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EDITORIAL

In memoriam: Eduardo Slatopolsky, MD, 1934-2024

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Dr. Eduardo Alberto Slatopolsky, the Joseph Friedman *Emeritus* Professor of Medicine at Washington University, one of the most outstanding and brilliant nephrologists, passed away on April 24th, 2024. Of his 89 years, he had dedicated nearly 60 to studying renal pathophysiology and mineral metabolism in chronic kidney disease. His meticulous experimental work transformed the practice of nephrology worldwide, introducing new therapies that are now standard. His extraordinary dedication and immense talent as a meticulous physician, diligent researcher, mentor, and educator leave a deep mark on the lives of countless patients and colleagues.

Eduardo Alberto Slatopolsky (Ed, as he preferred to be called) was born in Buenos Aires on December 12th, 1934. He received his medical degree in 1959 from the University of Buenos Aires, and that same year, he married Judith Hirsh Field, the love of his life.

Fascinated by the kidney and its metabolic and homeostatic functions, he moved to the United States in 1960, where he began his residency in Cleveland, Ohio. During an elective rotation at the Cleveland Clinic, he worked under Dr. Willem Kolff, the father of hemodialysis.

In 1960, Ed read the article *The Pathologic Physiology of Chronic Bright's Disease. An exposition of the "intact nephron hypothesis* published by Neil Bricker in the *American Journal of Medicine*[1]. The article made such an impact on him that he contacted Professor Bricker, the first head of nephrology at Washington University School of Medicine in St. Louis, Missouri, and asked for the opportunity to study and work under his direction. In 1963, he was accepted in the nephrology post-graduate program, where he found fertile ground for clinical practice, science, and research. He joined Saulo Klahr, another Latin American, and Richard Rieselbach, all of them young enthusiastic researchers.

Ed learned surgical techniques applied to animal models, laying the foundation for his life as a researcher. On this foundation, Bricker assigned him to study the regulation of phosphate excretion in uremia, which became his niche, from which he made multiple contributions throughout his fruitful career, establishing himself as a pioneer in the development of knowledge around secondary hyperparathyroidism in chronic kidney disease. Thus, more than 50 years ago, he and Bricker formulated the trade-off hypothesis, suggesting that the increase in serum phosphate resulting from the loss of glomerular filtration leads to a progressive elevation in parathyroid hormone (PTH) production to stimulate phosphate excretion, at the cost of the relentless development of secondary hyperparathyroidism. His early publications are considered milestones in the field of nephrology. By 1970, Slatopolsky had become an independent, original, and creative medical scientist, rising to the rank of Professor of medicine in 1975. In 1991, Washington University honored his contributions by awarding him the Joseph Friedman Professorship in renal diseases and medicine.

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Over the years, new findings from his lab and others advanced the understanding of the pathophysiology of secondary hyperparathyroidism and its clinical management. His scientific contributions can be summarized in several themes. The first is the role of phosphorus in secondary hyperparathyroidism. His observation that phosphorus retention by the diseased kidney can trigger events leading to hyperparathyroidism[2] led to the demonstration that this could be prevented by proportionally reducing phosphate intake in the diet[3], and that this improvement was independent of calcium and calcitriol. He showed that phosphorus *per se* could influence the parathyroid glands[4]. Furthermore, his demonstration that dietary phosphorus restriction was effective in controlling hyperparathyroidism led to the introduction of phosphate binders, starting with aluminum salts. With the recognition of the toxic effects of these compounds, he moved on to study other phosphate binders and played a major role in introducing calcium salts[5], now widely used in clinical practice. Thanks to his studies, generations of dialysis patients have been spared from the toxic effects of aluminum. Later on, he demonstrated the association between calcium-based phosphate binders and vascular calcification, and once again he pioneered the introduction of non-calcium, non-aluminum phosphate binder, sevelamer, which is now widely used in the clinical management of renal patients.

In the early 1970s, he developed a radioimmunoassay for PTH, using a highly sensitive antibody derived from a rooster, known as *Macho*, for a series of experiments on secondary hyperparathyroidism. At a time when determining PTH levels was extremely difficult, this antibody facilitated advances in hormonal metabolism and its clinical use. This tool attracted countless physicians to his laboratory, many of whom went on to have stellar careers.

Over the years, findings from his laboratory and others revealed dysfunctions in both the calcium-sensing receptor and the Vitamin D receptor in the parathyroid cell. Ed was the first to demonstrate that intravenous calcitriol directly suppresses PTH secretion in uremic patients[6]. Not satisfied with the clinical efficacy of calcitriol, mainly due to its potential to cause hypercalcemia, he sought calcitriol analogs with less calcemic effect, which are now extensively used in clinical practice.

Ed's studies were so comprehensive that it is impossible to summarize them all in this recollection. However, of note that he and his group went on to show the role of a decreased expression of the calcium-sensing receptor and the Vitamin D receptor in parathyroid function. These findings, along with the discovery of fibroblast growth factor 23 by others, and the calcitriol synthesis deficiency, contribute to the development of secondary hyperparathyroidism and expanded his theory.

There is no doubt that Dr. Slatopolsky was a splendid and diligent physician and researcher who understood early on the interplay of phosphorus, calcium, PTH, Vitamin D, and bone metabolism disorders that almost invariably occur in patients with chronic kidney disease.

Parallel to his lab work, Ed founded Washington University's chronic dialysis program and directed the Chromalloy American Kidney Center for 30 years. This dual role as a researcher and clinical nephrologist allowed him to apply his lab findings to managing patients with chronic kidney disease.

Dr. Slatopolsky et al. published over 350 articles, more than 200 invited publications, numerous books and book chapters, and have been cited over 30,000 times. He also gave hundreds of national and international lectures, earning recognition from colleagues and numerous awards and honors from universities and scientific societies. These works range from studies in living animals to sophisticated cellular and molecular studies that, together, consolidated his hypothesis and enabled new proposals to be made.

Among his many awards are the Frederic C. Bartter Award from the Bone and Mineral Metabolism Society, the Belding H. Scribner Award from the American Society of Nephrology, the Víctor Miatello Award from the Latin American Society of Nephrology and Hypertension, the Amgen International Award from the International Society of Nephrology, the Peter H. Raven Lifetime Achievement Award from the St. Louis Academy of Sciences, and the Master Clinician Award from Washington University School of Medicine/ Barnes-Jewish Hospital.

Ed had a great ability to form teams and collaborative projects, like the multidisciplinary group of researchers in bone and mineral diseases set up at Washington University. This networking ability made him not only a scientific innovator but also one of the pioneers in bringing sophisticated nephrology science to Latin American countries and the rest of the world.

Attracted by the "phosphate and PTH fever," many physicians and researchers traveled to Saint Louis to follow the *Pied Piper of Hamelin* and work alongside this researcher leading the field of mineral metabolism. Following him was easy: his generosity, kindness, and willingness to share his findings and wisdom smoothed the path. He was a direct and gregarious man with a magnetic personality. From the first contact, he would

ask colleagues, professors, fellows, and residents to call him by his first name. As a friend and fellow at Washington University said: "Eduardo was the soul of the nephrology division." Thanks to him and Saulo Klahr, many foreign nephrologists and researchers found the doors of Washington University open. This gave many, the opportunity to train in a highly scientific environment and spread the knowledge acquired around the world. Latin American doctors owe him a special debt of gratitude. Many collaborators carried samples of PTH antibodies in their luggage, facilitating their development as independent researchers in their home countries. With Eduardo and Saulo's inspiration and guidance, many laboratories and researchers flourished south of the border.

Ed will be remembered by legions of disciples worldwide. His legacy extends beyond the lab and the lecture hall; he also transmitted his tireless enthusiasm and zest for life. His passions were wine and fine dining, and he was also a lover of opera, tango, and salsa. But, above all, it was devotion to his wife Judith, with whom he shared 52 years of marriage until her death in 2012. He is survived by his children, Diana, Daniel, and Andrea, six grandchildren, and one great-granddaughter.

Eduardo will be greatly missed, but he will continue to inspire all of us who had the privilege and joy of knowing him.

References

1. Bricker NS, Morrin PA, Kime SW Jr. The pathologic physiology of chronic Bright's disease. An exposition of the "intact nephron hypothesis". Am J Med. 1960;28:77-98.
2. Slatopolsky E, Caglar S, Pennell JP, Taggart DD, Canterbury JM, Reiss E, et al. On the pathogenesis of hyperparathyroidism in chronic experimental renal insufficiency in the dog. J Clin Invest. 1971;50:492-9.
3. Slatopolsky E, Caglar S, Gradowska L, Canterbury J, Reiss E, Bricker NS. On the prevention of secondary hyperparathyroidism in experimental chronic renal disease using "proportional reduction" of dietary phosphorus intake. Kidney Int. 1972;2:147-51.
4. Slatopolsky E, Bricker NS. The role of phosphorus restriction in the prevention of secondary hyperparathyroidism in chronic renal disease. Kidney Int. 1973;4:141-5.
5. Slatopolsky E, Weerts C, Thielan J, Horst R, Harter H, Martin KJ. Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25-dihydroxy-cholecalciferol in uremic patients. J Clin Invest. 1984;74:2136-43.
6. Slatopolsky E, Weerts C, Lopez-Hilker S, Norwood K, Zink M, Windus D, et al. Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. N Engl J Med. 1986;315:157-61.

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ORIGINAL ARTICLE

Fabry nephropathy. Urinary expression of podocyte proteins mRNA and microRNAs in non-albuminuric patients

Nefropatía por Fabry. Expresión urinaria de ARNm de proteínas podocitarias y microRNAs en pacientes no-albuminúricos

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Abstract

Objective: *Determining the mechanisms involved in early stages of Fabry renal damage is useful to: (i) increase the probability of therapeutic efficacy and, (ii) develop new potential therapies. In present study, a Fabry population without pathological albuminuria was included to evaluate urinary biomarkers indicative of podocyte damage and renal fibrosis through transforming growth factor-βeta (TGF-β) pathway, compared to healthy controls.* **Material and methods:** *This was a cross-sectional design.* **Results:** *Nineteen patients with Fabry disease and ten healthy controls were included in the study. The expression of TGF-β-mRNA in urine of Fabry patients was significantly lower than that found in controls (p = 0.006). Antifibrotic microRNAs (miR-29 and miR-200) were significantly lower in Fabry patients (p = 0.009 and p = 0.005 respectively). A higher expression of podocalyxin mRNA (p = 0.484) were observed in Fabry patients versus controls. A diminished expression of CD2AP (p ≤ 0.001), α-actinin-4 (p = 0.002) and podocin (p = 0.003) mRNA were observed among Fabry disease patients. The overall decrease in miR-29 and miR-200 was significantly correlated with CD2AP (p = 0.005) and α-actinin-4 (p = 0.033) urinary mRNA lower expression.* **Conclusions:** *Fabry non-albuminuric patients have decreased urinary mRNA TGF-β expression compared to healthy subjects. In Fabry population, an association between decreased urinary excretion of antifibrotic microRNAs and CD2AP, α-actinin-4, and podocin was found, a result not previously described in Fabry nephropathy.*

Keywords: *Fabry disease. Renal disease. Biomarkers. Albuminuria. mRNA. microRNAs.*

Resumen

Objetivo: *Determinar los mecanismos involucrados en etapas tempranas del daño renal por Fabry es de utiidad para: (i) incrementar la probabilidad de eficacia terapéutica y, (ii) permitir el desarrollo de nuevas terapias. En el presente estudio, una población de pacientes Fabry sin albuminuria patológica fue incluida para evaluar biomarcadores urinarios indicativos de daño podocitario and fibrosis renal via TGF-β, comparados con sujetos sanos.* **Material y métodos:** *estudio de corte transversal.* **Resultados:** *19 patientes con enfermadad de Fabry y 10 controles fueron incluidos. La expresión de TGF-β-mRNA en orina de pacientes Fabry fue significativamente menor que la hallada en controles (p = 0.006). microRNAs anti-fibróticos*

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(miR-29 and miR-200) fueron significativamente bajos en pacientes Fabry (p = 0.009 and p = 0.005 respectively). Elevada expresión de ARNm de podocalixina (p = 0.484) fue observeda en pacientes Fabry versus controles. Una diminuida expresión de ARNm de CD2AP (p ≤ 0.001), α-actinina-4 (p = 0.002) y podocina (p = 0.003) fue observada en pacientes Fabry. La disminución de miR-29 y miR-200 se correlacionó significativamente con una baja expresión urinaria de ARNm de CD2AP (p = 0.005) y α-actinina-4 (p = 0.033). **Conclusiones:** *Pacientes Fabry no-albuminúricos tienen decrecida expresión urinaria de ARNm de TGF-β comparados con controles. En pacientes Fabry, una asociación entre menor excresión urinaria de microRNAs anti-fibróticos y CD2AP, α-actinina-4 y podocina fue hallada, un resultado no descripto previamente en la nefropatía por Fabry.*

Paabras clave: *Enfermedad de Fabry. Enfermedad renal. Biomarcadres. Albuminuria. ARNm. MicroRNAs.*

Introduction

Fabry disease (FD, OMIM 301500) is caused by deficient activity of lysosomal enzyme α-galactosidase-A (αGAL-A), due to variants in GLA gene (chromosome Xq21.3-22). This results in impaired catabolism of globotriaosylceramide (Gb-3) and related glycosphingolipids, in lysosomes, with progressive accumulation in various cell lineages, including renal, cardiac, neural, and vascular cells1. In kidney tissue, all cell types are affected by Gb-3 deposition[1].

Life expectancy in affected patients is shorter than the general population due to premature onset of kidney disease, cardiomyopathy, malignant arrhythmias, and cerebrovascular events[2].

FD nephropathy is manifested by pathological albuminuria on childhood and subsequent estimated glomerular filtration rate (eGFR) decrease on adulthood[1,3], end-stage kidney disease (ESRD) with requirement for renal function replacement therapy occurs at age 40 in males with "classic" FD phenotype (FD type 1)[4] In women with "classic" FD, kidney disease is more variable, usually onset later[5]; while in patients of both genders with the "late-onset" phenotype (FD type II), nephropathy may be the only manifestation or be absent[1]. Efficacy of available specific therapies, enzyme replacement therapy and pharmacological chaperone migalastat, is greater the earlier they are started, due to their impossibility to correct irreversible histological lesions, such as tissue fibrosis[6-8]. In renal tissue, both (i) glomerulosclerosis (GS) and (ii) fibrosis and tubule-interstitial atrophy have been described, although some authors have controversially reported glomerular histological involvement without interstitial fibrosis[9] while, in contrast, other researchers have found greater fibrotic histological involvement in the tubule-interstitium with almost not glomerular sclerosis[10]. Similarly, the pathophysiological mechanisms of kidney damage in FD are controversial; some authors highlight the central role of the podocyte, with podocyturia and podocyte phenotype changes as an early event[11-14], although others have emphasized the inflammatory phenomena that affect the tubule-interstitial compartment, with transforming growth factor-βeta (TGF-β) as the main mediator[10,15,16]. Determining the mechanisms involved in early stages of renal damage due to FD is useful to: (i) increase the probability of therapeutic efficacy, before renal fibrosis stage[10,17,18] and (ii) develop new potential therapies.

In the present study, a population of FD patients without pathological albuminuria was included to evaluate the profile behavior of urinary biomarkers indicative of podocyte damage and renal fibrosis through TGF-β pathway, compared to healthy controls.

Material and methods

Subjects

Patients with confirmed FD diagnosis of any age and gender, with urinary albumin/creatinine ratio (uACR) < 30 mg/g. Exclusion criteria: (i) patients with a cause of kidney disease other than FD, (ii) patients who at the moment of screening presented any clinical condition that potentially alters the results of biomarkers included in the study, and (iii) patients who fulfilled the inclusion criteria but refused to participate in the study. Healthy subjects with similar demographic characteristics were included as a control group. The study subjects gave their informed written consent, authorizing the publication of their results. The adults signed consent and those of pediatric age agreed and an adult representative also signed, according to local legislation.

Blood and urine samples were taken first thing in the morning on patients fasting.

Mutational diagnosis of FD was confirmed by direct sequencing and multiplex ligation-dependent probe amplification[19,20]. To classify GLA gene variants, www.omim.org/entry/301500 database was used.

The quantification of αGAL-A activity was performed by the fluorometric method; values greater than > 4.0 nmol/h/l were normal[21]. Plasma and urinary creatinine were determined by electrochemi luminescence (Roche Diagnostics). Albuminuria was determined by colorimetric method (Roche Diagnostics). The uACR was determined by the ratio albumin (mg)/creatinine (gr), values < 30 were inclusion criteria[21]. eGFR was estimated by the CKD-EPI equation in adults and Schwartz 2009 equation in pediatric patients[22].

Neuropathic pain, hypo-hidrosis, and gastrointestinal symptoms were determined by questioning[1]. Angiokeratomas were determined by physical examination[1]. Hearing impairment was assessed by logoaudiometry[1]. FD cardiomyopathy was assessed by typical abnormalities in cardiac magnetic resonance imaging (MRI) and/or color DOPPLER echocardiogram and/or 12-lead electrocardiogram[1]. Central nervous system (CNS) damage was determined by history of stroke and/or typical FD lesions in CNS MRI[1]. FD clinical manifestations present or absent were considered as qualitative variables (yes/not) for statistical analysis.

Preparation of urine samples and extraction of microRNAs

The first urine samples in the morning were immediately sent to laboratory for processing. A sample volume of 10 ml was centrifuged at 3000 × g for 15 min. Nine mL of the supernatant were discarded and the remaining 1 ml was centrifuged at 15,000 × g for 5 min. The urine sediment was stored at –80°C until use. MicroRNA extraction was performed according to the NucleoSpin miRNA plasma kits protocol, Macheney-Nagel, Germany. At present, there is no method available that can assess the exact quantity or quality of "small RNAs" and standard spectrophotometric methods for measuring the yield and quality of microRNAs are not suitable for biological samples. If the yield and concentration of microRNAs are sufficient, the quality evaluation of the extraction method can be performed by capillary electrophoresis or reverse transcription (RT) plus real-time polymerase chain reaction (qPCR)[23]. We evaluated the extractions by quantifying the small nucleolar RNA U6 (small nucleolar RNA U6) by RT-qPCR. The reaction conditions are described below.

microRNAs RT-qPCR

To detect the urinary expression of miR-21, miR-29, miR-192, miR-200, and miR-433 families, a RT-reaction with a stem-loop primer was used[24]. Stem-loop primers were designed according to Chen's protocol[25]. The sequences of the primers and the reaction conditions were previously reported by us[26,27]. The specificity of each primer was determined by an extension of six nucleotides at the 3' end, this extension is inverse and complementary to the 6 nucleotides at the 3' end of each microRNA[27]. For RT of each microRNA, a Transcriptor First Strand cDNA Synthesis Kit (Roche Diagnostics) was used. The protocol, preparation, conservation and reaction conditions, RT-qPCR, amplification of coding DNA, and use of U6 RNA as a reference control were previously described by us[26,27]. The qPCR reaction was performed according to the StepOne Plus System protocol (Applied Biosystems). To quantify the relative expression of each microRNA family, the 2-ΔΔCt method was used[26,27].

mRNA extraction and RT-qPCR

Total RNA extraction was performed according to the MagNA Pure Compact RNA Isolation Kit protocol, Roche Diagnostics, Switzerland. The integrity of the RNA was confirmed by running on an agarose gel, which was found to be suitable for PCR. RNA purity was confirmed using an IMPLEN 330 relative absorbance ratio 260/280 (Implen, Germany). Samples with a radius greater than 1.8 were used for PCR. A Transcriptor First Strand cDNA Synthesis Kit (Roche Diagnostics, Switzerland) was used for RT. Preparation, protocol, reaction conditions and storage were previously described by us[28]. mRNA quantification was performed with an ABI Step One Plus system (Applied Biosystems, USA). Human β-actin was used as a reference housekeeping gene[28]. A FastStart Universal SYBR Green Master/ROX system (Roche Diagnostics, Switzerland) was used for the q-PCR reaction. The quantification of each mRNA relative expression was performed by the ΔΔCt method[28].

