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Characterization of patients with diabetic kidney disease nonalbuminuric phenotype. A single-center observational study.

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Abstract

Introduction: The phenotypes with albuminuria and the nonalbuminuric phenotype in diabetic kidney disease (DKD) are known. The nonalbuminuric phenotype is defined with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2 associated with km il.;p.albuminuria- creatinuria ratio (ACR) less than 30 mg/gr. The objective of the present study was to describe the clinical characteristics of patients with DKD nonalbuminuric phenotype (nA-DKD).

Methods: This is an observational, descriptive study of patients treated at an IPS in Cartagena, Colombia, from 2021 to 2022.

Results: Of a total of 7698 patients with DKD criteria, 1714 patients (22.3%) had nA-DKD criteria, with a median age of 69 years (IQR 62-76), and women (75.73%). A total of 85% had hypertension, (22.3%) dyslipidemia, and the average BMI was in the overweight range. 9.5% had a history of smoking. Little presence of diabetic retinopathy was found.

Conclusion: Nonalbuminuric phenotype diabetic kidney disease is not uncommon in our environment. In general, the characteristics of our patients are very similar to those reported in other series.

Keywords:

Chronic kidney disease, Diabetic kidney disease, Mellitus diabetes, Albuminuria, Creatinuria, Glomerular filtration rate.

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The concept of diabetic kidney disease (DKD) was introduced by the National Kidney Foundation in 2007 to describe kidney disease attributable to diabetes mellitus (DM) to replace the term "diabetic nephropathy (DN)" [1], which is currently only attributable to biopsy-confirmed ERD [2].

DKD is the leading cause of chronic kidney disease (CKD), with a prevalence of 20–40% in individuals with type 2 diabetes mellitus (T2DM) [3]. As previously described, up to 40% of patients with T2DM who attend a first consultation already suffer from ERD, resulting in one of the most expensive complications for the health system [4- 6]. In Colombia, between 1.6 and 2.7% of the gross domestic product (GDP) is invested in the kidney population [7]. According to data from the Colombian High-Cost Account (CAC), for 2022, 790,117 people were notified of this diagnosis, which is still significant despite being lower than in 2021 [8].

ERD is defined as the loss of kidney function in patients with DM2 [9], which is framed by a decrease in the glomerular filtration rate (GFR), usually <60 mL/min/1.73 m^2, and the presence of albuminuria for three or more months [10]. The urinary albumin–creatinine ratio (ACR) [11] can be used to predict both the course of the disease and the risk of mortality, which is why it should be used in the screening of DKD [12] and time for classification by stage and severity of albuminuria [6, 13].

The classic presentation of ERD is the presence of albuminuria, which precedes the progressive decrease in the GFR [14, 15]. However, the disease develops despite the lack of linearity in the presentation of albuminuria. Between 19% and 32% of individuals have a >50% probability of presenting a nonlinear pattern in the appearance and progression of albuminuria. On the other hand, the lack of a widely accepted threshold for defining the GFR trajectory as nonlinear in a traditional way stands out [16], which suggests that a decrease in the GFR can occur independently of the presence of albuminuria [17].

Considering these findings, DKD can be divided into two phenotypes: the albuminuria phenotype (RAC ≥ 30 mg/g) and the nonalbuminuric phenotype (RAC <30 mg/g) [18, 19]. There are several patterns in the phenotypes associated with albuminuria, of which the most frequent and well-known is the classic phenotype. Although the prevalence of the nonalbuminuric phenotype has been increasing in several series, its clinical picture, pathological characteristics, prognosis, and mortality have not been thoroughly investigated [20, 21].

Research that has been carried out on the nonalbuminuric phenotype has shown that its prevalence is estimated to be 20-30% of all patients with DKD. It occurs at significantly older ages and is much more common in females [22]; however, in some reports, the male sex predominates [23], and it is more significantly associated with hypertension, increased pulse pressure, and hyperuricemia. In addition to a higher incidence of anemia, insulin, antihypertensives, and lipid-lowering agents are used. Much lower levels of glycosylated hemoglobin (Hba1c) [11] and the absence of diabetic retinopathy [24] have also been documented. Verma et al. reported that in diabetic patients with an ACR less than 30 mg/g, there were differences in the progression of kidney disease according to the degree of albuminuria. Patients with an AC more outstanding than 15 mg/g had a much greater progression of kidney damage than patients with an ACR less than 5 mg/g. This article states that even in patients with an ACR less than 30 mg/g, there is enormous disagreement regarding the value of albuminuria [24].

