The Prevalence of Severely Increased Albuminuria in the Type 2 Diabetes Population with Chronic Kidney Disease of Low Socioeconomic Status in San Juan: A Population in Need of Improved Accessibility to Disease-Modifying Therapy

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Objective: The aim of this study was to determine the prevalence of severely increased albuminuria and the percentage of patients with the indication for canagliflozin in the type 2 diabetes population with chronic kidney disease (CKD) and low socioeconomic status in the San Juan City Hospital.

Methods: This cross-sectional study examined the electronic records of 129 Hispanic type 2 diabetes patients. CKD in this population was defined according to the most recent nephrology and endocrinology guidelines. Albuminuria was diagnosed with two positive urine albumin/creatinine ratio results within 3-6 months. Data was obtained from July 2017 to January 2020 and analyzed utilizing descriptive statistics and correlations.

Results: The prevalence of moderately and severely increased albuminuria in patients with type 2 diabetes and CKD were 51.2% and 18.6% respectively. The number of patients with type 2 diabetes who filled the FDA indication for canagliflozin were 16.3%. The prevalence of hypertension, coronary artery disease (CAD) and heart failure (HF) was 61.2%, 15.5% and 10.1% respectively. Between albuminuria severity and decreased renal function, a tendency was observed although not statistically significant (r = -0.14, 95% CI: -0.31, 0.03; P = 0.109). While evaluating association between albuminuria groups and CAD, there was a noticeable tendency close to reaching statistical significance (P = 0.060).

Conclusion: There is a scarcity of studies regarding the prevalence of severely increased albuminuria in type 2 diabetics with CKD and this study contributes to the literature. On analysis of associations, statistical significance not reached likely due to small sample size. [*P R Health Sci J 2023;42(2):121-126*]

Key words: Macroalbuminuria, Diabetic kidney disease, Diabetes type 2

The diabetes epidemic is considered the main etiology of chronic kidney disease (CKD) and end-stage kidney disease worldwide (1, 2). Approximately 40% of patients with type 2 diabetes will develop diabetic kidney disease (DKD), which is associated with increased mortality risk in this population (3, 4). This condition is defined as chronic kidney disease which is primarily attributed to renal damage caused by diabetes (1, 5). It can be diagnosed clinically based on abnormal laboratory results such as albuminuria and/or reduced estimated glomerular filtration rate (GFR) without the presence of signs or symptoms of other causes of kidney damage (1). In current guidelines, GFR impairment is defined as a GFR below 60 ml/min per 1.73 m^2, while albuminuria is a urine albumin/creatinine ratio (UACR) ≥30 mg/g (6, 7, 8). Due to considerable biological variability, at least two abnormal UACR specimens in random spot urine collections, attained within 3-6 months are needed to detect albuminuria as stated in the American Diabetes Association (ADA) guideline (7, 8).

Studies report that GFR impairment is independently associated with increased risk of mortality in diabetic patients (6). In addition, albuminuria severity is associated with risk of CKD progression and cardiovascular disease, regardless of estimated GFR (9, 8). In a large cross-sectional study from data obtained from 33 countries, the global prevalence of moderately increased albuminuria (previously called microalbuminuria) was 38.8% and that of severely increased albuminuria (previously called macroalbuminuria) was 9.8% in the type 2 diabetes mellitus population. However, the highest prevalence of moderately and severely increased albuminuria is found in

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Asians and Hispanics with values of (43.2 and 43.8%) and (12.3 and 10.3%) respectively (5, 10, 11).

It is well known from large prospective randomized control trials that intensive glycemic control in patients with diabetes, delays albuminuria onset and progression in addition to decline in GFR (8). For the last decade, as an effect of the 2008 United States Food and Drug administration (FDA) guidance, a plethora of cardiovascular outcome trials done for safety, have brought considerable advances in the care of the type 2 diabetes population (12, 13). Recent large studies with relatively new classes of glucose-lowering agents have showed renal outcome benefits independent of glycemic control (8, 12).

