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Diabetic Retinopathy Confirms but Does Not Exclude Diabetic Nephropathy in Type 2 Diabetes: A Renal Biopsy Study of Diagnostic Accuracy and the Non-Diabetic Kidney Disease Spectrum

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ABSTRACT

Background. Non-diabetic kidney disease (NDKD) accounts for a clinically important proportion of renal disease in patients with type 2 diabetes mellitus (T2DM) undergoing kidney biopsy, and its management and prognosis differ from those of isolated diabetic nephropathy (DN). Absence of diabetic retinopathy (DR) is a widely cited clinical clue to NDKD. We evaluated the diagnostic performance of DR for predicting biopsy-proven DN and described the spectrum of NDKD in T2DM patients biopsied at a single centre.

Methods. Records of 60 T2DM patients who underwent renal biopsy were analysed. Biopsy diagnosis was the reference standard; DR (present/absent) was the index test. Sensitivity, specificity, predictive values, likelihood ratios and accuracy were calculated with 95% confidence intervals (CI); the DR–biopsy association was tested by Fisher's exact test. Baseline features were compared between groups and the NDKD spectrum described.

Results. Isolated DN was present in 44/60 (73.3%) and NDKD (including one mixed case) in 16/60 (26.7%). DR predicted DN with sensitivity 56.8% (95% CI 42.2–70.3), specificity 93.8% (71.7–98.9), PPV 96.2% (81.1–99.3), NPV 44.1% (28.9–60.5) and accuracy 66.7%; LR+ 9.09 and LR− 0.46 (Fisher p = 0.0004). Nearly half of DN patients (19/44, 43.2%) had no retinopathy. NDKD patients had markedly shorter diabetes duration (median 2 vs 12 years, $p < 0.001$), lower HbA1c ($p = 0.034$), more frequent low serum C3 ($p = 0.016$) and less advanced IFTA ($p = 0.007$). The commonest NDKD lesion was focal segmental glomerulosclerosis (25.0%).

Conclusions. In biopsied T2DM patients, the presence of retinopathy strongly rules in DN (high specificity and PPV), but its absence is a poor rule-out (low NPV). Short diabetes duration and low complement are more discriminating pointers to NDKD, and biopsy selection should not rest on retinopathy status alone.

Keywords: diabetic nephropathy; non-diabetic kidney disease; diabetic retinopathy; renal biopsy; type 2 diabetes mellitus.

INTRODUCTION

Kidney disease in T2DM is heterogeneous. While DN is the presumptive diagnosis in most patients with diabetes and chronic kidney disease, renal biopsy in selected patients reveals a substantial burden of NDKD, either in isolation or superimposed on DN. Distinguishing the two matters: several NDKD lesions are treatable and carry

a different prognosis, so misattributing them to DN risks withholding effective therapy.

Clinical predictors are used to decide who should be biopsied, and among these the presence or absence of DR is the most frequently invoked, on the rationale that microvascular disease in the eye and kidney tend to progress in parallel. The strength of this association, however, varies across cohorts, and its formal diagnostic performance against biopsy in the Indian setting remains incompletely characterised.

In this single-centre study we (i) quantified the diagnostic accuracy of DR for biopsy-proven DN in T2DM, and (ii) described the spectrum of NDKD lesions encountered, extending prior Indian observations. In the pooled meta-analysis of He et al., diabetic retinopathy predicted diabetic nephropathy with a sensitivity of about 65% and specificity of about 75%; the biopsy series of Das et al. and Prasad et al. reported NDKD in roughly one quarter to one third of biopsied T2DM patients, broadly in keeping with the 26.7% prevalence observed here.

MATERIALS AND METHODS

Study design and population

This was a retrospective analysis of 60 consecutive adult patients with established T2DM who underwent kidney biopsy at Rajarajeshwari Medical College and Hospital, Bengaluru, over the study period. Inclusion and exclusion criteria were as per the parent thesis protocol.

Definitions and reference standard

Kidney biopsy, reported by a nephropathologist with light microscopy, immunofluorescence and (where available) electron microscopy, was the reference standard. Each biopsy was classified as isolated DN, isolated NDKD, or mixed DN with superimposed NDKD. Diabetic retinopathy — the index test — was recorded as present or absent on dilated fundus examination.

