Nephrol Dial Transplant (2017) 32: 97–110
doi: 10.1093/ndt/gfw070
Advance Access publication 4 May 2016

Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies

Marco Fiorentino[1], Davide Bolignano[2,3], Vladimir Tesar[4], Anna Pisano[2], Wim Van Biesen[3], Giovanni Tripepi[2], Graziella D'Arrigo[2] and Loreto Gesualdo[1] on behalf of the ERA-EDTA Immunonephrology Working Group

[1]Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari, Bari, Italy, [2]CNR-Institute of Clinical Physiology, Reggio Calabria, Italy, [3]European Renal Best Practice (ERBP), University Hospital, Ghent, Belgium and [4]Department of Nephrology, 1st School of Medicine, Charles University, Prague, Czech Republic

Correspondence and offprint requests to: Loreto Gesualdo; E-mail: loreto.gesualdo@uniba.it

ORIGINAL ARTICLE

ABSTRACT

Background. The utility of renal biopsy in patients with diabetes is highly debated. Diabetics with rapidly worsening renal disease are often 'clinically' labelled as having diabetic nephropathy (DN), whereas, in many cases, they are rather developing a non-diabetic renal disease (NDRD) or mixed forms (DN + NDRD).

Methods. We performed a systematic search for studies on patients with diabetes with data on the frequency of DN, NDRD and mixed forms, and assessed the positive predictive values (PPVs) and odds ratios (ORs) for such diagnoses by meta-analysing single-study prevalence. Possible factors explaining heterogeneity among the different diagnoses were explored by meta-regression.

Results. In the 48 included studies ($n = 4876$), the prevalence of DN, NDRD and mixed forms ranged from 6.5 to 94%, 3 to 82.9% and 4 to 45.5% of the overall diagnoses, respectively. IgA nephropathy was the most common NDRD (3–59%). PPVs for DN, NDRD and mixed forms were 50.1% [95% confidence interval (CI): 44.7–55.2], 36.9% (95% CI: 32.3–41.8) and 19.7% (95% CI: 16.3–23.6), respectively. The PPV when combining NDRD and mixed forms was 49.2% (95% CI: 43.8–54.5). Meta-regression identified systolic pressure, HbA1c, diabetes duration and retinopathy as factors explaining heterogeneity for NDRD, creatinine and glomerular filtration rate for mixed forms and only serum creatinine for DN. ORs of DN versus NDRD and mixed forms were 1.71 (95% CI: 1.54–1.91) and 4.1 (95% CI: 3.43–4.80), respectively.

Conclusions. NDRD are highly prevalent in patients with diabetes. Clinical judgment alone can lead to wrong diagnoses and delay the establishment of adequate therapies. Risk stratification according to individual factors is needed for selecting patients who might benefit from biopsy.

Keywords: diabetes, diabetic nephropathy, meta-analysis, non-diabetic nephropathy, renal biopsy

INTRODUCTION

According to the WHO, in 2012 about 347 million people were affected by diabetes mellitus (DM) [1]. DM now ranks as the primary cause of end-stage kidney disease (ESKD) requiring chronic renal replacement therapy [1, 2] and the coexistence of DM and renal damage amplifies the risk of death and cardiovascular events [3].

About 30–40% of patients with diabetes with at least 10 years of history of disease usually present with a frank diabetic nephropathy (DN) [4] characterized by peculiar histological features at the glomerular level including nodular or diffuse mesangial sclerosis, arteriolar hyalinosis, micro aneurysms and exudative lesions. However, increasing evidence indicates that many patients with diabetes erroneously labelled as having progressive forms of DN are rather developing non-diabetic renal diseases (NDRD) or 'mixed' conditions where typical features of DN overlap with other kinds of histological damage.

The correct classification of such patients would be crucial to predict the natural course of their disease, thus allowing the establishment of appropriate therapeutic measures in a timely manner.

The utility of renal biopsy (RB) in patients with diabetes is currently an object of debate. As there is no overall consensus on timing and indications, the decision to perform RB is usually based on personal opinions or single-center policies [2]. RB is an invasive procedure that is not completely free from complications. Yet, in patients with diabetes presenting with rapidly worsening renal function and/or unusual clinical features (e.g. sudden appearance of heavy proteinuria in patients with short

duration of DM, haematuria, active urine sediment, no signs of other micro-vascular complications like retinopathy), RB would be crucial for identifying the presence of non-diabetic renal damage.

With this background in mind, we aimed at performing a systematic review and meta-analysis for clarifying the potential usefulness of RB in the diabetic setting by: (i) defining the cumulative epidemiology of DN, NDRD and 'mixed' forms (DN + NDRD), (ii) analysing the frequency and diagnostic likelihood of these conditions in a pooled meta-analysis and (iii) identifying factors associated with the different diagnoses by a meta-regression.

MATERIALS AND METHODS

Data source and search strategy

PubMed and Ovid MEDLINE were searched for articles without time and language restriction up to 15 September 2014 through a focussed search strategy (Supplementary data Table S1). References from relevant studies and reviews published on the same topic were screened for supplementary articles. The search was designed and performed by two authors (D.B. and M.F.).

Study selection

We included any study providing prevalence data on patients with diabetes undergoing RB on: (i) DN, defined by the presence of suggestive glomerular lesions like nodular sclerosis, diffuse mesangial sclerosis, mesangial expansion, basement membrane thickening, arteriolar hyalinosis, micro aneurysms and exudative lesions [5]; (ii) NDRD, defined by any histological alteration different from the above-mentioned and suggestive of other renal diseases [e.g. IgA nephropathy, membranous nephropathy (MN), focal-segmental glomerulosclerosis (FSGS), interstitial nephritis, vasculitis, nephroangiosclerotic lesions, etc.]; or (iii) mixed forms where histological signs of DN were superimposed on NDRD. Studies dealing with both Type 1 and Type 2 DM were considered. Studies were excluded if they were (i) dealing with empirical diagnoses not made by percutaneous RB, (ii) not focussing on diabetic patients or not including diabetic subpopulations with available data on renal histology, (iii) dealing with renal biopsies only performed on transplanted patients and (iv) not providing actual numbers (percentages) on the histological pictures found. Case reports, reviews, editorials and studies performed on children (age <18 years) or animals were excluded as well. Study selection was performed by two authors (D.B. and M.F.) separately. Discrepancies in study judgment were solved collegially.

Data extraction and meta-analysis

Data extraction and analysis were performed by two authors (M.F. and G.T.) and independently verified by another (D.B.). Single-study prevalence data were pooled in a meta-analysis using a random effect model to calculate the positive predictive values (PPVs) of clinical judgment for identifying DN, NDRD and mixed forms and the cumulative odds ratio (OR) of finding DN at RB compared with NDRD or mixed forms. Heterogeneity was assessed by I^2; I^2values of 25%, 50% and 75% were considered to correspond to low, medium and high levels of heterogeneity, respectively. Meta-regression analysis was implemented to investigate possible sources of heterogeneity. Possible publication bias was investigated by constructing the funnel plots and by applying the Egger's regression and the trim and fill tests. Statistical analyses were performed using Comprehensive Meta-analysis (Version 2.2, 2005; Biostat, Englewood, NJ, USA) and SPSS (Version 21; IBM Corporation, Armonk, NY, USA).

RESULTS

Search results

The flow diagram of the selection process is depicted in Figure 1. One thousand five hundred and ten potentially relevant references were evaluated for eligibility by title and abstract. A total of 1243 citations were excluded because of search overlap ($n = 100$), or because they were dealing with wrong topics or wrong populations ($n = 1143$). Among 267 studies selected for full text examination, 208 studies were excluded for not providing RB data in patients with diabetes and 11 for not providing percentage data on biopsy diagnosis. A total of 48 studies were therefore reviewed in detail and included in the quantitative analyses.

Study and participants' characteristics

The 48 studies reviewed included a total of 4876 diabetics undergoing RB. The number of subjects enrolled in each study ranged from 16 [6] to 611 [7].Thirty-six studies had a retrospective design [6–41], eight had a prospective design [42–49] and two presented a cross-sectional design [50, 51]. We also found useful data for our analyses from two randomized, double-blind trials. Cordonnier *et al.* [52] reported biopsy data of 22 Type 2 diabetics enrolled in a randomized controlled trial testing the effects of 4 mg Perindopril on kidney structure and function. Schwartz *et al.* [53] provided information on the glomerular histology of 36 diabetics enrolled in a multicenter pilot study investigating the effects of irbesartan on renal function and urine protein excretion.