For approximately two decades, there has been an anticipation for newer drugs with benefits for renal protection (12). Until recently, renin-angiotensin system blocking agents were the only approved treatment with renal benefits in type 2 diabetes patients (14). As Neuen et al. described, the ability of sodium-glucose cotransporter 2 (SGLT2) inhibitors to decrease albuminuria brought expectations for significant renal benefits (12). Studies have demonstrated that lowering of albuminuria by SGLT2 inhibitors, may be attributed to a direct renal effect through various possible mechanisms such as reduction of glomerular hyperfiltration and tubulointerstitial fibrosis (15).

In the SGLT2 inhibitor trials made with the purpose of establishing cardiovascular (CV) safety, secondary endpoints suggested possible renal benefit considering that these studies were not designed for this purpose and the populations were mostly low risk for renal disease progression (14). Recently, due to the results seen in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) renal outcomes trial, the SGLT2 inhibitor canagliflozin became the only type 2 diabetes therapy which has received FDA approval for the reduction of the risk of end-stage renal disease (ESRD), doubling of serum creatinine, cardiovascular death and heart failure hospitalizations in type 2 diabetes patients with CKD with UACR >300 mg/g. However, during the submission of our article, the renal outcomes trial for the SGLT2 inhibitor dapagliflozin was in process. In the CREDENCE trial, renal benefits were seen independent of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) which 99% of the patients used (14). Type 2 diabetes patients with CKD, as seen in different studies, are also at higher risk of heart failure hospitalizations and this medication reduces this risk (14).

This study aimed to determine the prevalence of severely increased albuminuria (UACR ≥ 300 mg/g) in type 2 diabetes patients with chronic kidney disease of low socioeconomic status in the San Juan City Hospital. Also, it assessed the percentage of patients who fulfilled the indication criteria for canagliflozin and would benefit from healthcare coverage of this medication for reno-protection. The study also evaluated the association of albuminuria with different laboratory parameters and conditions as seen in other studies.

Patients and Methods

This cross-sectional study examined the electronic health record of 129 Hispanic patients of 21 years or older with type 2 diabetes at the nephrology and endocrinology outpatient clinics at the San Juan City Hospital. These patients were required to have CKD and low socioeconomic status (defined as having government healthcare plan). The study evaluated the prevalence of severely increased albuminuria in these patients from the San Juan City Hospital from 1 July 2017 to 31 January 2020. The patients were obtained through the institutional electronic health record, under the care of nephrology and endocrinology attendings, utilizing the following ICD10 codes: E11.65, E11.22, E11.21, E11.9, N18.1, N18.2. N18.3, N18.9, R80.9 and R80.8.

The patients in this study had type 2 diabetes and were selected based on the availability of urine albumin creatinine ratio (UACR) as part of the annual workups. The patients were included if they reached one or both of the following criteria for CKD: estimated GFR (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation) below 60 ml/min per 1.73 m^2 and/or UACR ≥30 mg/g (utilizing 2 or more random spot urine collections of albumin and creatinine over at least a 3-month period). All of the patients included had a renin-angiotensin-aldosterone system (RAAS) blocker. The study also obtained demographic information such as sex, age, body mass index (BMI) and comorbidities such as coronary artery disease (CAD), heart failure (HF) and hypertension (HTN) by history. The diagnosis of HTN was obtained based on elevated blood pressures on record review. Patients were excluded if they had type 1 diabetes mellitus or end stage renal disease (ESRD).

The primary objective of the study was to determine the prevalence of severely increased albuminuria in the type 2 diabetes population with CKD of low socioeconomic status in San Juan in order to define the percentage of patients who fulfill the indication criteria for canagliflozin for renal benefits as described in the recently published CREDENCE trial. As a secondary objective, the study evaluated if there was a correlation between degree of albuminuria and lower estimated GFRs. In addition, correlation between other variables such as hemoglobin A1C and BMI with that of albuminuria, was evaluated. Lastly, the study evaluated for an association between albuminuria groups (normoalbuminuria, microalbuminuria and macroalbuminuria) and comorbidities such as CAD and HF. For simplification, these three albuminuria terms were used for this analysis. Normoalbuminuria is defined as UACR < 30 mg/g and microalbuminuria as UACR 30-300 mg/g. Nonetheless, it is important to mention that the currently used term for UACR < 30 mg/g is normal-mildly increased albuminuria (7). The normal UACR is considered to be less than 10 mg/g (7). For all the study analyses, UACR2 was used, meaning the most recent UACR value obtained in each patient.

