a multi-center study in China [61], membranous nephropathy (MN) was found to be the primary pathological type in NDKD (including mixed form) (40.8%), followed by immunoglobulin A nephropathy (IgAN) (19.8%)

As illustrated in Table 2, the proportion of NDKD cases identified in renal biopsy performed on patients with T2DM is not insignificant. In all continents, with the exception of Europe and Oceania, the proportion of patients with NDKD exceeds that with DN. These studies may overestimate the true prevalence of NDKD in T2DM patients, as indications for biopsy favor atypical cases, such as nephrotic syndrome, abnormal urine sediment, rapid decline of renal function or other NDKD indicators. On the other hand, in clinical practice, patients with T2DM rarely undergo diagnostic renal biopsy. In the absence of renal biopsy, the registry usually identifies patients with DM plus CKD as having DKD, resulting in an increase in the reported prevalence of DKD and a decrease that of NDKD [62]. In Asia, Africa (specifically Morocco and Tunisia) and Europe, the most commonly isolated NDKD pathological type is MN (Table 2), possibly associated with the increasing incidence of MN worldwide in the past decades. According to the literature [63], the incidence of MN in China increased from 6.48% in 1997–1999 to 22.79% in 2009–2011, while in Korea, idiopathic MN (IMN) was identified in 12.0% of all renal biopsies. Similar to Asia, the prevalence of IMN increased from 11.2 to 29.4% in Europe. A large-scale data study by Xu et al. [64] explained the high incidence of MN in China in the past decades in the context of environmental pollution (especially the increase in PM 2.5 levels). In areas with PM $2.5 > 70\ \mu g/m^3$, for every $10\ \mu g/m^3$ increase in concentration, the risk of developing MN was noted to increase by 14% (odds ratio 1.14, 95% confidence interval 1.10–1.18), while the effect in areas with PM $2.5 < 60\ \mu g/\ m^3$ was much lower. In support of this explanation, the prevalence of other major glomerular diseases remained relatively stable with increasing air pollution in China over the past decades, leading the authors to conclude that patients with long-term exposure to high levels of PM 2.5 may be more prone to MN than to other kidney diseases in a nonlinear pattern. In North America (specifically the USA), FSGS is the primary pathological type in patients with isolated NDKD (22%) (Table 2), which may be also related to the high incidence of FSGS. Consistent with previously published data [65], FSGS has always represented the primary pathological lesion in the USA, reported to be an average of 25.3% from 1986 to 2015.

Table 2 also illustrates the high rate of tubulointerstitial disease in the mixed group (21.7%), with the most common types being acute interstitial nephritis (AIN) (9.3%), followed by acute tubular necrosis (ATN) (9.0%). This high rate of tubulointerstitial disease may be associated with ischemic injury caused by diabetic vascular disease combined with other complex factors, such as susceptibility to

Table 2 Summary of renal biopsy results and pathological types in patients with type 2 diabetes mellitus in different continents

Continent	Number of cases diagnosed by pathology (%)			NDKD characteristics (%)[a]	Mixed characteristics (%)[a]
	DN	NDKD	Mixed		
Asia (n = 3173)	1322 (41.7)	1352 (42.6)	499 (15.7)	1. MN (24.1)	1. TIL (19.9)[b]
				2. IgAN (16.8)	2. IgAN (19.3)
				3. TIL (5.7)[b]	3. MN (15.2)
North America (n = 875)	304 (34.7)	350 (40.0)	221 (25.3)	1. FSGS (22.0)	1. ATN (32.1)
				2. HRD (11.1)	2. HRD (14.0)
				3. MN/ATN (10.9)	3. FSGS (10.9)
Africa (n = 131)	52 (39.7)	53 (40.5)	26 (19.8)	1. MN (15.1)	1. MN (23.1)
				2. IgAN/FSGS (13.2)	2. FSGS (19.2)
				3. PIGN (11.3)	3. PIGN/CTIN (15.4)
Europe (n = 862)	417 (48.4)	328 (38.1)	117(13.6)	1. MN (22.6)	1. PIGN (22.2)
				2. IgAN (21.3)	2. IgAN (12.8)
				3. FSGS (12.5)	3. MN (10.3)
Oceania (n = 263)	94 (35.7)	72 (27.4)	97 (36.9)	1. FSGS (63.9)	1. AIN (35.1)
				AIN (8.3)	2. FSGS (33.0)

[a] Given in order of reported prevalence (first (1), second (2) and third (3)
[b] TIL includes cases of IN, AIN, CIN, CTIN, TIN and ATN

infection, direct tubulointerstitial damage due to alterations in extracellular matrix synthesis and metabolism under the influence of glucose and/or the use of non-steroidal anti-inflammatory drugs, antibiotics, among others. These factors together lead to tubulointerstitial injuries. In conclusion, the high frequency of tubulointerstitial disease in patients with DKD may be related to the increased susceptibility of the kidney to ischemia and toxic injury [36].

