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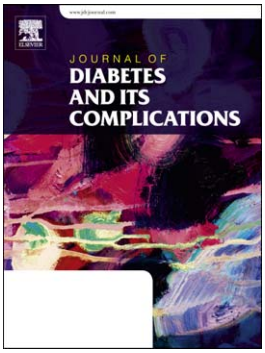

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Predicting non-diabetic renal disease in type 2 diabetic adults: The value of glycated haemoglobin

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Running Head: Predictors of renal disease in type 2 diabetes mellitus

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Structured Abstract

Aims: The indications for renal biopsy in type 2 diabetes mellitus (T2D) are not well established. We investigated the prevalence, spectrum, and predictors of biopsy-proven non-diabetic renal disease (NDRD) in T2D.

Methods: An observational, single-centre, retrospective study of T2D adults who underwent renal biopsies (*N*=51) over 10 years for nephrotic-range proteinuria, microscopic haematuria, or rapidly declining renal function.

Results: Thirty-five (68.6%) biopsies were diagnostic of NDRD, and 16 (31.4%) revealed isolated diabetic nephropathy. The most common NDRDs were interstitial nephritis (20%), progressive crescentic glomerulonephritis (14%), membranous nephropathy (11%), and focal segmental glomerulosclerosis (11%). The odds for NDRD declined by 97% in the presence of diabetic retinopathy (*P*<0.001). The deterioration of HbA1c during the year before biopsy predicted NDRD even after adjusting for diabetic retinopathy (OR, 7.65; 95% CI, 1.36-123.04; *P*=0.003). A model based on the interaction between the HbA1c values 12 months before biopsy and the absolute change in these values during the preceding year predicted NDRD with 73.7% sensitivity and 75% specificity (AUC, 0.77; 95% CI, 0.59-0.94).

Conclusions: This study demonstrated a considerably high prevalence of NDRD in T2D adults undergoing renal biopsy. The absence of diabetic retinopathy, lower HbA1c values 12 months before biopsy and greater deterioration in HbA1c prior to biopsy predicted NDRD in T2D. Further studies are needed to validate the findings.

Keywords: Glycated haemoglobin; Renal biopsy; Renal disease; Type 2 diabetes mellitus.

1. Introduction

Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus associated with end-stage renal disease requiring renal replacement therapy. A major contributor to development and progression of DN is glycaemic control as shown by major diabetes studies[1,2]. Other modifiable factors for DN include hypertension, obesity, smoking, and dyslipidaemia[3]. There is encouraging evidence suggesting that timely and long-term tight glycaemic control effectively delays the onset and slows the progression of DN in both type 1 and type 2 diabetes[4,5].

The diagnosis of DN is usually made through biochemical analyses of urine and blood. An early manifestation is persistent microalbuminuria. Estimated glomerular filtration rate (eGFR) declines prior to more severe macroalbuminuria in type 2 diabetes (T2D); hence a combination of eGFR and albuminuria can be used to stage and monitor patients[6,7]. While diabetes is the major cause of renal disease in patients with diabetes, in about a third of patients, renal dysfunction is due to other causes (non-diabetic renal disease; NDRD)[8-17]. In the NDRD group, the treatment of renal disease may require a different strategy. A renal biopsy is helpful in determining the underlying pathophysiology in NDRD.

The selection criteria for renal biopsy in diabetic patients are not well established. In type 1 diabetes, the presence of proteinuria with short diabetes duration and/or rapidly declining renal function, especially in the absence of diabetic retinopathy, have been suggested as a signal for the need for renal biopsy[18]. In T2D, the

criteria are less clear since dysglycaemia is present for many years prior to diagnosis. Commonly, proteinuria > 1 g/24 hours, renal involvement without diabetic retinopathy, or unexplained haematuria have been used as indicators for renal biopsy[19]. Identification of novel predictors of renal disease will improve the current selection criteria for renal biopsy and facilitate early detection of NDRD in T2D. Early diagnosis and appropriate treatment may help slow progression to end stage renal disease. In this study, we sought to investigate the prevalence, spectrum, and predictors of biopsy-proven NDRD in adults with T2D.

2. Subjects, Material and Methods

This was a retrospective observational study of T2D patients who underwent renal biopsies over 10 years in our centre. As this was an audit of retrospective data, the local research ethics committee felt that no formal ethics approval was required.

Fifty-one native renal biopsies obtained from 51 adults with a documented diagnosis of T2D, referred to our centre between 2002 and 2012, were analysed. In our centre, as a policy, DN is diagnosed on clinical grounds and kidney biopsies are only carried out if there are atypical clinical features. Indications for biopsy, in this cohort, included nephrotic range proteinuria (> 3 g/24 hours), significant microscopic haematuria (≥ ++), or rapidly declining renal function. Renal biopsy specimens were examined by light microscopy, direct immunofluorescence, and electron microscopy, where indicated.

