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ORIGINAL ARTICLE

Prevalence, Etiology and Clinical Characteristics of Biopsy Proven Non-Diabetic Renal Disease in a Population of 67 Diabetic Patients

Joana Monteiro Dias[1#*], Rita Valério Alves[2#], Mário Góis[3], Helena Viana[3] and Fernando Nolasco[3]

[1]*Serviço de Nefrologia e Transplantação Renal, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Portugal*

[2]*Serviço de Nefrologia, Hospital Rainha Santa Isabel, Portugal*

[3]*Laboratório de Morfologia Renal Prof. Adolfo Coelho, Serviço de Nefrologia, Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central, Portugal*

[#]*Equally contributing first authors.*

***Corresponding author:** *Joana Monteiro Dias, Serviço de Nefrologia e Transplantação Renal, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Avenida Professor Egas Moniz, 1649-035, Lisboa, Portugal, Tel: +351-217-805-317, Fax: +351-217-805-679*

Abstract

Background: Diabetic nephropathy (DN) has been historically the major cause of kidney disease in diabetic patients. However, recent studies have found a high proportion of diabetic patients with biopsy proven Non-diabetic renal disease (NDRD) or NDRD superimposed on DN. These findings have resurfaced the interest in establishing which of these patients may benefit most from a kidney biopsy. Our study aims to enlighten the prevalence and etiology of biopsy proven NDRD and to explore clinical and morphologic differences encountered in the diabetic patient with NDRD.

Methods: Medical records of all diabetic patients who underwent native kidney biopsy for suspected NDRD from January 2016 to December 2018 at Hospital Curry Cabral - Centro Hospitalar Universitário de Lisboa Central, EPE, were analysed retrospectively.

Results: We review medical records of 67 patients. All patients had a diabetes mellitus diagnosis at the time of biopsy and were biopsied for NDRD suspicion. In our population, 55.2% had DN (7.5% presented simultaneously DN and NDRD) and 41.8% had isolated NDRD. The most frequent causes of NDRD were IgA nephropathy (25%) and Chronic Interstitial Nephritis (10.8%). A shorter duration of diabetes had a statistically significant association with NDRD.

Conclusions: Nearly half diabetic patients proposed to kidney biopsy have a NDRD. Since kidney biopsy is essential to establish the diagnosis and subsequently provide adequate treatment, this resource should be used in the diabetic diabetic patient with NDRD suspicion, especially in those with a shorter duration of diabetes. Additional data is necessary to establish which patients should be proposed to earlier kidney biopsies.

Keywords

Non-diabetic renal disease, Type 2 diabetes mellitus, Kidney disease, Diabetic nephropathy

Introduction

Diabetic nephropathy (DN) is a notorious complication of diabetes mellitus and a frequent cause of kidney disease in diabetic patients, often resulting in end stage renal disease (ESRD). Significantly, DN remains the major cause of ESRD in most western countries [1-5].

Irrespective of DN frequency, it is nowadays well established that renal involvement in the diabetic patient may, alternatively, often be due to either non-diabetic renal disease (NDRD) or to both a NDRD superimposed on DN [6-9].

The atypical clinical features used to differentiate DN from NDRD are frequently unreliable in the evaluation of the individual patient [10,11]. Although kidney biopsy remains the gold standard for the diagnosis, indications for kidney biopsy in the diabetic patient remain debatable. As result, the prevalence

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of NDRD remains to some extent incompletely defined, also dependable on the wide variation of biopsy criteria [7,12-16].

Our study aims to enlighten the prevalence and etiology of biopsy proven NDRD and to explore clinical and morphologic differences encountered in the patient with type 2 Diabetes *Mellitus* (T2DM) and NDRD.

Methods

Medical records of all T2DM patients who underwent native kidney biopsy from January 2016 to December 2018 at Hospital Curry Cabral - Centro Hospitalar Universitário de Lisboa Central, EPE were analyzed retrospectively.

The data collected included baseline clinical characteristics at time of biopsy, namely age, gender, ethnicity, known duration of diabetes, presence of diabetic retinopathy, presence of comorbidities with possible correlations to kidney disease (hypertension, cardiovascular disease, chronic obstructive pulmonary disease, auto-immune disease, immunodeficiency virus, Hepatitis C virus, Hepatitis B virus, chronic liver disease, history of solid or hematologic neoplasia). Baseline laboratory findings recorded included 24-hour urine collection of protein (mg/24 h) or urinary protein to creatinine ratio, serum creatinine levels (g/dl), serum albumin levels (g/dL), immunological marker levels whenever present, including anti-nuclear antibodies (ANA), Anti-neutrophil cytoplasmic antibodies (ANCA) and cryoglobulins. Kidney anatomic characteristics, evaluated trough ultrasound, were also verified.