Clinical Indicators

The natural history of progression of T2DM/DKD to ESRD is not as clear as that of T1DM/DKD to ESRD. In addition, the clinical manifestations of this progression are varied. As such, many researchers have focused on trying to identify clinical indicators to distinguish DKD, single NDKD or a combination of the two in T2DM patients. Relevant clinical indicators include proteinuria, hematuria, duration of diabetes, diabetic retinopathy (DR), hypertension, hemoglobin, glycated hemoglobin (HbA1c), serum creatinine, serum cystatin C (CysC), C3, immunoglobulin, among others (Table 3)

As illustrated in Table 3, DR is an important clinical indicator predicting DKD or NDKD [18, 19, 21, 22, 24, 29, 31, 32, 37–40, 44, 46, 48, 51, 53, 54, 69–77, 80]. The presence of DR strongly suggests DKD, and the absence of DR is a major indicator to predict NDKD. In a multi-variate analysis, the overall diagnostic efficiency of DR was found to be quite significant [75, 76, 80]. In the study by Castellano et al. [51], the presence of retinopathy had a predictive value of 100% for DN. However, in a meta-analysis by Liang et al. [72], 23.6% of patients with biopsy-proven DKD did not have

Table3 Summary of clinical indicators for predicting diabetic kidney disease or nondiabetic kidney disease in patients with type 2 diabetes mellitus

Indicators	References
Family history	[15]
Duration of diabetes	[16, 21, 22, 24, 26, 29, 37, 41, 44, 48, 54, 69, 72, 74–76, 80]
Glycated hemoglobin (HbA1c)	[16, 26, 32, 33, 53, 72]
Diabetic retinopathy	[18, 19, 21, 22, 24, 29, 31, 32, 37–40, 44, 46, 48, 51, 53, 54, 69–77, 80]
Hematuria	[21, 26, 45, 48, 66, 74, 75]
Proteinuria	[20, 21, 23, 34, 37, 74, 80]
Serum total protein/albumin	[20, 33]
Hemoglobin	[24]
Serum creatinine	[20, 31, 79]
Fasting blood glucose	[32, 71, 73]
Hypertension	[44, 72]
Complement level	[68, 74]
Immunoglobin G (IgG)	[22, 68, 79]
Cystatin C	[67, 78]

DR and there was no evidence of co-existence of DN and DR in 17.6% of patients. In summary, the absence of DR can predict NDKD, but DKD cannot be ruled out. Similarly, even if DR is present, NDKD can also occur (DKD plus NDKD). As such, Zwi et al. [81] suggest that biopsy should be performed to exclude interstitial nephritis and FSGS even in the presence of retinopathy. Jiang et al. [77] also found that the severity of DR was not related to the presence of DKD.

The duration of diabetes is an important predictor of DKD and NDKD according to many published reports [16, 21, 22, 24, 26, 29, 37, 41, 44, 48, 54, 69, 72, 74–76, 80]. The major finding suggested by these reports is that a shorter duration of diabetes is suggestive of NDKD, while a longer duration is related to DKD. Some reports even provide a relatively specific time period: a duration of < 5 years from the time of diagnosing DM to developing a kidney disease is an independent predictor of NDKD [7, 16, 69, 75, 76], while a duration of > 10 years is an important indicator of DKD. More specifically, Yenigun et al. [[37] and Sharma et al. 41] identified a duration of > 12 years as a predictor of DKD and NDKD with high sensitivity and specificity.

Hematuria is also a common predicting factor of DKD and NDKD [21, 26, 45, 48, 66, 74, 75]. Jiang et al. [82] further found dysmorphic erythrocytes were more valuable than microhematuria in the diagnosis of a nondiabetic lesion in T2DM with proteinuria. Lower HbA1c can also predict NDKD [16, 26, 32, 33, 53, 72]. Wang et al. [83] further pointed out that both the ratio of glycated albumin to HbA1c and glycated albumin were better biopsy-proven DKD indicators than HbA1c.