The biopsy report, biochemical results, and clinical information at the time of renal biopsy and follow-up were studied. Glomerular filtration rate estimates were calculated using the 4-variable Modification of Diet in Renal Disease Study equation[20]. Glycaemic control was assessed by glycated haemoglobin (HbA1c) levels, measured using National Glycohemoglobin Standardization Program (NGSP) certified method, standardized to the Diabetes Control and Complications Trial assay. HbA1c values are reported in both NGSP percentage units with International Federation of Clinical Chemistry (IFCC) units (mmol/mol) in parentheses.

The primary outcome measure was the prevalence and nature of histologically-proven NDRD. The secondary outcome measures included predictors of NDRD vs. DN and the risk factors for adverse renal outcome. Adverse renal outcomes included reaching end stage renal disease requiring renal replacement therapy or chronic kidney disease (CKD) leading to death, or a composite of the two.

2.1 Statistical Analyses

The Shapiro–Wilk test was applied to assess normality of data distribution. Continuous variables with normal distribution are presented as means ± standard deviation (SD) and compared using the Student's t test. Continuous variables with non-normal distribution are presented as medians and interquartile ranges (IQR) and compared using the Wilcoxon rank-sum test or the Wilcoxon-matched pairs signed-ranks test. The chi-square test was applied to examine patterns between

categorical variables. Univariate and multivariate standard and exact logistic regression modelling were employed to identify the association between biopsy-proven NDRD and potential predictors. The logistic regression models were fitted using a stepwise bidirectional elimination algorithm, with inclusion and exclusion criteria of $P \leq 0.15$ and $P \geq 0.2$ respectively.

The number in whom complete data was available is mentioned in the text. Absolute changes (Δ) in eGFR and in HbA1c were calculated by subtracting values 12 months before biopsy from those at the time of biopsy. The follow-up ΔeGFR were calculated by subtracting the eGFR values at the time of biopsy from the values 12 months after.

Findings were considered to be statistically significant at the 5% level. Statistical calculations were performed using Stata 11.2 Special Edition (StataCorp LP, College Station, TX).

3. Results

3.1 Sample Characteristics and Renal Biopsy Findings

The entire cohort of renal biopsy patients (*N*=51) was predominantly male (64.7%), of mixed ethnicity (28 White Europeans, 18 South-Asians, 3 African Caribbeans, 2 with “not stated” ethnicity), aged 61 ± 12 years (mean ± SD). The median (IQR) duration of T2D was 9 (2-15) years (*N*=45). At the time of renal biopsy, the NGSP HbA1c was 7.2 (6.4-7.8) %, the IFCC HbA1c 55 (46-62) mmol/mol (*N*=42). Twenty-

two of 39 (56.4%) patients had diabetic retinopathy. The median (IQR) eGFR was 23.5 (11-39.5) ml/min/1.73m^2, and 60.4% of patients had stage 4–5 CKD. Twenty-one of 36 (58.3%) proteinuric patients had nephrotic range proteinuria (albumin/creatinine ratio > 250 mg/mmol or protein/creatinine ratio > 300 mg/mmol), and 16 of 35 (45.7%) had microscopic haematuria. Thirty-four of 46 (73.9%) patients were on renin-angiotensin-aldosterone system (RAAS) blockade therapy.

Thirty-five (68.6%) biopsies were diagnostic of NDRD, 16 (31.4%) revealed isolated DN, and 4 (7.8%) showed NDRD superimposed on DN. The spectrum of NDRD was as follows: interstitial nephritis 7 (20%), progressive crescentic glomerulonephritis 5 (14.3%), membranous nephropathy 4 (11.4%), focal segmental glomerulosclerosis 4 (11.4%), acute tubular necrosis 3 (8.6%)**,** immunoglobulin A nephropathy 2 (5.7%), ischaemic nephropathy 2 (5.7%), minimal change nephropathy 1 (2.9%), minimal change nephropathy + interstitial nephritis 1 (2.9%), mesangiocapillary glomerulonephritis 1 (2.9%), amyloidosis 1 (2.9%), oxalate nephropathy 1 (2.9%), myeloma cast nephropathy 1 (2.9%), fibrillary glomerulonephritis 1 (2.9%), and collagenofibrotic glomerulopathy 1 (2.9%). In more than 50% of NDRD, histology prompted alteration in therapeutic management.