Although most studies were published in the last decade, about half of the studies reported data obtained before 2000 [27–41, 47–49, 51–53]. Twenty-seven articles focussed on Asian populations [8–11, 13, 15–20, 23–25, 27, 28, 31, 34, 36, 41–46, 48, 50], fifteen were performed in European countries [12, 14, 26, 29, 30, 32, 35, 37–40, 47, 49, 51, 52], four in north America [7, 21, 33, 53] and two studies in African regions [6, 22]. All studies included patients with Type 2 diabetes. Type 1 diabetic patients represented a small percentage of the study population in six studies (ranging from 8 to 38% of participants) [12, 18, 32, 38, 40, 41]. No studies reported data based only on patients with Type 1 diabetes. Mean age of participants was variable across studies, spanning from 46 to 62 years. Male participants were predominant in all the studies (52–94% of participants) with the exception of Nzerue *et al.* [33] (48%). Information on

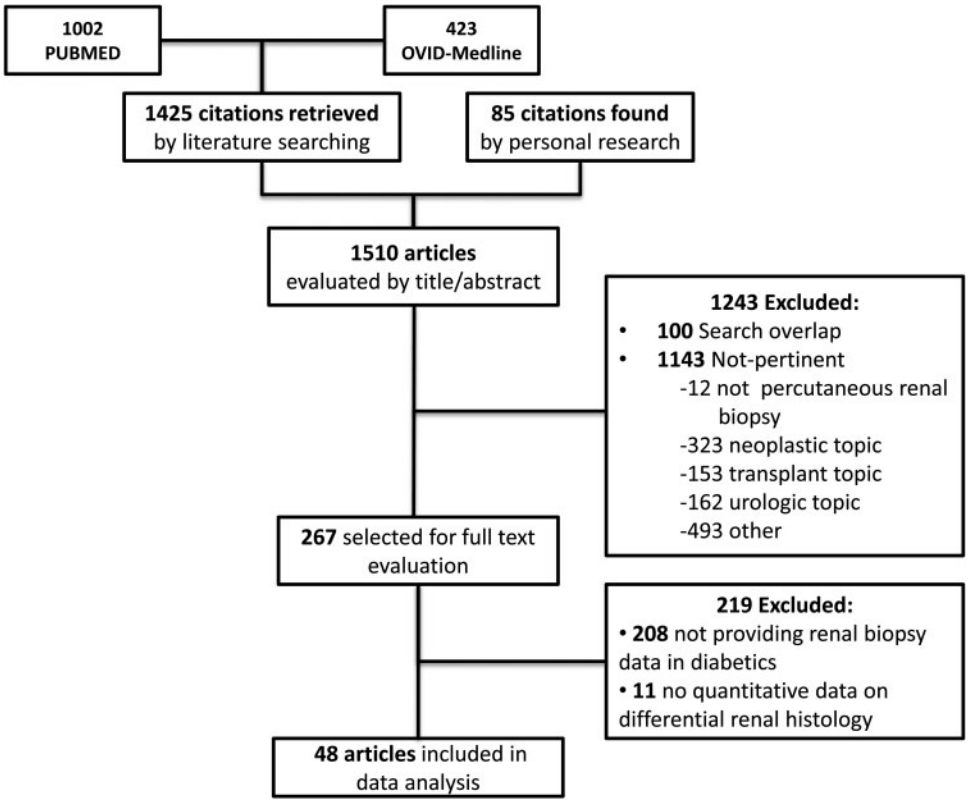

FIGURE 1: Flow of the study selection process.

body mass index (BMI) was provided in 12 studies only [14, 27, 28, 30, 34, 39, 42, 43, 49, 51–53]; in four studies [39, 51–53] the majority of diabetics were frankly obese (mean BMI ranging from 30.3 to 32 kg/m^2). Patients with diabetes undergoing RB were extremely heterogeneous with respect to renal function. Information on serum creatinine values was available in 34 studies [6, 7, 9–11, 13, 15–17, 19–21, 23–25, 27–29, 31, 33, 34, 37, 38, 42–48, 50–53]; in 10 of these studies the majority of patients had mean serum creatinine levels falling roughly within the normal range (<1.43 mg/dL) [16, 20, 25, 28, 31, 42–44, 51, 52]. In 12 studies mean values ranged from 1.44 to 3.00 mg/dL [7, 10, 13, 23, 25, 27, 29, 34, 37, 45, 47, 53] while the remaining 12 included patients with quite severely compromised renal function (serum creatinine >3 mg/dL) [6, 9, 11, 12, 15, 19, 21, 24, 33, 38, 46, 50]. Data on estimated glomerular filtration rate (eGFR) were available in 16 of the above-mentioned studies reporting information on serum creatinine [7, 10, 13, 15–17, 19–21, 28, 34, 42, 48, 51–53]. Three more studies [30, 40, 49] gave information on eGFR only. Biesenbach *et al.* [14] analysed 14 biopsies from diabetics with ESKD before their first dialysis and 70 cadaveric biopsy specimens of ESKD subjects post mortem. Mean proteinuria was reported in 36 studies [6, 7, 9, 11, 13, 15–17, 19–21, 23–31, 33–35, 37–39, 42–45, 47, 48, 50–53] and ranged from 1.07–8.9 g/24 h. Fioretto *et al.* [49] enrolled patients with a mean urinary albumin excretion rate of 44 μg/min. Glycaemic control was quite poor in the vast majority of studies where information on HbA1c was available (mean values spanning from 6.35 to 11.3%) [10, 11, 13, 14, 16, 17, 20, 23, 25, 28, 30, 31, 34, 39, 42–44, 48, 49, 51, 53]. Subjects were remarkably heterogeneous also with respect to the duration of diabetes, which ranged from 3.4 to 20 years [6–11, 13–15, 17, 19, 20, 24, 25, 27–35, 37–40, 42, 44–46, 48–51]. Data on the prevalence of retinopathy among the participants were available in 28 studies [6, 8, 11, 13, 15–17, 19–21, 23–25, 27, 30, 31, 33–35, 40, 42–46, 48, 49, 53]. In nine studies [17, 20, 27, 34, 39, 42, 48, 49, 53], the presence of diabetic retinopathy was described with different grading level according the classification of the Early Treatment of Diabetic Retinopathy Study (no retinopathy, non-proliferative and proliferative level). In three studies [18, 28, 51] none of the patients undergoing RB had signs of retinal damage. In the remaining, the prevalence of this condition ranged from 15 to 71%. Twenty-five studies [6, 9–11, 13, 15, 17, 19–21, 23–27, 30, 31, 34, 38, 39, 44, 46–48, 50] reported data on the frequency of haematuria in the analysed cohort (range 6–78%). Indications for RB in patients with diabetes were extremely variable across studies. Only five studies reported data of research-indicated RBs. In the remaining 43 studies based on clinically indicated biopsies, the major driver was represented by a clinical suspicion of NDRD defined as: (i) nephrotic-range proteinuria or renal impairment in the absence of diabetic retinopathy; (ii) nephrotic-range proteinuria or renal impairment with duration of diabetes <5 years; (iii) unexplained microscopic haematuria; (iv) unexplained acute kidney injury; (v) rapidly declining renal function in patients with previously stable renal function; or (vi) sudden onset of nephrotic-range proteinuria with normal kidney function. Other criteria less frequently adopted included sudden onset of non-nephrotic proteinuria (thresholds ranging from 0.5 to 2.5 g/24 h) or microalbuminuria [10, 16, 20, 23, 27, 28, 31, 39, 43, 44, 48–53]. Mazzucco *et al.* [29] compared a restricted biopsy policy (the

presence of haematuria, nephrotic syndrome, non-nephrotic proteinuria ≥2 g/day in the absence of diabetic retinopathy, rapidly progressive renal failure and renal insufficiency of unexplained origin) with an unrestricted policy (proteinuria > 0.5 g/day, alone or associated with haematuria and/or impairment of renal function). In five studies [6, 7, 21, 26, 41] the reasons for performing RB were not further specified. Main characteristics of the studies and participants are summarized in Tables 1 and 2.