Other clinical predictors studied are proteinuria and serum CysC. Proteinuria as a predictor, most of the published literature suggest that sub-nephrotic range proteinuria is associated with the presence of NDKD, while nephrotic range proteinuria suggests DKD [20, 23, 37, 74, 80]. Ghani [34] also found that

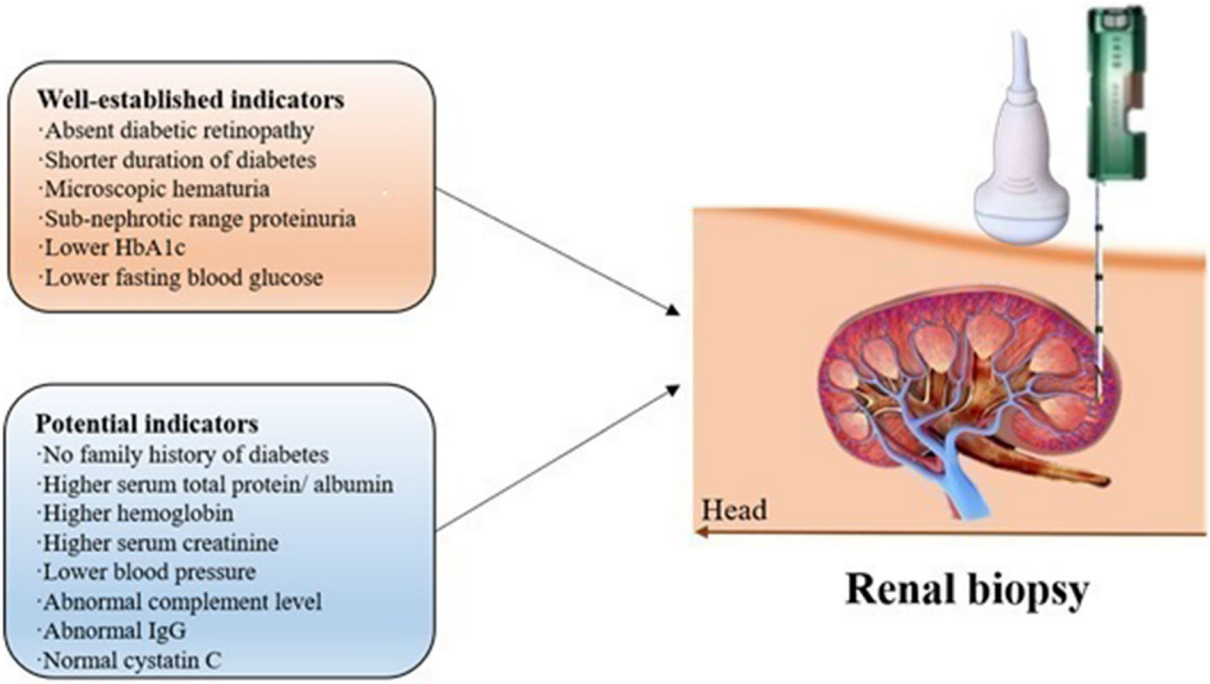

Fig. 1 Clinical indicators of nondiabetic kidney disease. *HbA1c* Glycated hemoglobin *IgG* immunoglobulin G

proteinuria level in patients with NDKD superimposed on diabetic glomerulosclerosis is typically higher; however, this finding needs to be supported by data from study with a large sample. Moreover, in a meta-analysis [67], researchers found that serum CysC was an early predictor of DN. Suzuki [78] also confirmed CysC can effectively detect grade 2 DN (urine albumin to creatinine ratio 30–300 mg/g) and will be especially useful for screening grade 2 CKD patients (K/DOQI–KDIGO [Kidney Disease Outcomes Quality Initiative–Kidney Disease Improving Global Outcomes] joint statement [3]).