Table 1 shows characteristics of the two subgroups based on renal biopsy findings. The patients with NDRD had better glycaemic control 12 months before biopsy (*N*=32), a smaller decrease in HbA1c during the year before biopsy (*N*=31; Figure

1A, Figure 1B), and a lower rate of diabetic retinopathy than those with isolated DN. There was a trend towards more South-Asians in the DN subgroup. We did not find any difference in eGFR prior to biopsy, at the time of biopsy, and 12 months after biopsy between the two subgroups. Following the therapeutic adjustments based on renal biopsy findings, the patients with NDRD had significantly greater improvement in eGFR 12 months after biopsy (*N*=38) than patients with isolated DN (Table 1). Similar numbers received RAAS blockade therapy in the two subgroups. There were no differences in duration of T2D (*N*=45) and in pharmacological treatment of diabetes (*N*=47; Table 1).

By the end of 2012, overall mortality was 29.4% with no difference between the subgroups. There was no difference in number of patients requiring renal replacement therapy. However, a composite adverse renal outcome (reaching end stage renal disease requiring renal replacement therapy + CKD leading to death; *N*=48) was higher in isolated DN subgroup (Table 1).

3.2 Predictors of Renal Disease and Risk Factors for Adverse Renal Outcomes

Table 2 presents the results of a univariate exact logistic regression analysis for unadjusted (crude) associations between NDRD and independent variables with odds ratios (OR), 95% confidence intervals (95% CI), and *P*-values. For subjects with diabetic retinopathy, the expected log odds of having NDRD decreased by 3.39, and the odds for NDRD declined by 97% ($P<0.001$). The unadjusted OR of the association between NDRD and HbA1c 12 months before biopsy was 0.60; for

every 1% (10.9 mmol/mol) increase in the HbA1c 12 months before biopsy, the odds for NDRD declined by 40% (*P*=0.018). There was a trend towards higher odds for NDRD with deterioration of HbA1c during the year before biopsy (*P*=0.054). We also observed a trend towards higher odds for NDRD with the increasing INTHbA1c (a variable consistent with the interaction between HbA1c 12 months before biopsy and ΔHbA1c during the year before biopsy); *P*=0.069.

The association between NDRD and deterioration of HbA1c during the year before biopsy remained significant even after adjusting for diabetic retinopathy in the final multivariate regression model (OR 7.65; 95% CI, 1.36 to 123.04; *P*=0.003). Our results further showed a statistically significant joint distribution of diabetic retinopathy and INTHbA1c. After adjusting for the diabetic retinopathy, the expected odds for NDRD increased by 1.28 for every one unit (1%) increase in INTHbA1c (OR 1.28; 95% CI, 1.03 to 1.82; *P*=0.013).

Figure 2 shows estimated predicted probabilities of having NDRD, by the HbA1c 12 months before biopsy, ranging from an approximately 85% probability of having NDRD in patients with a relatively low preceding HbA1c to a < 50% probability in patients with HbA1c of > 8.5% (69 mmol/mol). Of importance, the patients who experienced deterioration in HbA1c during the year prior to biopsy had at least 63% probability of having NDRD (Figure 2, plus symbols). The HbA1c 12 months before biopsy in these patients was < 8% (64 mmol/mol).

To further define the importance of HbA1c in predicting the NDRD, we performed receiver operating characteristic (ROC) curve analysis of three HbA1c-based

predictive models for NDRD (Figure 3). In the first model, the HbA1c 12 months before biopsy was used. The cut point of the HbA1c 12 months before biopsy of ≥ 6.2% (44 mmol/mol) was the best predictor of NDRD with 100% sensitivity. However, the 17% specificity reflected high rate (83%) of false positives (area under the curve AUC, 0.29; 95% CI, 0.07 to 0.51). In the second model, we measured predictive accuracy of the ΔHbA1c during the year prior to biopsy. The ΔHbA1c during the year prior to biopsy of ≥ -0.4% (-4.4 mmol/mol) was the best predictor of NDRD (73.7% sensitivity, 66.7% specificity; AUC, 0.75; 95% CI, 0.56 to 0.93). Since the preceding HbA1c and the ΔHbA1c during the year before biopsy are closely interrelated, the third predictive ROC curve model included an interaction term between the two aforementioned predictors (INTHbA1c; INTHbA1c = HbA1c 12 months before biopsy * ΔHbA1c during the year before biopsy). The ROC curve analysis showed that the INTHbA1c cut-off of ≥ -2.48% (-27.1 mmol/mol) was the best predictor of NDRD with 73.7% sensitivity and 75% specificity (AUC, 0.77; 95% CI, 0.59 to 0.94; Figure 3).