Statistics analysis

Descriptive statistics: Qualitative variables were expressed as percentages and continuous (quantitative) variables as mean ± standard deviation. Inferential statistics: parametric or non-parametric tests were used depending on the type of variable to be analyzed. A confidence interval of 95% was used. $p < 0.05$ were considered statistically significant. Data were processed in IBM SPSS Statistics 20 database.

Results

Twenty-nine subjects were studied; 19 FD patients and 10 healthy controls of similar age, gender, eGFR and albuminuria (Table 1). Among FD patients, 11 were pediatric and 8 adults; 17 patients presented "classic" type GLA variants (E398X, R227Q, L415P, L106R, C382Y; 6 males and 11 females) and two patients presented "later onset" GLA variants (R363H, R301Q; 2 females).

The expression of TGF-β mRNA in urine among FD patients was significantly lower than that found in controls ($p = 0.006$) (Fig. 1)

Urinary levels of pro-fibrotic microRNAs (miR-21, miR-192 and miR-433) were similar among FD patients versus controls ($p = 0.305$, $p = 0.128$ and $p = 0.128$ respectively), while anti-fibrotic microRNAs (miR-29 and miR-200) were significantly lower in FD patients compared to controls ($p = 0.009$ and $p = 0.005$, respectively) (Fig. 2).

Table 2 shows the result of multi-nominal logistic regression model with "decreased miR-29 and miR-200" as dependent variable for the variables "age", "gender", "genotype", "αGAL-A activity", "albuminuria"," eGFR", "neuropathic pain", "hypohidrosis", "gastro-intestinal symptoms", "angiokeratomas", "hearing loss", "cardiomyopathy," and "CNS involvement".

As seen in figure 3, Synaptopodin urinary mRNA expression ($p = 0.705$) from FD patients and controls was similar. A higher expression of podocalyxin mRNA ($p = 0.484$) was observed in FD patients compared to controls (Fig. 3). A diminished expression of CD2AP mRNA ($p \leq 0.001$), α-actinin-4 ($p = 0.002$) and podocin ($p = 0.003$) were observed in patients with FD compared to controls (Fig. 3).

Table 3 shows the associations found between each microRNAs family and renal function parameters versus urinary mRNA of podocalyxin, CD2AP, α-actinin-4 and podocin among FD patients. A significant correlation between miR-200 and CD2AP mRNA found in urine of with FD patients was found (Table 3).

Among the FD population, overall decrease of miR-29 and miR-200 was significantly correlated with CD2AP ($p = 0.005$) and α-actinin-4 ($p = 0.033$) urinary mRNA lower expression while it was not correlated with of synaptopodin ($p = 0.678$), podocalyxin ($p = 0.311$) and podocin ($p = 0.417$) mRNA urinary expression.

Table 1. Demographic characteristics and renal function of subjects classified as "Fabry" versus "Controls"

Variable	Fabry	Controls	p
Age (years)	21.15 ± 15.21	25.88 ± 15.25	0.472
Gender Male/ Female	6/13	4/6	0.664
eGFR (ml/min/m^2)	142.11 ± 35.45	120.72 ± 18.68	0.058
uACR (mg/g)	10.43 ± 7.41	8.55 ± 5.85	0.929

eGFR: estimated glomerular filtration rate; uACR: urinary albumin/creatinine ratio.

Table 2. Multi-nominal logistic regression model for dependent variable "decreased miR-29 and miR-200"

Variable	Association with "decreased miR-29 and miR-200"
Neuropathic pain	0.006*
Angiokeratomas	0.006*
Hipohidrosis	0.013*
αGAL-A activity	0.026*
GI symptoms	0.026*
eGFR	0.041*
Age	0.048*
Gender	0.077
Hearing loss	0.120
Cardiomyopathy	0.120
CNS involvement	0.179
Genotype	0.147
Albuminuria	0.342

*Statistically significant association.
-2 log verisimilitude: 0.000; R^2 Cox and Snell: 0.684; R^2 Nagelkerke: 1.000. αGAL-A: α-galactosidase-A; eGFR: estimated glomerular filtration rate; CNS involvement: Central nervous system involvement.

Discussion

GS and tubule-interstitial fibrosis (TIF) have been described in renal biopsies of FD patients; its presence is a factor of poor renal prognosis and favors progression to ESRD which occurs earlier and more severely in males with the "classic" FD variant[1,3,6]. TIF predominance and over-expression of TGF-β and VEGF-A in renal tissue of adult FD patients have been reported by some authors[10]; others however, have observed early podocyte involvement, without TIF[9].

In the present work, results of microRNAs related to renal fibrosis, growth factor TGF-β and urinary mRNA of podocyte proteins in non-albuminuric patients of both genders, adults and children, mostly with "classic" FD, are presented.

Table 3. Correlations between miR-21, miR-192, miR-433, miR-29, miR-200 and renal function parameters with synaptopodin, podocalyxin, CD2AP, α-actinin-4 and podocin mRNA in urine of patients with Fabry disease

	miR-21	miR-192	miR-433	miR-29	miR-200	uACR	eGFR
SIN	0.801	0.141	0.959	0.142	0.556	0.579	0.788
PXN	0.166	0.432	0.952	0.999	0.748	0.002*	0.777
CD2AP	0.920	0.594	0.802	0.189	0.023*	0.664	0.859
α-act-4	0.364	0.900	0.071	0.939	0.839	0.223	0.562
POD	0.314	0.132	0.118	0.144	0.953	0.954	0.015*

*Statistically significant correlation.
SIN: synaptopodin mRNA; PXN: podocalyxin mRNA; CD2AP: CD2AP mRNA; α-act-4: α-actinin-4 mRNA; POD: podocin mRNA; uACR: urine albumin/creatinine ratio; eGFR: estimated glomerular filtration rate.

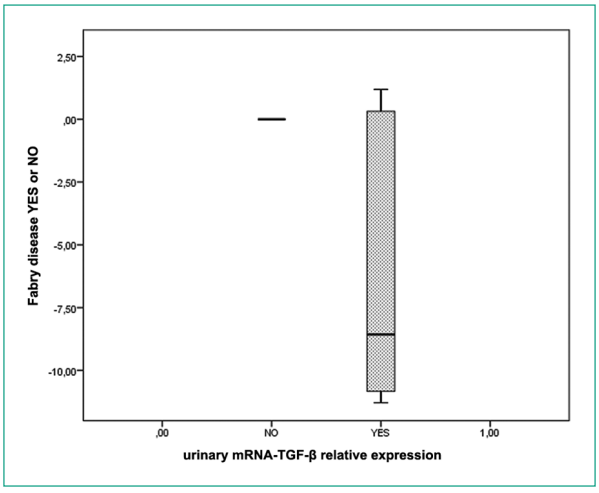

Figure 1. Relative expression of urinary TGF-β mRNA from patients with Fabry disease compared to controls.

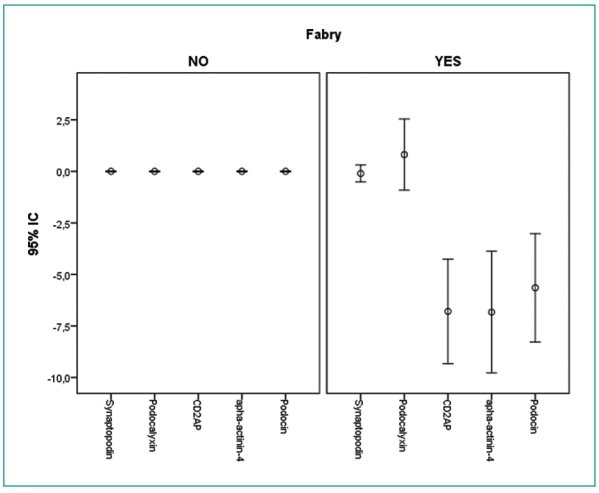

Figure 3. Urinary synaptopodin, podocalyxin, CD2AP, α-actinin-4, and podocin mRNA expression among patients with Fabry disease versus healthy controls.

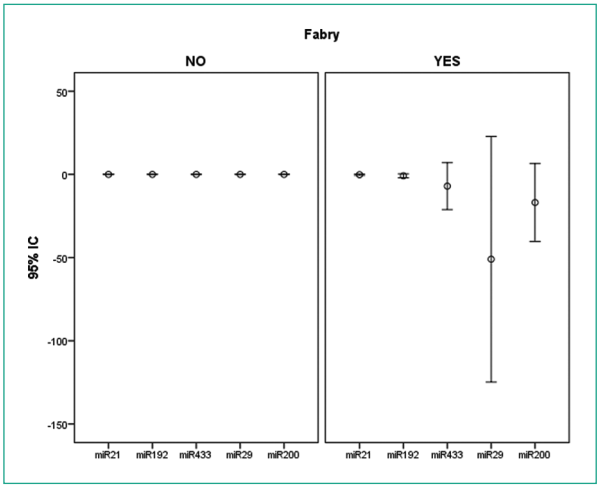

Figure 2. Comparative urinary levels of miR-21, miR-192, miR-433, miR-29, and miR-200 among Fabry disease patients versus healthy controls.

Renal over-expression of TGF-β in genetically modified animal models with FD[29] and adult human FD patients has been reported[16]; however, these results differ from those observed in our population, in which a significant urinary decrease expression of TGF-β mRNA was found.

During renal fibrosis process, miR-21, miR-192, and miR-433 (with pro-fibrotic function) are activated by TGF-β, while miR-29 and miR-200 (anti-fibrotic) are inhibited by TGF-β[30]. In the present study, a significant decrease in anti-fibrotic miR was observed in FD patients and similar quantification of pro-fibrotic miR among FD patients versus controls. These results coincide with our results from previous works, in which we had proposed a probable regulation of microRNAs related to renal fibrosis not mediated by TGF-β[26,27,31], at least in early FD renal damage stages, when

pathologic albuminuria is not present. The different expression of TGF-β in our study compared to that reported by other authors could be explained by the different populations included in each study; in our work, younger patients with a lower degree of nephropathy (non-pathological-albuminuria) were included compared to others studies where older patients with a lower eGFR were included in the study.

Urinary miR-29 and miR-200 decrease correlated with the typical early clinical manifestations of FD "classic" variant, and there was no correlation with major organic complications; probably because the patients included in the present study are non-albuminuric and present early stage of FD.

In contrast to the greater podocalyxinuria found in FD patients compared to controls, FD patients presented a significant decrease in urinary mRNA expression of podocyte cytoskeleton proteins components (CD2AP, α-actinin-4, and podocin). Podocalyxinuria is an adequate method to quantify podocyturia, because podocalyxin is a specific sialoglycoprotein and the main podocyte surface antigen; being located on the podocyte external surface, in contact with the uriniferous space, it allows early detection of podocyturia[13,32,33].

Decreased expression of CD2AP and α-actinin-4 correlated with decreased miR-29 and miR-200 in urine. This result could hypothesize new functions of miR-29 and miR-200 in FD nephropathy. In laboratory models of kidney disease, for example, the crucial role of miR-200 in podocyte maturation and differentiation has been demonstrated, in which miR-200 inhibition implies greater susceptibility to glomerular damage[34], early kidney tissue structure compromised early in FD patients[9].

Although the limitation of this study is the small number of patients included, studies with similar objectives have been reported with a similar population size, showing important results to the knowledge of FD renal pathophysiology[9,16].

The direct correlation between podocalyxinuria and albuminuria is an expected result, because in the early stages of kidney diseases with initial involvement of the glomerular structure, podocyturia is associated with greater albuminuria[12,32,35,36].

Conclusion

FD non-albuminuric patients have decreased urinary mRNA-TGF-β expression compared to healthy subjects. In this population, an association between decreased urinary excretion of anti-fibrotic microRNAs (miR-29 and miR-200) and podocyte cytoskeleton proteins (CD2AP, α-actinin-4, and podocin) was found, a result not previously described in FD nephropathy.

Author contributions

SJ: manuscript writing, patient evaluation, statistical analysis, and manuscript review. GP: carrying out laboratory tests and manuscript review. JII, NA, and FP: patient evaluation, data collection, and manuscript review. GV: statistical analysis and manuscript review.

Data availability statement

All data from the present study are available in the Research Department of "Instituto Universitario Italiano de Rosario" (investigacion@iunir.edu.ar).

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki). This study protocol was reviewed and approved by "Comité de Ética para la Investigación Clínica. Fundación Dr. J. R. Villavicencio" (annexed material), Alvear 854, S2000QGB, Rosario, Santa Fe, Argentina (www.villavicencio.org.ar).

The present study did not involve invasive interventions for the included subjects, because the biomarker determinations were carried out during routine medical check-ups. The ethical and technical procedures of this work were evaluated by the local research committees and departments.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data. Before the inclusion and publication of each subject's data, their vulnerability was evaluated.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document. Additional material regarding the data and procedures of the present study, as well as the informed consents, is available in Research Department of "Instituto Universitario Italiano de Rosario" (investigacion@iunir.edu.ar).

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30.
2. Zarate YA, Hopkin RJ. Fabry's disease. Lancet. 2008;372:1427-35.
3. Jaurretche S, Antongiovanni N, Perretta F. Prevalence of chronic kidney disease in Fabry disease patients: multicenter cross sectional study in Argentina. Mol Genet Metab Rep. 2017;12:41-3.
4. Jaurretche S, Antongiovanni N, Perretta F. Enfermedad vascular en pacientes varones con enfermedad de Fabry en hemodiálisis: estudio de cohorte retrospectivo en Argentina. Rev Nefrol Dial Transpl. 2019; 39:101-7.
5. Perretta F, Antongiovanni N, Jaurretche S. Major organic involvement in women with Fabry disease in Argentina. ScientificWorldJournal. 2018;2018:6515613.
6. Weidemann F, Sanchez-Niño MD, Politei J, Oliveira JP, Wanner C, Warnock DG, et al. Fibrosis: a key feature of Fabry disease with potential therapeutic implications. Orphanet J Rare Dis. 2013;8:116.
7. Ortiz A, Abiose A, Bichet DG, Cabrera G, Charrow J, Germain DP, et al. Time to treatment benefit for adult patients with Fabry disease receiving agalsidase β: data from the Fabry registry. J Med Genet. 2016;53:495-502.
8. Germain DP, Hughes DA, Nicholls K, Bichet DG, Giugliani R, Wilcox WR, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. N Engl J Med. 2016;375:545-55.
9. Tøndel C, Kanai T, Larsen KK, Ito S, Politei JM, Warnock DG, et al. Foot process effacement is an early marker of nephropathy in young classic Fabry patients without albuminuria. Nephron. 2015;129:16-21.
10. Rozenfeld PA, Bolla ML, Quieto P, Pisani A, Feriozzi S, Neuman P, et al. Pathogenesis of Fabry nephropathy: the pathways leading to fibrosis. Mol Genet Metab. 2020;129:132-41.
11. Trimarchi H, Canzonieri R, Schiel A, Costales-Collaguazo C, Politei J, Stern A, et al. Increased urinary CD80 excretion and podocyturia in Fabry disease. J Transl Med. 2016;14:289.
12. Trimarchi H, Canzonieri R, Schiel A, Politei J, Stern A, Andrews J, et al. Podocyturia is significantly elevated in untreated vs treated Fabry adult patients. J Nephrol. 2016;29:791-7.
13. Trimarchi H, Canzonieri R, Costales-Collaguazo C, Politei J, Stern A, Paulero M, et al. Early decrease in the podocalyxin to synaptopodin ratio in urinary Fabry podocytes. Clin Kidney J. 2019;12:53-60.
14. Trimarchi H, Ortiz A, Sánchez-Niño MD. Lyso-Gb3 increases αvβ3 integrin gene expression in cultured human podocytes in Fabry nephropathy. J Clin Med. 2020;9:3659.
15. Rozenfeld P, Feriozzi S. Contribution of inflammatory pathways to Fabry disease pathogenesis. Mol Genet Metab. 2017;122:19-27.
16. Feriozzi S, Rozenfeld P. Pathology and pathogenic pathways in Fabry nephropathy. Clin Exp Nephrol. 2021;25:925-34.
17. Jaurretche S, Antongiovanni N, Perretta F. Fabry nephropathy. Role of nephrologist and clinical variables associated with the diagnosis. Nefrologia (Engl Ed). 2019;39:294-300.
18. Jaurretche S. Pharmacological chaperones. New therapeutic alternative for Fabry disease nephropaty in Argentina. Rev Nefrol Dial Transpl. 2020;40:51-61.
19. Eng CM, Resnick-Silverman LA, Niehaus DJ, Astrin KH, Desnick RJ. Nature and frequency of mutations in the alpha-galactosidase a gene that cause Fabry disease. Am J Hum Genet. 1993;53:1186.
20. Schirinzi A, Centra M, Prattichizzo C, Gigante M, De Fabritiis M, Giancaspro V, et al. Identification of GLA gene deletions in Fabry patients by Multiplex Ligation-dependent Probe Amplification (MLPA). Mol Genet Metab. 2008;94:382-5.
21. Li Y, Scott CR, Chamoles NA, Ghavami A, Pinto BM, Turecek F, et al. Direct multiplex assay of lysosomal enzymes in dried blood spots for newborn screening. Clin Chem. 2004;50:1785-96.
22. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, et al. Kidney Disease: improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1-150.
23. Ach RA, Wang H, Curry B. Measuring microRNAs: comparisons of microarray and quantitative PCR measurements, and of different total RNA prep methods. BMC Biotechnol. 2008;8:69.
24. Kramer MF. Stem-loop RT-qPCR for miRNAs. Current protocols in molecular biology, 2011. 95(1), 15-10.
25. Chen C, Ridzon DA, Broomer AJ, Zhou Z, Lee DH, Nguyen JT, et al. Real-time quantification of microRNAs by stem-loop RT-PCR. Nucleic Acids Res. 2005;33:e179.
26. Jaurretche S, Venera G, Antongiovanni N, Perretta F, Perez GR. Urinary excretion of microRNAs in young fabry disease patients with mild or absent nephropathy. Open J Nephrol. 2018;8:71-83.
27. Jaurretche S, Venera G, Antongiovanni N, Perretta F, Pérez G. Urinary excretion profile of microRNAs related to renal fibrosis in Fabry disease patients. A pilot study. Meta Gene. 2019;19:212-8.
28. Jaurretche S, Venera G, Antongiovanni N, Perretta F, Perez GR. Possible role of transforming growth factor-βeta on podocyte injury and microRNAs regulation in early Fabry nephropathy stages. Br J Med Health Sci. 2020;6:594-601.
29. Lee MH, Choi EN, Jeon YJ, Jung SC. Possible role of transforming growth factor-β1 and vascular endothelial growth factor in Fabry disease nephropathy. Int J Mol Med. 2012;30:1275-80.
30. Chung AC, Lan HY. MicroRNAs in renal fibrosis. Front Physiol. 2015;6:50.
31. Jaurretche S, Perez G, Antongiovanni N, Perretta F, Venera G. Variables associated with a urinary MicroRNAs excretion profile indicative of renal fibrosis in Fabry disease patients. Int J Chronic Dis. 2019;2019: 4027606.
32. Pereira EM, da Silva AS, Labilloy A, do Monte Neto JT, do Monte SJ. Podocyturia in Fabry disease. J Bras Nefrol. 2016;38:49-53.
33. Doykov ID, Heywood WE, Nikolaenko V, Śpiewak J, Hällqvist J, Clayton PT, et al. Rapid, proteomic urine assay for monitoring progressive organ disease in Fabry disease. J Med Genet. 2020;57:38-47.
34. Li Z, Yin H, Hao S, Wang L, Gao J, Tan X, et al. miR-200 family promotes podocyte differentiation through repression of RSAD2. Sci Rep. 2016;6:27105.
35. Najafian B, Svarstad E, Bostad L, Gubler MC, Tøndel C, Whitley C, et al. Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease. Kidney Int. 2011;79:663-70.
36. Fall B, Scott CR, Mauer M, Shankland S, Pippin J, Jefferson JA, et al. Urinary podocyte loss is increased in patients with Fabry disease and correlates with clinical severity of Fabry nephropathy. PLoS One. 2016;11:e0168346.