Studies combining more than one predictor to distinguish DKD from NDKD have also been reported. Wong et al. [21] found that combination of absence of DR with hematuria or proteinuria ($\geq$ 2 g/day) was the most sensitive indicator of a nondiabetic lesion, and Soni [29] considered that a short duration of diabetes and absence of retinopathy, especially when associated with nephrotic proteinuria, strongly predicts a nondiabetic lesion, consistent with results from a research paper from Australia [69]. Our analysis of the published literature revealed some contradictions. For example, in a study by Lin et al. [20], duration of DM of > 10 years and absence of DR failed to rule out NDKD, and in a study by Tone et al. [76] microscopic hematuria and granular casts had low specificity and sensitivity for NDKD. Furthermore, a study by Zhang et al. [68] showed that with different levels of proteinuria, low IgG and high C3 were independent indicators of NDKD in patients with T2DM, while Byun et al. [22] described an association between higher levels of IgG and NDKD, and Kanodia et al. [74] described an association of NDKD with low levels of C3 and/or C4. All of these contradictions require further study and verification by analysis of large-scale data.

Although single or combined indicators have resulted in higher sensitivity and specificity, most have been derived from single sample studies, which cannot exclude the effect of small sample size, selection bias and other such limitations. Christensen et al. [50] clearly pointed out that clinical or laboratory data could not be used to separate diabetes and nondiabetic glomerular lesions based on

demographics. Clinically, if atypical DKD features are present, renal biopsy is still the only means to confirm the presence or absence of NDKD [2, 16–20, 22, 24–27, 31–34, 37–40, 46, 48, 50, 51, 69, 75, 80, 84]. To this end, we have divided these indicators from Table 3 into well-established indicators to NDKD and potential indicators to NDKD (Fig. 1). Whether potential indicators are able to predict NDKD requires more research data. However, when T2DM patients have the atypical DKD symptoms suggested by the above indicators, having kidney biopsy as early as possible to determine the presence and pathological type of NDKD is beneficial to the initiation of personalized treatment for patients.

DISCUSSION

Due to national policies and the paucity of relevant research, we were unable to collect comprehensive data for our review, particularly with regard to South America. Data from North America are limited to the USA, data from Oceania are also limited to New Zealand and data from Africa are only from Morocco and Tunisia; data from other countries on these three continents are lacking. However, our analysis of the available data allowed us to identify the high prevalence and wide spectrum of NDKD in patients with T2DM, as well as describe the sensitivity and specificity of the related clinical predictive indicators.

Overall, our findings suggest that, to date, renal biopsy is still an important strategy to differentiate between the three kinds of kidney disease complicating T2DM; this is particularly true when T2DM patients present atypical DKD symptoms (e.g. absence of DR, shorter duration of diabetes, microscopic hematuria, subnephrotic range proteinuria, lower HbA1c, lower fasting blood glucose). We look forward to collecting more data from Oceania, North America and Africa in the future to further verify or better explain our results.

Although the results from our review indicate the importance of kidney biopsy in T2DM complicated with renal disease, we admit that there are still some problems in applying this procedure. For example, kidney biopsy was considered to be safe in most studies [85–87], but patients with T2DM and kidney disease are usually older, and diabetes can cause damage to blood vessels and multiple systems, which might make renal biopsy more complicated. In addition, there is no consensus on the safety of kidney biopsy between kidney diseases complicating T2DM and kidney diseases without diabetes globally. Moreover, the decision-making process for kidney biopsy is mostly determined by the attending doctor, and research on the development of standardized criteria for performing renal biopsy in patients with diabetes is very limited.

In view of the above-mentioned issues, we suggest that future studies should focus on the identification of indicators of DKD and NDKD, not only those at the biochemical level but also at other levels, such as ultrasound and genomics. The availability of such indicators will increase the clinican's confidence in making a diagnosis and optimize the decision-making process regarding the implementation of kidney biopsy. In addition, future research can make full use of modern technological advances to achieve data sharing, conduct analyses of large datasets and apply innovative experimental designs. By carrying out dynamic monitoring of and long-term follow-ups on T2DM patients, future studies can gain a deeper understanding of the medical methods needed to identify DKD and NDKD and allow a more comprehensive interpretation and evaluation of renal biopsy's application value in T2DM complicated with renal diseases.

Our review has a number of limitations. First, we only used the PubMed database for our literature search, which may have resulted in omissions of some articles. In addition, we did not use additional statistical methods to quantify our conclusions, such as meta-analysis. In view of the deficiencies of our review, we will continue to pay attention to whether more research data appear, especially data from Africa, North America and Europe, and use a systematic approach to analyze the literature.

CONCLUSIONS

The high prevalence and various types of NDKD, as well as the complexity of DKD clinical manifestations, make it more difficult for clinicians to diagnose the three types of renal disease (DN, NDKD and DN plus NDKD [mixed form]). Although the application of renal biopsy in T2DM patients is controversial, our review suggests that, to date, renal biopsy is still an important strategy to identify T2DM complicated with renal disease, especially for patients with atypical DKD symptoms.

