Clinical and histopathological characteristics of diabetic patients with nephrotic proteinuria
A case series

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Abstract

Objective: to describe the clinical and histopathological characteristics of diabetic patients with nephrotic-range proteinuria.

Materials and methods: the kidney biopsies of diabetic patients with nephrotic proteinuria were reviewed. Descriptive analyses were performed along with a comparison of three groups according to the histopathological findings.

Results: the medical charts of 19 patients from 2018 through 2020 were collected, most of whom (94.7%) were diagnosed with type 2 diabetes mellitus (DM), with an average age of 58 years, and an average duration of DM of 9.9 years (SD: ±7.3). The findings from biopsies performed throughout the years prior to data collection showed that 26.3% had diabetic nephropathy as the only finding, 31.6% had a nephropathy other than diabetic nephropathy, and 42.1% had findings of both diabetic and nondiabetic nephropathy. A comparison of the groups showed a significant difference in the duration of DM, which was greater in patients with diabetic nephropathy (16.4 vs. 5 vs. 9.5 years, respectively, p: 0.024).

Conclusions: we present a case series of diabetic patients with nephrotic-range proteinuria in Colombia, showing that kidney biopsy lesions other than diabetic nephropathy may be a cause of proteinuria. We found that patients with a report of DN alone had a much longer duration of diabetes. **(Acta Med Colomb 2022; 47. DOI: https://doi.org/10.36104/amc.2022.2231).**

Keywords: *diabetic nephropathies, diabetes mellitus, proteinuria, biopsy, nephrotic syndrome*.

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Introduction

Diabetes-induced kidney disease is a complication of diabetes mellitus (DM) with high morbidity, mortality and costs, worldwide (1, 2). However, biopsy lesions other than diabetic nephropathy (a valid term only for histopathological description) have been described (3-7) and despite this, it is common in clinical practice to attribute any degree of proteinuria and kidney function deterioration only to diabetic nephropathy (DN), decreasing the chance of diagnosing other reversible or treatable causes. Some clinical characteristics of diabetic patients have been proposed as indications for performing a kidney biopsy, and have been associated with the presence of non-diabetic nephropathy (NDN) (8). One of these is nephrotic-range proteinuria, especially when it presents shortly after the diagnosis of DM or without retinopathy. In Colombia, no studies have been found which identify or describe the kidney lesions in patients with diabetes mellitus and nephrotic-range proteinuria. This study describes the clinical and histopathological characteristics found in this population and compares three groups according to the kidney biopsy findings (DN, NDN or mixed).

Materials and methods

A descriptive study was performed between 2018 and 2020, taking data from clinical charts and kidney biopsy reports of patients over the age of 18 with a diagnosis of type 1 or type 2 DM of any duration, who were being followed by nephrologists in various Colombian cities, and who had had a 24-hour urine protein greater than 3.5 gr, for which kidney biopsy had been performed. Given that kidney biopsies are uncommon in this group of patients, all Colombian nephrologists belonging to the Colombian Association of Nephrology (Asocolnef) were asked to participate in the study.

The only exclusion criterion was the presence of previously diagnosed glomerular disease. The study was

presented to and approved by the bioethics committee of Universidad de Caldas.

The variables collected were: age, sex, body mass index (BMI), type of DM, years since diagnosis, creatinine, urinalysis findings, 24-hour urine protein level, blood glucose level, glycosylated hemoglobin, the presence of arterial hypertension (HTN) and the kidney biopsy result including the evaluation of eight or more glomeruli, using immunofluorescence and light and electron microscopy. The Renal Pathology Society's 2010 histopathological classification of DN was used (9).

The SPSS version 22 program was used for analysis. Absolute and relative frequencies were used for categorical variables and measures of central tendency and dispersion were used for quantitative variables according to whether they had a normal or asymmetric distribution based on the Shapiro-Wilk test. The relevant statistics were used for comparisons between groups, taking a p less than 0.05 as statistically significant.