On the other hand, when comparisons have been made between the phenotypes, individuals with an albuminuric phenotype have a more unfavorable cardiovascular risk profile [25] despite the presence of macrovascular complications in both the albuminuric and nonalbuminuric phenotypes, according to some research. have behaved similarly [23]. In a Japanese study, it was established that patients with a history of cardiovascular disease had a greater risk of having a reduced glomerular filtration rate (GFR) or advanced kidney disease, indicating that a history of macrovascular complications could influence the renal prognosis in patients with these phenotypes [26]. Although albuminuria remains the most common phenotype, the nonalbuminuric variant occurs in many patients with DM2 and CKD [12].

The pathogenesis of the DKD nonalbuminuric phenotype (nA-DKD) still needs clarification. However, it has been associated with macroangiopathic damage with interstitial fibrosis, which differs from the glomerulosclerosis that characterizes the DKD albuminuric phenotype, resulting from the complex interaction of different pathways. The latter involves the hexosamine pathway, polyols, the protein kinase C pathway, and advanced glycosylation products (AGEs) [27-29].

Few studies have investigated the influence of risk factors (RFs) on kidney function trajectory in individuals with nonclassical phenotypes, such as nonalbuminuric phenotypes [24]. Hyperglycemia is one of the most common RFs, and independent of the presence or absence of ERD, poor glycemic control increases the deterioration of kidney function by disturbing the antioxidant system, which leads to the generation of AGEs [30]. The time of evolution of diabetes also plays a fundamental role in the presentation of this phenotype [31]. Among other RFs, we find race; it has been documented that the number of cases and the severity of ERD increase in individuals of Afro descent (3 to 6 times compared to Caucasians), Mexican Americans, and Pima Indians with a history of DM2, the latter of which have larger glomeruli than Caucasians. This characteristic can lead to greater susceptibility to glomerular damage caused by diabetes [32]. Furthermore, hypertension is significantly associated with the presentation of ERD, and hypertensive patients are known to have a greater risk of developing this pathology [11].

On the other hand, dyslipidemia plays an essential role in the progression of DKD since it causes podocyte apoptosis, which

ultimately translates to a decrease in high-density lipoprotein levels and an increase in triglyceride levels [28]. Obesity is a risk factor for DKD; however, its role in the physiopathogenesis of DKD is unclear [33]. Smoking is thought to be an independent risk factor for DKD development and progression; its role encompasses multiple factors, such as hyperlipidemia, oxidative stress, AGE storage, and glomerular sclerosis [28, 34].

Clinical studies have identified several clinicopathological characteristics of patients who suffer from nonalbuminuric DKD phenotypes. These findings remain controversial and motivate research to characterize our population with this pathology, evaluating the behavior of variables such as age, sex, clinical history, and laboratory data. The objective of this observational study was to describe the sociodemographic and clinical characteristics of patients with DM2 and nonalbuminuric diabetic kidney disease (RDnA) treated in the cardiovascular risk program of a primary care center in the city of Cartagena, Colombia.

Materials and methods

Research design

The present study is a cross-sectional observational study. The source is retrospective.

Scenery

The study was conducted in an IPS primary care center in Cartagena, Colombia, from January 1, 2021, to December 31, 2022.

Universe and sample

The study population corresponds to the anonymized documentary records of patients diagnosed with diabetic kidney disease at the institution. The following definitions were used to develop the study. The cases correspond to the records of patients with chronic kidney disease diagnosed with type 2 diabetes mellitus with a measured or estimated clearance <60 mL/min/1.73 m^2 and with ACR measurements for their classification.

Inclusion criteria

Patients over 18 years of age with a diagnosis of diabetic chronic kidney disease of a nonalbuminuric phenotype with an eGFR less than 60 cc/min and an ACR less than 30 mg/g were included.

Exclusion criteria

Patients with a history of kidney transplants and pregnant or lactating female patients were excluded. Records with incomplete data were removed from the inclusion analysis.

Variables

We included three variables in the final analysis; among the sociodemographic variables, we found age and sex. The variables corresponding to clinical history included chronic arterial hypertension, years of evolution of type 2 diabetes mellitus, dyslipidemia, diabetic retinopathy, previous acute myocardial infarction, heart failure, myocardial revascularization, cerebrovascular disease, and smoking habit. The macro variables corresponding to clinical characteristics included creatinine, creatinine, microalbuminuria, serum albumin, glomerular filtration rate, urinary albumin–creatinine ratio, glycosylated hemoglobin, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, and body mass index.