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ORIGINAL ARTICLE

Prevalence and treatment of chronic kidney disease in patients with type 2 diabetes in Mexico

Prevalencia y tratamiento de la enfermedad renal crónica en pacientes con diabetes tipo 2 en México

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Abstract

Objective: *In Mexico, chronic kidney disease (CKD) is among the top 10 causes of death in adults. Type 2 diabetes mellitus (T2DM) is responsible for 48.5% of cases. The objective of the study is to estimate the prevalence, treatment patterns, and costs associated with CKD in T2DM in Mexico by Kidney Disease Improving Global Outcomes (KDIGO) 2012 stage.* **Material and methods:** *This is a retrospective review of 1024 clinical charts of patients with T2DM treated in 10 public health centers in Mexico. Information from the private sector was obtained through a Delphi panel. The annual health resources use was quantified.* **Results:** *The prevalence of CKD in T2DM was stage G1 33.8%, G2 39.1%, G3 16.8%, G4 5%, and stage G5 5.4%. The proportion of patients with normal A1 albuminuria (< 30 mg/g) is 75, 39, 11, 10, and 4% for stages G1, G2, G3, G4, and G5, respectively, and for A3 (≥ 300 mg/g) it is 3, 18, 38, 43, and 71%, respectively. The annual cost in public hospital per stage is $17,398, $16,353, $21,293, $24,333, and $106,461; in the private settings is $1,900 for early stages (G1 and G2), $129,804 for G3, and $424,738 for G4 and G5 stages.* **Conclusions:** *Controlling and preventing the progression of CKD to advanced stages benefits patients and reduces the use of health services and health-care costs.*

Keywords: *Chronic kidney disease. Type 2 diabetes. Prevalence. Health resources use.*

Resumen

Objetivo: *En México, la enfermedad renal crónica (ERC) se sitúa entre las diez principales causas de muerte en adultos. La diabetes tipo 2 (DT2) es la causa del 48.5% de estas. Estimar la prevalencia, uso de recursos y costos de la ERC en DT2 en México por estadio KDIGO (Kidney Disease Improving Global Outcomes) 2012.* **Material y métodos:** *Estudio retrospectivo de 1,024 expedientes de pacientes con DT2 atendidos en diez centros de salud pública. La información del sector privado se obtuvo mediante un panel Delphi. Se cuantificó el uso de recursos anual necesarios para su atención.* **Resultados:** *La prevalencia de ERC en DT2 es del 33.8, 39.1, 16.8, 5 y 5.4% para los estadios G1, G2, G3, G4 y G5 respectivamente. La proporción de pacientes con albuminuria A1 (< 30 mg/g) es del 75, 39, 11, 10 y 4%, y A3 (≥ 300 mg/g) es del 3, 18, 38, 43 y 71% respectivamente. El costo anual a nivel institucional por estadio es de $17,398, $16,353, $21,293, $24,333 y $106,461; en el medio privado es de $1,900 en estadios G1 y G2, $129,804 en estadio G3 y $424,738 para los estadios G4 y G5.* **Conclusiones:** *El control y prevención de la progresión de la ERC a etapas avanzadas beneficia a los pacientes y reduce el uso de los servicios de salud y los costos de atención médica.*

Palabras clave: *Enfermedad renal crónica. Diabetes tipo 2. Prevalencia. Uso de recursos.*

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Introduction

In Mexico, chronic kidney disease (CKD) is one of the leading ten causes of death among people > 45 years, with 11,188 deaths reported in 2020 according to the National Institute of Statistics and Geography (INEGI)[1]. Type 2 diabetes mellitus (T2DM) accounts for 48.5% of chronic kidney disease (CKD) cases[2]. This equates to 6.2 million Mexicans with diabetes who have kidney failure[3]. This positions CKD in T2DM as a public health problem. In 2014, the public health institution spent 13.25 billion pesos; a cost incurred by just 0.8% of the beneficiaries (CKD population)[4]. However, there is no national registry that allows understanding of the real prevalence and treatment of CKD in T2DM in its different stages (according to the current kidney disease improving global outcomes [KDIGO] classification), to comprehend the unmet needs in treating this disease. Therefore, this study aims to provide data on prevalence through staging in both private and institutional practices.

Methods

Research questions and objective

What is the prevalence of the different stages of CKD in a population with T2DM in a nationally representative sample according to the KDIGO 2012 classification? The objective was to estimate the prevalence and related health resources needed to treat CKD in patients with T2DM > 20 years in Mexico, stratified by KDIGO 2012 stages.

Study design: Public sector

To address the study objective, a retrospective analysis was conducted on a cohort of patients with T2DM attending routine follow-up consultations at the Mexican Institute of Social Security (IMSS), starting data collection in June 2022 until reaching the target sample size. At present, IMSS serves 80% of patients on replacement therapy, such as dialysis and hemodialysis, in Mexico[2,5]. The sample was collected through ten sites across the country: Family Medicine Unit (UMF) #16 in Quintana Roo, UMF #35 (Nuevo León), UMF #58 in the State of Mexico, Regional General Hospital (HGR) #1 in Yucatán, HGR #1 in Colima, HGR #1 in Durango, HGR #2 in Coahuila; UMF #21, UMF #28, and La Raza National Medical Center in Mexico City. The selected centers are hospitals with at least 165 beds; all are representative of the northern, central, or southern regions of the country. National Scientific Research Committee Registration No: R-2022-785-028.

Sample size

The sample size was estimated at 1024 health records, with a margin of error of 3% and a 95% level of confidence (CI 95%). This considers a population in Mexico for 2023 of 131,230,255 inhabitants according to INEGI figures[6]; 70.1% of whom are 20 years or older[7], with a T2DM prevalence of 13.5% (CI95%: 8.1-16.7) in the population > 20 years according to the International Diabetes Federation[8], and considering that the prevalence of CKD in the T2DM population is 38%[9].

The sample size was calculated using the formula:

$$n = Z_a \times p_0 \times q_0$$

D^2 = 1024 patients

Where n is the sample size, Zα is the critical value for the standard normal distribution for a confidence level of 0.05, p0 is the prevalence or proportion (in this case 0.5), q0 = (1−p0)q0 = (1−p0), and d2 is the precision (0.05).

Operational

Patients' health records were selected from those attending follow-up consultations that met the inclusion criteria: men and women ≥ 20 years old; diagnosed for more than 24 months, as defined by the American Diabetes Association; with or without a CKD diagnosis; with at least one serum creatinine and albuminuria evaluation (within the past 12 months). Exclusion criteria included patients with nephrotoxic treatments in the past 2 weeks, pregnant or breastfeeding women, patients with malignant neoplasms, acute or chronic heart failure, pulmonary failure, hepatic failure, kidney disease due to another cause, or acute kidney injury reported in the past 3 months. Once a matching case was identified, data were collected using a specifically designed registration card in a centralized online database.

Variables included

Demographics: age, sex, education level. Clinical: duration of T2DM, CKD stages (determined by estimated glomerular filtration rate [eGFR] and albuminuria), risk factors for CKD progression (smoking, dyslipidemia, hypertriglyceridemia, obesity, hypertension), biochemistry (serum creatinine, urine albumin-to-creatinine ratio

[UACR], urinary albumin excretion rate [UAE], glycated hemoglobin [HbA1c], serum glucose, cholesterol, triglycerides, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and serum albumin), medical consultations, laboratory tests, hospitalizations, treatment of T2DM and CKD.

Study design: private sector

The private sector represents about 5% of patients on renal replacement therapy. However, it is a highly fragmented sector, with multiple actors operating in a disjointed manner, poorly regulated, and with a wide range of quality levels, leading to a lack of homogeneity in health records[10]. To address this issue, a panel of 10 medical experts (5 internists, 2 of them with dual specialties [1 internist/endocrinology and 1 internist/nephrology], 2 endocrinologists, and 3 nephrologists) with private clinical practice was integrated. On average, they had 20 years of experience and collectively saw over 1200 patients monthly.

To standardize the information collected in both sectors, the registration card used in the IMSS was used as the basis for the questionnaire applied to the Delphi panel. The Delphi method is a technique developed as a systematic method aiming to achieve consensus based on expert discussion through an iterative process. By applying a questionnaire that is answered individually, validating the results in repeated processes until reaching a certain level of consensus, conclusions are drawn from the statistical exploitation of the obtained data. Once the experts answered the first round individually, the responses were integrated and shared with the group. In a plenary session, they provided feedback with the information obtained from clinical records to identify similarities and differences between private and public settings; thus, they could adjust their responses and reach the final consensus on the prevalence and treatment of CKD among patients with T2DM in private medicine in Mexico. The panel results are grouped by specialty, endocrinology, and internal medicine for patients with CKD stages G3a and G3b; while nephrologists report for patients with CKD stages G4 and G5.

Data analysis

Categorical variables are expressed as proportions and continuous variables by mean or median, as appropriate. Costs were estimated based on the unit costs of medical care at IMSS 2023 (Official Journal of the Federation [DOF]: 29/11/2022)[11], identifying the total amount of health resources demanded during 1 year:

Total Cost per Patient: $TCP_{jkw} = n_z \Sigma RQ_{jkwi} - PR_i$

Where TCP_{jkw} is the total cost for patient k in medical event j with T2DM at severity grade w; RQ_{jkwi} the resource use and during 1 year for the management of a medical event j with T2DM at severity grade w; PRi is the price or unit cost of resource i; w is the severity grade of kidney disease (KDIGO stage); k are the patients {1,2... n1}; j is the type of medical event (1 medical consultation, 2 emergency consultation, 3 hospitalization, 4 lab tests, and 5 CKD treatment), and I refer to the resources used for medical care {1,2... n2}.

For handling missing data, a list-wise deletion approach was used. Assuming all missing data were missing at random, and because the sample size is large enough, statistical power is not an issue. Therefore, the available data were analyzed. The information was processed using the XLSTAT 2021.2.2 statistical program for Microsoft Excel.

Results

A total of 1607 cases of patients with T2DM attending scheduled follow-up consultations at any of the participating centers were identified, of which 1024 cases were retrospectively included and analyzed according to the inclusion and exclusion criteria. A prevalence of 27.2% of CKD stage ≥ 3 in patients with T2DM > 20 years was obtained, specifically identifying CKD stage G1 in 346 (33.8%) patients (eGFR ≥ 90 mL/min), G2 in 400 (39.1%) cases (eGFR 60-89 mL/min), G3 in 172 (16.8%) patients (eGFR 30-59 mL/min), G4 in 51 (5%) cases (eGFR 15-29 mL/min) and G5 in 55 (5.3%) patients (eGFR < 15 mL/min). Urinary albumin levels mg/24 h by CKD stage are shown in Fig. 1.

Overall, the cohort has a mean age of 64.2 years, 61% are women, with a body mass index (BMI) of 29.3, 61.4% are actively working, and a median of 14.4 years since T2DM diagnosis. With a mean HbA1c level of 8.1%, of which only 26.9% report HbA1c levels < 7.0%; plasma glucose 144.3 mg/dL; mean eGFR 77.5 mL/min; total cholesterol 185.7 mg/dL; HDL 45.8 mg/dL; LDL 105.9 mg/dL; triglycerides 193.3 mg/dL; urinary albumin 53.6 mg/24 h; serum creatinine 1.51 mg/dL and urea 44.4 mg/dL.

Among prevalent comorbidities, hypertension occurred in 70.8% of all patients, hyperlipidemia in 26%, obesity in 45.1%, hypertriglyceridemia in 14.5% of patients, and smoking in 3.2%. Regarding chronic complications, diabetic foot is reported in 2.3% of all cases,

diabetic retinopathy in 5.3%, cerebrovascular disease in 1.9%, neuropathy in 10.5%, and ischemic heart disease in 3.4% of all patients.

In the private sector, the prevalence of CKD (eGFR < 60 mL/min/1.73 m^2 and ACR < 30) in Mexican patients with T2DM goes from 20% up to 30%, reaching up to 33-50% in patients with a > 10-year diagnosis of T2DM and ≥ 60 years old. Regarding albuminuria levels, this seems to correlate with CKD progression, as shown in figure 2.

The mean age of patients in stages G3 is 56 years, while in late stages (G4 and G5) the mean age is 60 years; 54.5% of the total are women; 39.5% have a BMI > 30 in stages G3 versus 23.3% in late stages. Another difference is the time since T2DM diagnosis, with 28% of patients in stage G3 having a more than 10 years history versus 71.3% of patients in late stages. The most common comorbidities are hypertension 63% and 82.5% in stages G3 and late stages, respectively, hypertriglyceridemia ≥ 175 mg/dL 39.5% and 42.55%, smoking 13% and 8.75%, hyperlipidemia ≥ 240-250 mg/dL 53% for both groups. Regarding the prevalence of chronic complications by CKD stage, they are diabetic foot 7.4% and 14%, respectively, diabetic retinopathy 26.5% and 52.5%, stroke 8.5% and 13.75%, neuropathy 49% and 42.5%, ischemic heart disease 17.5% and 27.5%, CKD 39% and 92.5%, heart failure 17% and 62.5%, and arrhythmias 15.6% and 21.3% for patients in stages G3a and G3b versus stages G4 and G5.

From the analyzed patient base, they attend medical consultations on average 9.4 times a year, while the total visits are 7.15 in stages G1 and G2, 9.55 visits in stage G3, 9.07, and 8.96 visits per year for stages G4 and G5. The most demanded service is family medicine, with 3.7 consultations per year, followed by endocrinology with 1.4 consultations per year, and 1.2 consultations with the nutritionist, while nephrology stands out in patients in advanced stages with 2.7 consultations per year. The total number of laboratories per patient per year is 8.6 in stage G1, 9.1 tests in G2, 9.5 for G3, 9.4 in G4, and 9.3 tests for G5.

Regarding patient follow-up and monitoring in the private sector, in early stages (G1 and G2) it is mainly performed by the GP (or pharmacy) twice a year, while from stage G3, the patient may attend follow-up consultations between 6 and 10 times a year to different services (nephrology 2.6-4 consultations per year, nutrition 2.8-5 consultations per year, cardiology 2-2.5 consultations per year, endocrinology 2.2-2.9 consultations per year, and family medicine between 1.6 and 2.86 consultations per year). Approximately 5% of patients will require a consultation with the surgeon for transplantation. The total annual laboratory tests by CKD stage are G1 and G2, 3; G3, 36.6; and G4 and G5, 48.8.

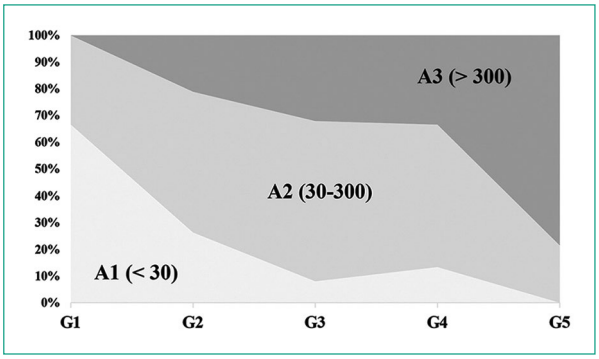

Figure 1. Urinary albumin Level mg/24 h by chronic kidney disease stage. These results should be analyzed carefully, as the urine albumin test is not yet commonly used within public health institutions. In this case, it was only present in 8.6% of the analyzed sample.

Metformin hydrochloride, NPH intermediate insulin, glargine insulin, sitagliptin, and pioglitazone are the most frequently used treatments in the analyzed population (Table 1).

While in the private sector, the most used alternatives are degludec insulin, glargine, lispro protamine, and intermittent NPH; along with linagliptin, metformin, and sitagliptin (Table 2).

Specifically, the use of sodium-glucose co-transporter type 2 inhibitors in stages G3 is intended for glycemic control, while their use in advanced stages is mainly to halt the progression of kidney disease.

Regarding CKD treatment, as the disease progresses, the number of drugs increases. Only 8% of cases in stage G1 report any CKD-related treatment drug, 19% of patients in stage G2 are on therapy, and 82% of all G3 patients, while those in stages G4 and G5 receive on average 2.2 and 3.5 drugs, respectively.