Results

Data were collected from 19 patients; the demographic and clinical characteristics are found in Table 1. An evaluation of the kidney biopsy findings showed that DN was reported as the only finding in 26.3%, NDN in 31.6% and mixed in 42.1%. In the DN group, 40% were classified as class IIA, 20% as class IIB, and 40% as class III. In the NDN group, IgA nephropathy was found in 33.3% of the patients, along with chronic interstitial nephritis, membranous glomerulopathy, interstitial nephritis associated with minimal change disease, and focal and segmental glomerulosclerosis in equal percentages of 16.6% each. In the group with both types of nephropathy (mixed), 50% had class IIB DN, 25% had class II, and 12.5% had class I and class IIA. The lesions other than DN were hypertensive nephropathy in 75%, and IgA nephropathy, focal glomerulosclerosis and the classic variant of primary segmental glomerulosclerosis in 12.5%.

Comparisons were made between three groups (Group 1: DN; Group 2: NDN and Group 3: mixed), which are shown in Table 2, with a statistically significant difference in the years elapsed since DM diagnosis at the time of kidney biopsy, this number being greater in the DN group. The group comparisons were significant between the DN and NDN groups (p=0.019), but not between the DN and mixed groups (p=0.178) nor between the NDN and mixed groups (p=0.422). An additional analysis was performed calculating the percentage of patients with five or more years since diagnosis, finding that 100% of the DN group and 66.7% of the mixed group had had the disease for five or more years, while 83.3% of the NDN group had been diagnosed for less than five years (p=0.018). In addition, 80% of those in the DN group had been diagnosed for more than 10 years, unlike the NDN and mixed groups, in which 83.3% had been diagnosed for less than 10 years (p=0.045).

Table 3 shows the additional comorbidities reported in the clinical chart, related to the finding reported on the kidney biopsy.

Discussion

This study described the clinical and histopathological characteristics of diabetic patients with nephrotic-range proteinuria, in whom we found similar demographic characteristics, such as age and sex, to those of other studies of kidney biopsies in diabetics, in which ages range from 49 to 65 years, with a predominance of males (4, 6, 10). The predominant type of diabetes was type 2, similar to most studies, which even only included this type of diabetes, as it is more frequent. Also, in patients with type 1 diabetes, the time of onset of proteinuria is clearer (around 10 years after diagnosis), and thus fewer biopsies are performed.

Comparing the frequencies of DN, NDN and mixed to other studies, we found a lower percentage of DN in this study (Table 4). However, there is a wide variety of percentages in the various studies due to the criteria used in each center for performing kidney biopsies, and the fact that some did not include the mixed category (11, 12).

In the group in which only NDN lesions were identified, the most frequently found lesion was IgA-mediated injury in 33.3%, which is strikingly similar to the percentages found in Asian studies, such as those reported by Zhou (5) and Zhuo (13), and even in the review by Kumar et al. (12),

Table 1. *Demographic and clinical characteristics*.

Variable	n=19
Sex Male, n (%)	 14 (73.7)
Age, mean in years (SD)	58.5 (10.4)
Type of Diabetes Mellitus Type 1, n (%) Type 2, n (%)	 1 (5.3) 18 (94.7)
Years since DM diagnosis, mean (SD)*	9.9 (7.3)
Creatinine, mean in mg/dL (SD)+	2.08 (1.0)
Glomerular filtration rate by MDRD, median (IQR) +	41.4 (21.2-56.6)
Presence of hematuria, n (%)°	6 (50)
Presence of leukocyturia, n (%)°	2 (16.7)
Proteinuria in a random sample in mg/dL, median (IQR)¡	300 (100-350)
24-hour urine protein in grams, median (IQR)	4.1 (3.6-7.6)
Fasting blood sugar in mg/dL, mean (SD)!	116.6 (27)
Glycosylated hemoglobin in %, mean (SD)#	6.7 (0.7)
High blood pressure, n (%)+	17 (94.4%)