The statistical analysis was done with MedCalc® for Windows Ver. 19.1.3. The analysis included descriptive statistics (frequency distributions, means and standard deviations) and

correlations of continuous variables using Pearson correlation coefficients and 95% Confidence Intervals. Also, Chi-squared test for trend was used to evaluate the prevalence rates of CAD and HF when comparing albuminuria groups. A P value of ≤ 0.05 was considered to indicate statistical significance. This investigation was approved by the San Juan City Hospital Institutional Review Board (IRB).

Results

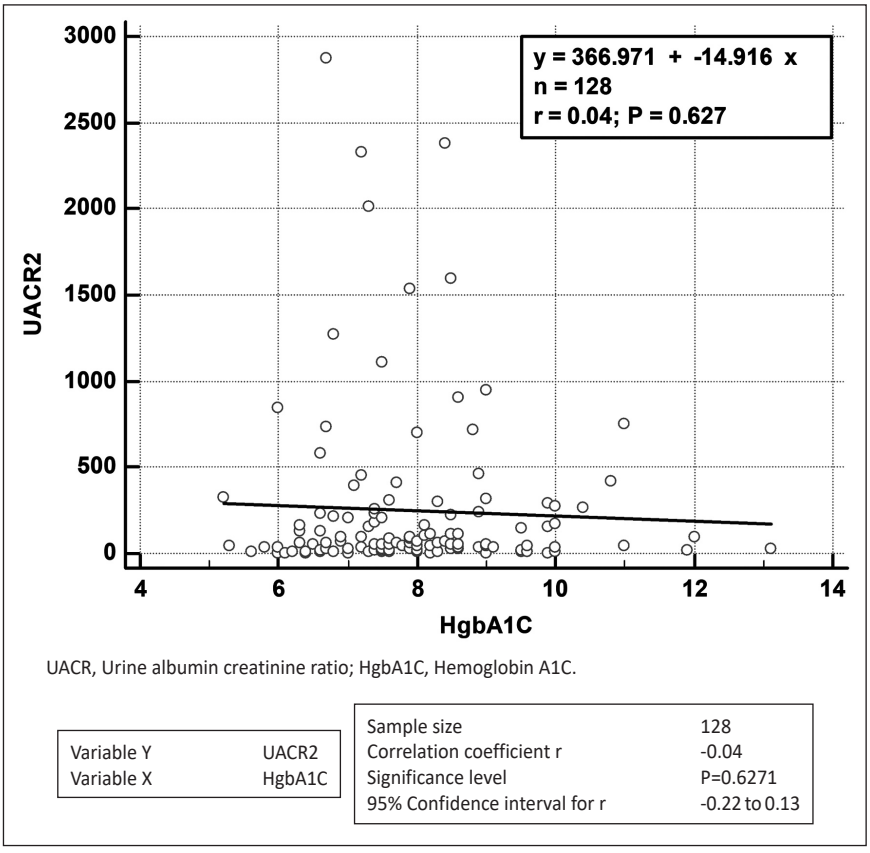
A total of 300 records from type 2 diabetes patients at the nephrology and endocrinology outpatient clinics were screened. Only 129 patients filled the requirements for chronic kidney disease and had two UACR measurements for inclusion in the analysis of this study.