4. Discussion

There were three major findings in the present study First, renal biopsies with histological confirmation of renal involvement revealed a considerably high prevalence of NDRD in a cohort of T2D patients with significant dipstick haematuria, nephrotic range proteinuria, and/or rapidly declining renal function. Second, this study confirmed the previously recognized associations between poor

long-term glucose control and presence of diabetic retinopathy and DN in T2D[2]. Third, besides the previously identified predictors of NDRD that include new onset nephrotic range proteinuria, shorter duration of diabetes, and the absence of diabetic retinopathy[21-23], this is the first study to demonstrate that in T2D, the HbA1c 12 months before biopsy and the absolute change in HbA1c during the year before biopsy predict the type of renal disease. This study also shows that those with biopsy-proven NDRD have a better composite outcome of end stage renal disease and death.

Our finding of high prevalence of NDRD in T2D is consistent with observations made by others[8-17]. These studies showed a variable prevalence of NDRD of 18-78%. This is attributed to selection criteria for renal biopsy and to the geographical and ethnic differences in the incidence of various NDRD. The finding of high prevalence of NDRD in this cohort of T2D patients with renal impairment and atypical features has important clinical implications; at least 50% of patients had NDRD that was treatable with steroids and immunosuppressive agents. The therapeutic adjustments based on histology and resultant modification of course of NDRD may explain the improvement in eGFR and the better composite adverse renal outcome in the NDRD subgroup. By contrast, there is no specific treatment for isolated DN[3,6,7]. Early and accurate diagnosis of NDRD is important for diabetic patients since treatment and prognosis may vary according to the underlying cause.

Several recent cross-sectional and longitudinal studies have reported associations between HbA1c and kidney function in T2D with mixed results[24-29]. Lee and colleagues[24] demonstrated a negative effect of preceding HbA1c (recorded 1 year before) on eGFR in T2D patients with CKD stages 3 and 4. In our study, a trend towards the positive association between the HbA1c 12 months before biopsy and eGFR was observed in the subgroup with isolated DN (r=0.56; *P*=0.058; *N*=12). There was no association between the preceding HbA1c and eGFR even after the patients were grouped according to CKD stages. Of importance, our results show that both the HbA1c 12 months before biopsy and the absolute change in HbA1c during the year before biopsy differ between patients with isolated DN and NDRD with similarly decreased eGFR at the time of renal biopsy. Our study is consistent with previous observations that annual variation in HbA1c could predict DN in patients with T2D and that long-term variability of HbA1c predicts microalbuminuria[26,27] and development/progression of renal and cardiovascular complications of T2D[28,29].

The ROC curve analysis of the three proposed HbA1c-based predictive models showed that although both the HbA1c 12 months before biopsy and its change during the year before biopsy predicted type of renal disease, the model based on the interaction between the two variables (INTHbA1c) had the best predictive accuracy for NDRD. Since different predictors may be sensitive to different aspects of renal diseases, this “new” predictor may improve the overall predictive capability of the HbA1c-based models.

In the present study, the patients histologically diagnosed with NDRD had fairly good long-term diabetes control 12 months prior to biopsy. Our findings indicate that the HbA1c either remains stable or gradually deteriorates in patients with NDRD despite the decline in renal function during the year prior to renal biopsy. This observation may be explained by the adverse impact of inflammatory and immune responses to progressive NDRD on glucose control. Both acute and chronic inflammation leads to stress hyperglycaemia, consistent with a maladaptive and detrimental response to stress and inflammation[30]. Furthermore, in patients with isolated DN, the elevated preceding HbA1c levels improved significantly during the year before renal biopsy. Decreased renal degradation of insulin typically ensues later in the course of CKD[31], which could account for the "improved" glucose control prior to biopsy in patients with isolated DN.

There are several limitations to our study that should be considered in relation to the findings. The relatively small sample size and retrospective nature precluded examination of influence of ethnicity, arterial hypertension, anaemia, smoking, and others. Data on some clinical variables and characteristics were not available for some patients and thus could not be included in our analyses. The exact stages of diabetic retinopathy could not be established in each case to further correlate with the type of renal disease. A final limitation concerns the applicability of the results to practical decision making in the general diabetic population, as only T2D adults with suspicion of underlying NDRD were enrolled.

Despite these limitations, our study demonstrates a considerably high prevalence of histologically-proven NDRD in T2D adults undergoing renal biopsy. It also shows the HbA1c levels during the year before renal biopsy differ between NDRD and isolated DN. Besides the predictive value of diabetic retinopathy, we have identified the HbA1c 12 months before biopsy and ΔHbA1c as important novel candidate predictors of NDRD and DN in T2D. While HbA1c remains the best long-term marker of glycaemic control in patients with T2D, our findings suggest that annual evaluation of HbA1c and its dynamic changes along with the assessment of diabetic retinopathy could facilitate early detection of NDRD in T2D. Clinical significance of this finding is emphasized by the fact that the selection criteria for renal biopsy in T2D adults are still not well established and novel predictors of renal disease are critically needed. Prospective studies are needed to validate the proposed HbA1c-based predictive models for NDRD with a view to refining the current selection criteria for renal biopsy in T2D patients, and identify patients that will benefit from specific therapeutic interventions that will reduce adverse renal outcomes.