Specifically, the use of angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) increases as kidney disease progresses. ARBs are present in 1%, 3%, 12%, 25%, and 36% of cases in stages G1, G2, G3, G4, and G5, respectively; and 2%, 4%, 9%, 18%, and 15%, respectively in the case of ARBs (Table 3).

In the private sector, the most used antihypertensives in stage G3 are telmisartan (37%), losartan (16.5%), and amlodipine (12%); while in stages G4 and G5 they are nifedipine (27.5%), telmisartan (15%), or any other ACEI/

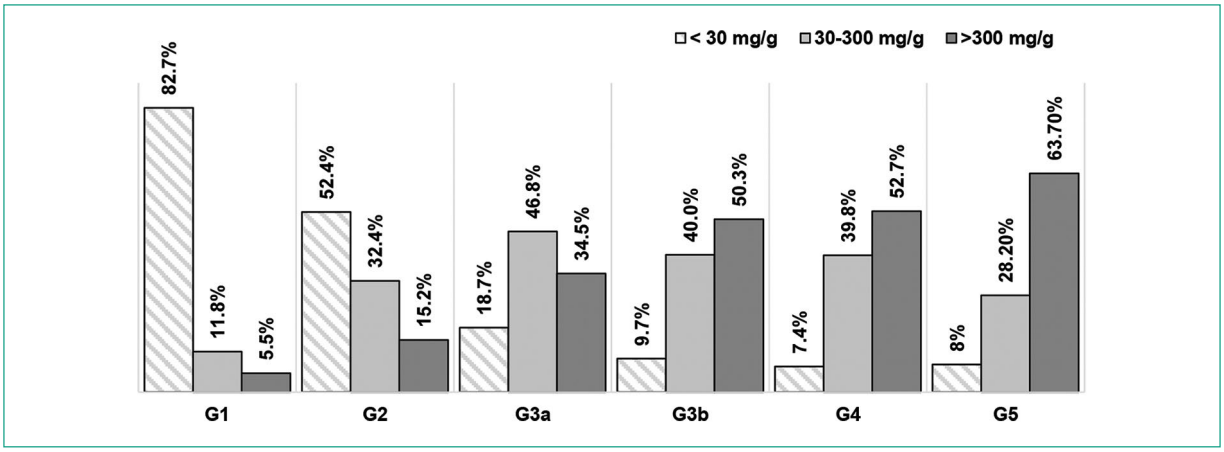

Figure 2. Albuminuria according to the chronic kidney disease stage. Private sector.

Table 1. Management of type 2 diabetes mellitus by KDIGO stage in centers from the public sector

Treatment	G1 (%)	G2 (%)	G3 (%)	G4 (%)	G5 (%)
Metformin	74.7	77.0	67.9	26.2	13.3
Insulin glargine	26.6	20.6	24.1	23.0	31.1
Sitagliptin	22.5	17.4	17.0	13.1	2.2
Intermediate NPH insulin	19.1	16.7	28.3	55.7	37.8
Dapagliflozin	14.0	13.0	9.4	4.9	0.0
Glibenclamide	12.6	12.1	9.9	5.0	6.7
Insulin lispro	10.2	6.7	5.7	9.8	6.7
Pioglitazone	9.6	3.9	8.0	19.7	6.7
Linagliptin	7.0	7.0	13.7	4.9	8.9
Insulin lispro/protamine	5.1	6.0	8.5	4.9	6.7
Other treatments	19.1	14.9	11.2	16.4	8.8

KDIGOL: Kidney Disease. Improving Global Outcomes.

ARB (25%). Among diuretics, furosemide (52%) is the most used in stage G3, followed by spironolactone (10%) and bumetanide (6%). For terminal stages, furosemide (40%), chlorthalidone (23.8%), and bumetanide (17.50%). Calcium carbonate as a supplement is used in 23% and 25% in stages G3 and G4-5, respectively. Vitamin D is preferably applied in the form of calcitriol (22%) and cholecalciferol (18%) in stage G3, and as calcitriol (20%) and cholecalciferol (12.5%) in stages G4 and G5. The use of erythropoietin is predominant in stages G4 and G5, with a preference for alfa-erythropoietin (45%), followed by methoxy-polyethylene glycol-epoetin beta (13.8%). In patients requiring transplantation, the preferred immunosuppressants are tacrolimus (32.5%), mycophenolate mofetil (16.3%), mycophenolic acid (15%), and prednisone (15%).

Of all the CKD G5 stage patients analyzed, 65.5% (n = 36) do not report replacement treatment, 18.2% (n = 10) report being on intermittent peritoneal dialysis, 9.1% (n = 5) on continuous ambulatory peritoneal dialysis, and 7.3% (n = 4) on hemodialysis. In contrast, in the private sector, only 14.7% would not receive replacement therapy. The distribution by treatment type is shown in figure 3.

No information was collected on the length of stay in the series of cases attended at IMSS, only outpatient

Table 2. Management of type 2 diabetes mellitus by KDIGO Stage in centers from the private sector

Treatment	G1-G3 (%)	G4-G5 (%)
Insulin degludec	52.5	27.5
Insulin glargine	44.0	45.0
Metformin hydrochloride 850 mg	33.0	20.0
Insulin lispro	26.3	21.3
Intermediate NPH insulin	21.4	60.0
Linagliptin 5 mg	20.3	17.5
Sitagliptin 100 mg	19.0	26.3
Canagliflozin	16.4	10.5
Insulin lispro protamine 75/25	13.1	20.0
Liraglutide 6 mg	10.6	6.8
Pioglitazone 15 mg	7.6	14.3
Rapid-acting insulin	6.8	7.5
Glibenclamide 5 mg	6.0	5.0
Dapagliflozin 10 mg	5.1	6.3
Other treatments	13.2	2.5

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Table 3. Use of resources and management of chronic kidney disease at the institutional level

Treatments	G1 (%)	G2 (%)	G3 (%)	G4 (%)	G5 (%)
Erythropoiesis-stimulating agents	0%	1	5	14	38
ARBs	1	3	12	25	36
Furosemide	0	0	7	9	32
Iron sulfate	0	1	4	11	30
Folic acid	0	1	4	16	30
Allopurinol	0	1	5	20	23
Beta-blockers	1	0	5	9	23
KA/EAA	0	1	7	20	21
Statins	4	6	9	20	21
Calcitriol	0	0	3	16	19
Prazosin	0	0	3	9	19
iECA	2	4	9	18	15
Nifedipine	0	0	1	2	15
Amlodipine	0	1	2	5	11
Hydralazine	0	0	1	0	6
Other treatments	0	0	5	25	8

KA/EAA: keto-analogues and essential amino acid supplements; ARBs: angiotensin II receptor blockers; ACE: inhibitors (iECA); angiotensin-converting enzyme inhibitors.

services were provided. However, it can be inferred from the information obtained through the expert panel. Thus, it is observed that as CKD progresses, not only does the percentage of hospitalized patients increase, from 20% in stage G3 up to 40% in stages G4-G5, but also the length of stay, with 1.4 and 3.4 admissions per year, respectively.

As a result of the patient's health deterioration, the proportion of active workers at the institutional level is higher than 60% in stages G1 to G3, decreases to 45.5% in stage G4, and 36.2% in stage G5. CKD progression not only reduces the proportion of active workers but also increases the number of work disabilities. This means more patients are absent from work (16% vs. 38% in stages G3 and G4-G5, respectively) and for longer periods (5 vs. 11.8 days), as reported by the expert panel.

Once CKD is established, the annual institutional costs of care increase by 26.2%, 44.2%, and 531% as patients progress to stages G3, G4, and G5, respectively. The annual cost of patients on replacement therapy is $225,041.84 (between $57,305 and $612,300 depending on whether it is dialysis or hemodialysis), however, it should be noted that only 34.5% of G5 stage cases report replacement therapy, so the expected population cost in G5 stage is $77,742. Regarding the annual cost of renal replacement therapy in the private sector, it ranges from $81,850.73 to $255,459.07 depending on the medical specialty group consulted, with a total annual CKD cost (excluding T2DM medications or antihypertensives) of $1,899.58 for early stages, $129,804.05 per year for stage G3, and $424,738.10 for end-stage renal disease (Table 4).

Discussion

Although this study does not present data on mortality associated with CKD progression, it is important to consider that the population with T2DM and CKD has a high cardiovascular and renal risk, and interventions to reduce this risk and delay CKD progression in T2DM patients are essential. In this regard, it has been reported that eGFRs < 60 mL/min (stages IIIa and IIIb) have adjusted hazard ratios for mortality of 1.2 and 1.8,

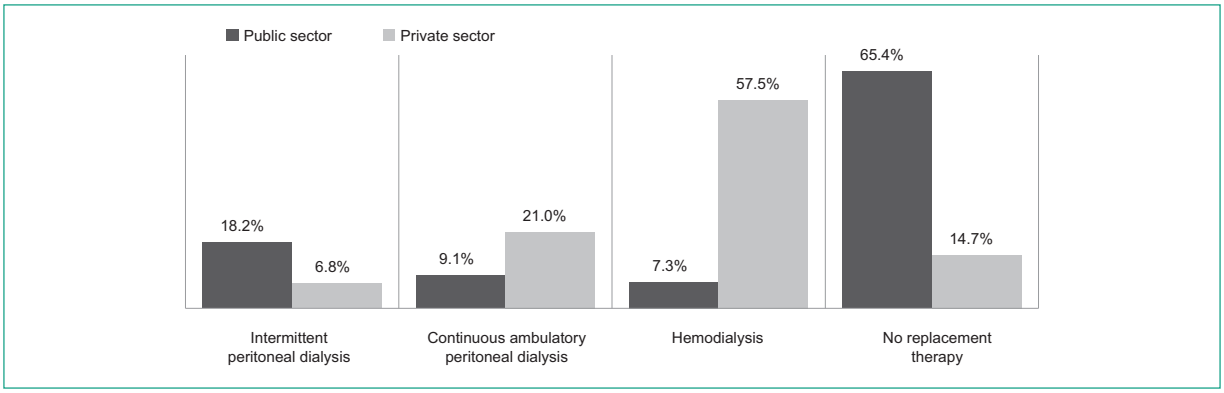

Figure 3. Renal replacement therapy (chronic kidney disease stage G5).

respectively, versus patients with levels > 60 mL/min[12]. This is clearly seen in Mexico, where death is the main cause of dropout in dialysis programs[2].

Regarding resource use, patients in CKD stages G1 and G2 attend medical consultations an average of 6.87 times a year, similar to the six visits per year reported by Rodríguez et al. in 2010[13] for patients with T2DM without chronic complications. As for outpatient visits in patients in stages G3, G4, and G5, 9.54 visits are reported; slightly higher than the eight outpatient visits per year in those T2DM patients undergoing peritoneal dialysis reported by Cortés-Sanabria et al. (2013)[14]. Similarly, the results reported by Sánchez-Cedillo et al. (2020)[15], who estimated the cost of kidney failure in patients on dialysis and hemodialysis in public health institution patients. However, despite the differences in the approach used to identify the necessary resources for the care of patients on dialysis and hemodialysis based on the experience of treating physicians versus the retrospective review of clinical records conducted in the present work, the estimates of the number of inputs and/or resources used during 1 year are similar to those reported in the present work, with eight consultations/year and approximately 9 laboratory tests and imaging modalities[15].

In particular, the annual cost per patient of renal replacement therapy in the public sector was estimated between $331,502 and $718,760/year; figures similar to the lower range reported by Villareal (2021)[16], who conducted a review of patients > 18 years undergoing hemodialysis in public outsourced hemodialysis units, with an average annual cost per patient with CKD managed with hemodialysis between $257,866 and $296,938 (figures updated to 2023)[17]. In contrast, the management of patients on hemodialysis reported at $320,848 by the consulted expert panel is lower than the institutional cost. This is mainly due to the differential in session cost, while in the institution's fee schedule, it is $3,925 per session[11], and the average cost reported by experts is $1,941.67/session.

We should mention that the findings in treatment patterns and resource utilization of outpatient services for patients with T2DM without CKD are not necessarily a reflection of compliance with the health-care guidelines established in the Comprehensive T2DM care protocol prevention, diagnosis, and treatment (IMSS, 2022)[18]. In it, medical follow-up is divided based on the glycemic control level of patients, resulting in 11 and 31 outpatient visits for controlled and uncontrolled patients, respectively, equivalent to $15,077 and $41,549 annually. Considering that approximately 26.9% of all analyzed patients are controlled, we can infer a weighted average annual follow-up cost of $34,428; the percentage of patients with glycemic control was slightly lower than reported by Calvo-Vázquez (2015)[19], who, through a retrospective review conducted at a single IMSS center in Mexico City, found that 66.5% of the analyzed population reported having poor glycemic control (HbA1c > 7%)[19].

Conclusion

Regarding diagnosis, the determination of creatinine, the calculation of eGFR, and the determination of UACR remain the main methods for diagnosing and monitoring the severity of CKD, so their standardized use in all patients with T2DM at least once a year should be promoted.

As it occurs in the public sector, in the private sector the use of resources during monitoring and follow-up of the patient with CKD in T2DM is determined by the severity of CKD. Thus, control and prevention of CKD

Table 4. Annual cost of CKD in T2DM according to stage

Public sector costs					
Service	**G1**	**G2**	**G3**	**G4**	**G5**
Laboratory tests	$1,165	$1,239	$1,286	$1,277	$1,259
Outpatient consultations	$9,505	$9,490	$13,585	$12,898	$12,923
T2DM treatment	$6,564	$5,149	$3,751	$3,535	$1,011
CKD treatment	$164	$475	$2,671	$6,624	$13,525
Replacement therapy	-	-	-	-	$77,742
Total annual	$17,398	$16,353	$21,293	$24,333	$106,461

Private sector costs			
Service	**G1-G2**	**G3**	**G4-G5**
Laboratory tests	$420	$6,530	$9,418
Outpatient consultations	$1,480	$11,526	$8,529
Hospital admissions	-	-	$29,897
Replacement therapy	-	$81,851	$255,459
Total annual	$1,900	$129,804	$424,738

T2DM: type 2 diabetes mellitus; CKD: chronic kidney disease.

progression to advanced stages benefit not only the health and quality of life of individuals but also lead to reduced use of health services, laboratory, and pharmacological treatment, and therefore the cost of medical care.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

References

1. Estadística de Defunciones Registradas 2020. México: INEGI; 2020. Available from: https://www.inegi.org.mx/contenidos/programas/mortalidad/doc/defunciones_registradas_2020_nota_tecnica.pdf [Last accessed on 2023 May 05].
2. Méndez-Durán A, Méndez-Bueno JF, Tapia-Yáñez T, Muñoz-Montes A, Aguilar-Sánchez L. Epidemiología de la insuficiencia renal crónica en México. Dial Traspl. 2010;31:7-11.
3. Obrador GT, Rubilar X, Agazzi E, Estefan J. The challenge of providing renal replacement therapy in developing countries: the Latin American perspective. Am J Kidney Dis. 2016;67:499-506.
4. Cortés-Sanabria L, Ayala-Cortés RA, Calderón-García CE, Silva-Ocegueda A. Retos y perspectivas de la enfermedad renal crónica en México: a propósito del día mundial del riñón, 2017. Rev Sal Jal. 2017;4:6-9.
5. Serna-Soto JL, Ortega-Mendoza RA, Rivera-Ramírez OA, Pérez-Peláez GC. Prevalencia de enfermedad renal crónica en pacientes con diabetes mellitus e hipertensión arterial en el Hospital Escandón. Salud Publica Mex. 2016;58:338-9.
6. Indicadores Demográficos de la República Mexicana, en el Año 2023. México: INEGI; 2023 Available from: https://www.conapo.gob.mx/work/models/conapo/mapa_ind_dem18/index_2.html [Last accessed on 2023 Jul 07].
7. Proyecciones de la Población de México y de las Entidades Federativas, 2016-2050. CONAPO; 2023. Available from: https://datos.gob.mx/busca/dataset/proyecciones-de-la-poblacion-de-mexico-y-de-las-entidades-federativas-2016-2050 [Last accessed on 2023 May 05].

8. Atlas de la Diabetes de la Federación Internacional de Diabetes. Novena Edición 2019. Versión On-Line. International Diabetes Federation; 2019. Available from: https://www.diabetesatlas.org/upload/resources/material/20200302_133352_2406-idf-atlas-span-book.pdf
9. United States Renal Data System. 2022 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2022.
10. Tamayo y Orozco JA, Lastiri Quirós HS. La Enfermedad Renal Crónica en México, Hacia una Política Nacional Para Enfrentarla. Academia Nacional de Medicina de México (ANMM). México, DF: Intersistemas; 2016.
11. Costos Unitarios por Nivel de Atención Médica Actualizados al año 2023. Gopbierno de México, Diario Oficial de la Federación; 2022. Available from: https://www.dof.gob.mx/nota_detalle.php?codigo=5672661&fecha=29/11/2022#gsc.tab=0 [Last accessed on 2023 Jan 15].
12. Wright JD, Folsom AR, Coresh J, Sharrett R, Couper D, Wagenknecht LE, et al. The ARIC (atherosclerosis risk in communities) study. JACC focus seminar 3/8. J Am Coll Cardiol. 2021;77:2939-59.
13. Rodríguez Bolaños RA, Reynales Shigematsu LM, Jiménez Ruiz JA, Juárez Márquez SA, Hernández Ávila M. Costos directos de atención médica en pacientes con diabetes mellitus tipo 2 en México: análisis de microcosteo. Rev Panam Salud Publica. 2010;28:412-20.
14. Cortés-Sanabria L, Rodríguez-Arreola BE, Ortiz-Juárez VR, Soto-Molina H, Pazarín-Villaseñor L, Martínez-Ramírez H, et al. Comparison of direct medical costs between automated and continuous ambulatory peritoneal dialysis. Perit Dial Int. 2013;33:679-86.
15. Sánchez-Cedillo A, Cruz-Santiago J, Mariño-Rojas FB, Hernández-Estrada S, García-Ramírez C. Carga de la enfermedad: insuficiencia renal, diálisis-hemodiálisis y trasplante renal en México. Costo de la enfermedad. Rev Mex Traspl. 2020;9:15-25.
16. Villarreal-Ríos E, Palacios-Mateos A, Galicia-Rodríguez L, Vargas-Daza E, Baca Moreno C, Lugo-Rodríguez A. Costo institucional del paciente con enfermedad renal crónica manejada con hemodiálisis. Rev Med Inst Mex Seguro Soc. 2021;58:698-708.
17. Cifras Actualizadas Mediante la Calculadora de Inflación del INEGI. Inflación Acumulada de Ene 2021 a Ene 2023 de 15.54%. México: INEGI. Available from: https://www.inegi.org.mx/app/indicesdeprecios/calculadorainflacion.aspx [Last accessed on 2023 Jun 05].
18. Protocolo de Atención Integral (PAI) Diabetes Mellitus Tipo 2. Prevención, Diagnóstico y Tratamiento. CDMX, México: IMSS; 2022. Available from: https://www.imss.gob.mx/sites/all/statics/profesionalesSalud/investigacionSalud/historico/programas/03-pai-dm-prevencion-diagnostico-y-tratamiento.pdf
19. Calvo-Vázquez I, Sánchez-Luna O, Yáñez-Sos AL. Prevalencia de enfermedad renal crónica no diagnosticada en pacientes con diabetes mellitus tipo 2 en atención primaria a la salud. Med Int Méx. 2015;31:41-9.