The mean age in this study was 64 years with 64.3% of the patients being women. The mean glycated hemoglobin (HgbA1C) was 8.0% (64 mmol/mol) and the mean BMI was 31.2 kg/m^2. The lowest estimated GFR (eGFR) was 22 ml/min per 1.73 m^2 while the highest eGFR was 103 ml/min per 1.73 m^2 with a mean eGFR of 57.7 ml/min per 1.73 m^2 and a mean creatinine value of 1.38 mg/dL. The maximum UACR value was 2,868 mg/g and the mean UACR was 247 mg/g (Table 1). The prevalence of moderately and severely increased albuminuria in patients with type 2 diabetes and CKD were 66 (51.2%) and 24 (18.6%) respectively (Table 1). The patients with type 2 diabetes who filled the FDA indication for canagliflozin (eGFR ≥ 30 ml/min per 1.73 m^2 in addition to UACR > 300 mg/g) were 16.3% of the population. The prevalence of HTN, CAD and HF were 61.2%, 15.5% and 10.1% respectively. All the patients had a RAAS blocking agent, with 54.3% using an angiotensin II receptor blocker (ARB). In this patient population with type 2 diabetes, there was no correlation between HgbA1C and degree of albuminuria (r = -0.04, 95% confidence interval (CI): -0.22, 0.13; P = 0.627) (Figure 1). Also, upon analysis, there was no correlation between BMI and degree of albuminuria (r = 0.005, 95% CI: -0.170, 0.181; P = 0.952) (Figure 2). Between severity of albuminuria and lower eGFR, a tendency was observed although not statistically significant (r = -0.14, 95% CI: -0.31, 0.03; P = 0.109) (Figure 3). Upon evaluation of the association between the albuminuria groups and CAD, a noticeable tendency was observed close to reaching statistical significance (P = 0.060) (Table 2). Lastly, no association was found between albuminuria groups and HF (P = 0.521).

Table 1. Patient characteristics and the prevalence of albuminuria by groups in patients with T2DM and CKD.

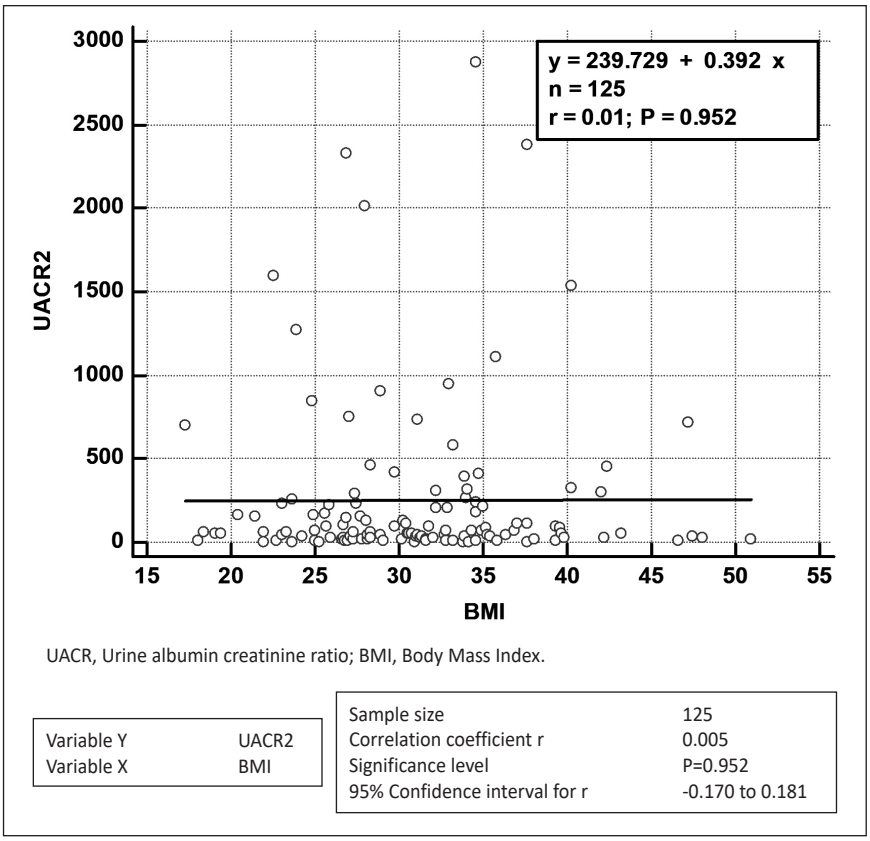
Characteristics	All	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
No. (%)	129 (100)	39 (30.2)	66 (51.2)	24 (18.6)
Mean age yr *	64.2 (9.9)			
Male (%)	46 (35.7)			
Female (%)	83 (64.3)			
ACEI (%)	59 (45.7)			
ARB (%)	70 (54.3)			
HgbA1C mean % *	8.0 (1.4)			
BMI Mean *	31.2 (6.8)			
Creatinine Mean *	1.38 (0.46)			
GFR mean *	57.7 (20.9)			
UACR mean *	247 (487.6)			
HTN (%)	79 (61.2)			
CAD (%)	20 (15.5)			
HF (%)	13 (10.1)			