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Tables

Table 1: Characteristics of patients (*N*=51) according to renal biopsy findings

Variable	Patients with NDRD (*N*=35)	Patients with isolated DN (*N*=16)	*P*
Age (years)	63 ± 11	58 ± 14	0.167
Sex - females (%)	40	25	0.298
South-Asian ethnicity (%)	30.3	61.5	0.051
Duration of diabetes (years)	7.5 (1-13)	9 (4-19)	0.433
Diabetes treatment - diet only (%)	9.4	6.7	0.757
Diabetes treatment - OHA/GLP-1 agonists (%)	53.1	66.7	0.382
Diabetes treatment - insulin/insulin + OHA (%)	37.5	26.7	0.465
HbA1c at the time of biopsy			
- NGSP HbA1c (%)	7.2 ± 0.88	7.7± 1.76	
- IFCC HbA1c (mmol/mol)	55 ± 9.6	61 ± 19.2	0.188
HbA1c 6 months before biopsy			
- NGSP HbA1c (%)	7.4 (6.3-8.0)	8.9 (6.6-12.2)	
- IFCC HbA1c (mmol/mol)	57 (45-64)	74 (48-110)	0.288
HbA1c 12 months before biopsy			
- NGSP HbA1c (%)	6.9 (6.5-8.0)	9 (7.2-10.6)	
- IFCC HbA1c (mmol/mol)	52 (48-64)	75 (55-92)	0.047
ΔHbA1c during the year before biopsy			
- NGSP HbA1c (%)	-0.1 (-0.5; +0.3)	-0.9 (-1.75; -0.3)	
- IFCC HbA1c (mmol/mol)	-1.1 (-5.5; +3.3)	-9.8 (-19.1; -3.3)	0.023
Diabetic retinopathy (%)	34.6	100	<0.001
eGFR 12 months before biopsy (ml/min/1.73m^2)	58 (40-77)	55 (46-63)	0.648
eGFR 6 months before biopsy (ml/min/1.73m^2)	45 (39-81)	41 (28-56)	0.244
eGFR at the time of biopsy (ml/min/1.73m^2)	16 (10-36)	29 (17-49)	0.158
eGFR 6 months after biopsy (ml/min/1.73m^2)	33 (17-47.5)	28.5 (18-36)	0.550
eGFR 12 months after biopsy (ml/min/1.73m^2)	37.8 ± 22	32.1 ± 24.4	0.318
ΔeGFR during the year before biopsy (ml/min/1.73m^2)	-31.3 ± 25.8	-21.1 ± 16	0.233
ΔeGFR 12 months after biopsy (ml/min/1.73m^2)	6.8 ± 17.4	-7.1 ± 16.4	0.015
Urine PCR at the time of biopsy (mg/mmol)	367 (265-1015)	441 (130.5-871)	0.685
RAAS blockade therapy at the time of biopsy (%)	74.2	73.3	0.950
Adverse renal outcome (%)	34.4	68.8	0.024
-- Renal replacement therapy after biopsy (%)	18.2	25	0.579
-- Mortality (%)	22.9	43.8	0.129
- the time until death (months)	29 ± 22.9	24 ± 27.4	0.738

Continuous variables with normal distribution are presented as means ± SD. Continuous variables with non-normal distributions are presented as medians (IQR). *DN,* diabetic nephropathy; *eGFR,* glomerular filtration rate estimates; *ΔeGFR*, an absolute change in eGFR; *GLP-1*, glucagon-like peptide-1; *HbA1c,* glycated haemoglobin; *ΔHbA1c,* an absolute change in HbA1c; *IFCC,* International Federation of Clinical Chemistry; *NDRD,* non-diabetic renal disease; *NGSP*, National Glycohemoglobin Standardization Program; *OHA,* oral hypoglycemic agents; *PCR,* Protein to Creatinine Ratio; *RAAS,* renin-angiotensin-aldosterone system.