Prevalence of DN, NDRD and mixed forms, and pooled analyses

Prevalence data of DN, NDRD and mixed forms are summarized in Table 2. Information on the three histological pictures in the same study cohort was available in 30 papers [7–13, 17, 20, 21, 23–27, 29, 33–39, 41, 42, 45–48, 50]. Thirteen studies [6, 14, 22, 28, 30, 32, 40, 43, 44, 49, 51–53] compared only DN with NDRD while three studies [15, 19, 31] presented only diagnosis of DN or mixed forms. The prevalence of DN was extremely variable, ranging from 6.5 [8] to 94% [53] of the overall histological pictures, as well as that of NDRD (3% [35] to 82.9% [8]) and mixed forms (4% [38] to 45.5% [15]). In the study by Hashim Al-Saedi [18] all diabetics undergoing RB had histological evidence of NDRD. Differential diagnoses of NDRD were specified in 43 studies [6–11, 13–21, 23–40, 42–48, 50, 51, 53]. IgA nephropathy was the most frequent NDRD in 16 studies [6, 8, 15, 25–27, 31, 34, 35, 37, 42, 44, 47, 48, 51, 53] with a prevalence ranging from 3 [35] to 59% [48]. MN was the predominant NDRD in nine studies [13, 20, 28–30, 38, 40, 45] (7 [38] to 35% [30]). FSGS prevailed in six cohorts [12, 16, 21, 32, 33, 50], (17 [12] to 37.7% [16]). Acute interstitial nephritis was the main NDRD in four studies [9, 11, 17, 24] (18 [24] to 48.8% [11]). The analysis of the different histological pictures of NDRD according to the population background showed a significantly higher percentage of IgA diagnosis in studies on Asian populations compared with European (mean percentage of IgA diagnosis: 21.3 versus 8.2%, P = 0.003) and American studies (21.3 versus 9.4, P = 0.04). A higher frequency of FSGS was described in European studies compared with studies from the USA (mean percentage of FSGS diagnosis: 19 versus 10%, P = 0.03). Moreover, the percentage of membrano-proliferative glomerulonephritis in Asian populations was higher than that in Europeans (mean percentage: 17.6 versus 7.3%, P = 0.016). The performance of clinical judgment for correctly classifying the type of nephropathy in patients with diabetes was assessed by calculating the PPVs, i.e. the proportion of patients who are really affected by a specific nephropathy at RB among those considered as affected by DN or NDRD or by mixed forms on the basis of clinical judgment. PPVs (pooled data) of clinical judgment for identifying DN, NDRD and mixed forms were 50.1% [95% confidence interval (CI): 44.9–55.3], 36.9% (95% CI: 32.3–41.8) and 19.7% (95% CI: 16.3–23.6), respectively (Figure 2). When considering NDRD and mixed forms together, the PPV of such diagnoses was 49.2% (95% CI: 43.8–54.5) (Figure 2d). The PPV of NDRD in retrospective studies (38%, 95% CI: 32–43) was significantly higher than in prospective studies (27%, 95% CI: 20–35, P = 0.007), as well as in studies after 2000 (40%, 95% CI: 35–45) compared with PPV of studies before 2000 (26%, 95% CI: 17–37, P = 0.03). The PPVs of DN (49 versus 65%, P = 0.25) and NDRD (39 versus 25%, P = 0.18) did not differ between studies based on clinically or research-indicated biopsies; however, a higher percentage of IgA nephropathy was described in clinically indicated biopsy studies (P = 0.03). The Egger's regression test (i.e. a test indicating whether the joint distribution of standard errors and logit event rates statistically deviates from an ideal funnel plot) suggested statistical evidence of publication bias in pooled analyses of DN and mixed forms (P-values ranging from 0.003 to 0.006) (Supplementary data Figure S1). However, such a bias, although statistically significant, was not meaningful from a quantitative point of view because the Trim and Fill method (a test quantifying the potential distortion attributable to selection bias of studies in a meta-analysis) showed that the pooled PPVs for DN (0.50, 95% CI: 0.45–0.55), NDRD (0.37, 95% CI: 0.32–0.42) and mixed forms (0.20, 95% CI: 0.16–0.24) as calculated in the standard meta-analysis did not materially differ from those derived by the Trim and Fill method (DN: 0.43, 95% CI: 0.37–0.48; NDRD: 0.37, 95% CI: 0.32–0.42; mixed forms: 0.20, 95% CI: 0.16–0.24), indicating that the publication bias was not enough to introduce a distortion in the pooled estimates. There was high heterogeneity in all the three analyses (I^2 90%, 88% and 86%, respectively). Meta-regression identified systolic blood pressure ($r = -0.53$, P = 0.02), HbA1c ($r = -0.49$, P = 0.02), duration of diabetes ($r = -0.36$, P = 0.04) and diabetic retinopathy ($r = -0.59$, P = 0.001) as factors explaining heterogeneity among PPVs of NDRD. The same analysis indicated serum creatinine ($r = -0.42$, P = 0.01) as the only factor underlying heterogeneity among studies for DN and creatinine ($r = 0.52$, P = 0.006) and, even more, GFR ($r = -0.73$, P = 0.007) as the only two factors elucidating heterogeneity among studies for mixed forms. Overall, the crude OR of finding DN at RB was 69% higher (OR: 1.71, 95% CI: 1.54–1.92, P < 0.001) than that of NDRD and more than four times higher (OR: 4.1, 95% CI: 3.43–4.80, P < 0.001) than that of mixed forms.

DISCUSSION

Worldwide, roughly 3% of newly diagnosed patients with Type 2 diabetes have overt nephropathy and about 20–30% of patients with Type 1 or Type 2 diabetes develop such complications throughout their life [54]. The early identification of DN is mandatory to delay ESKD, but early biomarkers (e.g. albuminuria) often fail to predict disease course as they might not reflect the real histological damage or the possible presence of other, superimposed renal diseases. The importance of RB was studied in a large double-blind controlled trial on 285 patients with Type 1 diabetes (Renin-Angiotensin System Study, RASS), which showed the role of renin–angiotensin system (RAS) blockade on the progression of diabetic retinopathy [55]. However, most nephrologists do not advocate RB in patients with diabetes, arguing that this procedure would simply confirm the presence of DN in the majority of patients [10, 43].

Our systematic analysis of 48 studies indicates that, in patients with diabetes with suspicion of DN, the prevalence of non-diabetic renal damage is indeed seriously high (up to 82.9%

Table 1. Main characteristics and indications for renal biopsy of the reviewed studies

Study	Year	Country	Design	No. of patients	Age (years)	Gender (male %)	sCr (mg/dL)	GFR (mL/min)	uPr (g/24 h)	HbA1c (%)	DM vintage (years)	DR (%)	Indications
Zhuo *et al.* [8]	2013	China	Retrospective	216	∼48	–	–	–	–	–	3.4	18	Clinical renal biopsies, Type 2 DM, presence of urinary abnormalities or renal impairment
Sharma *et al.* [7]	2013	USA	Retrospective	620	∼62	61	2.5	29.1	4.3	–	9.31	–	Clinical renal biopsies, Type 2 DM
Harada *et al.* [42]	2013	Japan	Prospective	55	∼58	67	1.29	49.83	2.75	7.69	10.1	38	Clinical renal biopsies, Type 2 DM, presence of urinary abnormalities or renal impairment
Zajjari *et al.* [6]	2012	Morocco	Retrospective	16	∼60	81	4.5	–	4.75	–	6.5	37.5	Clinical renal biopsies, Type 2 DM
Yaqub *et al.*[9]	2012	Pakistan	Retrospective	68	∼56	75	4.5	–	5.98	–	9	–	Clinical renal biopsies, Type 2 DM, nephrotic-range proteinuria, absence of diabetic retinopathy, duration of diabetes <5 years, unexplained microscopic haematuria, unexplained acute kidney injury, rapidly declining renal function in patients with previously stable renal function
Oh *et al.* [10]	2012	South Korea	Retrospective	126	∼60	68.3	2.38	45.4	–	7.1	8.3	–	Clinical renal biopsies, Type 2 DM, proteinuria more than 1 g/day, renal involvement without retinopathy, renal involvement within 5 years, unexplained haematuria
Chong *et al.* [11]	2012	Malaysia	Retrospective	110	∼53	58	3.35	–	7.06	8	12	60	Clinical renal biopsies, Type 2 DM, uncertain cause of acute renal failure, acute or chronic renal failure, relatively short duration of diabetes or without retinopathy, heavy proteinuria (>1 g/day), and microscopic haematuria
Biesenbach *et al.* [14]	2011	Austria	Retrospective	84	∼60	53	–	ESKD	–	7.7	20	–	Clinical renal biopsies, Type 2 DM with ESKD
Haider *et al.* [12]	2011	Austria	Retrospective	567	∼56	–	–	–	–	–	–	–	Clinical renal biopsies, Type 1 and 2 DM with CKD
Chang *et al.* [13]	2011	South Korea	Retrospective	119	∼53	53.8	1.7	51.54	7.4	8.1	7.95	42.9	Clinical renal biopsies, Type 2 DM, strong suspicion of NDRD (rapidly increasing amount of proteinuria or nephrotic syndrome), short duration of diabetes, absence of retinopathy, unexplained impaired or rapidly declining renal function, persistent haematuria
Bi *et al.* [15]	2011	China	Retrospective	220	∼51	69	4.37	38	3.74	–	9.24	46	Clinical renal biopsies, Type 2 DM, with haematuria (40% of cases), rapid deterioration of renal function (19.5%), massive proteinuria without retinopathy (34.5%)
Zhang *et al.* [43]	2011	China	Prospective	130	∼49	61	1.3	–	1.8	6.9	–	41.5	Clinical renal biopsies, Type 2 DM, microalbuminuria and/or haematuria or unexplained renal dysfunction; overt proteinuria especially heavy proteinuria; rapid progression in renal function
Mou *et al.* [16]	2010	China	Retrospective	69	∼53	52.2	1.34	57.86	3.74	6.65	–	42	Clinical renal biopsies, Type 2 DM, with proteinuria over 1 g or GFR <60 mL/min
Lin *et al.* [17]	2009	Taiwan	Retrospective	50	∼61	64	3.15	34.38	5.07	7.06	9.97	48	Clinical renal biopsies, Type 2 DM, heavy proteinuria or renal impairment, absence of retinopathy or overt neuropathy, duration of diabetes <10 years, unexplained haematuria of glomerular origin, unexplained acute renal failure
Ghani *et al.* [19]	2009	Kuwait	Retrospective	31	∼50	54.8	4.47	38.6	3.18	–	9.33	45.2	Clinical renal biopsies, Type 2 DM, clinical suspicion of NDRD
Arif *et al.* [50]	2009	Pakistan	Cross-sectional	73	∼51	59	3.8	–	2.3	–	–	–	Clinical renal biopsies, Type 2 DM, clinical suspicion of NDRD (presence of haematuria, nephrotic