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REFERENCES

1. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017;12:2032–45.
2. Bullard KM, Cowie CC, Lessem SE, et al. Prevalence of diagnosed diabetes in adults by diabetes type—United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67:359–61.
3. KDOQI. KDOQI Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis. 2007;49:12–154.
4. Gosmanov AR, Wall BM, Gosmanova EO. Diagnosis and treatment of diabetic kidney disease. Am J Med Sci. 2014;347:406–13.
5. Reutens AT, Atkinstkins RC. Epidemiology of diabetic nephropathy. Contrib Nephrol. 2011;170:1–7.
6. Assogba FG, Couchoud C, Hannedouche T, et al. French Renal Epidemiology and Information Network Registry. Trends in the epidemiology and care of diabetes mellitus-related end-stage renal disease in France, 2007–2011. Diabetologia. 2014;57:718–28.
7. Bramlage P, Lanzinger S, van Mark G, et al. Patient and disease characteristics of type-2 diabetes patients with or without chronic kidney disease: an analysis of the German DPV and DIVE databases. Cardiovasc Diabetol. 2019;18:33.
8. Chou YH, Lin WC, Chen YM. Clinical outcomes in patients with biopsy-proved diabetic nephropathy compared to isolated lupus or crescentic glomerulonephritis. Diabetes Res Clin Pract. 2019;148:144–51.

9. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care. 2014;37:2864–83.

10. Doshi SM, Friedman AN. Diagnosis and management of Type 2 diabetic kidney disease. Clin J Am Soc Nephrol. 2017;12:1366–73.

11. Thomas MC, Brownlee M, Susztak K, et al. Diabetic kidney disease. Nat Rev Dis Primers. 2015;1:1–19.

12. Fiorentino M, Bolignano D, Tesar V, et al. Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. Nephrol Dial Transpl. 2017;32:97–110.

13. Olsen S. Identification of non-diabetic glomerular disease in renal biopsies from diabetics–a dilemma. Nephrol Dial Transpl. 1999;14:1846–9.

14. Fioretto P, Caramori ML, Mauer M. The kidney in diabetes: dynamic pathways of injury and repair. The Camillo Golgi Lecture 2007. Diabetologia. 2008;51:1347–55.

15. Xu J, Hu XF, Huang W, et al. The clinicopathological characteristics of diabetic nephropathy and non-diabetic renal diseases in diabetic patients. Zhonghua Nei Ke Za Zhi. 2017;56:924–9.

16. Wang J, Han Q, Zhao L, et al. Identification of clinical predictors of diabetic nephropathy and non-diabetic renal disease in Chinese patients with type 2 diabetes, with reference to disease course and outcome. Acta Diabetol. 2019;56:939–46.

17. Zhuo L, Zou G, Li W, Lu J, Ren W. Prevalence of diabetic nephropathy complicating non-diabetic renal disease among Chinese patients with type 2 diabetes mellitus. Eur J Med Res. 2013;18:4–11.

18. Bi H, Chen N, Ling G, Yuan S, Huang G, Liu R. Nondiabetic renal disease in Type 2 diabetic patients: a review of our experience in 220 cases. Ren Fail. 2011;33:26–30.

19. Liu S, Guo Q, Han H, et al. Clinicopathological characteristics of non-diabetic renal disease in patients with type 2 diabetes mellitus in a north-eastern Chinese medical center: a retrospective analysis of 273 cases. Int Urol Nephrol. 2016;48:1691–8.

20. Lin YL, Peng SJ, Ferng SH, Tzen CY, Yang CS. Clinical indicators which necessitate renal biopsy in type 2 diabetes mellitus patients with renal disease. Int J Clin Pract. 2009;63:1167–76.

21. Wong TY, Choi PC, Szeto CC, et al. Renal outcome in type 2 diabetic patients with or without coexisting nondiabetic nephropathies. Diabetes Care. 2002;25:900–5.

22. Byun JM, Lee CH, Lee SR, et al. Renal outcomes and clinical course of nondiabetic renal diseases in patients with type 2 diabetes. Korean J Intern Med. 2013;28:565–72.

23. Lee YH, Kim KP, Kim YG, et al. Clinicopathological features of diabetic and nondiabetic renal diseases in type 2 diabetic patients with nephrotic-range proteinuria. Medicine. 2017;96:e8047.