All biopsies were evaluated using standards for kidney biopsy, namely hematoxylin and eosin, periodic acid-Schiff and silver stains for light microscopy, and immunofluorescence staining using antibodies anti-IgA, IgG, IgM, C3, C1q, and kappa and lambda light chains. Kidney biopsy data regarding the diagnosis, characteristics of the vessels, interstitial fibrosis and infiltrate where gathered, and the lesions were grouped into absent or present. Classification as Diabetic Nephropathy was based in the Pathologic Classification of Diabetic Nephropathy published by Tervaert in 2010 [17].

Statistical analysis was performed using SPSS version 23.0 (Chicago, USA) for Mac OS X. Continuous variables were presented as mean and standard deviation, or median and interquartile range (IQR) for variables with skewed distributions and other nominal variables were presented as number (frequency) and percentage. Independent-sample t-tests were used to analyze the mean Diabetic Nephropathy and continuous variables (age and diabetes mellitus duration). Data are presented as a mean [95% confidence interval (CI)]. A Mann-Whitney test was also made to analyze the mean Diabetic Nephropathy and continuous variables with skewed distributions (serum creatinine levels, 24-hour proteinuria, serum albumin).

We used the chi-square test to analyze Diabetic Nephropathy versus the following dichotomous variables: diabetic retinopathy, gender, ethnicity, presence of hematuria, history of solid tumors, hepatic transplant, changes in kidney ultrasound, presence of fibrosis in renal biopsy, changes in vessels in renal biopsy or presence of hyalinosis in renal biopsy. Underlying assumptions were met, unless otherwise indicated. A p-value of < 0.05 was considered statistically significant.

One-way ANOVA was used to determine whether there were differences between the means of different diabetic nephropathy classes and age and duration of diabetes, a Games-Howell post hoc test was also performed.

Results

A total of 67 patients with T2DM underwent native kidney biopsy. All patients were biopsied for suspicion of NDRD. Indications for kidney biopsy were recent onset of nephrotic syndrome or nephrotic proteinuria - considered has 24-hour proteinuria or protein to creatinine ratio in the spot urine analysis equal or superior to 3.5 mg/dL, non-nephrotic proteinuria acute kidney injury, rapidly progressive renal failure, chronic kidney disease active sediment or presence of another suggestive systemic disease culprit. The more frequent indications for kidney biopsy in this cohort was Nephrotic proteinuria (n = 22; 37.3%). In 8 (11.9%) of kidney biopsies, indication for biopsy could not be retrieved from medical records. The distribution of the indications for kidney biopsy is presented in Table 1.

Our data showed that 49.3% (n = 33) of patients had either NDRD 41.8% (n = 28) or simultaneous DN and NDRD 7.5% (n = 5).

In our cohort, 74.6% (n = 50) were males, the mean age was 64.09 ± 10.09 years (range 41-84 years) and 85.1% (n = 57) were caucasian. The mean time since the diabetes mellitus diagnose was 12.29 ± 6.86 years

Table 1: Indications for kidney biopsy.

	Frequency	Percent
Nephrotic proteinuria	22	37.3%
Non-nephrotic proteinuria	9	15.3%
Chronic kidney disease	8	13.6%
Acute kidney injury	5	8.5%
Nephrotic Syndrome	5	8.5%
Systemic disease	5	8.5%
AKI rapidly progressive	4	6.8%
Asymptomatic urinary abnormalities	1	1.7%
TOTAL	59	100%

AKI: Acute kidney injury.

Table 2: Comorbidities.

	Total Population n = 67		DN n = 37		NDRD n = 28		p
	n	%	n	%	n	%	
Hypertension	61	91%	35	94.6%	24	85.7%	0.221
Liver transplant	9	13.4%	2	5.4%	7	25%	0.067
HCV	8	11.9%	3	8.1%	4	14.3%	0.426
Cardiovascular Disease	7	10.4%	3	8.1%	4	14.3%	0.426
Chronic Liver Disease	6	9%	3	8.1%	2	7.1%	0.885
Solid Tumors	6	9%	1	2.7%	5	17.9%	0.037
Autoimmune disease	4	6%	1	2.7%	3	10.7%	0.183
Hematologic Neoplasia	4	6%	2	5.4%	2	7.1%	0.773
COPD	3	4.5%	2	5.4%	1	3.6%	0.727
HIV	2	3%	1	2.7%	1	3.6%	0.841
HBV	1	1.5%	3	8.1%	2	7.1%	0.247

COPD: Chronic obstructive pulmonary disease; DN: Diabetic nephropathy; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; NDRD: Non-diabetic renal disease.

Table 3: Laboratory findings.