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ORIGINAL ARTICLE

Percutaneous implantation of the catheter for peritoneal dialysis by the nephrologist

Implantación percutánea del catéter para diálisis peritoneal por el nefrólogo

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Abstract

Objective: *A functioning peritoneal access without complications is crucial for carrying out dialysis treatment and achieving optimal results. Determine the clinical evolution of patients with peritoneal catheters (PCs) placed by the nephrologist, in the Dr. Abelardo Buch López Institute of Nephrology, from January 2014 to May 2022.* **Material and methods:** *Observational, descriptive, retrospective (historical) cohort study. A sample universe was used (92 patients), who received peritoneal dialysis and whose catheters were implanted by a nephrologist. A review of outpatient medical records was performed. The results were analyzed in Statistical Package for the Social Sciences v25. Descriptive statistics and the Kaplan–Meier technique were used.* **Results:** *In 76.1% the time elapsed between implantation and use was adequate. The average hospital stay was 1.03 days. The most frequent cause of late use of peritoneal access was implantation complications (63.6%): late (70.7%) and early (17.4%) complications. Peritonitis was the most prevalent infectious complication (30.4%) and non-infectious PC dysfunction (22.8%). Survival of the PC was high, showing 63.2% at 5 years.* **Conclusions***: The survival of the PC was high, with minimal complications and an adequate overall clinical evolution of the patients.*

Keywords: *Peritoneal dialysis/peritoneal catheter. Interventional nephrology. Percutaneous implantation.*

Resumen

Objetivo: *Un acceso peritoneal funcionante y sin complicaciones es crucial para la realización del tratamiento dialítico y para conseguir resultados óptimos. Determinar la evolución clínica de los pacientes con catéteres peritoneales (CP) colocados por el nefrólogo, en el Instituto de Nefrología Dr. Abelardo Buch López, de enero de 2014 a mayo de 2022.* **Material y métodos:** *Estudio observacional, descriptivo, de cohorte retrospectiva (histórica). Se utilizó universo muestral (92 pacientes), que recibían diálisis peritoneal (DP) y cuyos catéteres fueron implantados por nefrólogo. Se realizó una revisión de las historias clínicas ambulatorias. Los resultados fueron analizados en SPSS v25. Se utilizó estadística descriptiva y técnica de Kaplan-Meier.* **Resultados:** *En el 76.1% el tiempo transcurrido entre implantación y uso fue adecuado. La media de estadía hospitalaria fue de 1.03 días. La causa del uso tardío del acceso peritoneal más frecuente fue por complicaciones propias de la implantación (63.6%): tardías (70.7%) y tempranas (17.4%). La peritonitis fue la complicación infecciosa más prevalente (30.4%) y no infecciosa la disfunción del CP (22.8%). La supervivencia del CP fue elevada, el 63.2% a los cinco años.* **Conclusiones:** *La supervivencia del CP fue elevada, con mínimo de complicaciones y una evolución clínica global de los pacientes adecuada.*

Palabras clave: *Diálisis peritoneal/catéter peritoneal. Nefrología intervencionista. Implantación percutánea..*

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Introduction

Chronic kidney disease (CKD) is considered a clinical syndrome due to definitive changes in kidney function and/or structure and is characterized by an irreversible, slow, and progressive evolution[1-4].

Various studies have been conducted for the management of the disease, leading to the emergence of renal replacement therapies (RRT): hemodialysis (HD), kidney transplantation, and peritoneal dialysis (PD)[5].

PD constitutes an intracorporeal purification method that uses not an artificial dialyzing membrane as occurs in HD, but a biological membrane whose surface characteristics, vascularization, and cellular composition allow for exchange between an electrolyte solution infused on one side and the patient's blood. The peritoneum possesses such characteristics[6].

The development of a PD program will also depend, to a large extent, on establishing safe and durable peritoneal access with a functioning and problem-free peritoneal catheter (PC). Nothing is more detrimental to the development of a PD program than recurrent problems with catheter implantation or the existence of multiple complications related to peritoneal access[7].

The importance of functioning and complication-free peritoneal access is crucial for the execution of dialysis treatment and for achieving optimal results. Improvements in peritoneal access are attributed to advancements in the design of new catheters, the methods of implanting them, and post-insertion care. All of this has led to better catheter function and a decrease in complications arising from peritoneal access[7].

The main function of the PD catheter is to facilitate consistent bidirectional flow of the dialysate solution without requiring significant effort or causing discomfort or pain; a function governed by basic physical principles[7,8]. The PC must be implanted by an expert who is knowledgeable about the functions and complications of peritoneal access to ensure a greater chance of success[7-11].

There are two catheter insertion techniques: surgical and percutaneous; however, due to modifications made to these two techniques, the number of described techniques can be expanded[7-11].

It is important to consider that a series of factors will influence the achievement of stable and safe access. Among these, the most significant are related to the type of catheter, the method of implantation, the experience of the implanting physician, the body's reaction to the catheter, immediate care, and the characteristics of the patient. The implantation of the catheter should always be regarded as a surgical intervention that may have complications, so risks must be minimized, and the surgical procedure must be performed with the utmost care[6,7,9-11].

PCs are inserted by nephrologists, interventional radiologists, and surgeons. All that is required from them is experience and good outcomes with any of the techniques they utilize, although it is known that sometimes the choice of a technique is conditioned by the available resources and the experience of the implanting physician with that particular technique[6,7,9,11,12].

The insertion of the PC has become a procedure routinely performed primarily by surgeons worldwide. However, in recent years, there seems to be a new trend encouraging the involvement of nephrologists in the catheter placement process, within the framework of the development of interventional nephrology[13].

At the Nephrology Institute, the Seldinger puncture technique is currently preferred, and since 2013, the procedure has been predominantly performed by nephrology specialists. A scientific problem was identified: what are the main outcomes obtained in the percutaneous implantation of chronic peritoneal access in PD patients by nephrologists at Instituto de Nefrología Dr. Abelardo Buch López, Havana, Cuba?

The primary objective of this article was to determine the clinical evolution of patients with PCs placed by nephrologists at the above-mentioned health-care center.

Materials and methods

We conducted an observational, descriptive, retrospective cohort study with the aim of determining the clinical progression of patients with PCs placed by nephrologists at Instituto de Nefrología Dr. Abelardo Buch López from 2014 through 2022.

A sample universe was utilized, which included 92 patients on PD whose catheters (n = 92) were implanted by a nephrologist using the percutaneous technique, as they had access and the availability of the studied variables.

A review of the outpatient health records of patients participating in the PD program was performed, along with the documentation for the implantation procedure of the PD catheter in the operating room and the database (in Excel) of the program compiled by the co-author of the research, with monthly updates of the indicators.

When analyzing the study patients, it was confirmed that, following the choice of PD, the first action taken was a physical examination which, along with the medical history, allowed for determining whether the placement of a PC was feasible. In the medical history and

physical examination, the presence of previous surgical interventions that may have caused residual adhesions, and the presence of hernias (umbilical, inguinal, femoral, rectus diastasis, etc.) were evaluated; these clinical aspects constituted contraindications for the use of the investigated technique. In addition, the entry site of the catheter into the abdominal cavity and the exit point of the catheter on the skin were identified.

The Seldinger puncture technique was used for catheter implantation, using a trocar, dilator, tunneler, and guide for catheter placement. Local anesthesia was used, and in some cases, the patient was also sedated. The catheter was generally placed 3 cm below the left or right paramedian umbilicus; an incision was performed in the skin until reaching the fascia of the rectus abdominal muscles, followed by a small transverse incision to the one made in the skin, securing a stitch on each side. The peritoneal cavity was accessed with a needle, through which a metal guide was introduced, after which the needle was removed. Then, the dilator with its sheath was introduced through the guide; the guide and dilator were removed, leaving only the plastic sheath through which the catheter was introduced. Afterward, the sheath, the internal ring, or cuff, was removed, and it was left beneath the aponeurosis of the rectus muscle, tying the stitches so that the catheter was well adjusted to the muscle. The subcutaneous tunnel was then created, placing the external ring no < 3 cm from the exit site, ensuring it was appropriately positioned caudally to prevent fluid leakage and the entry of microorganisms.

In all evaluated patients, a group of requirements was monitored, including when to implant the catheter, patient preparation, catheter placement in the abdominal wall, creation of the subcutaneous tunnel and exit site, post-operative care, and conditioning before its use.

These patients started being followed in the outpatient clinic of the PD service at the center with monthly frequency, and a mean of 15 days after catheter implantation, they began their dialysis treatment in the different modalities of PD (manual and automated), with their variants.

The cohort study began in January 2014, when nephrologists started applying this technique at the center. The operationalized variables were collected from the referred information sources, with a follow-up trend until December 2022.

In evaluating the types of complications, they were divided according to two fundamental aspects: time of occurrence and etiology. The former described early complications that occurred within 30 days of PC implantation. A thorough analysis included complications related to the implantation of the PC *per se*, describing them according to their appearance 4 days after the technique was performed.

The microbiological profile of the peritonitis was analyzed at the center microbiology department[9].

All the information was processed automatically; the Statistical Package for the Social Sciences statistical package version 25 was used. Descriptive statistics were used with frequency distribution analysis, calculating absolute and relative frequencies for each qualitative variable. To determine catheter survival for PD, the Kaplan–Meier technique was used; for the test performed, a significance level of 95% was set ($\alpha = 0.05$, p [significance level] significant < 0.05).

The project for this research was previously approved by the hospital ethics committee and scientific council.

Results

In 76.1% of the study patients, the elapsed time was appropriate (12 and 16 days after implantation). In the series, the PCs were not used early, and in 23.9% of the sample, the use of the PC was delayed. Most patients were in an outpatient care regimen (80.4%), followed by those with lengths of stay of < 3 days (15.2%). The mean length of stay was 1.03 days, with a standard error of 0.154 (Table 1).

Table 2 shows the main causes that justified the late use of peritoneal access, which included complications related to implantation in 63.6% of the patients in this group (22 patients), followed by learning difficulties at 27.3%.

Table 3 shows the complications; 81 complication events occurred at the 8-year follow-up. Of note, most events presented late (70.7%), and only 17.4% occurred early. Only 6 events (7.4%) were related to the implantation of the PC *per se*, as they occurred within the first 4 days following the procedure. There was almost similar behavior between non-infectious complications and infectious complications (44.6% and 43.5%, respectively, of the total study sample).

The most frequent infectious complications included peritonitis (30.4%) and tunnelitis (17.4%). However, these were analyzed throughout the study period. Among the peritonitis cases, only 9 episodes (32.1%) occurred within the first 15 days after catheter implantation.

When identifying non-infectious complications in the study patients, the presence of episodes of PC dysfunction stood out (22.8%), as well as dislocation

(16.3%) and entrapment of the PC by the omentum with seven episodes being reported (7.6%).

The survival rate of the PC was high (Table 4 and Fig. 1), showing a 63.2% survival rate at the 5-year follow-up, and it was also observed that from 3 to 5 years, the same survival rate was achieved. The median survival in the sample was 6.398, with a standard error of 1.938. The results demonstrated a statistically significant association.

Discussion

A currently widely used technique is the percutaneous placement of the PD catheter. Apparently, it has the same efficacy and no greater complications than surgical placement. The main advantages of this technique are cost-effectiveness and short lengths of stay, as well as the use of local anesthesia and sedation during placement, thereby avoiding the potential complications of general anesthesia[14-16].

Regarding the time elapsed between placement and use of the PC, length of stay, and the causes that justify the late use of peritoneal access, several related studies were found. However, the results obtained in this research correspond with the implementation of the protocols approved by the center, which support use after 15 days of placement.

Montenegro[7] asserts that it is advisable to wait at least 2 weeks before starting to use the catheter. At 6 weeks, the catheter should be well secured, and care for the exit site is reduced to using soap and water, whether during or outside of showering, followed by vigorous drying.

The investigator himself supports the idea that, such as any permanent access to dialysis, the PC needs time for healing, settling, and ultimately maturation. Therefore, it is recommended to perform the insertion, at least, 1 month earlier than planned for its use to avoid complications arising from immediate commencement[7].

A favorable element in the investigated series was the non-early use, which reflects the opportunity in the implementation of the PC and adherence to appropriate patient selection criteria.

The application of this PC implantation method is commendable in terms of reducing the days of hospital admission. In the series, stays > 2 days were largely associated with patients who lived far from the hospital center. Sánchez et al. showed a mean length of stay of 4 ± 3.8 days in their patients[17].

On the late use of the PC, it is necessary to identify the learning needs of patients, a variable that has been widely studied. Daugirdas et al.[18] reported that optimal results were achieved in the development of the patient's therapy, strengthening self-care capacity, and development of skills and knowledge that facilitate adherence to nursing recommendations given during training[18].

The author agrees with Parra[19] and Gómez[20], who support the importance of education provided by nurses in training courses to prevent complications, especially infectious ones.

Table 1. Time elapsed between catheter placement and use and length of stay in the study patients

Variables/scales	Frequency	%
Time elapsed (days)		
< 12	0	0.0
12-16	70	76.1
> 16	22	23.9
Total	92	100.0
Length of stay scale	**No.**	**%**
Outpatient	74	80.4
≤ 3 days	14	15.2
> 3 days	4	4.4

Table 2. Reasons for delayed use of peritoneal access

Causes	Frequency	%
Patient learning difficulties	6	27.3
Difficulties in home conditions	2	9.1
Access complications	14	63.6
Total	22	100.0

Table 3. Complications by time of occurrence and etiology

Complications by time of occurrence		
Complications	**Frequency**	**%**
Early	16	17.4
Late	65	70.7
Complications by etiology		
Complications	**Frequency**	**%**
Infectious	40	43.5
Non-infectious	41	44.6

Table 4. Survival of the peritoneal catheter

Time (years)	Survival (%)	Standard error
1	85.2	3.8
2	73.6	5.3
3	63.2	6.6
4	63.2	6.6
5	63.2	6.6

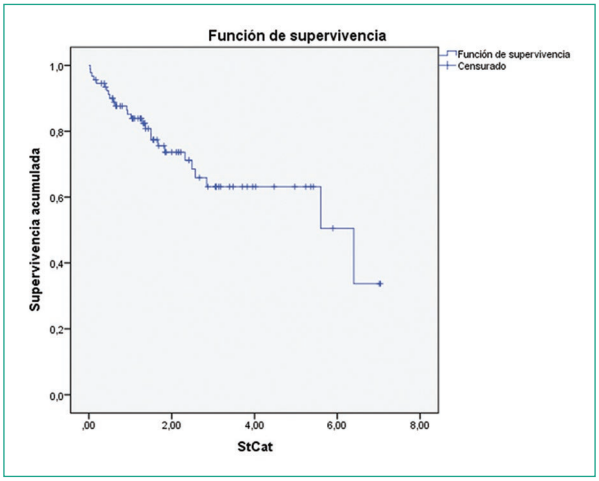

Figure 1. Survival of the peritoneal catheter. Instituto de Nefrología Dr. Abelardo Buch López. 2014-2022.

In the author's view, the pace of learning and the practical expression of the skills required to execute the technique vary considerably, and the factors are numerous. Therefore, it is essential to use flexible and individualized training methods.

Randomized and non-randomized prospective studies have demonstrated that peritoneoscopically placed PD catheters by nephrologists have fewer complications and longer catheter survival rates than those surgically inserted[21].

Various authors suggest that potential complications should be monitored daily within the first 10 days, and then monthly for 12 months after the initiation of PD[17,22,23].

In their series, Castro Gayoso et al.[17] found that 78.6% of patients did not present complications, with the most prevalent being catheter dysfunction (14.3%), hemoperitoneum (4.3%), and peritonitis (2.9%).

In general, catheter malfunction problems occur within the first few months after the initiation of RRT and largely depend on the correct catheter placement technique[24]. It represents a significant cause of failure of the technique, which can reach up to 20% due to inadequate dialysis, insufficient ultrafiltration, and multiple manipulations and interventions that may lead the patient to request a change in technique[24].

Several authors have studied the role of PC as an invasive device that can serve as a reservoir for bacteria[25,26]. In this regard, peritonitis is one of the most frequent complications of PD, impacting the patient's quality of life, survival, and nutritional status. It is characterized by the presence of cloudy dialysate fluid, abdominal pain, and a cytological examination of the dialysis fluid showing more than 100 leukocytes/mm^3, with, at least, 50% polymorphonuclear cells, which could be due to chemical irritation, local necrosis, direct contusion, or bacterial invasion, being the most common cause of therapeutic failure in PD[27,28].

Guidelines from the International Society for PD recommend a benchmark of 0.5 episodes per patient per year, or one episode every 2 years. Reducing the incidence of peritonitis is a multifaceted process that begins with extensive patient training, focusing on the appropriate technique[29,30].

The results in our series amounted to just 0.3 episodes per patient per year, which supports our program. Although HD and PD have been associated with similar mortality rates in incident patients, some studies have shown greater benefits of PD for early (2 years) and long-term survival[22,31,32].

Álvarez et al. identified catheter survival at 57.0 ± 1.5 months[33]. Various studies support the role of interventional nephrology, particularly the role of the nephrologist in catheter placement, concerning a reduction in complications and the use of a less invasive method[25,26,34-37]; in our more than 9-year experience at the above-mentioned center, without trying to establish any comparison with those placed by surgical specialists, favorable and adequate results are shown, while economically, it allows for a considerable saving of resources.

The literature review related to the topic in question supports that, in the current context in Latin America, a reality that is no stranger to Cuba, the incidence and prevalence of CKD are very heterogeneous (but among the highest in the world) and its growth rate is constant; PD is the least used dialysis modality in the region (contrasting with HD), and its growth has recently decreased. Moreover, clinical outcomes of PD are similar to HD, but costs are lower in most cases[38]; in this scenario, the development of interventional nephrology imposes new challenges and needs.