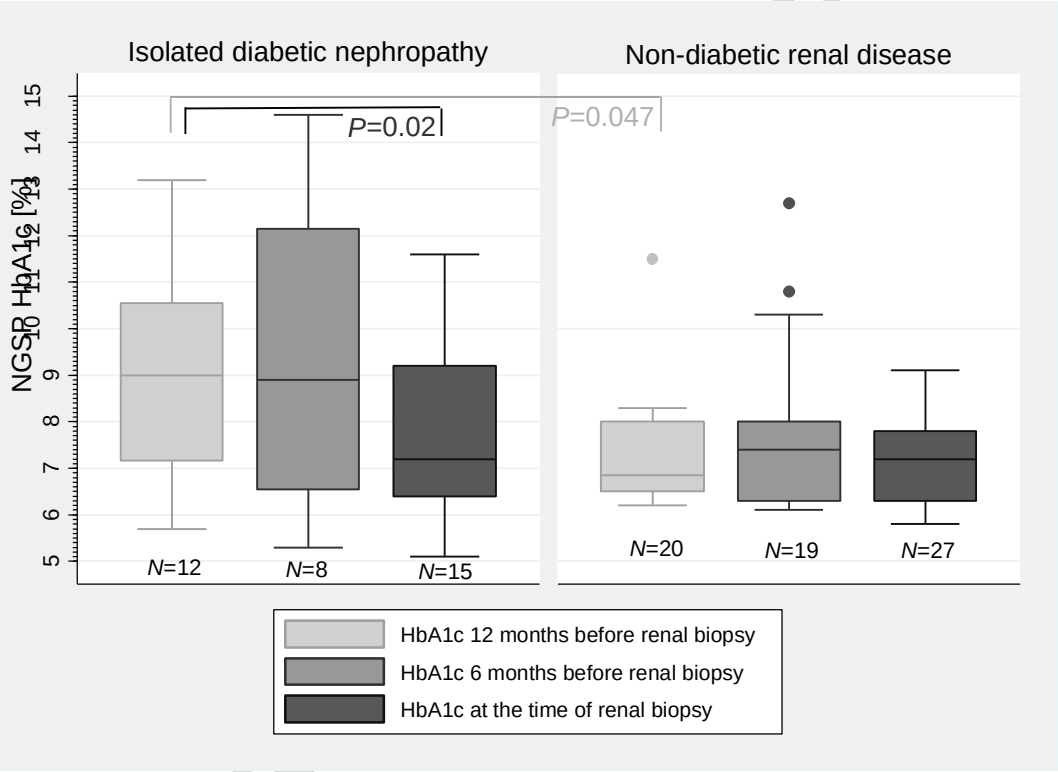
Table 2: Unadjusted (crude) associations between non-diabetic renal disease and independent variables

Variable	*P*-value	OR	95% CI
Age	0.171	1.04	0.99 to 1.09
Sex			
• female		1.00 (reference)	
• male	0.474	0.51	0.10 to 2.14
Ethnicity			
• White European		1.00 (reference)	
• South-Asian	0.107	0.28	0.06 to 1.25
Duration of diabetes	0.493	0.97	0.89 to 1.06
Diabetes treatment			
• diet only		1.00 (reference)	
• OHA/GLP-1 agonists	0.607	0.53	0.05 to 5.86
• insulin/insulin + OHA	0.950	1.08	0.09 to 13.54
HbA1c 12 months before biopsy	0.018	0.60	0.35 to 0.93
HbA1c at the time of biopsy	0.200	0.71	0.41 to 1.19
ΔHbA1c during the year before biopsy	0.054	1.89	0.99 to 4.46
INTHbA1c	0.069	1.06	1.00 to 1.14
Diabetic retinopathy	<0.001	0.03	0.00 to 0.24
eGFR 12 months before biopsy	0.401	1.02	0.98 to 1.06
eGFR at the time of biopsy	0.374	0.99	0.96 to 1.02
ΔeGFR during the year before biopsy	0.211	0.98	0.94 to 1.01
Microscopic hematuria	0.116	4.86	0.75 to 56.13
Nephrotic proteinuria	1.000	1.02	0.19 to 5.17
Urine PCR at the time of biopsy	0.384	1.00	1.0 to 1.0
RAAS blockade therapy at the time of biopsy	1.000	1.04	0.19 to 5.03

CI, confidence interval; *eGFR,* glomerular filtration rate estimates; *ΔeGFR*, an absolute change in eGFR; *GLP-1*, glucagon-like peptide-1; *HbA1c,* glycated haemoglobin; *ΔHbA1c,* an absolute change in HbA1c; *INTHbA1c*, a variable consistent with the interaction between HbA1c 12 months before biopsy and ΔHbA1c during the year before biopsy; *OHA,* oral hypoglycemic agents; *OR,* odds ratio; *PCR,* Protein to Creatinine Ratio; RAAS, renin-angiotensin-aldosterone system.