24. Chang TI, Park JT, Kim JK, et al. Renal outcomes in patients with type 2 diabetes with or without coexisting non-diabetic renal disease. Diabetes Res Clin Pract. 2011;92:198–204.

25. Oh SW, Kim S, Na KY, et al. Clinical implications of pathologic diagnosis and classification for diabetic nephropathy. Diabetes Res Clin Pract. 2012;97:418–24.

26. Kritmetapak K, Anutrakulchai S, Pongchaiyakul C, Puapairoj A. Clinical and pathological characteristics of non-diabetic renal disease in type 2 diabetes patients. Clin Kidney J. 2018;11:342–7.

27. Yaqub S, Kashif W, Hussain SA. Non-diabetic renal disease in patients with type-2 diabetes mellitus. Saudi J Kidney Dis Transpl. 2012;23:1000–7.

28. Das U, Dakshinamurty KV, Prayaga A, Uppin MS. Nondiabetic kidney disease in type 2 diabetic patients: a single center experience. Indian J Nephrol. 2012;22:358–62.

29. Soni SS, Gowrishankar S, Kishan AG, Raman A. Non diabetic renal disease in type 2 diabetes mellitus. Nephrology. 2006;11:533–7.

30. Moger V, Kumar SK, Sakhuja V, et al. Rapidly progressive renal failure in type 2 diabetes in the tropical environment: a clinico-pathological study. Ren Fail. 2005;27:595–600.

31. Chong YB, Keng TC, Tan LP, et al. Clinical predictors of non-diabetic renal disease and role of renal biopsy in diabetic patients with renal involvement: a single centre review. Ren Fail. 2012;34:323–8.

32. Harada K, Akai Y, Sumida K, et al. Significance of renal biopsy in patients with presumed diabetic nephropathy. J Diabetes Investig. 2013;4:88–93.

33. Suzuki D, Takano H, Toyoda M, et al. Evaluation of renal biopsy samples of patients with diabetic nephropathy. Intern Med. 2001;40:1077–84.

34. Ghani AA, Al Waheeb S, Al Sahow A, Hussain N. Renal biopsy in patients with type 2 diabetes mellitus: indications and nature of the lesions. Ann Saudi Med. 2009;29:450–3.

35. Jalalah SM. Non-diabetic renal disease in diabetic patients. Saudi J Kidney Dis Transpl. 2008;19: 813–6.

36. Heybeli C, Oktan MA, Arda HU, et al. Predictors and histopathological characteristics of non-diabetic renal disorders in diabetes: a look from the tubulointerstitial point of view. Intern Med J. 2019;49: 1524–33.

37. Yenigun EC, Dede F, Ozturk R, et al. Non-diabetic renal disease in diabetes mellitus: clinical features and renal biopsy findings. Hippokratia. 2015;19: 148–52.

38. Erdogmus S, Kiremitci S, Celebi ZK, et al. Non-diabetic kidney disease in type 2 diabetic patients: prevalence, clinical predictors and outcomes. Kidney Blood Press Res. 2017;42:886–93.

39. Soleymanian T, Hamid G, Arefi M, et al. Non-diabetic renal disease with or without diabetic nephropathy in type 2 diabetes: clinical predictors and outcome. Ren Fail. 2015;37:572–5.

40. Pham TT, Sim JJ, Kujubu DA, Liu IL, Kumar VA. Prevalence of nondiabetic renal disease in diabetic patients. Am J Nephrol. 2007;27:322–8.

41. Sharma SG, Bomback AS, Radhakrishnan J, et al. The modern spectrum of renal biopsy findings in patients with diabetes. Clin J Am Soc Nephrol. 2013;8:1718–24.

42. Nzerue CM, Hewan-Lowe K, Harvey P, Mohammed D, Furlong B, Oster R. Prevalence of non-diabetic renal disease among African-American patients with type II diabetes mellitus. Scand J Urol Nephrol. 2000;34:331–5.

43. Zajjari Y, Aatif T, Hassani K, Benbria S, El Kabbaj D. Renal histology in diabetic patients. Saudi J Med Med Sci. 2019;7:22–7.

44. Zajjari Y, Benyahia M, Ibrahim DM, et al. Non-diabetic renal disease in type II diabetes mellitus patients in Mohammed V Military Hospital, Rabat, Morocco. East Mediterr Health J. 2012;18:620–3.