	Total Population n = 67		DN n = 37		NDRD n = 28	
	Median	IQR	Median	IQR	Median	IQR
24-h Proteinuria (mg/24 h)	3200	[1100;5300]	3000	[1250;6000]	3600	[925;5000]
Serum Albumin (g/dL)	3.7	[3;4]	3.6	[2.9;4]	3.8	[3.18;4.09]
Serum Creatinine (mg/dL)	2.39	[1.56;3.5]	2.39	[1.58;3.5]	2.35	[1.43;3.95]
	n	%	N	%	n	%
ANA	2	3%	2	5.4%	0	0%
ANCA	2	3%	1	2.7%	1	3.6%
Cryoglobulins	1	1.5%	0	0%	0	0%
Hematuria	15	22.4%	3	8.1%	12	42.9%

ANA: Anti-nuclear antibodies; ANCA: Anti-neutrophil cytoplasmic *antibodies; IQR: Inter-quartile range.*

(range 3-32 years) and 28.4% (n = 19) of our patients had diabetic retinopathy. Regarding additional comorbidities, detailed in Table 2, 91% (n = 61) were hypertense and 10.4% had cardiovascular disease.

The patients presented with a median creatinine of 2.39 mg/dL, a median 24-hours proteinuria of 3200 mg/24 h, median albuminemia of 3.7 g/dL and 28.4% (n = 19) with hematuria. All the laboratory findings are presented in Table 3.

Kidney ultrasound was reviewed in 66 patients. Among these, 22.7% (n = 15) presented ultrasound changes: 26.7% (n = 4) with enlarged kidneys, 26.7% (n = 4) with bosselated kidneys, 20% (n = 3) with kidney asymmetry, 13.3% (n = 2) with small kidneys and 13.3% (n = 2) with undifferentiated kidneys.

The most common histological lesion in our cohort was Diabetic Nephropathy (n = 37; 55.2%) although 5 of these patients presented both DN and superimposed NDRD. Twenty-eight (41.8%) patients presented solely NDRD and two (3%) patients had biopsies with an inadequate/insufficient sample. In patients with isolated NDRD, the most common histological lesion was IgA Nephropathy (n = 7, 25%) and in patients with both NDRD and DN the most common histological lesion was Nephroangiosclerosis (n = 2, 40%). The histological lesions observed are summarized in Table 4 and Table 5.

We compared patients with DN or DN plus NDRD to the patients with solely NDRD. We found that the relation between DN and Diabetic Retinopathy was significant ($X^2 = 9.012$, $p = 0.003$), as the relation between DN and absence of Hematuria ($X^2 = 9.698$, $p = 0.002$), presence of fibrosis in histological findings ($X^2 = 5.119$, $p = 0.041$), presence of vascular changes in kidney biopsy ($X^2 = 12.633$, $p < 0.001$) and presence of vascular hyalinosis ($X^2 = 32.485$, $p < 0.001$).

No significant between-group differences (DN or DN plus NDRD vs. solely NDRD) were observed with respect to seric creatinine ($U = 493$; $p = 0.74$), albuminemia ($U = 329$; $p = 0.278$) and proteinuria ($U = 483$; $p = 0.643$).

Table 4: Histological diagnosis.

		Partial	Total
	N	**%**	**%**
	67	**100%**	**100%**
Diabetic Nephropathy	**37**	**100%**	**55.2%**
I	1	2.7%	1.5%
IIa	5	13.5%	7.5%
IIb	13	35.2%	19.4%
III	10	27%	14.9%
IV	8	21.6%	11.9%
NDRD	**28**	**100%**	**41.8%**
IgA Nephropathy	7	25%	10.4%
Chronic Interstitial Nephritis	3	10.7%	4.5%
Amyloidosis AA	2	7.1%	3%
Chronic Glomerulonephritis	2	7.1%	3%
FSGS	2	7.1%	3%
Interstitial Nephritis	2	7.1%	3%
Membranous Nephropathy	2	7.1%	3%
I	1	3.55%	1.5%
III	1	3.55%	1.5%
Proliferative endocapillary GN	2	7.1%	3%
Amyloidosis AL	1	3.6%	1.5%
Drug-induced Nephropathy	1	3.6%	1.5%
Fibrillary GN	1	3.6%	1.5%
Glomerular hypertrophy in relation with Metabolic Syndrome	1	3.6%	1.5%
Hypertensive nephrosclerosis	1	3.6%	1.5%
Unclassified Chronic Nephropathy	1	3.6%	1.5%
Inadequate/Insufficient sample	**2**		**3%**

FSGS: Focal segmental glomerular sclerosis; GN: Glomerulonephritis; Ig: Immunoglobulin; NDRD: Non-diabetic renal disease.

Note: Patients with simultaneous ND and NDRD were considered as part of the DN group.

Table 5: Histological diagnosis NDRD superimposed on ND.