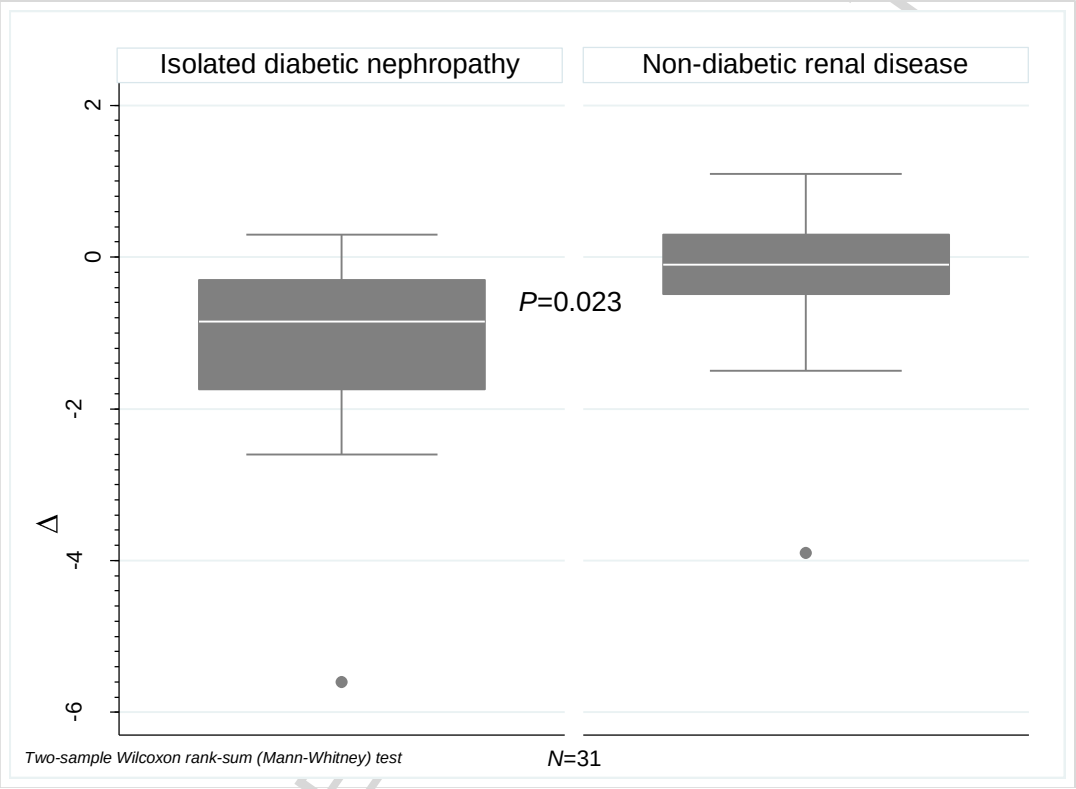
Figures

Figure 1A: Long-term glucose control in type 2 diabetic patients with isolated diabetic nephropathy vs. non-diabetic renal disease



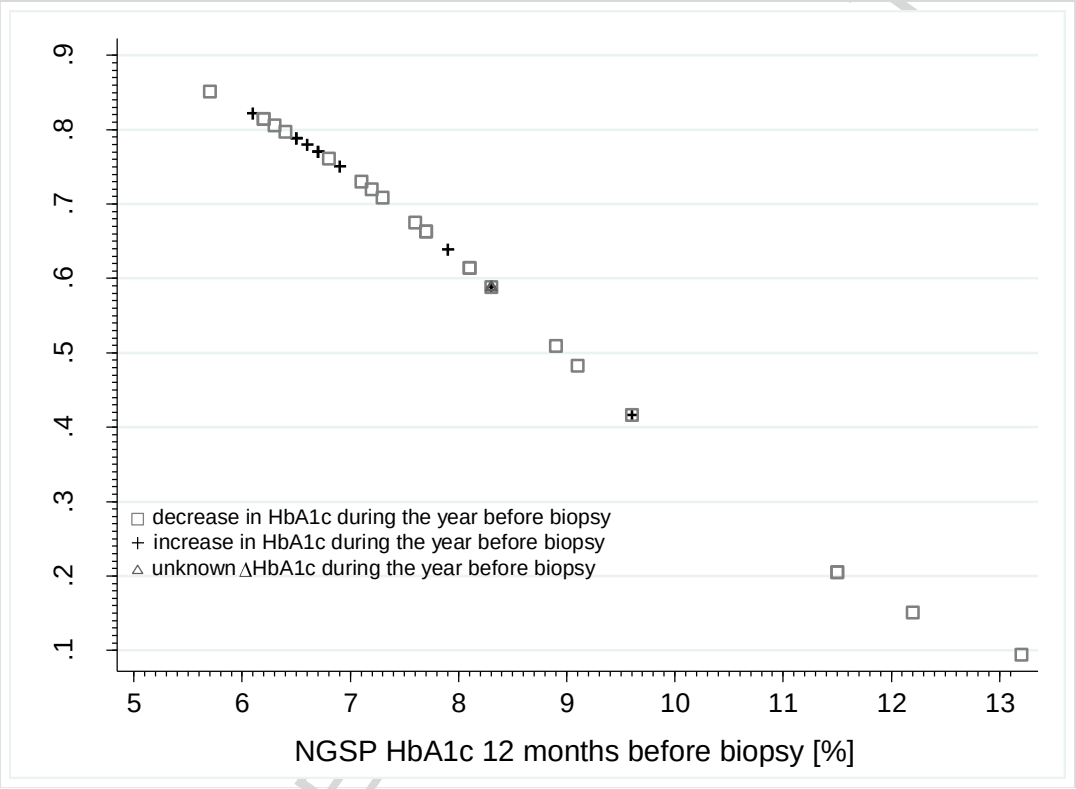
HbA1c, glycated haemoglobin; *NGSP*, National Glycohemoglobin Standardization Program.