Data sources/measurements

The source was indirect; the institutional electronic file and the internal medicine and nephrology services registry were reviewed. Laboratory results were obtained from the electronic laboratory records. The diagnosis of diabetic kidney disease was made using the CKD-EPI formula and serum creatinine. To measure RAC, proteinuria in an isolated urine sample was divided by urinary creatinine in the same sample, equating the units to obtain mg/g.

Biases

To avoid possible interviewer, information, and memory biases, the leading researcher always safeguarded the data with a guide and records approved in the research protocol. Observation and selection biases were avoided by applying the participant selection criteria. All clinical and paraclinical variables from the previous period were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their agreement was verified.

Study size

The sample was probabilistic; with an incidence of 3849 annual cases of ERD, there were 7698 cases for the 2-year study period. With an expected frequency of 50% and a confidence limit of 5%, the sample size with a confidence level of 99.99% was 1265 cases. The StatCaclc program from Epi Info TM (version 7.2.6. CDC, Clifton Road, Atlanta, USA) was used.

Quantitative variables

Descriptive statistics were used. The scaled results are expressed as the means and standard deviations. Categorical data, such as sex, are presented as proportions.

Statistical analysis

Noninferential statistics were used. The confidence intervals for the proportions of prevalence data are presented. We used the Kolmogorov–Smirnov test to evaluate the data distribution, assuming that P values <0.05 were significant. The categorical variables are expressed as absolute and relative frequencies. In contrast, the quantitative variables are presented as the median (Me) and interquartile range (IQR) because they were not normally distributed. The data were analyzed using the R studio statistical program.

Results

Study participants and prevalence of nA-DKD

Among the 7698 patients with DKD, 1714 had nA-DKD (22.3%). The 95% confidence intervals for the proportions ranged from 21.3% to 23.2%. Table 1 and Figure 1 present the cases classified by RAC.

Table 1. Prevalence of diabetic kidney disease of nonalbuminuric phenotype.

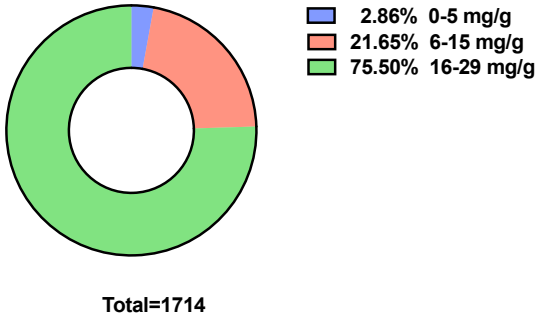
RAC	Frequency n=1714	Proportion, 95% confidence interval.
0-5 mg/g	49	0.6 (0.5-0.8)
6-15 mg/g	371	4.82 (4.34-5.30)
16-29 mg/g	1294	16.81 (15.97-17.64)

ACR: albumin–creatinine ratio (mg/g).

Characteristics of the study group

The median age of the patients was 69 years (IQR 62-76), and they were primarily women, with 1298 patients being 75.73% female. Table 1 shows the baseline characteristics of the population included in the study.

Figure 1. Distribution by albumin-creatinine ratio.



Regarding the clinical history of the patients, we found that the most frequently associated comorbidity was arterial hypertension (85.24%, 1461 patients), followed by dyslipidemia (22%, 382 patients). The median number of years of DM evolution was 5 (IQR 3-8). A total of 1018 (59.3%) patients reported a history of smoking. A total of 151 (8.81%) patients reported ex-smoking, 12 (0.7%) patients reported active smoking, and in 533 (31.1%) patients, no data were found in the medical charts. Only 16 (0.96%) patients reported the presence or absence of diabetic retinopathy. The presence of cardiovascular disease and heart failure was also reported in less than 10% of patients. For the rest of the data, see Table 2.

Regarding the clinical variables of the patients, 77% had stage 3b CKD, with a median glomerular filtration rate (GFR) of 52 ml/min/m2 (IQR 45-56). The median body mass index (BMI) was 27, with an IQR of 24-30; 38% of patients were overweight, and 27.3% were obese. Regarding laboratory parameters, the median value for glycated hemoglobin was 6.5% (IQR 6-7.3%), that for creatinine was 1.21 mg/dL (IQR 1.11-1.40), and the albuminuria/creatinineuria ratio was 20 mg/g (IQR 16-25). Table 3 describes the clinical variables and laboratory parameters of the patients included in the study.

Table 2. Prevalence of diabetic kidney disease of non albuminuric phenotype .