*Abbreviations: SD: standard deviation; DM: diabetes mellitus; MDRD: Modification of Diet in Renal Disease study. *Calculation based on data from 17 patients. +Calculation based on data from 18 patients. ° Calculation based on data from 12 patients.! Calculation based on data from 14 patients. ¡ Calculation based on data from 11 patients. # Calculation based on data from 15 patients.*

Table 2. *Comparison of demographic and clinical variables between the different groups.*

Variable	Group 1 – DN (n=5)	Group 2 – NDN (n=6)	Group 3 - Mixed (n=8)	P value
Sex Male, n (%) Female, n (%)	 5 (100) 0	 3 (50) 3 (50)	 6 (75) 2 (25)	0.171
Age, mean in years (SD)	64.8 (9.2)	58.0 (8.9)	55.1 (11.5)	0.279
Type of diabetes mellitus Type 1, n (%) Type 2, n (%)	 0 5 (100%)	 0 6 (100%)	 1 (12.5) 7 (87.5)	0.484
Years since DM diagnosis, mean (SD)*	16.4 (5.4)	5 (4.7)	9.5 (7.44)	0.024
Creatinine, mean in mg/dL (DE)+	2.28 (0.88)	2.08 (1.25)	1.95 (0.98)	0.865
GFR by MDRD, median (IQR) +	28.2 (21.1-56.8)	46.33 (18.7-63.4)	38.7 (21.3-86.5)	0.87
Presence of hematuria, n (%)°	2 (50)	2 (50)	2 (50)	1.0
Presence of leukocyturia, n (%)°	4 (80)	1 (25)	1 (25)	0.54
Random proteinuria in mg/dL, median (IQR)!	300 (165-400)	300 (150-450)	300 (100-400)	0.926
24-hour urine protein in grams, median (IQR)	10 (3.7-12.2)	4.55 (3.9-5,8)	3.7 (3.5-4.5)	0.14
Fasting blood sugar in mg/dL, mean (SD)¡	126 (22.9)	94 (22.03)	122 (33.2)	0.274
Glycosylated hemoglobin in %, mean (SD)#	7.18 (0.8)	6.58 (0.55)	6.54 (0.72)	0.321
Comorbidity High blood pressure, n (%)+	 5 (100)	 4 (80)	 8 (100)	0.252

*Abbreviations: SD: Standard deviation; DM: Diabetes mellitus; MDRD: Modification of Diet in Renal Disease study. *Calculation based on data from 17 patients. +Calculation based on data from 18 patients. ° Calculation based on data from 12 patients.. !Calculation based on data from 14 patients. ¡Calculation based on data from 11 patients.. # Calculation based on data from 15 patients.*

in which they compared the lesions found in the various studies, with IgA nephropathy predominating in reports from Korea, Hong Kong and China. Nevertheless, the percentage of this nephropathy is higher than that reported in studies in the United States, Spain, and even in Colombia (7, 13.2 and 12.5%, respectively) (6, 7, 14). However, another study recently performed in Colombia by García et al. (15), which described the clinical and histological characteristics of 269 kidney biopsies between 2002 and 2017, found that IgA nephropathy was the most common primary glomerulonephropathy, concluding that, despite being similar to other world populations, it does differ from prior studies in Latin America.

A high percentage of hypertensive nephropathy was found in the mixed nephropathy group, even greater than that in other studies (6,10). This was probably due to the prevalence of HTN in the study population's age range, in addition to the high comorbidity of type 2 DM patients and some DM mechanisms which can worsen HTN, such as endothelial dysfunction and activation of the renin-angiotensin-aldosterone and sympathetic systems (5, 16).

Regarding 24-hour proteinuria, a higher level was found in the DN group, although it was not statistically significant, probably due to the small number of patients. This coincides with studies reported in the United States (6) and Spain (7, 10), in which a higher degree of proteinuria was a predictor for DN and even for a greater severity of DN (7).