Continued

Table 1. Continued

Study	Year	Country	Design	No. of patients	Age (years)	Gender (male %)	sCr (mg/dL)	GFR (mL/min)	uPr (g/24 h)	HbA1c (%)	DM vintage (years)	DR (%)	Indications
													syndrome, non-nephrotic proteinuria <3 g/day in the absence of retinopathy, rapidly progressive glomerulonephritis and renal insufficiency of unknown origin)
Hashim Al-Saedi [18]	2009	Iraq	Retrospective	80	Range 17–62	70	–	–	–	–	–	0	Clinical renal biopsies, Type 1 and 2 DM, nephrotic-range proteinuria, absence of retinopathy
Zhou *et al.* [44]	2008	China	Prospective	110	∼46	70	1.29	–	3.6	7.8	∼5	46.3	Clinical renal biopsies, Type 2 DM, persistent proteinuria (>500 mg/day)
Akimoto *et al.* [20]	2008	Japan	Retrospective	50	∼53	58	1.1	68.8	5	7.1	6.08	56	Clinical renal biopsies, Type 2 DM, proteinuria >0.5 g/day, clinical suspicion of NDRD
Pham *et al.* [21]	2007	USA	Retrospective	232	∼58	53	3.4	38.7	5.9	–	–	17	Clinical renal biopsies, Type 2 DM
Huang *et al.* [23]	2007	China	Retrospective	52	∼54	62	2.14	–	3.34	7.46	NA	34	Clinical renal biopsies, Type 2 DM, overt proteinuria (>0.5 g/day), elevated sCr and/or the development of haematuria
Prakash *et al.* [45]	2007	India	Prospective	23	∼53	65	2.97	–	3.97	–	6.19	65.2	Clinical renal biopsies, Type 2 DM, clinical suspicion of NDRD
Soni *et al.* [24]	2006	India	Retrospective	160	∼51	73.7	4.18	–	3.72	–	7.2	61	Clinical renal biopsies, Type 2 DM, massive proteinuria, the absence of retinopathy, haematuria and unexplained change in renal function
Tone *et al.* [25]	2005	Japan	Retrospective	97	∼53	59	1.43	–	3.75	6.35	5.76	24	Clinical renal biopsies, Type 2 DM, short duration of diabetes (<5 years), and/or absence of diabetic retinopathy and/or presence of microscopic haematuria
Moger *et al.* [46]	2005	India	Prospective	26	∼47	80	Range 3.2–10.8	–	–	–	6.9	76	Clinical renal biopsies, Type 2 DM, with documented doubling of sCr in <4 weeks or recently diagnosed advanced renal failure were identified
Rychlik *et al.* [26]	2004	Czech Republic	Retrospective	163	∼58	65	–	–	8.9	–	–	–	Not reported
Serra *et al.* [47]	2002	Spain	Prospective	35	∼59	63	2.39	–	2.01	–	–	–	Clinical renal biopsies, Type 2 DM, absence of diabetic retinopathy and/or presence of microhaematuria and/or presence of sudden unexpected change in renal function
Castellano *et al.* [30]	2002	Spain	Retrospective	20	∼60	55	–	63.4	5.3	6.4	4.13	15	Clinical renal biopsies, Type 2 DM, short duration of diabetes (<5 years), absence of diabetic retinopathy and/or presence of microscopic haematuria
Mazzucco *et al.* [29]	2002	Italy	Retrospective	393	∼61	67	2.45	–	4.89	–	9.39	–	Clinical renal biopsies, Type 2 DM, restricted policy (presence of haematuria, nephrotic syndrome, non-nephrotic proteinuria >2 g/day, absence of diabetic retinopathy, rapidly progressive renal failure) versus unrestricted policy (proteinuria >0.5 g/day, and/or haematuria, and/or impairment of renal function)
Wong *et al.* [27]	2002	China	Retrospective	68	∼49	55	1.76	–	2.08	–	6.27	39.6	Clinical renal biopsies, Type 2 DM, proteinuria 1 g/day, renal involvement, absence of retinopathy, duration of diabetes <5 years, unexplained haematuria of glomerular origin
Premalatha *et al.* [28]	2002	India	Retrospective	18	∼54	56	1.39	76	4.28	8.5	8.4	0	Research renal biopsies, Type 2 DM, proteinuria >1 g/day, absence of retinopathy

Izzedine *et al.* [32]	2001	France	Retrospective	21	~48	71	–	–	–	–	15.5	–	Clinical renal biopsies, Type 1 (38%) and 2 (62%) DM, microscopic haematuria and/or proteinuria > 2.5 g/day without retinopathy
Suzuki *et al.* [31]	2001	Japan	Retrospective	109	~48	67	1.22	–	1.77	8.82	7.26	49	Clinical renal biopsies, Type 2 DM with proteinuria
Nzerue *et al.* [33]	2000	USA	Retrospective	31	~49.5	48	4.7	–	4.5	–	10.1	48	Clinical renal biopsies, Type 2 DM, severe nephrotic syndrome in three patients, suspected nephritis in nine patients and rapid deterioration of renal failure
Christensen *et al.* [51]	2000	Denmark	Cross-sectional	51	~55	80	0.99	93.2	1.36	8.44	4.68	0	Research renal biopsies, Type 2 DM, albuminuria > 300 mg/day, without diabetic retinopathy
Lee *et al.* [34]	1999	South Korea	Retrospective	22	~51	63	1.57	52.8	3.97	7.79	4.2	27	Clinical renal biopsies, Type 2 DM, nephritic syndrome or haematuria, significant proteinuria, absence of retinopathy, rapidly progressive renal failure, normal-size kidney
Cordonnier *et al.* [52]	1999	UK	RCT	26	~47	81	0.93	123	1.07	–	–	–	Research renal biopsies, Type 2 DM, proteinuria ranging from 70 to 4210 mg/day and relatively preserved GFR (creatinine clearance 60 mL/min)
Schwartz *et al.* [53]	1998	USA	RCT	36	~58	68	1.53	65.9	4.68	8.58	–	71	Research renal biopsies, Type 2 DM, proteinuria >500 mg/day, sCr <3 mg/dL, hypertension
Mak *et al.* [48]	1997	China	Prospective	51	~55	70	1.9	86.1	5.26	11.3	7.23	58	Clinical renal biopsies, Type 2 DM, proteinuria >1 g/day
Olsen *et al.* [35]	1996	Denmark	Retrospective	33	~62	–	–	–	5.37	–	8	60	Clinical renal biopsies, Type 2 DM, clinical suspicion of NDRD
Fioretto *et al.* [49]	1996	Italy	Prospective	34	~58	76	–	101	44 µg/min	8.5	11	67	Research RB, Type 2 DM, microalbuminuria
John *et al.* [36]	1994	India	Retrospective	80	~47	60	–	–	–	–	–	–	Clinical renal biopsies, Type 2 DM, nephritic syndrome or unexplained haematuria, clinically significant proteinuria, absence of retinopathy, rapid progressive renal failure
Gambara *et al.* [37]	1993	Italy	Retrospective	52	~62	57	2.65	–	3.1	–	9.72	–	Clinical renal biopsies, Type 2 DM, proteinuria
Richards *et al.* [38]	1992	UK	Retrospective	68	~52	–	5.45	–	3.07	–	11.05	–	Clinical renal biopsies, Type 1 (32%) and 2 (68%) DM, severe nephrotic syndrome (25 cases), no retinopathy (18), haematuria (13), rapid decline in renal function (11), unexplained renal failure at presentation (5), no neuropathy (3)
Parving *et al.* [39]	1992	Denmark	Prospective	35	~55	94	–	75.2	1.78	8.87	9.54	–	Clinical renal biopsies, Type 2 DM, albuminuria > 300 mg/day
Kleinknecht *et al.* [40]	1992	France	Retrospective	53	~51	56	–	51.5	–	–	13.2	53	Clinical renal biopsies, Type 1 (34%) and 2 (66%) DM, clinical suspicion of NDRD
Hironaka *et al.* [41]	1991	Japan	Retrospective	35	~49	60	1[a]	–	6.8[a]	–	9.2[a]	20[a]	Clinical renal biopsies, Type 1 (8%) and 2 (92%) DM

CKD, chronic kidney disease; DM, diabetes mellitus; DR, diabetic retinopathy; ESKD, end stage kidney disease; GFR, glomerular filtration rate; RCT, randomized controlled trial; sCr, serum creatinine; uPr, proteinuria; NA, not available.
[a]Data on 10 patients with NDRD.