45. Mami I, Harzallah A, Kaaroud H, et al. Nondiabetic renal disease in patients with type 2 diabetes. Saudi J Kidney Dis Transpl. 2017;28:842–50.

46. Horvatic I, Tisljar M, Kacinari P, et al. Non-diabetic renal disease in Croatian patients with Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2014;104: 443–50.

47. Grujicic M, Salapura A, Basta-Jovanovic G, Figurek A, Micic-Zrnic D, Grbic A. Non-diabetic kidney disease in patients with type 2 diabetes mellitus—11-year experience from a single center. Med Arch. 2019;73:87–91.

48. Wągrowska-Danilewicz M, Danilewicz M. Spectrum of biopsy-proven renal diseases in patients with type 2 diabetes mellitus. A single center study. Pol J Pathol. 2015;66:361–7.

49. Mazzucco G, Bertani T, Fortunato M, et al. Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies. Am J Kidney Dis. 2002;39:713–20.

50. Christensen PK, Larsen S, Horn T, Olsen S, Parving HH. Causes of albuminuria in patients with type 2 diabetes without diabetic retinopathy. Kidney Int. 2000;58:1719–31.

51. Castellano I, Covarsí A, Novillo R, Gómez-Martino JR, Ferrando L. Renal histological lesions in patients with type II diabetes mellitus. Nefrologia. 2002;22: 162–9.

52. Rychlík I, Jancová E, Tesar V, et al. The Czech registry of renal iopsies. Occurrence of renal diseases in the years 1994–2000. Nephrol Dial Transpl. 2004;19:3040–9.

53. Pallayova M, Mohammed A, Langman G, Taheri S, Dasgupta I. Predicting non-diabetic renal disease in type 2 diabetic adults: the value of glycated hemoglobin. J Diabetes Complicat. 2015;29:718–23.

54. Tan J, Zwi LJ, Collins JF, Marshall MR Cundy T. Presentation, pathology and prognosis of renal disease in type 2 diabetes. BMJ Open Diabetes Res Care. 2017;5:e000412.

55. Liang S, Li Q, Zhu HY, et al. Clinical factors associated with the diagnosis and progression of diabetic nephropathy. Cell Biochem Biophys. 2014;70: 9–15.

56. Dong ZY, Qiu Q, Chen XM. Clinical significance of renal biopsy in diabetic patients with kidney injury. Chin J Kidney Dis Investig. 2015;4:32–6.

57. Gonzalez Suarez ML, Thomas DB, Barisoni L, Fornoni A. Diabetic nephropathy: is it time yet for routine kidney biopsy? World J Diabetes. 2013;4: 245–55.

58. Prakash J, Sen D, Usha KNS. Non-diabetic renal disease in patients with type 2 diabetes mellitus. J Assoc Phys India. 2001;49:415–20.

59. John GT, Date A, Korula A, Jeyaseelan L, Shastry JC, Jacob CK. Nondiabetic renal disease in noninsulin-dependent diabetics in a South Indian hospital. Nephron. 1994;67:441–3.

60. Kitiyakara C, Kopp JB, Eggers P. Trends in the epidemiology of focal segmental glomerulosclerosis. Semin Nephrol. 2003;23:172–82.

61. Liu D, Huang T, Chen N, et al. The modern spectrum of biopsy-proven renal disease in Chinese diabetic patients-a retrospective descriptive study. PeerJ. 2018;6:e4522.

62. Anders HJ, Huber TB, Isermann B, Schiffer M. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. Nat Rev Nephrol. 2018;14:361–77.

63. Xu J, Hu X, Xie J, Chen N. Management of membranous nephropathy in Asia. Kidney Dis (Basel). 2015;1:119–25.

64. Xu X, Nie S, Ding H, Hou FF. Environmental pollution and kidney diseases. Nat Rev Nephrol. 2018;4:313–24.

65. O'Shaughnessy MM, Hogan SL, Poulton CJ, et al. Temporal and demographic trends in glomerular disease epidemiology in the Southeastern United States, 1986–2015. Clin J Am Soc Nephrol. 2017;12:614–23.

66. Lin HY, Niu SW, Kuo IC, et al. Hematuria and renal outcomes in patients with diabetic chronic kidney disease. Am J Med Sci. 2018;356:268–76.

67. Zhou B, Zou H, Xu G. Clinical utility of serum cystatin c in predicting diabetic nephropathy among patients with diabetes mellitus: a meta-analysis. Kidney Blood Press Res. 2016;41:919–28.