Characteristics	Sample n =1714	(%)
Women	1298	75.73
Men	416	24.27
Clinical History		
Years of evolution of DM (Me, RIC)	5 (3 – 8)	
Arterial hypertension	1461	85.24%
Dyslipidemia	382	22.29%
Active Smoking	12	0.70%
Former smoker	151	8.81%
has never smoked	1018	59.39%
No data on smoking	533	31.10%
Ischemic stroke	6	0.35%
Diabetic retinopathy	16	0.96%
Acute myocardial infarction	5	0.29%
Previous angioplasty	2	0.12%
Heart failure	2	0.12%

DM: Diabetes mellitus. Me: Average. IQR: Interquartile range .

Discussion

The present study characterizes patients with DM2 syndrome who suffered from nA-DKD at a single institution in Cartagena, Colombia, between January 2021 and December 2022. We found that 1714 patients had this condition, accounting for 22.3% of the patients during the follow-up period. Studies carried out worldwide have observed a prevalence similar to that in our population. First, in the United Kingdom Prospective Diabetes Study (UKPDS), which included 3687 diabetic individuals, 60% of patients developed kidney disease without having previously manifested albuminuria after many years of follow-up [35].

An investigation carried out in China with a total of 1620 hospitalized patients with DM2 revealed a significant association between ERDnA and female sex, older age, and higher serum uric acid levels, as well as a greater incidence of anemia and greater use of insulin and antihypertensive and lipid-lowering drugs [11]. Our research revealed similar characteristics, such as predominantly female older adult patients; a high incidence of HTN and little association with retinopathy were also documented. However, our study could not demonstrate a high prevalence of anemia or dyslipidemia, as described in the cited study [11].

Regarding the paraclinical variables, we found that the HbA1 levels were similar to those described in the literature; our population had a median of 6.5% (IQR 6-7.3), indicating that they generally had

adequate metabolic control. These values are similar to those of other studies, where the average value of HbA1 was approximately 6.5% [11].

Regarding the stage of CKD, there are similarities with what is described in the literature. In an investigation carried out in India in 3534 individuals with DM2, 121 patients (3.4%) had nA-DKD, with a smaller proportion found in patients with more advanced renal stages, with a proportion of 45.1% in renal stage 3a, 31.3% in stage 3b and 10.0% between stages 4 and 5. In the present analysis, we obtained very similar results: 77% (1320/1714) had renal stage 3a disease, 17% (291/1714) had renal stage 3b disease, 5% (80/23) had stage 4 disease, and only 1% had stage 5 disease [23].

Debasish Kar et al. concluded in a meta-analysis that smoking is a strong predictor of albuminuria in patients with DM2 [30]. In our analysis, we found that 9.5% of patients with nA-DKD (163/1714) had some history of smoking, which is considered a low prevalence; however, a significant percentage of the data reported as missing could explain this finding.

Verma et al., in their clinical study in which they included 1629 patients and all people with diabetes with normoalbuminuria (ACR less than 30 mg/kg), demonstrated that there are differences in the progression of kidney disease in this group of patients, depending on the level of albuminuria. Patients with an ACR greater than 15 mg/g had more significant progression of kidney disease than patients with an ACR less than 5 mg/g [24]. This may indicate the impact of the presence and level of albuminuria on the progression of kidney disease. Another study carried out in Japan with a total of 2953 patients with DM and nA-DKD established that those with a history of cardiovascular disease had a greater risk of having a reduced glomerular filtration rate or advanced kidney disease, which could suggest that a history of macrovascular complications could influence the renal prognosis in patients with this phenotype [26, 36]. This variable was not evaluated; the patients had an average ACR of 20 mg/g CI between 16 and 25 mg/g.

Table 3. Clinical and laboratory characteristics of the study group.

Characteristics	Sample N=(1714)	Percentage (%)
Clinical Variables		
CKD stage classification		
Stage 3a	1320	77.01%
Stage 3b	291	16.98%
Stage 4	80	4.67%
Stage 5	23	1.34%
Body mass index (kg/m ^{2}), (Me, IQR)	27 (24 – 30)	
Abdominal perimeter (cts.), (Me, RIC)	94.5 (90 – 102)	
Systolic blood pressure (mm/Hg), (Me, RIC)	120 (120 – 140)	
Diastolic blood pressure (mm/Hg), (Me, RIC)	80 (80-80)	
Nutritional status classification		
Underweight	24	1.40%
Normal weight	547	31.91%
Overweight	675	38.38%
Obesity	468	27.30%
Laboratory variables		
Glomerular filtration rate (ml/min/m ^{2}), (Me, RIC)	52 (45 – 56)	
Creatinine (mg/dL), (Me, RIC)	1.21 (1.11 – 1.40)	
Hemoglobin (mg/dL), (Me, RIC)	12.6 (11.7 – 13.6)	
Albumin (mg/dL), (Me, RIC)	4.2 (3.98 – 4.48)	
Total cholesterol (mg/dL), (Me, RIC)	185 (172 – 200)	
HDL cholesterol (mg/dL), (Me, RIC)	48 (47.1 – 48.9)	
LDL cholesterol (mg/dL), (Me, RIC)	107 (94.7 – 118.9)	
Triglycerides (mg/dL), (Me, RIC)	147 (124 – 175)	
Glycosylated hemoglobin (%), (Me, RIC)	6.5 (6 – 7.3)	
Microalbuminuria (mg/L), (Me, RIC)	12 (10 – 15)	
Creatinuria (mg/dL), (Me, IQR)	55 (50 – 71)	
RAC (mg/g) Me, RIC)	20 (16 – 25)	