Figure 1B: Changes in HbA1c during the year before renal biopsy in patients with isolated diabetic nephropathy vs. non-diabetic renal disease



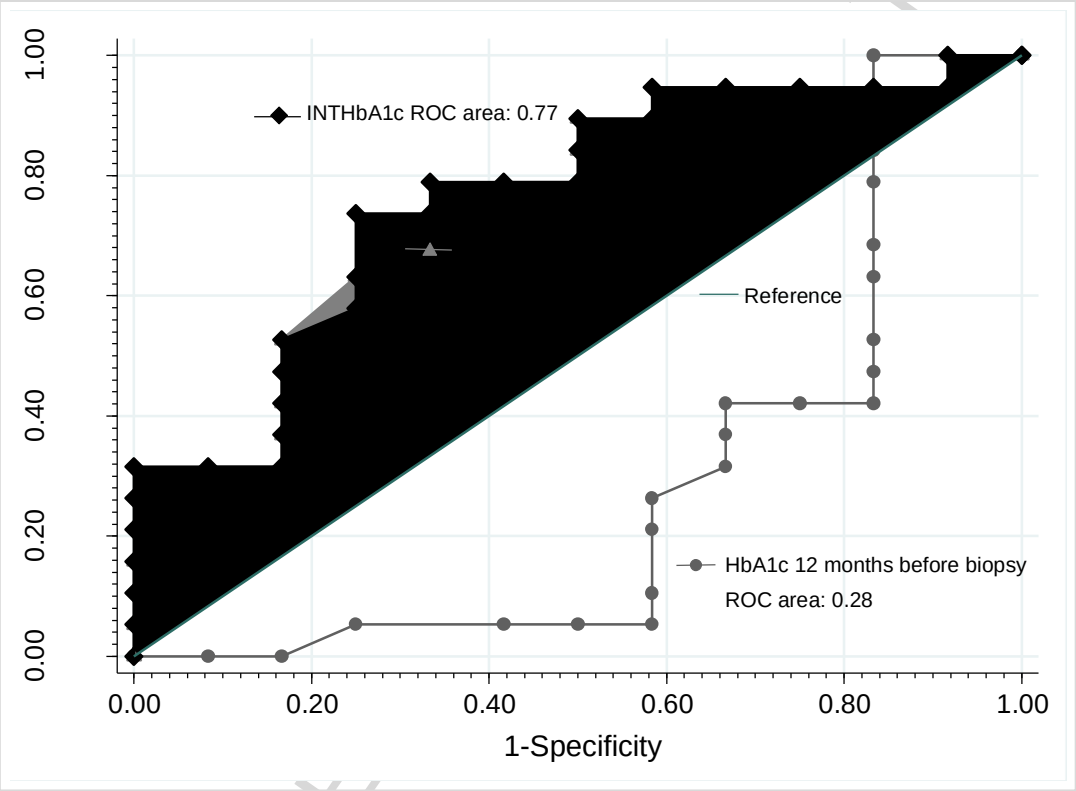
HbA1c, glycated haemoglobin; *ΔHbA1c,* an absolute change in HbA1c; *NGSP*, National Glycohemoglobin Standardization Program.

Figure 2: Predicted probabilities of having non-diabetic renal disease in type 2 diabetes, by the HbA1c 12 months before biopsy



HbA1c, glycated haemoglobin; *ΔHbA1c,* an absolute change in HbA1c; *NDRD,* non-diabetic renal disease; *NGSP*, National Glycohemoglobin Standardization Program.

Figure 3: ROC curve of the three HbA1c-based predictive models for non-diabetic renal disease



HbA1c, glycated haemoglobin; *ΔHbA1c,* an absolute change in HbA1c during the year prior to biopsy; *INTHbA1c*, an interaction term between the HbA1c 12 months before biopsy predictor and the ΔHbA1c during the year before biopsy predictor; *NDRD,* non-diabetic renal disease; *ROC,* receiver operating characteristic.