Handling of mixed disease

For the primary accuracy analysis, the target condition ("DN") was defined as isolated DN; the single mixed case (acute tubular injury superimposed on DN class III) was grouped with NDKD, because the clinical question is whether retinopathy identifies patients who can be spared a biopsy. A pre-specified sensitivity analysis repeated the calculation with the mixed case counted as DN.

Statistical Analysis

Continuous variables are summarised as mean ± SD (independent-samples t-test) or median (IQR) for skewed data (Mann–Whitney U test); categorical variables as counts (percentages), compared by Fisher's exact test. From the 2×2 cross-tabulation of DR against biopsy diagnosis, sensitivity, specificity, predictive values, likelihood ratios and accuracy were derived with 95% CI (Wilson method for proportions; log method for likelihood ratios). A two-sided $p < 0.05$ was significant. Analyses were performed in Python (SciPy/statsmodels); a reproducible script accompanies this analysis.

RESULTS

Of 60 biopsied T2DM patients, 44 (73.3%) had isolated DN (25 class III, 19 class IV), 15 (25.0%) had isolated NDKD and 1 (1.7%) had mixed disease; NDKD (including the mixed case) thus accounted for 16/60 (26.7%). Baseline characteristics are shown in Table 1. The groups were similar in age, sex, proteinuria and hematuria, but DN patients had substantially longer diabetes duration (median 12 vs 2 years, $p < 0.001$), higher HbA1c ($p = 0.034$), more advanced interstitial fibrosis ($p = 0.007$) and more frequent retinopathy, while low serum C3 occurred only in NDKD ($p = 0.016$).

The cross-tabulation of retinopathy against biopsy diagnosis (Table 2) yielded a significant association (Fisher $p = 0.0004$). Diagnostic performance is summarised in Table 3: retinopathy showed high specificity (93.8%) and PPV (96.2%) but modest sensitivity (56.8%) and low NPV (44.1%); LR+ was 9.09 and LR− 0.46. Notably, 19 of 44 DN patients (43.2%) had no retinopathy. In the sensitivity analysis (mixed case

counted as DN), specificity and PPV rose to 100% (95% CI 79.6–100 and 87.1–100), as the single false positive was reclassified. The spectrum of NDKD (Table 4) was led by focal segmental glomerulosclerosis (25.0%), followed by membranous nephropathy, IgA nephropathy and acute tubular injury.

Table 1. Baseline clinical and laboratory characteristics of the DN and NDKD groups.

Variable	DN (n = 44)	NDKD (n = 16)	p-value
Age, years (mean ± SD)	47.8 ± 8.0	50.9 ± 11.4	0.328
Male sex, n (%)	26 (59.1)	8 (50.0)	0.568
Duration of diabetes, years (median, IQR)	12.0 (9.0–16.3)	2.0 (1.0–3.0)	<0.001
HbA1c, % (mean ± SD)	10.7 ± 1.9	9.1 ± 2.6	0.034
Blood urea, mg/dL (median, IQR)	30.2 (17.8–39.5)	17.0 (12.0–24.8)	0.114
Serum creatinine, mg/dL (median, IQR)	2.70 (1.88–4.43)	1.85 (1.38–3.20)	0.072
eGFR, mL/min/1.73m² (mean ± SD)	27.7 ± 15.2	44.1 ± 33.5	0.076
24-h proteinuria, g/day (median, IQR)	3.40 (2.17–5.33)	2.86 (1.48–6.88)	0.547
Nephrotic-range proteinuria, n (%)	22 (50.0)	6 (37.5)	0.559
Microscopic hematuria, n (%)	16 (36.4)	6 (37.5)	1.000
Diabetic retinopathy present, n (%)	25 (56.8)	1 (6.2)	<0.001
Low serum C3, n (%)	0 (0.0)	3 (18.8)	0.016
Advanced (moderate–severe) IFTA, n (%)	27 (61.4)	3 (18.8)	0.007

SD, standard deviation; IQR, interquartile range; eGFR by CKD-EPI 2021; IFTA, interstitial fibrosis and tubular atrophy. NDKD group includes the one mixed DN+NDKD case. Continuous variables: t-test (mean ± SD) or Mann–Whitney U (median, IQR); categorical: Fisher's exact test. Shaded p-values are significant (p < 0.05).