Conclusion

In most patients, the time elapsed between catheter implantation and its use was appropriate, and the outpatient care regimen predominated. No patients were reported who had early use of the PC, and the main causes of late use were complications related to implantation and difficulties with learning the dialysis technique in more than half of the affected patients. A low rate of complications related to catheter implantation *per se* was reported, and late complications were below the mean international standards; the main infectious complication was peritonitis, and the main non-infectious complication was catheter dysfunction. The survival of the PC placed by nephrologists using the percutaneous technique in our center was high, with minimal complications and an adequate overall clinical progression of the patients.

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References

1. Ammirati AL. Chronic kidney disease. Rev Assoc Med Bras (1992). 2020;66 Suppl 1:S03-9.
2. Saran R, Robinson B, Abbott KC, Agodoa LY, Bhave N, Bragg-Greshman J, et al. US Renal Data system 2017 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2018;71 3 Suppl 1:S1-S688.
3. Martínez G, Guerra E, Pérez D. Enfermedad renal crónica, algunas consideraciones actuales. Multimed. 2020;24:464-9.
4. Almaguer M. Prevención de la enfermedad renal crónica. In: Treviño A, editor. Tratado de Nefrología. 5th ed. México, DF: Ediciones Prado; 2019.
5. Herrera CA, Arratia JC. Diálisis peritoneal. RMB. 2021;15:70-5.
6. Correa R, Mehrotra R, Saxena A, editors. Diálisis Peritoneal. In: El riñón. España: Editorial Elsevier, 11na edición en español; 2021. Disponible en: https://www.buscalibre.com/int-es/libro-brenner-y-rector-el-rinon/9788491138969/p/53451498
7. Montenegro J, Correa R, Riella MC. Tratado de Diálisis Peritoneal. España: Elsevier; 2020.
8. Fajardo-Leitzelar FA, Sierra M, Barahona-López DM, Sánchez-Sierra LE, Matute-Martínez CF, Mendoza-Sabillón DE, et al. Analysis of patients in peritoneal dialysis: clinical-epidemiologic factors and peritoneal transport type with hypertonic replacement. Análisis de pacientes en diálisis peritoneal: factores clínico-epidemiológicos y tipo de transporte peritoneal con recambio hipertónico. Rev Colomb Nefrol. 2018;5:146-55.
9. Bohorques R, Álvarez Y, Martínez A. Diálisis peritoneal. In: Alfonso JP, editor. Nefrología. La Habana: Editorial de Ciencias Médicas; 2016. p. 383-92.
10. Vizcarra CA. ¿Es la diálisis peritoneal la mejor opción de tratamiento durante la pandemia por COVID-19? Rev Colomb Nefrol. 2020;7 Suppl 2:379-81.
11. Quiná González ED. Complicaciones de la Implantación de Catéteres de Tenckhoff por Cirugía Abierta Versus Cirugía Mínimamente Invasiva [Tesis de Grado en Internet]. [Guatemala]: Universidad de San Carlos Guatemala; 2019. Available from: https://repositoriosiidca.csuca.org/record/repousac13520/details
12. González F, Marrero S, Vega NJ. Materiales Para Diálisis Peritoneal. Catéteres. Nefrología al día; 2019. Available from: https://www.nefrologiaaldia.org/es-articulo-implantacion-del-cateter-peritoneal-tecnica-459 [Last accessed on 2022 Dec 21].
13. Sánchez E. ¿La colocación del catéter peritoneal por el nefrólogo influye en la tasa de utilización de la diálisis peritoneal? NefroPlus. 2016;8:41-3.
14. Cullis B, Al-Hwiesh A, Kilonzo K, McCulloch M, Niang A, Nourse P, et al. ISPD guidelines for peritoneal dialysis in acute kidney injury: 2020 update (adults). Perit Dial Int. 2021;41:15-31.
15. Khudari HE, Abdel-Aal AK, Abaza M, Almehmi SE, Sachdeva B, Almehmi A. Peritoneal dialysis catheter placement: percutaneous and peritoneoscopic techniques. Semin Intervent Radiol. 2022;39:23-31.
16. Zhao S, Zhu X, Li Q, Zhu B, Wang Y, Cui W, et al. A simplified percutaneous technique for inserting Tenckhoff catheters for peritoneal dialysis. Clin Nephrol. 2019;91:17-24.
17. Sánchez Carmona E, García Torres O, Segura Trujillo M, Villaseñor AS. Percepción de redes de apoyo del paciente con enfermedad renal crónica en terapia sustitutiva con diálisis peritoneal. Med Gen Fam. 2020;9:173-7.
18. Daugirdas JT, Blake PG, Ing TS. Manual de Diálisis. 5th ed. Barcelona: Wolters Kluwer; 2015.
19. Parra M, Serrano L. Conocimientos sobre los cuidados enfermeros en diálisis peritoneal. Rvt Cient Hygia Enf. 2016;91:20-4.
20. Gomez YI, Constantino F. Percepción del paciente de diálisis peritoneal sobre la educación que brinda el profesional de enfermería. ACC CIETNA. 2021;8:32-44.
21. Uribe JM, Molano AP. Diálisis peritoneal en tiempos difíciles. Rev Colomb Nefrol. 2021;8:e428.
22. Constantino F, Romero AY. Autocuidado en el hogar del paciente en tratamiento de diálisis peritoneal. Paraninfo Digit. 2018;13:e161.
23. San Juan P, Pérez A, Barrientos C. Aspectos clínicos y microbiológicos de la peritonitis asociada a diálisis peritoneal en pacientes adultos con insuficiencia renal crónica en el Servicio de Urgencias. Rev Chil Infectol. 2018;35:225-32.
24. Grefberg N, Danielson BG, Benson L, Pitkänen P. Right-sided hydrothorax complicating peritoneal dialysis. Report of 2 cases. Nephron. 1983;34(2):130-4. doi: https://doi.org/10.1159/000182995.
25. Htay H, Johnson DW, Craig JC, Schena FP, Strippoli GF, Tong A, et al. Catheter type, placement and insertion techniques for preventing catheter-related infections in chronic peritoneal dialysis patients. Cochrane Database Syst Rev. 2019;5:CD004680.
26. Lynch Mejía MF. Peritonitis bacteriana secundaria a diálisis peritoneal. Rev Med Legal Costa Rica. 2019;36:108-14.
27. López Vélez WA. Determinación de Causas Para el Cambio de Tratamiento de Diálisis Peritoneal a Hemodiálisis, Hospital de Especialidades Carlos Andrade Marín Durante el Periodo 2015 a 2018 [Tesis]. [Quito]: Universidad Central del Ecuador, Facultad de Ciencias Médicas; 2020. Available from: https://www.dspace.uce.edu.ec/bitstream/25000/21907/1/t-uce-0006-cme-230-p.pdf

28. Salzer WL. Peritoneal dialysis-related peritonitis: challenges and solutions. Int J Nephrol Renovasc Dis. 2018;11:173-86.
29. Hui J, Kim MJ, Ye M, Kim JH, Kim MJ, Kim S, et al. Percutaneous peritoneal dialysis catheter implantation with no break-in period: a viable option for patients requiring unplanned urgent-start peritoneal dialysis. Kidney Res Clin Pract. 2020;39:365-72.
30. Bravo J, Larrarte C, Quiñonez S, Echeverri J, Quiroga C, Gómez C. *Candida haemulonii*: causa infrecuente de peritonitis asociada a diálisis peritoneal. Infectio. 2018;22:58-60.
31. Marshall M. The benefit of early survival on PD versus HD-why this is (still) very important. Perit Dial Int. 2020;40:405-18.
32. Chang HH, Chang CH, Hsiao CY, Kao SY, Chen JY, Chen TH, et al. Diabetes is the most critical risk factor of adverse complications after peritoneal dialysis catheter placement. Front Med (Lausanne). 2021;8:719345.
33. Álvarez Y, Bohorques R, Vega PD, Noa FL. Alteraciones cardiovasculares de pacientes en un programa de diálisis peritoneal domiciliaria en el Instituto de Nefrología de Cuba. Rev Cubana Cardiol Cir Cardiovasc. 2017;23:479-8.
34. Wong B, Ravani P, Oliver MJ, Holroyd-Leduc J, Venturato L, Garg AX, et al. Comparison of patient survival between hemodialysis and peritoneal dialysis among patients eligible for both modalities. Am J Kidney Dis. 2018;71:344-51.
35. Hsieh Y, Chang C, Wen Y, Chiu P, Yang Y. Predictors of peritonitis and the impact of peritonitis on clinical outcomes of continuous ambulatory peritoneal dialysis patients in Taiwan-10 years' experience in a single center. Perit Dial Int. 2014;34:85-94.
36. Molina Fàbrega R, Torregrosa de Juan E, Revert Espi R, Pallardó Calatayud Y. Diagnóstico por Imagen de las Complicaciones Asociadas a la Diálisis Peritoneal: Revisión de la Técnica, los Hallazgos Radiológicos y el Papel de la TC Peritoneografía. Seram; 2018. Available from: https://piper.espacio-seram.com/index.php/seram/article/view/1271/679 [Last accessed on 2023 Jan 28].
37. Archila B, Beltrán B, Tejada M, Arucha S. Percepción de calidad de vida en usuarios de un programa ambulatorio de diálisis peritoneal. Rev Cient Inst Nac Salud. 2018;1:35-41.
38. Parapiboon W, Ponce D, Cullis B. Acute peritoneal dialysis in COVID-19. Perit Dial Int. 2020;40:359-62.

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CLINICAL CASE

Case of idiopathic nodular glomerulosclerosis

Caso de glomeruloesclerosis nodular idiopática

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Abstract

Nodular glomerulosclerosis is a histopathological pattern characterized by increased hyaline deposition in the mesangial matrix in a nodular form. This pattern can be observed in a variety of clinical entities, leading to a diagnostic challenge, which, in many cases, is concluded as an idiopathic nodular glomerulosclerosis because the etiology is not determined. A clinical case of a patient with grade I obesity, non-smoking and non-diabetic, who consulted for nephrotic syndrome and alteration of kidney function, who presented a pattern of nodular glomerulosclerosis in the renal biopsy, with exclusion of all causes is presented.

Keywords: *Idiopathic nodular glomerulosclerosis. Hypertension. Diabetic nephropathy.*

Resumen

La glomeruloesclerosis nodular es un patrón histopatológico caracterizado por aumento del depósito hialino en la matriz mesangial en forma nodular. Este patrón puede observarse en una variedad de entidades clínicas, conduciendo a un desafío diagnóstico, que en muchos casos se concluye acuñando a la glomeruloesclerosis nodular como idiopática por no arribar a la etiología. Se presenta el caso clínico de un paciente obeso grado I, no tabaquista y no diabético, que consultó por síndrome nefrótico y alteración de la función renal, que presentó en la biopsia renal patrón de glomeruloesclerosis nodular con exclusión de todas las causas de la misma.

Palabras claves: *Glomeruloesclerosis nodular idiopática. Hipertensión arterial. Nefropatía diabética.*

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Introduction

Nodular glomerulosclerosis is a histopathological finding that can appear in multiple entities, with diabetes being the most common disease associated with this histopathological pattern. Histologically, nodular glomerulosclerosis is characterized by an increase in the hyaline deposition of the mesangial matrix, which is acellular and stains positive with periodic acid-Schiff (PAS). It is accompanied by thickening of the glomerular basement membrane (GBM) and tubular basement membrane (TBM), and associated with arteriolar hyalinosis/sclerosis[1,2]. Tubulointerstitial fibrosis and tubular atrophy can be observed in up to 58% of patients. Immunofluorescence (IF) shows linear deposits of IgG at the GBM and TBM, and sometimes IgG and C3 trapped in areas of sclerosis[1,2].

In addition to diabetes, this glomerular pattern can be observed in amyloidosis, where it stains positively with Thioflavin T, and with Congo Red, it exhibits birefringence under polarized light. Some cases of membranoproliferative glomerulonephritis may present PAS-positive nodular glomerulosclerosis, but optical microscopy reveals hypercellularity and duplication of the GBM. Monoclonal immuglobulin deposition disease can also present PAS-positive nodules, but IF shows linear deposits of light chains in the GBM or TBM[1,3]. Fibrillary and immunotactoid glomerulonephritis may exhibit this pattern, but often accompanied by membranoproliferative glomerulonephritis pattern[1]. In fibrillary glomerulonephritis, IF is positive for polyclonal IgG and C3 in the majority of cases, while in immunotactoid glomerulonephritis, monoclonal IgG is more common; however, electronic microscopy is required to diagnose these two entities. Another differential diagnosis is fibronectin glomerulopathy, where dense subendothelial deposits are observed on electron microscopy (EM), with definitive diagnosis provided by immunohistochemistry[1]. Finally, idiopathic nodular glomerulosclerosis is histologically indistinguishable from diabetic nephropathy in all aspects, except that the patient does not have diabetes[1].

Idiopathic nodular glomerulosclerosis has been associated with risk factors such as hypertension, smoking, and obesity. Regarding the pathogenesis of the disease, it has been observed that these risk factors generate advanced glycation end products and oxidative stress, creating a lesion very similar to the one observed in diabetes[4,5]. It has also been evidenced that they release cytokines and growth factors, such as vascular endothelial growth factor and transforming growth factor-beta 1 causing podocyte apoptosis and perpetuating glomerulosclerosis[4,6].

Most patients with idiopathic nodular glomerulosclerosis clinically manifest with deteriorating renal function and nephrotic-range proteinuria; however, presentations such as nephrotic syndrome have also been described. Around 50% of cases require dialysis within a period of < 5 years[1].

Clinical case

The clinical case of a 50-year-old male patient with history of grade I obesity (BMI 32), non-smoker, and without medical follow-ups, who presented to our hospital with an overfill nephrotic syndrome, is presented. On admission, his blood pressure was 200/100 mmHg with anasarca. Laboratory tests showed urea 162 mg/dL, creatinine 5.5 mg/dL, albumin 2.3 g/dL, total cholesterol 227 mg/dL, and glomerular type proteinuria of 7.1 g/24 hs with negative immunofixation. Urine sediment analysis showed no hematuria but presence of lipiduria. The main diagnostic methods are summarized in table 1. Due to anasarca refractory to diuretics treatment and worsening renal function, hemodialysis was initiated. During hospitalization, it was discovered that patient had signs of chronic hypertension (compatible fundoscopy and echocardiogram). Infectious causes of nephrotic syndrome were ruled out (negative serology for hepatitis B and C viruses, HIV, and syphilis), and also, diabetes mellitus was ruled out (fasting glucose, oral glucose tolerance test, and fundoscopy showed no diabetic retinopathy). The patient presented ANA 1/160, negative Anti-DNA, ANCA, PR3, MPO, and normal C3 and C4, but due to the sole presence of ANA with other negative antibodies and normal complements levels, it was interpreted as a false positive and autoimmune disease was also discarded. Monoclonal gammopathy was excluded (negative serum and urine protein electrophoresis) along with other secondary causes of nephrotic syndrome. Once the patient's clinical condition stabilized, a renal biopsy was performed (Table 1 and Fig. 1). The biopsy shows the presence of nodular glomerulosclerosis, they were PAS positive and negative with Thioflavin T (Ruling out Amyloidosis); also, it was observed thickening of GBM and TBM and arterioles with mild hypertrophy of their muscular layer and segmental hyalinosis. In the IF, there was only a linear reinforcement of IgG in basement membranes, with negative light chains in the IF

Table 1. Diagnostic methods used during the patient's hospitalization

24 hs urine	Amount: 1660 mL, proteinuria 7.1 g/24 hs, Electrophoretic uroproteinogram: glomerular, median selectivity. Immunofixation negative
Immunologic findings	ANA positive 1/640, Anti-nDNA: negative, ANCA: negative, PR3 and MPO: negative, C3: 113 mg/dL, C4: 36 mg/dL
OGTT	Fasting blood sugar 71 mg/dL. At hour 2: 120 mg/dL
Renal echography	Both kidneys with preserved shape and echogenicity, regular and smooth borders, with preserved corticomedullary relationship. Non-dilated pelvicalyceal system, without cysts or renal macro lithiasis. Right kidney: average parenchymal thickness 19 mm. Dimensions: 118 × 57 × 55 mm in longitudinal, AP and transverse axes. Volume: 193 cc. Left kidney: average parenchymal thickness 19 mm. Dimensions: 112 × 46 × 53 mm in longitudinal, AP and transverse axes. Volume: 142 cc
Echo cardiogram	Concentric hypertrophy with preserved systolic function with severe left atrial dilatation and mild right atrial dilatation. Grade II diastolic dysfunction. Pleural effusion and ascites.
Renal biopsy	14 glomeruli: all enlarged in size, diffusely affected by the presence of sclerosed nodules, irregular, or different sizes, some of them lamellar, others hypercellular, PAS-positive and Silver Metanamine positive, they stain blue with Masson's Trichrome and are negative with the Thioflavin T technique. They are associated with microanerysms, loaded with proteinaceous material and fibrosis of the urinary space. Thickening of capillary and tubular basement membranes are also recognized. Tubular atrophy and diffuse interstitial fibrosis to a moderate degree (45%). Arterioles with mild hypertrophy of their muscular layer and segmental hyalinosis. Immunofluorescence: IgG: mild linear reinforcement of glomerular capillaries and tubular basemen membranes, IgA and IgM: negatives. C3 and C1q: trapped in sclerosis foci. Fibrinogen: negative. Kappa and Lambda light chains: negatives.

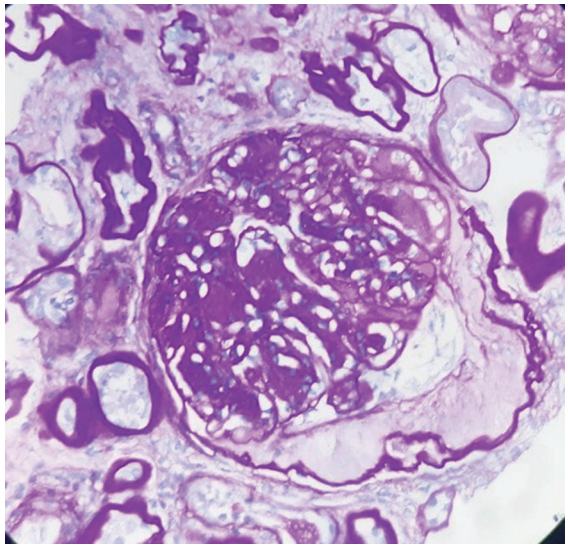

Figure 1. Optic microscopy with periodic acid-Schiff technique showing glomeruli with a nodule of sclerosis.

(excluding monoclonal gammopathy). However, there was an impossibility to perform electronic microscopy to exclude fibrillary or immunotactoid glomerulonephritis, which are differential diagnosis. With all this data, we decided to conclude with the diagnosis of nodular glomerulosclerosis. In the subsequent days, there was no improvement in renal function, and the patient continued hemodialysis up to the present day.