*Data presented as mean (standard deviation); ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; HgbA1C, Hemoglobin A1C; BMI, Body Mass Index; GFR, Glomerular filtration rate; UACR, Urine albumin creatinine ratio; HTN, Hypertension; CAD, Coronary artery disease; HF, Heart Failure.



UACR, Urine albumin creatinine ratio; HgbA1C, Hemoglobin A1C.

Figure 1. Correlation between HgbA1C and albuminuria as continuous variables.



UACR, Urine albumin creatinine ratio; BMI, Body Mass Index.

Variable Y	UACR2
Variable X	BMI

Sample size	125
Correlation coefficient r	0.005
Significance level	P=0.952
95% Confidence interval for r	-0.170 to 0.181

Figure 2. Correlation between BMI and albuminuria as continuous variables.

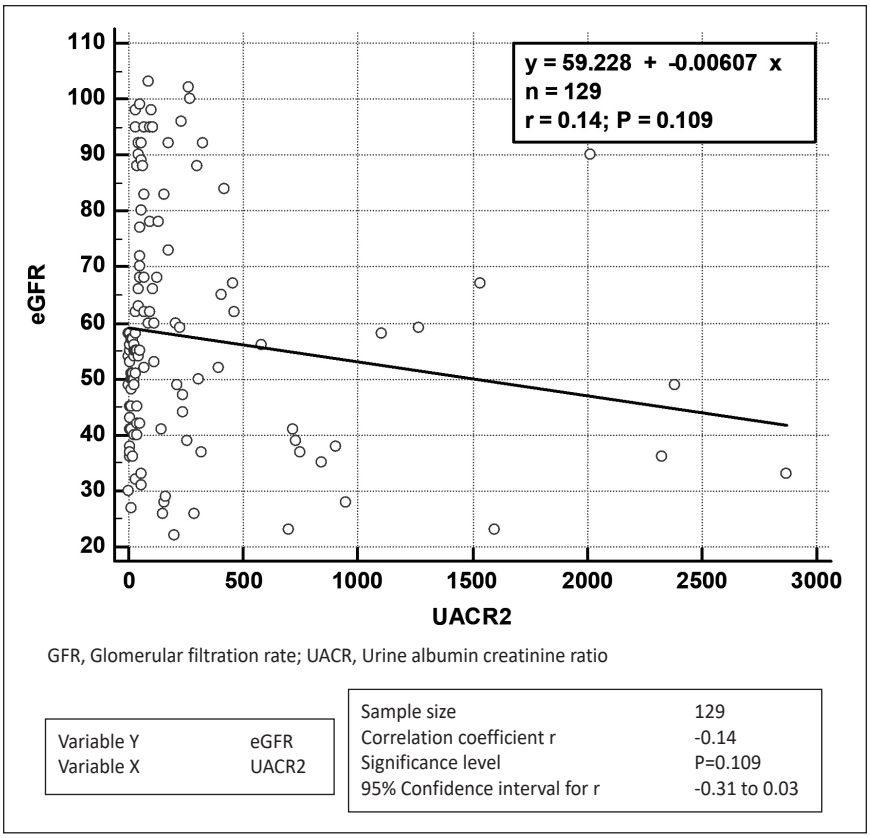
Discussion

In this study, we found that the prevalence of moderately and severely increased albuminuria (previously known as micro and macroalbuminuria) in the Hispanic type 2 diabetes patients with CKD at our institution was 51.2% and 18.6% respectively. Upon review of the literature, the prevalence of severely increased albuminuria in patients with DKD has been seldom studied. Most of the previous studies found in literature have evaluated the prevalence of albuminuria in the type 2 diabetes population in general. As Geith et al. (10) states, Hispanics with type 2 diabetes have the second highest prevalence (10.3%) of severely increased albuminuria. It is reasonable to think that the prevalence of severely increased albuminuria in type 2 diabetes patients with CKD would be considerably higher than the prevalence found in type 2 diabetes patients in general, as evidenced from the data in our study population.