Table 2. Cross-tabulation of diabetic retinopathy against biopsy diagnosis (2×2).

Diabetic retinopathy	DN on biopsy	NDKD on biopsy	Total
Present	25 (TP)	1 (FP)	26
Absent	19 (FN)	15 (TN)	34
Total	44	16	60

TP, true positive; FP, false positive; FN, false negative; TN, true negative. Target condition = isolated DN. The one false positive was the mixed DN+NDKD case. Fisher's exact p = 0.0004.

Table 3. Diagnostic performance of diabetic retinopathy for predicting biopsy-proven DN.

Diagnostic index (retinopathy for DN)	Estimate	95% CI
Sensitivity	56.8%	42.2–70.3
Specificity	93.8%	71.7–98.9
Positive predictive value	96.2%	81.1–99.3
Negative predictive value	44.1%	28.9–60.5
Positive likelihood ratio (LR+)	9.09	1.34–61.71
Negative likelihood ratio (LR−)	0.46	0.32–0.66
Diagnostic accuracy	66.7%	54.1–77.3

CI, confidence interval (Wilson for proportions; log method for likelihood ratios). Sensitivity analysis with the mixed case counted as DN: sensitivity 57.8%, specificity 100% (79.6–100), PPV 100% (87.1–100), NPV 44.1%.

Table 4. Spectrum of non-diabetic kidney disease lesions (n = 16).

NDKD histological diagnosis	n	% of NDKD
Focal segmental glomerulosclerosis	4	25.0
Membranous nephropathy	2	12.5
IgA nephropathy*	2	12.5
Acute tubular injury†	2	12.5
Chronic granulomatous interstitial nephritis	1	6.2
Chronic interstitial nephritis	1	6.2
Fibrillary glomerulonephritis	1	6.2
Chronic glomerulosclerosis	1	6.2
Thrombotic microangiopathy (malignant HTN)	1	6.2
Glomerular organoid deposit disease	1	6.2
Total NDKD	**16**	**100**

**Includes one IgA nephropathy with focal mesangial proliferation and segmental sclerosis. †Includes the mixed case (acute tubular injury superimposed on DN class III). Percentages of total NDKD.*

DISCUSSION

In this cohort of 60 biopsied T2DM patients, retinopathy behaved as a strong rule-in but weak rule-out test for DN. When present, it predicted DN with 96% PPV and 94% specificity (LR+ 9.1) - only one NDKD patient had retinopathy. When absent, however, it excluded DN poorly: the NPV was just 44%, and 43% of biopsy-proven DN patients had no retinopathy. This tempers the common teaching that absent retinopathy points away from DN; in this population it did not reliably do so.

The strongest discriminator was diabetes duration: NDKD occurred predominantly in patients with short-duration diabetes (median 2 vs 12 years), consistent with the clinical intuition that early-onset renal disease in T2DM warrants suspicion of NDKD. Lower HbA1c, less advanced interstitial fibrosis, and low serum C3 (seen only in NDKD, in keeping with immune-complex or complement-mediated lesions) were additional pointers. Together these suggest that a biopsy-selection strategy combining short diabetes duration, absent retinopathy and low complement discriminates better than retinopathy status alone.

The NDKD spectrum — led by FSGS, then membranous and IgA nephropathy — is consistent with the pattern reported in Indian biopsy series, several of which are potentially treatable, reinforcing the value of biopsy in appropriately selected diabetic patients.

These findings sit comfortably within the wider literature. In the meta-analysis by He et al., diabetic retinopathy predicted diabetic nephropathy with moderate sensitivity and specificity, mirroring the strong rule-in but weak rule-out behaviour seen here. The observed NDKD prevalence of 26.7% is consistent with the single-centre Indian experience of Das et al. and with the more recent series of Prasad et al., in which NDKD accounted for a comparable share of biopsied T2DM patients and short diabetes duration and absent retinopathy were similarly discriminating.

Limitations

The single-centre design and modest sample (n = 60, with only 16 NDKD) limit the precision of the accuracy estimates - reflected in wide confidence intervals, particularly for LR+ - and preclude robust multivariable modelling. Selection is conditioned on the decision to biopsy (spectrum/verification bias), and retinopathy was recorded as a binary without grading. Point estimates should therefore be read alongside their confidence intervals.

Declaration by Authors
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