Table 2. Main histological findings of the reviewed studies

Study	Year	Population ($n =$)	Histological diagnosis			NDRD characteristics
			DN (%)	NDRD (%)	Mixed (%)	
Zhuo *et al.* [8]	2013	216	6.5	82.9	10.7	In patients aged 17–59 years, IgAN (29–34%), MN (11–15%), FSGS (8.8–5.4%) In patients aged >60 years, MN (25.7%), AIN (17%), MPGN (11%)
Sharma *et al.* [7]	2013	620	37	36	27	ATN (17–43%), FSGS (13–22%), hypertensive nephrosclerosis (19%), IgAN (7–11%)
Harada *et al.* [42]	2013	55	54.5	34.5	10.9	IgAN (23.6%), FSGS (5.4%), MN (1.8%)
Zajjari *et al.* [6]	2012	16	62.5	37.5	–	IgAN (19%), myeloma (6%)
Yaqub *et al.* [9]	2012	68	31	52	17	AIN (26.4%), post-infectious GN (10.3%), MN (5.9%), PICGN (5.9%)
Oh *et al.* [10]	2012	126	39.7	51.6	8.7	IgAN (16%), MN (11.9%), FSGS (7.6%), MPGN (4.7%)
Chong *et al.* [11]	2012	110	62.7	18.2	19.1	AIN (48.8%), hypertensive nephrosclerosis (24.4%), MCD (7.3%)
Biesenbach *et al.* [14]	2011	84	78.5	21.5	–	–
Haider *et al.* [12]	2011	567	46.6	32	31.4	FSGS (17%), AIN (13%), IgAN (9%), MN (3%)
Chang *et al.* [13]	2011	119	36.2	53.8	10	MN (32.9%), MCD (15.8%), FSGS (11.8%), IgAN (11.8%)
Bi *et al.* [15]	2011	220	54.5	–	45.5	IgAN (34%), MN (22%), mesangial-proliferative GN (14%)
Zhang *et al.* [43]	2011	130	73.9	26.1	–	IgAN (16.9%), MN (6.15%)
Mou *et al.* [16]	2010	69	47.8	52.2	–	FSGS (37.7%), IgAN (15.9%), MCD (15.9%), MN (8.7%)
Lin *et al.* [17]	2009	50	48	22	30	AIN (46%), MN (19.2%), IgAN (11.5%)
Ghani *et al.* [19]	2009	31	54.8	–	45.2	PICGN (21.4%), AIN (14.4%), IgAN (7.1%)
Arif *et al.* [50]	2009	73	27.3	31.7	41	FSGS/MCD (30.56%), MN (8.3%), IgAN (5.5%)
Hashim Al-Saedi [18]	2009	80	–	100	–	MPGN (40%), FSGS (25%), MN (20%), MCD (10%), amyloidosis (5%)
Zhou *et al.* [44]	2008	110	54.5	45.5	–	IgAN (34%), MN (22%), MPGN (14%)
Akimoto *et al.* [20]	2008	50	68	26	6	MN (8%), IgAN (6%), MPGN (6%)
Pham *et al.* [21]	2007	232	27.5	53.2	19.3	FSGS (21%), MCD (15.3%), IgAN (15.3%), MN (13.3%)
Huang *et al.* [23]	2007	52	55.7	38.5	5.8	Mesangial-proliferative GN (9.6%), MCD (7.7%)
Kharrat *et al.* [22]	2007	72	34.1	69.5	–	–
Prakash *et al.* [45]	2007	23	56.5	30.5	13	MN (8.7%), FSGS (8.7%)
Soni *et al.* [24]	2006	160	27.5	42.5	30	AIN (18.1%), post-infectious GN (17.2%), MN (11.2%), FSGS (7.7%)
Tone *et al.* [25]	2005	97	36	47.5	16.5	IgAN (16%), MN (13%), MCD (8%), FSGS (5%)
Moger *et al.* [46]	2005	26	34.6	23.1	42.3	Proliferative GN (27%), AIN (15.3%), PICGN (11.5%)
Rychlik *et al.* [26]	2004	163	42.4	47.5	10.1	IgAN (15%), MN (12%), PICGN (12%)
Serra *et al.* [47]	2002	35	74.3	17.1	8.6	IgAN (8%), FSGS (3%)
Castellano *et al.* [30]	2002	20	45	55	–	MN (35%), renal vasculitis (15%), IgAN (5%)
Mazzucco *et al.* [29]	2002	393	39.7	43	17.3	MN (23.1%), IgAN (20.3%), post-infectious GN (20.9%), MCD (12.4%), FSGS (12.4%), extra capillary GN (9.6%)
Wong *et al.* [27]	2002	68	35	46	19	IgAN (19%), nephrosclerosis (13%), MN (12%), MCD (6%)
Premalatha *et al.* [28]	2002	18	50	50	–	MN (33.3%), AIN (12.5%), MCD (12.5%)
Izzedine *et al.* [32]	2001	21	62	38	–	FSGS, IgAN, vascularnephropathy
Suzuki *et al.* [31]	2001	109	73.3	–	26.7	IgAN (44.8%), proliferative GN (37.9%), MN (6.9%), AIN (6.9%), FSGS (3.4%)
Nzerue *et al.* [33]	2000	31	41.9	19.4	38.7	FSGS (18%), nephrosclerosis (17%), MN (6%), PICGN (6%)
Christensen *et al.* [51]	2000	51	69	13	–	IgAN (8%), MPGN (4%)
Lee *et al.* [34]	1999	22	36.4	50	13.6	IgAN (22%), MN (21%), MCD (21%), AIN (5%)
Condonnier *et al.* [52]	1999	26	85	15	–	–
Schwartz *et al.* [53]	1998	36	94	6	–	IgAN (3%), MN (3%)
Mak *et al.* [48]	1997	51	67	16	17	IgAN (59%), hypertensive nephrosclerosis (24%)
Olsen *et al.* [35]	1996	33	88	3	9	IgAN (3%), mesangio-proliferative GN (3%), crio-GN (3%)
Fioretto *et al.* [49]	1996	34	29.4	41.2	–	–
John *et al.* [36]	1994	80	18.7	60	21.3	MCD (16%), IgAN (8%), MN (8%), AIN (6%), FSGS (6%)
Gambara *et al.* [37]	1993	52	36.5	33	30.5	IgAN, MN, FSGS, MCD, PICGN (4%)
Richards *et al.* [38]	1992	68	62	34	4	MN (7%), IgAN (2%), PICGN (2%), MPGN (2%)
Parving *et al.* [39]	1992	35	77.1	20	2.9	Mesangial-proliferative GN
Kleinknecht *et al.* [40]	1992	53	64	36	–	MN (14%), FSGS (14%), AIN (3%)
Hironaka *et al.* [41]	1991	35	71.4	14.3	14.3	–

AIN, acute interstitial nephritis; ATN, acute tubular necrosis; Crio-GN, crioglobulinemic glomerulonephritis; DN, diabetic nephropathy; FSGS, focal-segmental glomerulosclerosis; GN, glomerulonephritis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; MPGN, membrano-proliferative glomerulonephritis; NA, not available; NDRD, non-diabetic renal disease; PICGN, Pauci-immune crescentic glomerulonephritis.

of the overall diagnoses). Similarly, the calculated PPVs for NDRD and mixed forms (36.9% and 19.7%, respectively) and the combined PPV (NDRD + mixed forms, 49.2%) strengthen the hypothesis that non-diabetic renal damage at RB is not as unlikely as commonly believed. Furthermore, there was high heterogeneity in the type of NDRD histologically assessed, IgA nephropathy being the most common finding (3 to 59%). The prevalence of different histological pictures of NDRD has been analysed in this systematic review and differences between population settings have been described. A higher prevalence of diagnosis of IgA nephropathy in Asian population has been described in the selected studies compared with other populations (European, American, African studies). IgA nephropathy is considered to be multifactorial disease in which pathogenesis

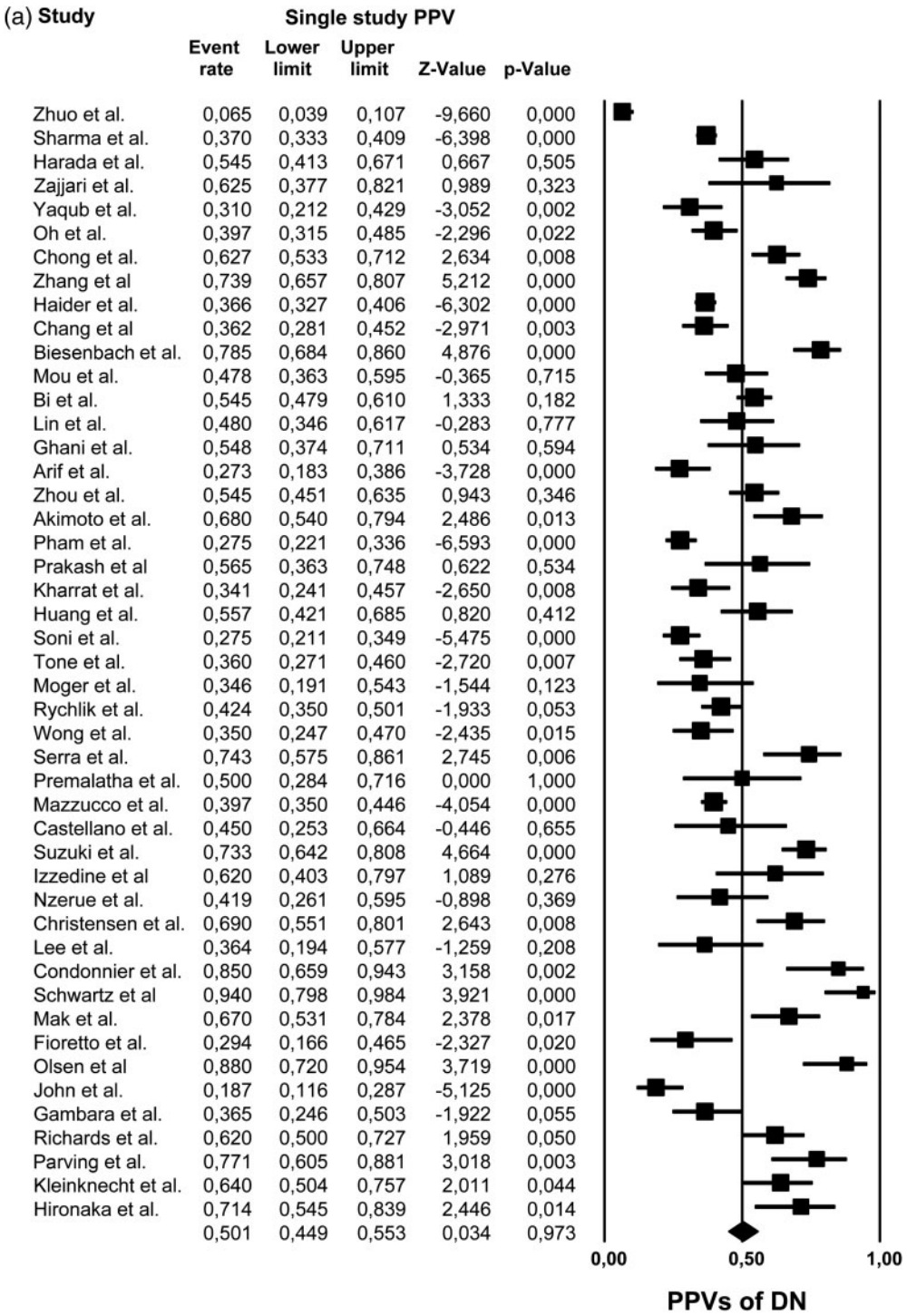

FIGURE 2: PPVs of clinical judgment for the diagnosis of DN (**a**), NDRD (**b**), mixed forms (**c**) and NDRD + mixed forms (**d**) from pooled meta-analysis. DN, diabetic nephropathy; NDRD, non-diabetic renal disease; PPVs, positive predictive values.

involves genetic and environmental factors. Our results are in line with the prevalence of glomerular disease in non-diabetic patients in previous studies [56, 57]. A similar prevalence of IgA nephropathy and MN was found in studies on European populations, contrary to what is reported in several RB registries [26, 58, 59].