Discussion

There are few published cases in the literature regarding idiopathic nodular glomerulosclerosis, with three major studies collecting data from patients with this glomerular pattern[7-9]. These studies showed that patients did not have alteration in glycemic metabolism, nor did they develop it during short-term follow-up. However, the same studies showed that patients with this histopathology in renal biopsy had risk factors such as hypertension, smoking, and/or obesity. In most published cases of idiopathic nodular glomerulosclerosis, renal biopsy showed varying degrees of mesangial matrix increase with nodular formations associated with thickening of the GBM and TBM and arteriolar hyalinosis. Moreover, this arteriolar hyalinosis strongly correlates with coronary artery disease. Our patient shares many similarities with those presented in the literature. Like other cases, our patient had risk factors, being obese and hypertensive. Unlike other studies, our patient had no history of smoking. The presentation was similar to other clinical cases, with nephrotic syndrome and renal function impairment. Regarding histopathology, our patient's renal biopsy showed the same alterations described in the literature: diffuse sclerosed nodules, PAS-positive and Thioflavin T-negative, thickening of the GBM and TBM, segmental arteriolar hyalinosis, and linear IgG reinforcement in the GBM and TBM with negative light chain IF. The limitation in our case was the impossibility to perform EM. Our patient

required hemodialysis from the onset of clinical symptoms to the present day, without recovery of renal function, similar to several cases reported in the literature.

Conclusion

Idiopathic nodular glomerulosclerosis is a clinical entity with very few reported cases and preventable risk factors (hypertension, smoking, and obesity), which can present as nephrotic-range proteinuria, nephrotic syndrome, or even end-stage renal disease. It is a disease with a high incidence of requiring renal replacement therapy in a short period, making it crucial to learn more about this disease, identify risk factors, and eliminate them to prevent the progression of renal damage once established.

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References

1. López-Revuelta K, Abreu A, Gerrero-Márquez C, Stanescu R, Marín M, Fernández E. Diabetic nephropathy without diabetes. J Clin Med. 2015;4:1403-27.
2. Herzenberg AM, Holden JK, Singh S, Magil AB. Idiopathic nodular glomerulosclerosis. Am J Kidney. 1999;34:560-64.
3. Muller-Hocker J, Weiss M, Thoenes G, Grund A, Nerlich A. Case of idiopathic nodular glomerulosclerosis mimicking diabetic glomerulosclerosis (Kimmelstiel-Wilson type). Pathol Res Pract. 2002;198:375-9.
4. Nasr S, D'Agati V. Nodular glomerulosclerosis in the nondiabetic smoker. J Am Soc Nephrol. 2007;18:2032-6.
5. Navaneethan S, Singh S, Choudhry W. Nodular glomerulosclerosis in a non-diabetic patient: case report and review of literature. J Nephrol. 2005;18:613-5.
6. Pedrosa A, Gomes W, Gonçalves M, Teles F, Modesto V. Glomeruloesclerosis nodular en un tabaquista hipertenso no-diabético con dislipemia. An Sist Sanit Navar. 2011;34:301-6.
7. Markowitz G, Lin J, Valeri A, Avila C, Nasr S, D'Agati V. Idiopathic nodular glomerulosclerosis is a distinct clinicopathologic entity linked to hypertension and smoking. Hum Pathol. 2002;33:826-35.
8. Li W, Verani R. Idiopathic nodular glomerulosclerosis: a clinicopathologic study of 15 cases. Hum Pathol. 2008;39:1771-6.
9. Wu J, Yu S, Tejwani V, Mao M, Muriithi A, Ye C, et al. Idiopathic nodular glomerulosclerosis in Chinese patients: a clinicopathologic study of 20 cases. Clin Exp Nephrol. 2014;18:865-75.

PERMANYER

CASE REPORT

Rituximab in young adults with steroids dependence nephrotic syndrome: a case series

Rituximab en adultos jóvenes con síndrome nefrótico corticodependiente: serie de casos

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Abstract

We aim to assess the efficacy of rituximab (RTX) in treating adults with steroid-dependent nephrotic syndromes (SDNS) or frequently relapsing nephrotic syndromes (FRNS), whose disease was diagnosed during childhood. We analyzed the clinical course of patients with nephrotic syndromes (NS) onset in childhood who received RTX treatment for SDNS or FRNS after childhood (> 16 years). All patients had minimal change disease (MCD) or focal and segmental glomeruloesclerosis (FSG) proven by biopsy. We analysed patient characteristics and outcomes. Twelve patients (n = 8 MCD, n = 4 FSG). The median exposure time to steroids prior to RTX was 19 years (range: 2-31.5 years). NS was diagnosed at a median age of 3 years (range: 1.5-6.0 years), the median age when patients received their first RTX dose was 24 years (range: 16-42 years). After RTX treatment, all patients achieved remission not needing any immunosuppressive drugs. The relapse rate decreased by 8 times (rate ratio: 8.7; 95% CI: 2.1-40.5) and the average prednisone dose was reduced (19.6 ± 17.5 mg vs. 4.6 ± 8.6 mg/dL; p = 0.0027). RTX was effective in reducing the number of relapses and steroid loading in young adults with SDNS or FRNS with an adequate safety profile.

Keywords: *Nephrotic syndrome. Young adult. Minimal change disease. Focal segmental glomerulosclerosis. Rituximab.*

Resumen

Nos propusimos evaluar la respuesta al tratamiento con rituximab (RTX) en adultos con síndrome nefrótico corticodependiente (SNCD) y recaedor frecuente (SNRF). Se analizaron pacientes con diagnóstico de SNCD y SNRF en la infancia que tenían estudio histológico renal y recibieron RTX siendo adolescentes o adultos jóvenes (> 16 años). Analizamos características clínicas y analíticas de los pacientes y su evolución. Se incluyeron 12 pacientes (n = 8 con lesión glomerular mínima, n = 4 con glomeruloesclerosis focal y segmentaria). La mediana de exposición a esteroides previa al RTX fue 19 años (rango: 2-31.5 años). El SN fue diagnosticado con una mediana de edad de 3 años (rango: 1.5-6.0 años) y la mediana de edad al recibir la primera dosis de RTX fue 24 años (rango: 16-42 años). Luego del tratamiento con RTX, y al final del seguimiento, todos los pacientes lograron remisión sin fármacos inmunosupresores. La tasa de recaídas luego del tratamiento con RTX disminuyó ocho veces (8.7; IC95%: 2.1-40.5) y la dosis de prednisona promedio se redujo (19.6 ± 17.5 mg vs. 4.6 ± 8.6 mg/dl; p = 0.0027). El rituximab fue eficaz en reducir el número de recaídas y la carga de esteroides en adultos jóvenes con SNCD o SNRF, con un adecuado perfil de seguridad.

Palabras claves: *Síndrome nefrótico. Adulto joven. Lesión glomerular mínima. Glomeruloesclerosis focal y segmentaria. Rituximab.*

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Introduction

A total of 90% of idiopathic nephrotic syndromes (NS) in childhood remit with steroid therapy[1-3]. However, up to 60% of children will frequently relapse or develop dependence on corticosteroids, a condition known as corticosteroid-dependent nephrotic syndrome (CDNS). This situation leads to a significant cumulative dose of steroids with increased morbidity, reaching adolescence with adverse effects, some of which are irreversible[3], including Cushing's syndrome, dyslipidemia, diabetes, hypertension[4], early vascular aging, and osteopenia. In addition, these children and adolescents will often require other immunosuppressants, including calcineurin inhibitors, mycophenolate mofetil (MMF), or cyclophosphamide (CF)[2].

The Kidney Disease: Improving Global Outcomes guidelines for the management and treatment of glomerulopathies recommend treatment with rituximab (RTX) in patients with renal failure and corticosteroid dependence with minimal change disease (MCD)[4].

Multiple studies suggest that B cells are involved in the pathogenesis of these nephropathys, supported by the clinical benefit observed following anti-CD20 therapy[5]. More than a decade ago, Benz et al. reported the very first case of a change in the clinical course of a CDNS after RTX therapy[6]. A 16-year-old adolescent with more than 35 relapses of NS received anti-CD20 for the treatment of idiopathic thrombocytopenic purpura and progressed without subsequent relapses of his NS/purpura[6]. At present, there is sufficient evidence from randomized clinical trials on the benefit of RTX in the treatment of CDNS in children, with a significant effect in reducing the number of relapses and steroid burden[3,7,8].

Evidence in adults is somewhat more limited; however, prospective and retrospective studies suggest similar benefits to those observed in pediatrics[9]. Several studies have reported results from the use of RTX in the treatment of CDNS and steroid-resistant nephrotic syndrome (SRNS) in the subgroup of adolescents or young adults who started their disease in childhood[10].

The objective of this study was to analyze the progression of patients with CDNS or SRNS that started in childhood who received RTX in young adulthood in our setting. We compared the initial status, number of relapses, doses of immunosuppressants/steroids before and after RTX, as well as their clinical progression.

Methods

Study population

Patients were included from the analysis of the Uruguayan Registry of Glomerulopathies (RUG). A description of the characteristics of this registry has been reported previously[11]. The RUG was established in 1970 and since 1989 has become a national reference registry that groups information from all kidney biopsies performed in the national territory, reported by nephrologists and pathologists[11]. From 1990 through 2014, a total of 3390 native kidney biopsies were performed in patients > 14 years[11]. For this study, we selected patients with NS who started in childhood who were diagnosed with CDNS or SRNS through renal biopsy confirming MCD or focal segmental glomerulosclerosis (FSGs) and who received RTX as young adults (after the age of 16). We reported all CDNS or SRNS patients on RTX from July 2018 to 2021.

Protocol (#4018) was approved by Hospital Manuel Quintela Ethics Committee (Universidad de la República, Uruguay) and all patients signed their informed consent forms. The information was handled confidentially in full compliance with current legislation.

Clinical and laboratory presentation

The clinical characteristics of the population were analyzed at 3 time periods: Before the histological study, at the time of RTX initiation, during, and at the end of follow-up. We recorded complications related to NS, steroid burden, and their adverse effects, use of other immunosuppressive (IS) drugs, and doses of RTX. We analyzed all available information until the end of the follow-up.

Laboratory test results reported on creatinine levels, albumin levels, and total serum proteins. Proteinuria (PRO) was measured in 24-h urine and/or using the urine protein-creatinine ratio (UPCR)[12]. Serum creatinine was measured using the modified Jaffe method. This method was calibrated with isotope dilution mass spectrometry as a reference and used in full compliance with current recommendations[13]. The variables measured before and after the administration of RTX included: number of relapses, need for steroids, and use of IS drugs.

Definitions

The NS was defined as the presence of urine PRO > 3.5 g/24 h or a UPCR > 3 g/g and hypoalbuminemia

(serum albumin < 3.5 g/dL). Complete remission was defined as urine PRO levels < 0.3 g/24 h, a UPCR < 0.3 g/g, or a negative urine test strip. Relapse was defined as PRO levels > 3.5 g/24 h a UPCR > 3 g/g and hypoalbuminemia (serum albumin < 3.5 g/dL) after a period of partial or complete remission. CDNS was considered when a relapse occurred during the tapering of corticosteroids or within the following 14 days after discontinuation. SRNS was defined as ≥ 2 relapses within 6 months or 4 relapses in 1 year[4].

Treatment with RTX

RTX was administered after achieving remission (complete or partial) of NS with corticosteroid treatment. The infusion was preceded by 100 mg of IV methylprednisolone, 10 mg of chlorpheniramine maleate, and 1000 mg of acetaminophen.

Statistical analysis

For database management and statistical analysis, we used IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, United States). Data are expressed as means and standard deviations or medians and ranges. We compared means and proportions using the t-test for paired observations. To compare the relapse rates before and after RTX, we used a 95% confidence interval (95% CI) for the pre-RTX and post-RTX relapse rates and the comparison between rates before and after RTX[14,15]. Statistical significance was set at $\alpha = 0.05$.

Results

A total of 12 patients were included according to the established inclusion criteria. Diagnosis for all patients was confirmed by histological study, 8 were classified as MCD and 4 as FSGs. The patients' median at the onset of NS was 3 years (range, 1.5-6 years), with a sex distribution of 6:6 females/males. Eight of the 12 kidney biopsies were performed in adulthood[16]. The median time elapsed from the onset of NS to the kidney biopsy was 14 years (range, 0-24.5 years).

Clinical progression and IS treatment at the onset of nephrotic syndrome

Most patients (11/12) achieved complete remission with steroids. All patients were steroid-sensitive, nine behaved as SRNS, and 10 as CDNS. The mean duration of corticosteroid exposure was 18.9 ± 8.4 years (median, 19; range, 2-31 years). Most patients (11/12; 0.92) required at least one IS drug in addition to steroids, including cyclosporine A (CyA), MMF, or CF. Nine patients (0.75) experienced NS-related complications, including: cerebral vein thrombosis (n = 1), stroke (n = 1), deep vein thrombosis (n = 2), superficial vein thrombosis (n = 1), pneumonia (n = 6), upper respiratory infection (n = 6), urinary tract infection (n = 1), pelvic inflammatory disease (n = 1), spontaneous bacterial peritonitis (n = 1), acute kidney injury in the context of nephrosis, and pathophysiological treatment of nephrosis (n = 3), 1 of whom required renal replacement therapy. At least 10 patients reported adverse events related to steroid/IS therapy, including: osteopenia (n = 3), vertebral compression (n = 1), hypertension (n = 5), dyslipidemia (n = 9), overweight (n = 3), hirsutism (n = 2), gastroduodenal ulcer (n = 1), human papillomavirus infection (n = 1), tuberculous pleurisy (n = 1), and glucose intolerance (n = 2). One patient reported a decline in glomerular filtration associated with the initiation of CyA.

The characteristics of the patients, treatments, and complications of NS before RTX are summarized in table 1.

Treatment with RTX

The median age of patients at the time of receiving the first dose of RTX was 24 years (range, 16-42 years). At this time, 11 patients were in complete remission and 1 in partial remission with non-nephrotic PRO. In all cases, patients were on blockers of the renin-angiotensin-aldosterone system, and 11 on other immunosuppressants, including: prednisone (PDN) (n = 1), PDN + CyA (n = 5), PDN + CyA + MMF (n = 2), PDN + CyA + CF (n = 3), and PDN + CyA + MMF + CF (n = 1). The median dose of PDN at the start of RTX was 19 ± 16.5 mg/day, and the median time from the onset of NS to RTX treatment was 17.5 years (range, 11-38 years). The initial dose of RTX was 1000-2000 mg, administered in 1 or 2 infusions separated by 2 weeks. To consolidate treatment, three patients received an additional dose of RTX (500-1000 mg) after the initial dose.

Clinical progression and IS treatment after RTX

After 12 months into RTX, all 11 patients were in complete remission without IS treatment, and one was in partial remission.

Table 1. Clinical characteristics, complications, immunosuppressive treatment, and relapses before RTX

Cases	Age NS (years)	Time SN-PRB (years)	Age at 1st RTX (years)	NS-RTX time (years)	Steroid Response	Pre-RTX tx	NS-related Complications	Relapses pre-RTX (in 12 months)	Cr pre-RTX	Alb pre-RTX
1	1.5	16	34	32.2	CD, FR	PDN, CyA, CF, MMF	Ischemic stroke, CAP	3	1.39	4.2
2	3	19	26	23	CD, FR	PDN, CyA, CF	CVT, UTI, CAP	8	0.61	4.1
3	3	14	17	14	CD	PDN	DVT, SVT, CAP, upper respiratory infection	-	2	0.50
4	6	0	17	11	CD, FR	PDN, CyA	SBP, NAC, DVT, upper respiratory infection	3	0.90	3
5	4	14	42	38	CD, FR	PDN, CyA	No	5	0.65	4.1
6	3	11	22	19	CD, FR	PDN, CyA, CF	No	2	0.80	4
7	4	3	16	12	CD, FR	PDN, CyA	No	2	0.80	4.1
8	7	12	21	14	CD, FR	PDN, CyA, MMF	CAP, PID	4	0.82	4.4
9	2	15	30	28	CD	PDN, CyA, CF	Upper respiratory infection, CAP	2	0.48	3.9
10	3	5	19	16	CD	PDN, CyA	Upper respiratory infection	2	0.87	4.1
11	2	17	28	26	CD, CD, FR	PDN, CyA	Upper respiratory infection	4	0.77	3.9
12	1.5	24.5	31	29.5	CD, FR	DFZ, CyA, MMF	Upper respiratory infection	5	0.56	3.12
Median (range)	3 (1.5-6)	14 (0-24)	24 (16-42)	17.5 (11-38)	NA	NA	NA	3 (2-8)	0.77 (0.48-1.39)	3.5 (3-4.9)

Alb: albuminemia (g/L); CD: corticosteroid-dependent; CF: cyclophosphamide; Cr: creatinine (mg/dL); CyA: cyclosporine A; PID: pelvic inflammatory disease; HD: hemodialysis; AKI: acute kidney injury; UTI: urinary tract infection; MMF: mycophenolate mofetil; CAP: community-acquired pneumonia; NA: not applicable; SBP: spontaneous bacterial peritonitis; PRB: percutaneous renal biopsy; PDN: prednisone; FR: frequent relapser; RTX: rituximab; NS: nephrotic syndrome; tx: treatment; CVT: cerebral venous thrombosis; DVT: deep vein thrombosis; SVT: superficial vein thrombosis.

The mean follow-up was 24 months (range, 1-60 months). Eight patients did not relapse after the initial RTX dose. Beyond 12 months, three patients relapsed once (36-72 month follow-up) and entered remission with PDN, remaining relapse-free after the dose #3 of RTX. The remaining patient experienced 2 relapses (36-month follow-up), achieving partial remission with PDN and dose #3 of RTX (Table 2).

The dose of PDN was significantly lower after RTX (19.6 ± 17.5 mg vs. 4.6 ± 8.6 mg/dL; p = 0.0027) (Fig. 1). The relapse rate of NS significantly decreased after RTX, being pre-RTX 0.25 versus 0.01 relapses/patient/month post-RTX. The rate ratio was 16.7 (95% CI, 6.5-54.5) (Fig. 2).

RTX -related adverse events

No serious adverse events were reported during or after the RTX infusion, and no infections occurred at the follow-up. Three mild hypersensitivity reactions were reported, characterized by rash and pruritus during the infusion, which resolved with antihistamines, and it was not necessary to interrupt the dose.