As described in the literature, one of the most important risk factors for diabetic kidney disease progression is albuminuria, in addition to uncontrolled glycemia and arterial hypertension (2). Also, the first clinical sign of classic diabetic renal damage is the occurrence of albuminuria (16). It is noteworthy to mention that albuminuria has been proven to be an independent risk factor for cardiovascular disease in multiple epidemiologic studies (17). Duru et al. (2) and Gerstein et al. (17) both describe albuminuria as a continuous risk factor thereby increasing risk of ischemic CV events and progression of kidney disease, as UACR increases. In our study, although we did not see a significant association between the degree of albuminuria and lower eGFR, there was a tendency. Evaluation for association between albuminuria groups and CAD was close to reaching statistical significance. Most likely, statistical significance not reached due to the small size of the study population. Similarly, the association with HF was assessed but was not statistically significant. The fact that HF diagnosis was obtained by history could contribute to underestimating this diagnosis in a population that is at high risk for HF. All these facts underscore the importance of type 2 diabetes screening for early detection, blood pressure evaluation and at least annual evaluation of renal function and urine spots for albumin/creatinine ratio in order to achieve timely initiation of reno-protective medications (16, 18).

Persson and Rossing highlight the fact that when DKD is not treated, there is a yearly decrease in eGFR between 2 to 20 ml/min per 1.73 m^2 (16). Nonetheless, if the condition is managed by reducing the mayor risk factors and implementing RAAS blockade, eGFR yearly decline is significantly diminished to 2 to 5 ml/min per 1.73 m^2 (16). There is clear evidence that ACE inhibitors (ACEI) and ARBs reduce progression of CKD in hypertensive patients with diabetes with UACR ≥ 300 mg/g (8). However, the residual risk is significant despite the use of these medications (19), underscoring the need for availability of new proven treatment modalities such as SGLT2 inhibitor therapy for this high-risk population for renal outcomes. The landmark randomized clinical trial CREDENCE, was adequately powered to show that canagliflozin significantly reduced clinically significant renal outcomes, cardiovascular events, in addition to heart failure hospitalizations (8, 14). These benefits were seen independent of glycemic control. Also, recently the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) in type 2 diabetes patients was stopped early due to the impressive benefits seen, making dapagliflozin another potential future treatment option for these patients.

As mentioned above, a significant number of patients (16.3%) in our population of low socioeconomic status, have the indication for canagliflozin 100 mg as studied in the CREDENCE trial. These patients at high risk of progression to ESRD, would greatly benefit from this medication if they



GFR, Glomerular filtration rate; UACR, Urine albumin creatinine ratio

Variable Y	eGFR
Variable X	UACR2

Sample size	129
Correlation coefficient r	-0.14
Significance level	P=0.109
95% Confidence interval for r	-0.31 to 0.03

Figure 3. Correlation between severity of albuminuria and eGFR as continuous variables.

Table 2. Prevalence Rates of Coronary Artery Disease (CAD) and Heart Failure (HF) comparing groups according to Albuminuria.

Variable	Normoalbuminuria N (%)	Microalbuminuria N (%)	Macroalbuminuria N (%)	p-value*
CAD	2 (10)	13 (65)	5 (25)	0.060
HF	3 (23.1)	7 (53.8)	3 (23.1)	0.521

*Chi-squared test for trend. P value ≤ 0.05 considered to indicate statistical significance CAD, Coronary artery disease; HF, Heart Failure.

had access to better healthcare coverage. SGLT2 inhibitors are relatively expensive treatments in this day and age, however the healthcare costs of preventable cardio-renal complications and hospitalizations are far superior. Thus, we greatly emphasize that cost-effectivity studies should be undertaken in order to compare costs of early use of these medications with the costs of not adequately treating these patients.