Several factors may explain such a high histological variability. In particular, criteria used to select patients with diabetes who would benefit from RB were very different among the studies reviewed. As alluded to before, only a small number of studies evaluated research-indicated biopsies while the vast majority analysed clinically indicated biopsies. Percentages of DN and NDRD diagnoses were not statistically different between these two groups, whereas a higher percentage of IgA nephropathy was showed in clinically indicated biopsies. Although interesting, these observations may be influenced by the substantial discrepancy in the number of patients in which RB was driven by research or clinical purposes. Hence,

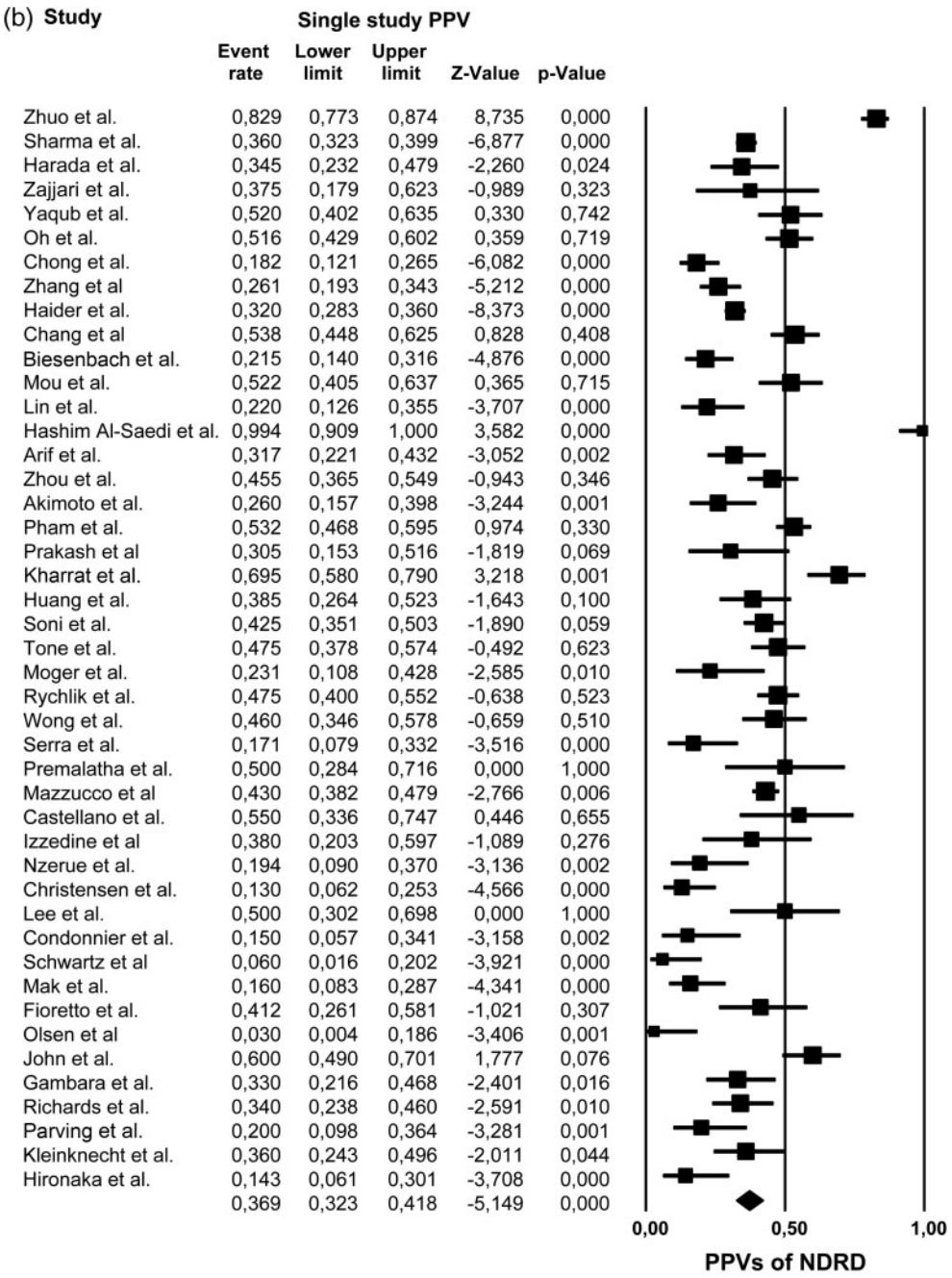

FIGURE 2: *Continued*

statistical analyses could be underpowered to detect such a significant difference in the overall percentage of diagnoses made. The most common indications were represented by a sudden onset of nephrotic-range proteinuria or renal impairment in the absence of diabetic retinopathy or in the presence of a history of diabetes <5 years, the presence of active urinary sediment, an unexplained acute kidney injury or a rapid renal function decline in patients with previously stable renal function.

The evaluation of factors explaining heterogeneity identified systolic blood pressure, HbA1c, duration of diabetes and diabetic retinopathy as inversely correlated with NDRD diagnosis. Serum creatinine was the only factor underlying heterogeneity for DN. Finally, serum creatinine and, even more, GFR elucidated heterogeneity among studies for mixed forms.

In previous studies exploring clinical predictors of the presence of DN or NDRD, Zhuo *et al.* [8] pointed at longer diabetic duration, higher systolic blood pressure, higher HbA1c and the presence of retinopathy as clinical signs highly suggestive of classic DN. The role of retinopathy was very well analysed by the RASS study [60], which described a significant association between diabetic retinopathy and preclinical histological damage in patients with Type 1 DM. Tone *et al.* [25] confirmed that diabetic retinopathy had the highest sensitivity (87%) and sensibility (93%) in predicting the presence of DN. However, the presence of proliferative retinopathy is associated with the classical nodular sclerosis of DN [49, 53], and patients with both DN and retinopathy showed a more severe renal histology than those without retinal damage [42]. Patients with other