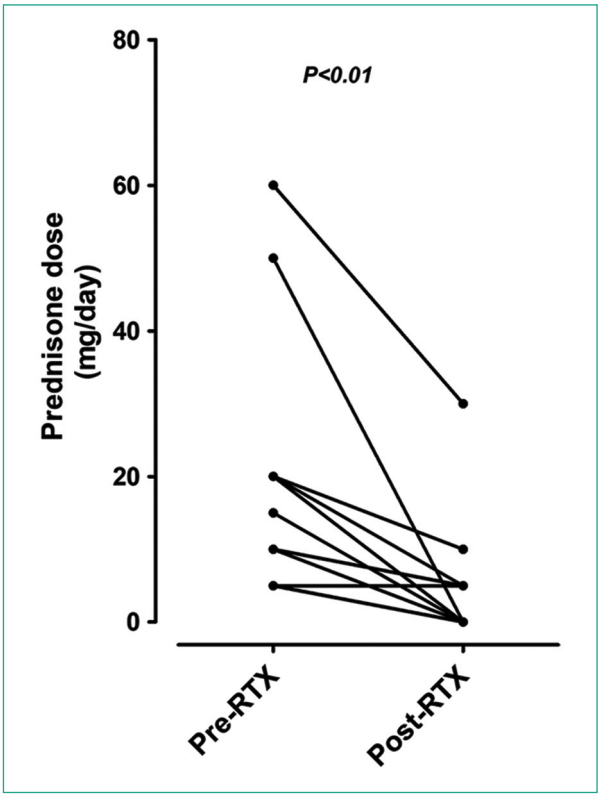

Figure 1. Dose of PDN before and after RTX. Level of significance (p) of the difference resulting from the comparison of means. PDN: prednisone; Pre-RTX: dose immediately before receiving RTX; Post-RTX: dose at the end of follow-up; RTX: rituximab.

Discussion

Our work supports the available evidence and demonstrates the clinical benefit of using RTX in young adults with frequent relapses, often corticosteroid-dependent, with NS onset in childhood. RTX proved effective in reducing the relapse rate, and remission was maintained with minimal or no immunosuppression in most patients. RTX was safe and well tolerated by the patients.

The relapse rate significantly decreased after RTX (0.25 vs. 0.01 relapses/patient/month; p < 0.0001). The rate ratio was 16.7 (95% CI, 6.5-54.5) (Fig. 2).

Most patients (n = 8) remained in remission without the need for immunosuppression during the follow-up, which are results consistent with former studies[17]. Several prospective studies have demonstrated the efficacy of RTX in achieving sustained remission in steroid-dependent NS (SDNS) or SRNS in young adults (< 50 years)[3]. A randomized prospective clinical study by Ruggenenti et al. allocated 10 children and 20 adults (age range, 22.7-47.4 years) with SDNS and SRNS to RTX therapy. This study showed a significant decrease in the relapse rate after RTX (2.5 vs. 0.5 relapses/patient/year). This study also demonstrated a decrease in the cumulative steroid dose after RTX (from 56.8 down to 0.5 mg/kg; p < 0.001). All patients remained in remission at the end of the observation period, and 14 patients did not require further immunosuppressors[3]. A prospective Asian study compared clinical and analytical expression 12 months before and after RTX, reporting a decrease in the number of relapses[18]. A subsequent analysis of the same population reported that this remission was sustained over time[19]. The significant decrease in the total number of relapses observed at the 24-month follow-up after the RTX dose was lower versus the 24 months before the infusion (108 vs. 8; p < 0.001)[19]. Similarly, in a multicenter retrospective study of 41 patients on 2 doses of RTX (1 g/15 days) Guitard et al. showed partial or complete remission in 78% of cases[17].

The GLOSEN group (Spanish Working Group for Glomerular Disease Study) compared RTX versus standard treatment and retrospectively analyzed 50 adults with SDNS and SRNS. In the RTX group, 80% achieved complete remission, and 70% did not relapse at the follow-up (26 ± 22 months). Furthermore,

Table 2. Immunosuppressive treatment, follow-up, and treatment response

Cases	Steroid Exposure (years)	PDN (mg) pre-RTX	PDN (mg) at follow-up completion	CyA, MMF at follow-up completion	RTX Dose (mg)	Relapses/12 months pre-RTX	Relapses/ months post-RTX	Follow-up (months)
1	26	5	5	No	1000 + 500 + 500	3	2	36
2	24	60	30	No	1000 + 1000	8	1	72
3	2	20	0	No	1000 + 500 + 500	2	1	60
4	12	20	10	No	500 + 500	3	0	12
5	28	10	0	No	1000 + 1000 + 500	5	1	36
6	19	10	0	No	1000	2	0	36
7	12	10	0	No	1000 + 1000	2	0	36
8	14	5	0	No	500 + 500	4	0	12
9	28	50	0	No	500 + 1000	2	0	12
10	17	20	5	No	1000 + 500	2	0	12
11	26	10	5	No	1000 + 1000	4	0	12
12	31.5	15	0	No	1000 + 1000	5	0	10
Median (range)	19 (2-31.5)	13 (5-60)	0 (0-30)		NA	3 (2-8)	0 (0-2)	24 (10-60)

CF: cyclophosphamide; CyA: cyclosporine A; MMF: mycophenolate mofetil; NA: not applicable; PDN: prednisone; RTX: rituximab.

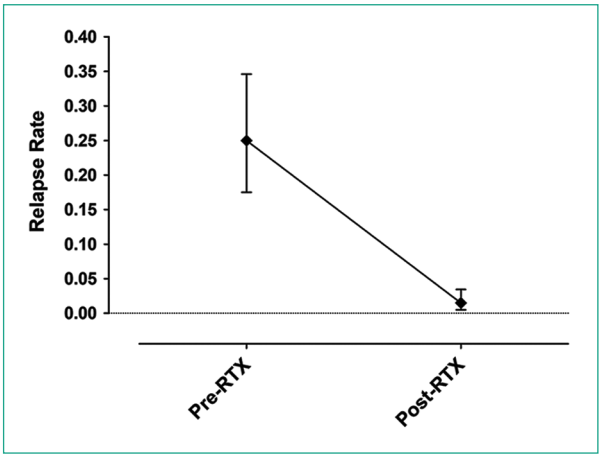

Figure 2. Relapse rate (patient/month) and 95% CI before and after RTX. 95% CI: 95% confidence interval; RTX: rituximab.

IS therapy could be discontinued in, at least, 50% of the patients[20].

All patients from our study received RTX after achieving remission, which improves the efficacy of this drug. Munyentwali et al. showed a lower number of relapses in patients on RTX while in remission[21]. The authors suggest that this may be explained by the loss of RTX via urine in patients with PRO.

Fernández-Fresnedo et al. retrospectively analyzed eight patients with corticosteroid-resistant NS[22] who received high doses of RTX during the period of severe nephrotic PRO, observing a significant reduction in PRO in only two patients, who had received the highest cumulative doses[22]. The lower plasma levels of RTX in patients with NS may explain the poorer response in patients with severe PRO.

Our results should be interpreted considering the limitations of the study. First, it is a small sample; however, most of the available evidence in the literature is based on small to medium-sized studies[3]. Similarly, we found positive results in the use of RTX in a particular subgroup of adults with SDNS or SRNS that began in childhood. Second, we reported on a retrospective study; however, the information for this analysis comes from a robust National Glomerulopathy Registry, and we drew comparisons before and after treatment[11]. Finally, the RTX dose used was not standardized, varying from case to case. However, several accepted therapeutic schemes are available in the literature. Initial reports used weekly plans of four doses of 375 mg/m^2,

while later publications showed efficacy with 1 or 2 doses separated by 6 months[23]. However, there was no correlation between the RTX protocol used and the number of relapses. In this regard, Munyentwali et al. reported similar relapse rates between groups on high doses of RTX (1 dose per week for 4 weeks of 375 mg/m^2 and 1000 mg on days 1 and 15) and those on only 2 doses of 375 mg/m 1 week apart[2,21].

Used according to recommendations and with premedication, RTX has proven to be a safe drug that has demonstrated benefits in treating NS in children and young adults with steroid dependency and frequent relapses. However, some aspects remain not entirely established, including the need for maintenance.

Clearly, there are benefits for the population of young adults suffering from frequent relapses, complications of NS, and corticosteroid overload. These benefits are further enhanced by the prevention of long-term corticosteroid complications (carbohydrate metabolism, cardiovascular risk, osteopenia, esthetic changes, and psychological damage), minimizing the loss of study or workdays and ultimately improving the quality of life.

Conclusion

Our work supports and demonstrates the efficacy of RTX in reducing relapses and steroid burden in young adult patients with SDNS or SRNS that began in childhood.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant Clinical Research Ethics Committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. J Am Soc Nephrol. 1997;8:769-76.
2. Waldman M, Crew RJ, Valeri A, Busch J, Stokes B, Markowitz G, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. Clin J Am Soc Nephrol. 2007;2:445-53.
3. Ruggenenti P, Ruggiero B, Cravedi P, Vivarelli M, Massella L, Marasa M, et al. Rituximab in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. J Am Soc Nephrol. 2014;25:850-63.
4. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100:S1-276.
5. Mallat SG, Itani HS, Abou-Mrad RM, Abou Arkoub R, Tanios BY. Rituximab use in adult primary glomerulopathy: where is the evidence? Ther Clin Risk Manag. 2016;12:1317-27.
6. Benz K, Dötsch J, Rascher W, Stachel D. Change of the course of steroid-dependent nephrotic syndrome after rituximab therapy. Pediatr Nephrol. 2004;19:794-7.
7. Magnasco A, Ravani P, Edefonti A, Murer L, Ghio L, Belingheri M, et al. Rituximab in children with resistant idiopathic nephrotic syndrome. J Am Soc Nephrol. 2012;23:1117-24.
8. Ravani P, Magnasco A, Edefonti A, Murer L, Rossi R, Ghio L, et al. Short-term effects of rituximab in children with steroid-and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol. 2011;6:1308-15.
9. Iijima K, Sako M, Nozu K, Mori R, Tuchida N, Kamei K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2014;384:1273-81.
10. Guigonis V, Dallocchio A, Baudouin V, Dehennault M, Hachon-Le Camus C, Afanetti M, et al. Rituximab treatment for severe steroid-or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. Pediatr Nephrol. 2008;23:1269-79.
11. Garau M, Cabrera J, Ottati G, Caorsi H, Gonzalez Martinez F, Acosta N, et al. Temporal trends in biopsy proven glomerular disease in Uruguay, 1990-2014. PLoS One. 2018;13:e0206637.
12. Schwedt E, Olascoaga A, Sánchez MF, Piana A, Raymondo S, De Souza N, et al. Primer Consenso Nacional sobre Proteinuria en el diagnóstico y la evaluación de la Enfermedad Renal Crónica en Adultos. Arch Med Int. 2012;34:3-11.
13. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem. 2006;52:5-18.
14. Sahai H, Khurshid A. Statistics in Epidemiology: Methods, Techniques and Applications. United States: CRC Press; 1995.
15. Rothman KJ, Greenland S, Lash TL. Types of epidemiologic studies. In: Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology. 2nd ed. Philadelphia, PA: Lippincott Raven; 1998. p. 74-5.

16. KDIGO Work Group. Chapter 10: Immunoglobulin A nephropathy. Kidney Int Suppl. 2012;2:209-17.
17. Guitard J, Hebral AL, Fakhouri F, Joly D, Daugas E, Rivalan J, et al. Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance. Nephrol Dial Transplant. 2014;29:2084-91.
18. Takei T, Itabashi M, Moriyama T, Kojima C, Shiohira S, Shimizu A, et al. Effect of single-dose rituximab on steroid-dependent minimal-change nephrotic syndrome in adults. Nephrol Dial Transplant. 2013;28:1225-32.
19. Iwabuchi Y, Takei T, Moriyama T, Itabashi M, Nitta K. Long-term prognosis of adult patients with steroid-dependent minimal change nephrotic syndrome following rituximab treatment. Medicine (Baltimore). 2014; 93:e300.
20. DaSilva I, Huerta A, Quintana L, Redondo B, Iglesias E, Draibe J, et al. Rituximab for steroid-dependent or frequently relapsing idiopathic nephrotic syndrome in adults: a retrospective, multicenter study in Spain. BioDrugs. 2017;31:239-49.
21. Munyentwali H, Bouachi K, Audard V, Remy P, Lang P, Mojaat R, et al. Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. Kidney Int. 2013;83:511-6.
22. Fernandez-Fresnedo G, Segarra A, González E, Alexandru S, Delgado R, Ramos N, et al. Rituximab treatment of adult patients with steroid-resistant focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2009;4:1317-23.
23. Bruchfeld A, Benedek S, Hilderman M, Medin C, Snaedal-Jonsdottir S, Korkeila M. Rituximab for minimal change disease in adults: long-term follow-up. Nephrol Dial Transplant. 2014;29:851-6.

Uremic frost: a case of severe azotemia

Escaracha urémica: an caso de azotemia grave

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75-year-old woman observed in the emergency department with asthenia, nausea, and anorexia for 2 weeks.

She exhibited confusion, slurred speech, continuous fine tremor, tachypnea, blood pressure 165/70 mmHg, and pulse 71 bpm. White crystalline deposits observed along eyebrows, forehead, and nose (Figure 1).

Analytical results revealed sCr 31 mg/dL, urea 526 mg/dL, sodium 140 mmol/L, potassium 6.6 mmol/L, total calcium 11.0 mg/dL, phosphate 10.3 mg/dL, and metabolic acidosis. She began hemodialysis for severe azotemia.

Neurological status normalized and crystals disappeared within a week. Investigation revealed myeloma cast nephropathy.

Uremic frost translates high urea and nitrogenous product concentrations in sweat, forming crystals after water evaporation[1,2]. This is a rare finding nowadays.

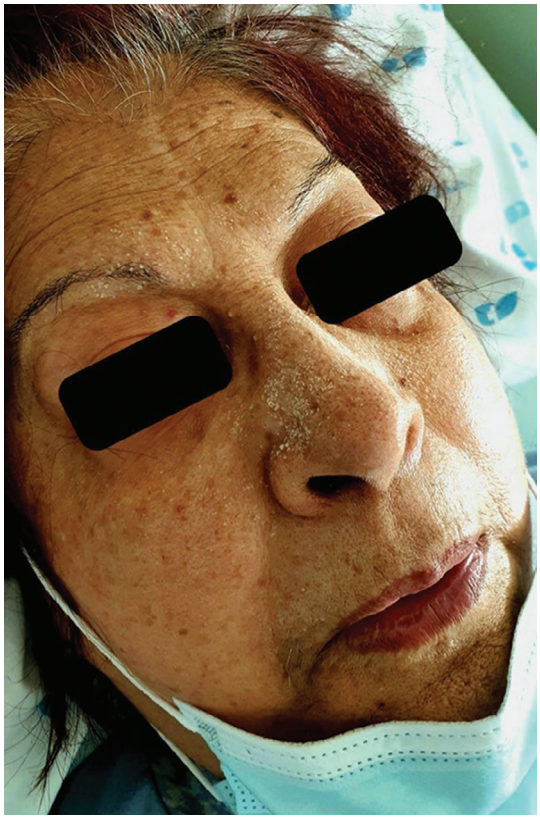

Figura 1. Uremic Frost. White crystalline deposits which translate high concentrations of urea and nitrogenous products in sweat.

References

1. Saardi KM, Schwartz RA. Uremic frost: a harbinger of impending renal failure. Int J Dermatol. 2016;55:17-20.
2. Delaney KL, Lerma EV, Nunley JR. Uremic frost. In: Nunley J, Lerma E, editors. Dermatological Manifestations of Kidney Disease. New York: Springer; 2015.

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Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes

Efecto de semaglutide sobre la enfermedad renal crónica en pacientes con diabetes mellitus tipo 2

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Dear Editor, we would like to congratulate Dr. Perkovic and colleagues demonstrating that semaglutide reduced by 24% the risk of kidney outcomes and death from cardiovascular causes in persons with type 2 diabetes (T2D) and chronic kidney disease (CKD)[1]. In SUSTAIN 6, semaglutide showed renal benefits mainly in terms of albuminuria reduction, interestingly the metabolic effects (blood sugar control and body weight) were higher in the 1 mg dose as compared to 0.5 mg[2]. In concordance, in the SUSTAIN FORTE, the 2 mg weekly dose was also better in metabolic control[3], indicating that the effect is in part dose-dependent. In addition, when studying kidney function Shaman et al. found that 1 mg of semaglutide has a higher effect in reducing albuminuria and delaying glomerular filtration rate progression as compared to liraglutide 1.8 mgs/day and low semaglutide dose 0.5 mgs/weekly[4]. The SELECT trial clearly demonstrated renal benefit of 2.4 mgs/weekly semaglutide in obese persons without diabetes[5]. Although the results of FLOW study are impressive, we are wondering if the beneficial effects could be in part dose-dependent. By now, FLOW trial demonstrated that semaglutide is a cardiorenal protective drug in patients with T2D and CKD, but it is not known if the higher doses used in persons with obesity may exert better renal benefits in comparison to the doses used in patients with T2D.

Conflicts of interest

The authors declare that:

J.R.F received honoraria as a speaker and consulting fees from Novo Nordisk, AstraZeneca, Eli Lilly, Bayer, Sanofi, Boehringer-Ingelheim, Merck and MSD.

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References

1. Perkovic V, Tuttle K, Rossing P, Mahaffey K, Man J, Bakris G, et al. Effects of semaglutide on chronic kidney disease in patients wtih Type 2 diabetes. N Engl J Med. 2024;391:109-21.
2. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834-44.
3. Frías JP, Auerbach P, Bajaj HS, Fukushima Y, Lingvay I, Macura S, et al. Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. Lancet Diabetes Endocrinol. 2021;9:563-74.
4. Shaman AM, Bain SC, Bakris GL, Buse JB, Idorn T, Mahaffey KW, et al. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and leader. Circulation. 2022;145:575-85.
5. Ryan DH, Lingvay I, Deanfield J, Kahn SE, Barros E, Burguera B, et al. Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial. Nat Med. 2024;30:2049-57.

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Errata

Fe de erratas: Documento de consenso sobre nuevas terapias para retrasar la progresión de la enfermedad renal crónica con énfasis en los iSGLT-2: implicaciones para Latinoamérica [Revista Nefrología Latinoamericana 2024;21(Supl.):1-18]

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En este artículo se han detectado los siguientes errores:

– Figura 3: en el cuarto subtítulo, en lugar de "Enfermedad renal hipertensiva o isquémica", debe decir "Otras enfermedades renales o causa desconocida"
– Figura 4: donde dice "iSGLT-2 si TFGe ≥ 20 ml/min y RAC < 200 mg/g[3‡] (2B)", debe decir "iSGLT-2 si TFGe ≥ 20 a 45 ml/min y RAC < 200 mg/g[3‡] (2B)"
– Página 13, párrafo 2, línea 6: donde dice "el estudio EMPA-REG incluyó", debe decir "el estudio EMPA-KIDNEY incluyó"

Véase el contenido relacionado en DOI: 10.24875/NEFRO.M24000037