NDRD superimposed on DN	N = 5	100%
FSGS	1	20%
Drug-induced Nephropathy	1	20%
Hypertensive nephrosclerosis	2	40%
Tubular necrosis	1	20%

DN: Diabetic nephropathy; FSGS: Focal segmental glomerular sclerosis; NDRD: Non-diabetic renal disease.

Our study showed that NDRD patients had statistically significantly less years of diabetes duration (10.07 ± 6.33 years) compared with biopsy proven DN patients (14.06 ± 6.83 years), t (59) = -2.94, p = 0.02.

There was statistically significant difference between different diabetic nephropathy classes as determined by one-way ANOVA (p = 0.002). A Games-Howell post hoc test revealed that the duration of diabetes was statistically significantly lower in class 2a (8.8 2.17 years) compared with class 2b (18.75 ± 6.52 years, p = 0.002) and duration of diabetes in class 2b (18.75 ± 6.52 years) was significantly higher compared with class 4 (10 ± 4.14 years, p = 0.009). There was no significant difference between the other classes.

Discussion

Since DN has been historically the most important kidney disease in diabetic patients, most renal abnormalities are primarily attributed to DN, frequently without further investigation of other possible causes. The pursuit of an alternative diagnosis is further discouraged by the high frequency of other comorbidities with a known association to kidney disease -as hypertension and cardiovascular disease- since a histologic differentiation of these entities would be of unlikely clinical significance.

Additionally, kidney biopsy remains the only reliable test to differentiate NDRD from DN but it can be considered invasive and bothersome, which may seem to supplant the eventual benefits of a formal diagnosis in many patients with a stable or slowly declining kidney function. Attending to these, it is possible that NDRD is still underestimate and underdiagnosed in the diabetic population, leading to delays or to overall non-implementation of the appropriate treatment.

Our data showed that 49.3% (n = 33) of patients had either NDRD 41.8% (n = 28) or simultaneous DN and NDRD 7.5% (n = 5). In our population, the most frequent cause of NDRD was IgA nephropathy (25%, n = 7), followed by chronic interstitial nephritis (10.7%, n = 3), although several diagnosis were encountered, namely membranous nephropathy, Focal Segmental Glomerular Sclerosis (FSGS), AA and AL amyloidosis or Fibrillary Glomerulonephritis. The high frequency of NDRD in biopsied diabetic patients was, for comparison, similarly high in previous studies although the prevalence of isolated NDRD vs superimposed NDRD and the main causes in each tend to differ [12,13,18].

Our data showed a statistically significant difference in the duration of DM in NDRD patients to DN patient, with a significant shorter course of disease in the previous group (10.07 vs. 14.06 years). This difference, also previously encountered in other studies [12], may suggest that shorter known durations of diabetes at the onset of kidney disease, namely those equal or below 10 years, may herald a valuable clinical clue for the suspicion of NDRD.

In our cohort, there was a statistically significant association of fibrosis, vascular changes and hyalinosis to DN, reinforcing the relation of diabetes mellitus to vasculopathy. There was an statistically significant association from absence of hematuria and DN. Additionally, and irrespective of the high frequency of hypertension in this cohort, hypertensive nephroangiosclerosis was only found in three patients (one with NDRD and two with both DN and NDRD), underpinning the importance of questioning our clinical bias in the evaluation of diabetic patients with additional long-standing hypertension presenting with kidney disease.

There was also a statistically significantly relation of diabetes length to DN morphologic class, with a longer duration being associated to class 2b compared with class 2a and to class 4.

There are limitations to our paper, namely an important selection bias, since all biopsied patients had clinical suspicion of NDRD, which might result in an overestimation of NDRD prevalence in our cohort when compared to an unselected population of diabetic patients with kidney disease. Additionally, because of our center inherent characteristics, our cohort has a high percentage of patients (22.4%) submitted to an hepatic transplant or with hepatic chronic disease, leading to a lower mimicry of the characteristics of other diabetic patients population. Moreover, this aforementioned group of patients might represent an additional bias when interpreting the major causes of NDRD of our cohort, since the association of hepatic disease to IgA Nephropathy - the main diagnosis in our study NDRD group - is well known. Nevertheless, it is worth mention that IgA Nephropathy has consistently been reported as a main cause of NDRD in analogous studies [12,14,18].

Conclusion

Our data showed that almost half (41.8%) of diabetic patients who present for kidney biopsy for NDRD suspicion will have NDRD or both DN and NDRD. It suggests that clinical clues alone might be insufficient in the approach to the diabetic patient with kidney disease and may lead to NDRD underdiagnosis and undertreatment.

Although different results should be expected in an unselected population of diabetic patients with nephropathy, these results emphasize the importance of a kidney biopsy, in patients with a higher likelihood of NDRD, namely those with a shorter course of diabetes mellitus and those with no retinopathy.

Additional data to establish which patients should be proposed to earlier kidney biopsies are needed.

Conflict of Interest Statement

None declared.

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