Limitations

This is a small study of 129 patients, greatly due to the fact that there was a considerable number of patients who did not have at least two reported UACRs upon review of patient records mostly at the nephrology clinics. As Persson and Rossing (16) have stated, there is a paucity of testing for annual screening for albuminuria even though the guideline recommendations are not new. Therefore, the prevalence of severely increased albuminuria in Hispanic type 2 diabetes patients with CKD needs future studies with a considerably larger pool of patients. This study also serves the purpose of increasing physician awareness of the importance of annual screening for diabetic kidney disease in this population since a vast amount of information demonstrates that renal disease progression can be delayed with different evidence-based interventions.

In conclusion, this study evaluated the prevalence of severely increased albuminuria in Hispanic type 2 diabetes patients with CKD. There is a paucity of data regarding this topic in the DKD population. Nonetheless, there is substantial evidence supporting the fact that albuminuria is a continuous risk factor for renal function deterioration as UACR increases (2). Larger epidemiologic studies are needed pertaining albuminuria in DKD, especially in high-risk ethnicities such as Hispanics in which the prevalence of macroalbuminuria has been reported to be among the highest in type 2 diabetes patients in general. However, the future looks brighter for high risk DKD patients given the recently reported evidence in the CREDENCE trial which showed prevention of clinically significant renal outcomes in type 2 diabetes patients with GFR ≥ 30 ml/min per 1.73 m^2 and UACR > 300 mg/g. This study underscores the fact that there are vulnerable populations with scarce resources who are constantly faced with healthcare disparities limiting their access to healthcare and innovative treatments with solid benefits. Cost-effectiveness studies are greatly needed to help create awareness of the costs of DKD complications to improve healthcare coverage of these valuable medications.

Resumen

Objetivo: El propósito de este estudio era determinar la prevalencia de albuminuria severamente aumentada y el porciento de pacientes con indicación para canagliflozin en pacientes diabéticos tipo 2 (DMT2) con enfermedad renal crónica (ERC) de bajos recursos en el Hospital Municipal de San Juan. Métodos: Este studio transversal examinó record electrónico de 129 pacientes Hispanos con DMT2. ERC en esta

población fue definida de acuerdo a las guías más recientes de nefrología y endocrinología. Albuminuria fue diagnosticada con dos resultados positivos de la razón de albumina/creatinina en orina dentro de 3-6 meses. Los datos fueron obtenidos desde Julio 2017 a Enero 2020 y analizados utilizando estadísticas descriptivas y correlaciones. Resultados: La prevalencia de albuminuria moderadamente y severamente aumentada en pacientes con DMT2 y ERC fue 51.2% y 18.6% respectivamente. El numero de pacientes con DMT2 que llenaron los requisitos del FDA para canagliflozin fue 16.3%. La prevalencia de hipertensión, enfermedad coronarina (EAC) y fallo cardiaco fue 61.2 %, 15.5% y 10.1% respectivamente. Entre severidad de albuminuria y function renal, se observó una tendencia aunque no estadísticamente significativa (r = -0.14, 95% CI: -0.31, 0.03; P = 0.109). Al evaluar asociación entre grado de albuminuria y EAC, hubo una tendencia notable cerca de ser estadísticamente significativa (P = 0.060). Conclusión: Hay una escazes de estudios relacionados a la prevalencia de albuminuria severamente aumentada en pacientes de DMT2 con ERC y este estudio aporta a la literature. En el análisis de asociaciones, no hubo significancia estadística probablemente por la muestra pequeña.

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Dr. Irizarry-Villafañe wrote the manuscript, and researched data. Dr. González-Bóssolo, endocrinologist, involved in manuscript writing and revision. The authors acknowledge Dr. Ivan Iriarte, independent service, for his work in the statistical analysis of this study.

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