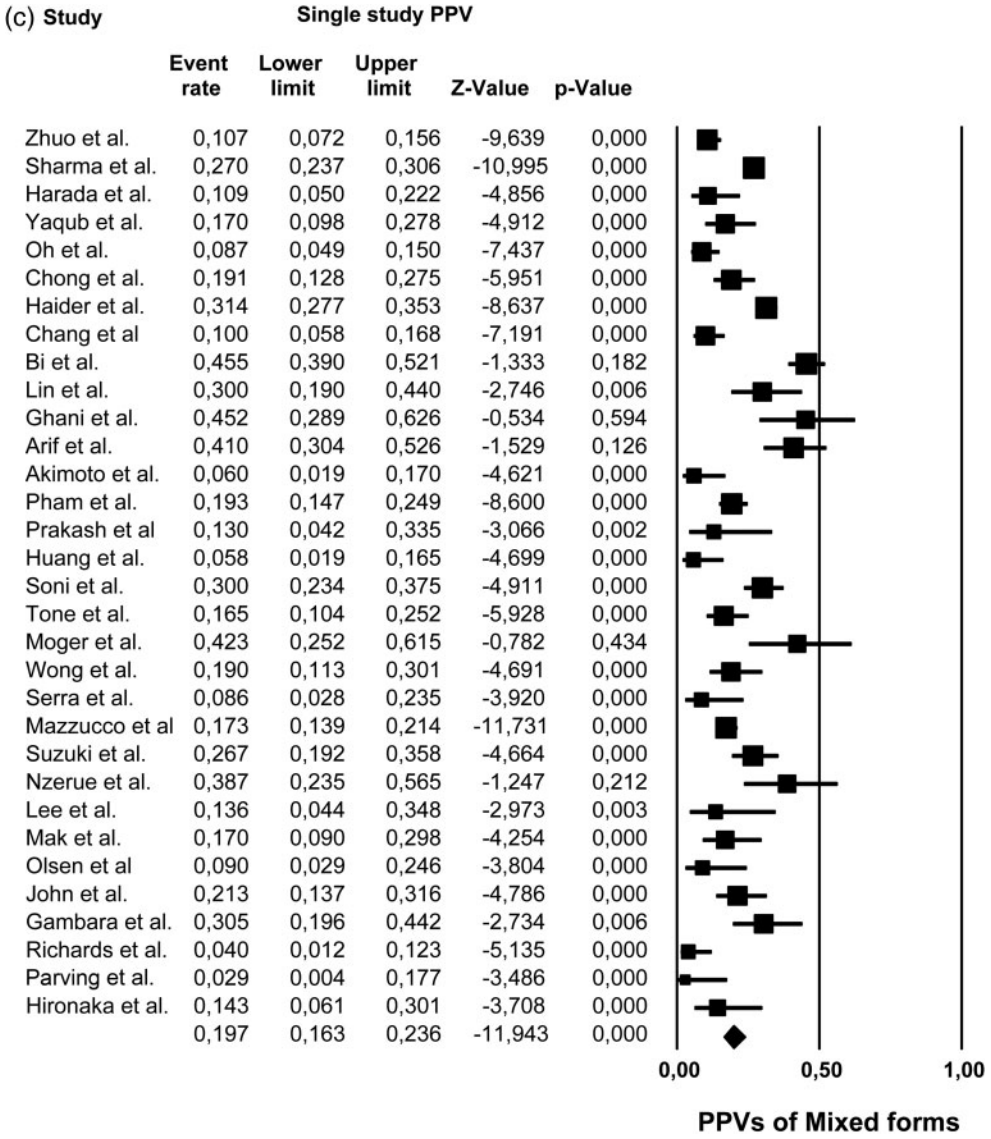

FIGURE 2: *Continued*

histological lesions more frequently have no evidence of diabetic retinopathy or only have minimal damage and none of the patients with NDRD had proliferative retinopathy [34, 39, 49, 53]. In the study by Liang *et al.* [3], the presence of dysmorphic erythrocytes and erythrocytes casts was strongly indicative of NDRD. However, in the same study the predictive role of diabetic retinopathy with respect to DN was questioned since the absence of such complication was, in some cases, associated with the presence of DN. The hypothesis that retinopathy might be a poor predictor of DN was supported by another study [45], in which DN was present in about 50% of diabetics without DR, while 40% of patients with DR had other renal diseases.

RB might be fundamental for clarifying the epidemiology of renal disease in patients with diabetes and for planning proper therapeutic management [17]. Furthermore, although this procedure is invasive, the risk profile in subjects with diabetes is comparable to that of the general population [43]. As described in a large research biopsy study on patients with Type 1 DM [55], specific histological lesions, such as thickening of glomerular basement membrane or an increase of mesangial fractional volume, can be evident early on, before the development of overt DN and initiation of treatment (such as RAS inhibition) based on clinical manifestations may be inadequate to delay the natural history of the disease. Indeed, treatment approaches for DN and NDRD may diverge: for instance, IgA nephropathy, FSGS, membranous glomerulonephritis and other primary and secondary glomerular diseases usually benefit from personalized treatments (e.g. immunosuppressive therapies) rather than from general approaches [54]. The prognostic importance of RB is another aspect that should be seriously taken into consideration [2, 10]. Oh *et al.* [10] found that ESKD occurred in 44% of DN, in 18.2% of mixed forms and in only 12.3% of NDRD. Diabetics with frank DN usually have a worse prognosis compared with patients with NDRD [13, 27] and the severity of DN correlates with histological (glomerular and tubule-interstitial damage) and clinical (eGFR, proteinuria) predictors of ESKD [10, 54]. Nevertheless, NDRD may have better outcomes, particularly if these conditions are identified early and specific treatments are predisposed [1].

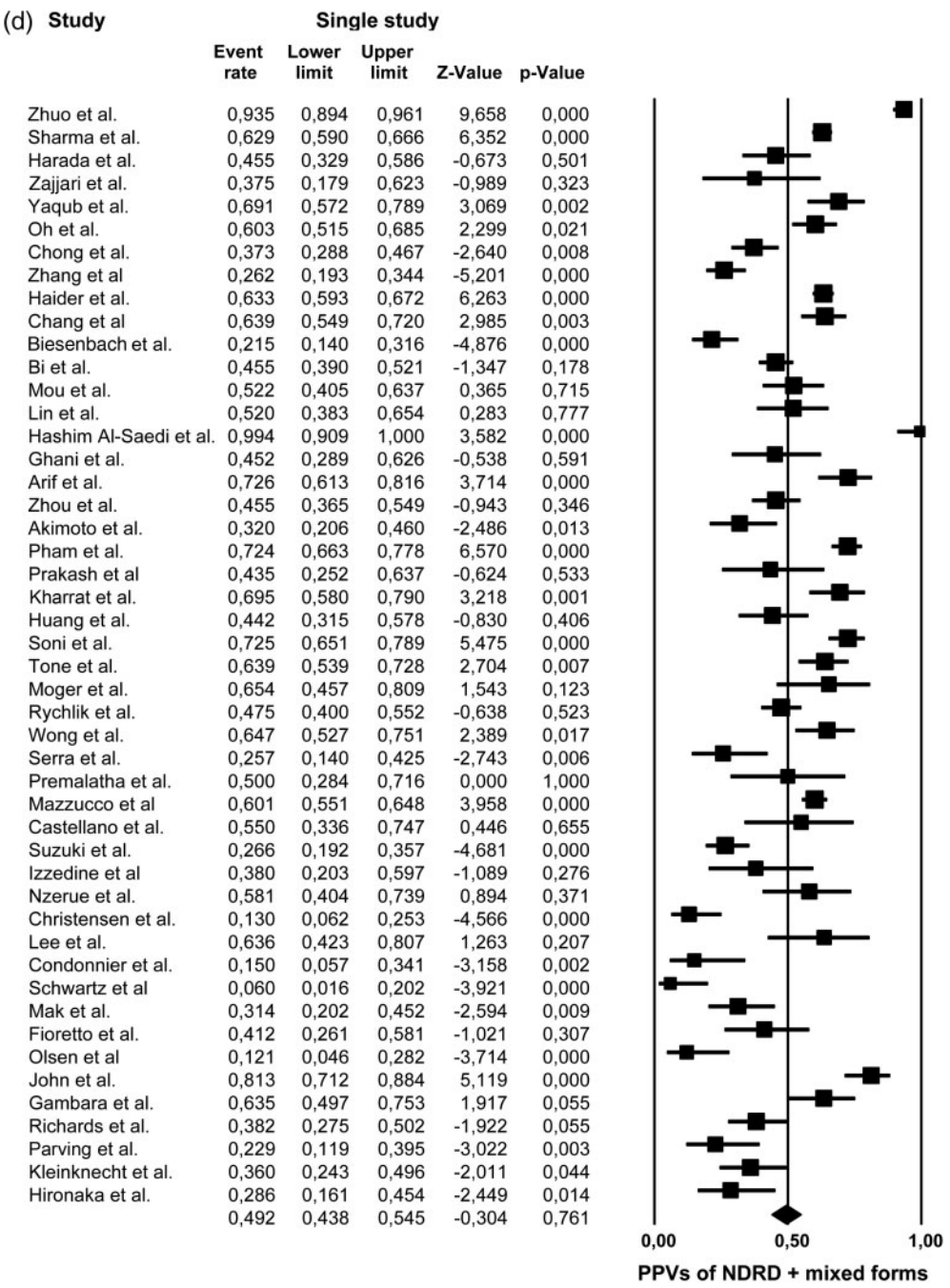

FIGURE 2: *Continued*

Our review has some strengths and limitations that deserve mentioning. The main strength is represented by the systematic approach to the existing literature by implementing high-sensitivity and focussed search strategies according to current methodological standards. This, however, cannot fully rule out residual publication bias. The main limitation of our findings is related to the observational nature of the included studies (most of which had a retrospective design) and the more or less evident presence of selection bias. Furthermore, as shown, there was high heterogeneity with respect to the number of subjects enrolled, the criteria used for performing RB, the degree of renal impairment, the duration of diabetes and the frequency of diabetic retinopathy; this may hamper the possibility of drawing unique and definitive conclusions and generalizing findings to the whole diabetic population.

In conclusion, our study shows proof that RB might represent an important tool in patients with diabetes, particularly for identifying subjects with NDRD who would benefit from personalized treatment for retarding ESKD. Future, well-planned studies on this issue are eagerly awaited for clarifying the exact role of this procedure in the clinical management of patients with diabetes.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

We are grateful of the European Renal Best Practice (ERBP) and ERA-EDTA Immunonephrology Working Group (both sponsored by ERA-EDTA) for the incessant support to the project. This study was financed by Italian National Health (RF09ED01: 'Prevalence and impact on total mortality of chronic kidney disease in patients with type 2 diabetes in Apulia; a paradigm for a region-based study whose data may be specifically implemented in the management of chronic metabolic and vascular diseases in a Mediterranean area') and by a grant of Italian Society of Nephrology (SIN).
The results presented in this paper have not been published elsewhere in whole or part.

AUTHORS' CONTRIBUTIONS

M.F., D.B. and L.G. collaborated on research idea, study design, study selection and wrote the paper. V.T. helped in drafting the paper. A.P. collaborated on study selection and data collection. W.V.B. helped in full-text research and in drafting the paper. G.T. and G.D. helped in statistical analysis and data interpretation. All authors approved the final version of the submitted manuscript.

CONFLICT OF INTEREST STATEMENT

All the authors have declared no competing interest.