ACR: albumin creatinine ratio. Me: average. IQR: Interquartile range .

In addition, we found little data on a history of cardiovascular disease, so it was not possible to perform such an analysis; however, regarding cardiovascular risk factors, the majority of patients had a BMI in the range of overweight or obesity, a fact that contrasts with other studies where the population with a nonalbuminuric phenotype has reported a lower prevalence of this condition [37].

The present study has several strengths. We highlight two crucial points: first, the number of populations included with this phenotype despite being in a single center; second, this is the first characterization study carried out in the region on this specific population of patients with DKD, which could open lines of research in the future.

On the other hand, this study has several limitations. First, it is a descriptive, retrospective study that does not allow for establishing an association between the variables studied or a causal relationship. Second, this was a study carried out in a single healthcare center, so it may not reflect the reality of the entire diabetic patient population. Third, we analyzed several clinical and laboratory variables without including the use of drugs for DM2 that could influence the behavior and progression of patients with the nonalbuminuric DKD phenotype. Additionally, as this was a review of medical records, several data on some variables that were reviewed probably needed to be recorded in the medical records; it is necessary to carry out new clinical analytical or intervention studies to establish an association and better define the behavior of patients with an ERD nonalbuminuric phenotype.

Conclusions

DKD can have several trajectories in its presentation and evolution, so it is essential to know that several phenotypes have already been described. The nonalbuminuric phenotype of diabetic kidney disease is uncommon in our population. In this work, we describe the clinical and laboratory characteristics of this group of patients in our population, similar to those reported in the literature. It is necessary to carry out studies that evaluate the risk and cardiorenal prognosis of this phenotype and, in this way, to obtain a clearer picture and interventions that can modify its impact.

Abbreviations

DKD: Diabetic kidney disease.
nA-DKD: Nonalbuminuric diabetic kidney disease.
CKD: chronic kidney disease.
DM2: Diabetes mellitus type 2.
BMI: Body mass index.
Me: Median.
ACR: urinary albumin–creatinine ratio.
IQR: Interquartile range.

Supplementary information
The supplementary materials have not been provided.

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Does not apply.

Contributions of authors

Yerina Hortensia Salas Carmona: Conceptualization, methodology, research, Writing – Original draft.
Dagoberto Serpa Diaz: Conceptualization, methodology, Writing – Original draft.
Yuris C Salas Carmona: Conceptualization, visualization, validation, Writing-review and editing, formal analysis.
Enrique C Ramos Clason: Conceptualization, visualization, validation, Writing-review and editing, formal analysis.
María Raad Sarabia: Conceptualization, visualization, validation, Writing-review and editing, formal analysis.
Rodrigo Daza-Arnedo: Conceptualization, Project administration, Supervision, validation, visualization, Writing – review and editing.
María Ximena Cardona Blanco: Conceptualization, methodology, research
Paula Parra Sánchez, Conceptualization, methodology, research.
Jorge Rico-Fontalvo: Conceptualization, Project administration, Supervision, validation, visualization, Writing – review and editing.
All the authors have read and approved the final version of the manuscript.

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The study was self-financed by the authors.

Availability of data or materials

Does not apply.

Statements

Ethics committee approval and consent to participate

The Universidad del Sinú Section Cartagena-Colombia Ethics Committee approved the research protocol.

Consent for publication

This does not apply when patient-specific magnets, X-rays, or photographs are not published.

Conflicts of interest

Dagoberto Serpa declares that he has received speaking fees for Novo Nordisk.
Rodrigo Daza has received speaking fees from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Bayer.
Jorge Rico Fontalvo declares that he has received speaking fees from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lilly, Sanofi, Novartis, AbbVie, Merck, and Bayer and has participated in their advisory boards.
The other authors declare that they have no conflicts of interest.

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