68. Zhang J, Wang Y, Zhang R, et al. Serum levels of immunoglobulin G and complement 3 differentiate non-diabetic renal disease from diabetic nephropathy in patients with type 2 diabetes mellitus. Acta Diabetol. 2019;56:873–81.

69. Teng J, Dwyer KM, Hill P. Spectrum of renal disease in diabetes. Nephrology (Carlton). 2014;19:528–36.

70. He F, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. Diabetologia. 2013;56:457–66.

71. Fan JZ, Wang R. Non-diabetic renal disease in patients with type 2 diabetes: a single centre study. Intern Med J. 2018;48:451–6.

72. Liang S, Zhang XG, Cai GY, et al. Identifying parameters to distinguish non-diabetic renal diseases from diabetic nephropathy in patients with type 2 diabetes mellitus: a meta-analysis. PLoS ONE. 2013;8:e64184.

73. Mou S, Wang Q, Liu J, et al. Prevalence of non-diabetic renal disease in patients with type 2 diabetes. Diabetes Res Clin Pract. 2010;87:354–9.

74. Kanodia KV, Vanikar AV, Nigam L, Patel RD, Suthar KS, Patel H. Clinicopathological study of nondiabetic renal disease in type 2 diabetic patients: a single center experience from India. Saudi J Kidney Dis Transpl. 2017;28:1330–7.

75. Dong Z, Wang Y, Qiu Q, et al. Clinical predictors differentiating non-diabetic renal diseases from diabetic nephropathy in a large population of type 2 diabetes patients. Diabetes Res Clin Pract. 2016;121:112–8.

76. Tone A, Shikata K, Matsuda M, et al. Clinical features of non-diabetic renal diseases in patients with type 2 diabetes. Diabetes Res Clin Pract. 2005;69:237–42.

77. Jiang S, Yu T, Zhang Z, et al. Diagnostic performance of retinopathy in the detection of diabetic nephropathy in Type 2 diabetes: a systematic review and meta-analysis of 45 studies. Ophthalmic Res. 2019;62:68–79.

78. Suzuki Y, Matsushita K, Seimiya M, et al. Serum cystatin C as a marker for early detection of chronic kidney disease and grade 2 nephropathy in Japanese patients with type 2 diabetes. Clin Chem Lab Med. 2012;50:1833–9.

79. Weng CH, Hu CC, Yu CC, et al. Immunoglobulin G levels can predict non-diabetic renal disease in patients with type 2 diabetes mellitus. J Diabetes. 2012;4:37–40.

80. Wang X, Li J, Huo L, et al. Clinical characteristics of diabetic nephropathy in patients with type 2 diabetic mellitus manifesting heavy proteinuria: a retrospective analysis of 220 cases. Diabetes Res Clin Pract. 2019;157:107874.

81. Zwi LJ, Yiu TS, Marshall MR, Lam-Po-Tang MK. Non-diabetic renal diseases in a multi-ethnic New Zealand cohort with type 2 diabetes mellitus: clinical and histopathological features. Pathology. 2014;46:424–32.

82. Jiang S, Wang Y, Zhang Z, Dai P, Yang Y, Li W. Accuracy of hematuria for predicting non-diabetic renal disease in patients with diabetes and kidney disease: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2018;143:288–300.

83. Wang N, Xu Z, Han P, Li T. Glycated albumin and ratio of glycated albumin to glycated hemoglobin are good indicators of diabetic nephropathy in type 2 diabetes mellitus. Diabetes Metab Res Rev. 2017;33:e2843.

84. Bermejo S, Pascual J, Soler MJ. The current role of renal biopsy in diabetic patients. Minerva Med. 2018;109:116–25.

85. Wilczek HE. Percutaneous needle biopsy of the renal allograft. A clinical safety evaluation of 1129 biopsies. Transplantation. 1990;50:790–7.

86. Soares SM, Fervenza FC, Lager DJ, Gertz MA, Cosio FG, Leung N. Bleeding complications after transcutaneous kidney biopsy in patients with systemic amyloidosis: single-center experience in 101 patients. Am J Kidney Dis. 2008;52:1079–83.

87. Hergesell O, Felten H, Andrassy K, Kühn K, Ritz E. Safety of ultrasound-guided percutaneous renal biopsy-retrospective analysis of 1090 consecutive cases. Nephrol Dial Transpl. 1998;13:975–7.