(See related article by Caramori. Should all patients with diabetes have a kidney biopsy? *Nephrol Dial Transplant* 2017; 32: 3–5)

REFERENCES

1. Prakash J. Non-diabetic renal disease (NDRD) in patients with type 2 diabetes mellitus (type 2 DM). *J Assoc Physicians India* 2013; 61: 194–199
2. Gonsalez Suarez ML, Thomas DB, Barisoni L *et al.* Diabetic nephropathy: Is it time yet for routine kidney biopsy? *World J Diabetes* 2013; 4: 245–255
3. 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
4. Bolignano D, Mattace-Raso F, Sijbrands EJ *et al.* The aging kidney revisited: a systematic review. *Ageing Res Rev* 2014; 14: 65–80
5. Tervaert TW, Mooyaart AL, Amann K *et al.* Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol* 2010; 21: 556–563
6. 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: 620–623
7. 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: 1718–1724
8. Zhuo L, Ren W, Li W *et al.* Evaluation of renal biopsies in type 2 diabetic patients with kidney disease: a clinicopathological study of 216 cases. *Int Urol Nephrol* 2013; 45: 173–179
9. Yaqub S, Kashif W, Hussain SA. Non-diabetic renal disease in patients with type-2 diabetes mellitus. *Saudi J Kidney Dis Transpl* 2012; 23: 1000–1007
10. Oh SW, Kim S, Na KY *et al.* Clinical implications of pathologic diagnosis and classification for diabetic nephropathy. *Diabetes Res Clin Pract* 2012; 97: 418–424
11. 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: 323–328
12. Haider DG, Peric S, Friedl A *et al.* Kidney biopsy in patients with diabetes mellitus. *Clin Nephrol* 2011; 76: 180–185
13. 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
14. Biesenbach G, Bodlaj G, Pieringer H *et al.* Clinical versus histological diagnosis of diabetic nephropathy—is renal biopsy required in type 2 diabetic patients with renal disease? *Q J Med* 2011; 104: 771–774
15. Bi H, Chen N, Ling G *et al.* Nondiabetic renal disease in type 2 diabetic patients: a review of our experience in 220 cases. *Ren Fail* 2011; 33: 26–30
16. 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: 354–359
17. Lin YL, Peng SJ, Ferng SH *et al.* Clinical indicators which necessitate renal biopsy in type 2 diabetes mellitus patients with renal disease. *Int J Clin Pract* 2009; 63: 1167–1176
18. Hashim Al-Saedi AJ. Pathology of nondiabetic glomerular disease among adult Iraqi patients from a single center. *Saudi J Kidney Dis Transpl* 2009; 20: 858–861
19. Ghani AA, Al Waheeb S, Al Sahow A *et al.* Renal biopsy in patients with type 2 diabetes mellitus: indications and nature of the lesions. *Ann Saudi Med* 2009; 29: 450–453
20. Akimoto T, Ito C, Saito O *et al.* Microscopic hematuria and diabetic glomerulosclerosis—clinicopathological analysis of type 2 diabetic patients associated with overt proteinuria. *Nephron Clin Pract* 2008; 109: c119–e64126
21. Pham TT, Sim JJ, Kujubu DA *et al.* Prevalence of nondiabetic renal disease in diabetic patients. *Am J Nephrol* 2007; 27: 322–328
22. Kharrat M, Kammoun K, Charfeddine K *et al.* Renal biopsy findings in diabetes mellitus. *Tunis Med* 2007; 85: 216–219
23. Huang F, Yang Q, Chen L *et al.* Renal pathological change in patients with type 2 diabetes is not always diabetic nephropathy: a report of 52 cases. *Clin Nephrol* 2007; 67: 293–297
24. Soni SS, Gowrishankar S, Kishan AG *et al.* Non diabetic renal disease in type 2 diabetes mellitus. *Nephrology* 2006; 11: 533–537
25. 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: 237–242
26. Rychlik I, Jancova E, Tesar V *et al.* The Czech registry of renal biopsies. Occurrence of renal diseases in the years 1994–2000. *Nephrol Dial Transplant* 2004; 19: 3040–3049
27. 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: 900–905
28. Premalatha G, Vidhya K, Deepa R *et al.* Prevalence of non-diabetic renal disease in type 2 diabetic patients in a diabetes centre in Southern India. *J Assoc Physicians India* 2002; 50: 1135–1139
29. 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: 713–720
30. Castellano I, Covarsi A, Novillo R *et al.* Renal histological lesions in patients with type II diabetes mellitus. *Nefrologia* 2002; 22: 162–169
31. Suzuki D, Takano H, Toyoda M *et al.* Evaluation of renal biopsy samples of patients with diabetic nephropathy. *Intern Med.* 2001; 40: 1077–1084
32. Izzedine H, Fongoro S, Pajot O *et al.* Retinopathy, hematuria, and diabetic nephropathy. *Nephron* 2001; 88: 382–383
33. Nzerue CM, Hewan-Lowe K, Harvey P *et al.* Prevalence of non-diabetic renal disease among African-American patients with type II diabetes mellitus. *Scand J Urol Nephrol* 2000; 34: 331–335
34. Lee EY, Chung CH, Choi SO. Non-diabetic renal disease in patients with non-insulin dependent diabetes mellitus. *Yonsei Med J* 1999; 40: 321–326

35. Olsen S, Mogensen CE. How often is NIDDM complicated with non-diabetic renal disease? An analysis of renal biopsies and the literature. *Diabetologia* 1996; 39: 1638–1645
36. John GT, Date A, Korula A *et al.* Nondiabetic renal disease in noninsulin-dependent diabetics in a south Indian Hospital. *Nephron* 1994; 67: 441–443
37. Gambara V, Mecca G, Remuzzi G *et al.* Heterogeneous nature of renal lesions in type II diabetes. *J Am Soc Nephrol* 1993; 3: 1458–1466
38. Richards NT, Greaves I, Lee SJ *et al.* Increased prevalence of renal biopsy findings other than diabetic glomerulopathy in type II diabetes mellitus. *Nephrol Dial Transplant* 1992; 7: 397–399
39. Parving HH, Gall MA, Skott P *et al.* Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. *Kidney Int.* 1992; 41: 758–762
40. Kleinknecht D, Bennis D, Altman JJ. Increased prevalence of non-diabetic renal pathology in type II diabetes mellitus. *Nephrol Dial Transplant* 1992; 7: 1258–1259
41. Hironaka K, Makino H, Ikeda S *et al.* Nondiabetic renal disease complicating diabetic nephropathy. *J Diabet Complications* 1991; 5: 148–149
42. 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
43. Zhang PP, Ge YC, Li SJ *et al.* Renal biopsy in type 2 diabetes: timing of complications and evaluating of safety in Chinese patients. *Nephrology (Carlton)* 2011; 16: 100–105
44. Zhou J, Chen X, Xie Y *et al.* A differential diagnostic model of diabetic nephropathy and non-diabetic renal diseases. *Nephrol Dial Transplant* 2008; 23: 1940–1945
45. Prakash J, Lodha M, Singh SK *et al.* Diabetic retinopathy is a poor predictor of type of nephropathy in proteinuric type 2 diabetic patients. *J Assoc Physicians India* 2007; 55: 412–416
46. 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
47. Serra A, Romero R, Bayes B *et al.* Is there a need for changes in renal biopsy criteria in proteinuria in type 2 diabetes? *Diabetes Res Clin Pract* 2002; 58: 149–153
48. Mak SK, Gwi E, Chan KW *et al.* Clinical predictors of non-diabetic renal disease in patients with non-insulin dependent diabetes mellitus. *Nephrol Dial Transplant* 1997; 12: 2588–2591
49. Fioretto P, Mauer M, Brocco E *et al.* Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia* 1996; 39: 1569–1576
50. Arif M, Arif MK, Arif MS. An evaluation of renal biopsy in type-II diabetic patients. *J Coll Physicians Surg Pak* 2009; 19: 627–631
51. Christensen PK, Larsen S, Horn T *et al.* Causes of albuminuria in patients with type 2 diabetes without diabetic retinopathy. *Kidney Int* 2000; 58: 1719–1731
52. Cordonnier DJ, Pinel N, Barro C *et al.* Expansion of cortical interstitium is limited by converting enzyme inhibition in type 2 diabetic patients with glomerulosclerosis. The Diabiopsies Group. *J Am Soc Nephrol* 1999; 10: 1253–1263
53. Schwartz MM, Lewis EJ, Leonard-Martin T *et al.* Renal pathology patterns in type II diabetes mellitus: relationship with retinopathy. The Collaborative Study Group. *Nephrol Dial Transplant* 1998; 13: 2547–2552
54. An Y, Xu F, Le W *et al.* Renal histologic changes and the outcome in patients with diabetic nephropathy. *Nephrol Dial Transplant* 2015; 30: 257–266
55. Mauer M, Zinman B, Gardiner R *et al.* ACE-I and ARBs in early diabetic nephropathy. *J Renin Angiotensin Aldosterone Syst* 2002; 3: 262–269
56. Chang JH, Kim DK, Kim HW *et al.* Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience. *Nephrol Dial Transplant* 2009; 24: 2406–2410
57. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: Analysis based on 13 519 renal biopsies. *Kidney Int* 2004; 66: 920–923
58. Gesualdo L, Di Palma AM, Morrone LF *et al.* The Italian experience of the national registry of renal biopsies. *Kidney Int* 2004; 66: 890–894
59. Rivera F, Lopez-Gomez JM, Perez-Garcia R *et al.* Frequency of renal pathology in Spain 1994–1999. *Nephrol Dial Transplant* 2002; 17: 1594–1602
60. Klein R, Zinman B, Gardiner R *et al.* The relationship of diabetic retinopathy to preclinical diabetic glomerulopathy lesions in type 1 diabetic patients: the Renin-Angiotensin System Study. *Diabetes* 2005; 54: 527–533

Received for publication: 11.7.2015; Accepted in revised form: 1.3.2016