We found statistically significant differences in the time elapsed since DM diagnosis, with this being much greater in the DN group than in the NDN group. In fact, when the groups were compared, the difference persisted if the time elapsed was more than five or 10 years, concurring with García-Martín et al.'s study (10), which found that DM lasting longer than 10 years had an OR of 2.71 as an independent predictor for histological DN findings, and was even one of the risk factors included in the score proposed by these authors to predict the presence of this nephropathy. This is in line with Bermejo et al.'s report in 2016, who, on multivariate analysis, found that a shorter duration of diabetes was one of the variables independently associated with non-diabetic lesions on kidney biopsy (7). These findings suggest that, in patients with nephrotic-range proteinuria and less than five or even 10 years' duration of diabetes, a cause of the marked proteinuria other than diabetes should be suspected. Recently, the Sociedad Italiana de Nefrología [Italian Society of Nephrology] published its position on the indications for kidney biopsy in patients with diabetes (8), which include, among others, less than five years' duration of diabetes, especially if the patients have type 1 diabetes, and the rapid onset and progression of albuminuria or the sudden onset of nephrotic syndrome. Notably, that same ar-

Table 3. *Other reported comorbidities, according to kidney biopsy diagnosis.*

Kidney biopsy finding	Additional comorbidity
Diabetic and hypertensive nephropathy	Familial dysbetalipoproteinemia, 2 phenotype
Diabetic and hypertensive nephropathy	Rheumatoid arthritis
Interstitial nephritis associated with minimal change disease	Suspected systemic sclerosis

ticle mentions that, historically, kidney biopsies in diabetic patients were extremely limited, as it was assumed that the clinical presentations in these patients were attributable to diabetic nephropathy. However, the evidence over the last few years shows that a percentage of patients are affected by non-diabetic nephropathy (including the 51.7% reported by this same society in the Italian kidney biopsy registry), in whom a delayed diagnosis by kidney biopsy can have an impact on long-term outcomes (8, 17). It is also important to highlight that the most recent Colombian clinical practice guidelines for diabetic kidney disease (18) do not provide specific recommendations for ordering kidney biopsies, as this tool should be analyzed within the diagnostic context of kidney disease.

The limitations are related to the small number of patients, despite diabetes mellitus being highly prevalent, which can be explained by the fact that nephrotic proteinuria is infrequent in diabetics and kidney biopsies are rarely performed on this group of patients. Even prior studies with larger samples of diabetic patients with any degree of proteinuria carried out data collection over 10 to 23 years, compared to our data collection which covered two years (4, 5, 7, 10). Keeping this limitation in mind, we reiterate that the comparison between groups was exploratory. In the future, with larger case series or prospective data collection, comparisons with greater statistical power may be carried out.

Variables of interest such as the presence of diabetic retinopathy or medications used were not included either, as they were not reported in the reviewed clinical charts.

Conclusions

We show, and encourage the medical staff who care for diabetic patients to consider, that not all kidney disorders in these patients are secondary to DN, and the attending physicians should always be alert to atypical manifestations which could lead to an early diagnosis and affect these patients' treatment and prognosis.

Table 4. *Comparison of frequencies of the groups in different studies.*

Study: Country, author and reference	Diabetic nephropathy	Non-diabetic nephropathy	Mixed
India. Prakash et al. (3)	87.7%	12.3%	NR
China. Bi et al. (4)	54.5%	NR	45.5%
China. Zhou J et al. (5)	54%	46%	NR
USA. Sharma et al. (6)	37%	36%	27%
Spain. Bermejo et al. (7)	34.5%	61.8%	3.6%
Spain. García-Martín et al. (10)	61%	39%	NR
Colombia. Aristizábal et al. (14)	28%	71%	NR
Current study	26.3%	31.6%	42.1%
Abbreviations: NR: Not reported.			

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