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EDITORIAL

Are your kidneys ok? Detect early to protect kidney health

¿Están bien sus riñones? Detecte tempranamente para proteger su salud renal

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Introduction

Timely treatment is the primary strategy to protect kidney health, prevent kidney disease progression and related complications, reduce cardiovascular disease (CVD) risk, and prevent premature kidney-related and cardiovascular mortality[1-3]. International population assessments show low awareness and low detection of kidney disease and substantial gaps in treatment[2]. People with kidney failure universally express the preference for having been diagnosed early in their disease trajectory to allow more time for educational, lifestyle, and pharmacologic interventions[4]. Therefore, increasing knowledge and implementing sustainable solutions for the early detection of kidney disease to protect kidney health are public health priorities[2,3].

Epidemiology and complications of kidney disease

Chronic kidney disease (CKD) is prevalent, affecting 10% of the world's population, or over 700 million people[5]. Almost 80% of the population with CKD reside in low-income countries (LICs) and lower-middle-income countries (LMICs), with approximately 1/3 of the known affected population living in China and India alone[5,6]. Prevalence of CKD was increased by 33% between 1990 and 2017[5]. Increasing prevalence of CKD is driven by population growth, aging, and the obesity epidemic, resulting in higher prevalence of two major risk factors for CKD: type-2 diabetes (T2DM) and hypertension. In addition, risk factors for CKD beyond cardiometabolic conditions contribute to the rising burden of kidney disease, including social deprivation, pregnancy-related acute kidney injury (AKI), preterm birth, and increasing environmental threats (infections, toxins, climate change, and air pollution)[5,7]. These threats disproportionately affect people in LICs and LMICs[8].

Undetected and untreated CKD is more likely to progress to kidney failure and cause premature morbidity and mortality. Globally, more people died in 2019 of CVD attributed to reduced kidney function (1.7 million people) than kidney disease alone (1.4 million)[5]. CKD is expected to rise to the 5th most common cause of years of life lost by 2040, surpassing type 2 diabetes,

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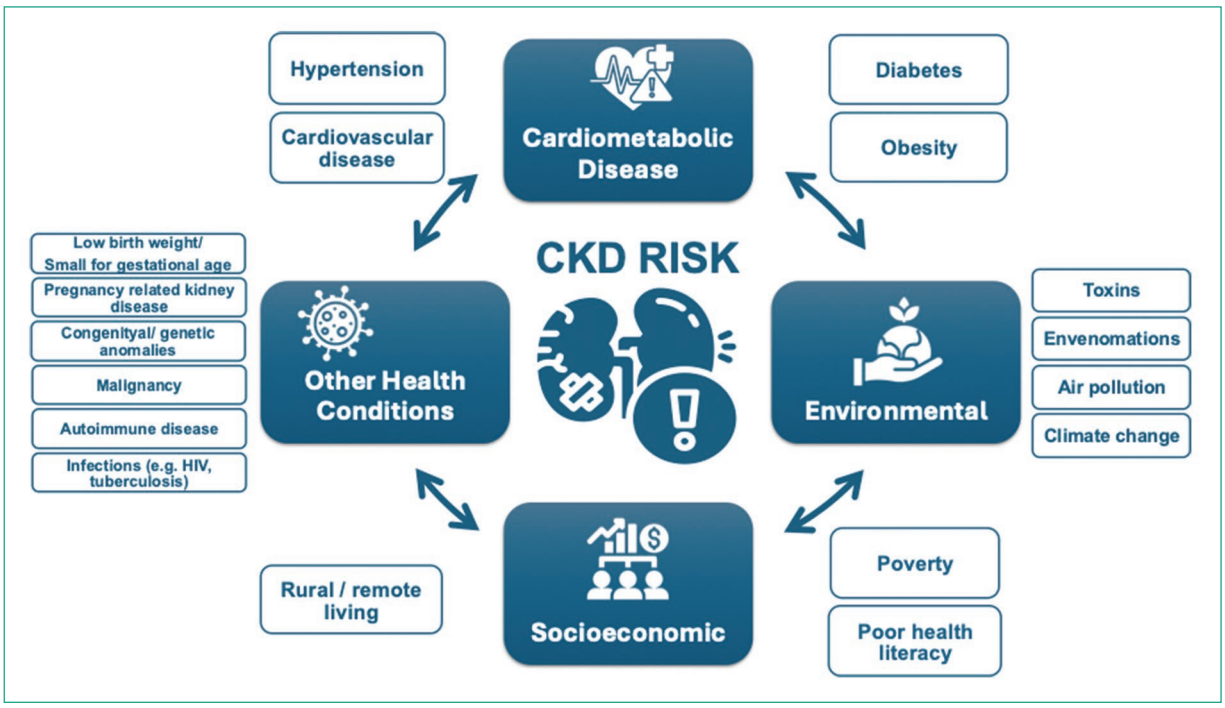

Figure 1. Risk factors for chronic kidney disease.

Alzheimer's disease, and road injuries[9]. The rising mortality of kidney disease is remarkable in contrast to other non-communicable diseases (NCDs) such as CVD, stroke, and respiratory disease, which are projected to experience a decline in mortality[8]. Even in early stage CKD, multi-system morbidity decreases quality of life. In particular, mild cognitive impairment is associated with early stage CKD and it is possible that early CKD detection and treatment could slow cognitive decline and reduce the risk of dementia[10]. CKD in children has profound additional effects, threatening growth, and cognitive development and with lifelong health and quality of life implications[11,12]. The number of people on kidney failure replacement therapy (KFRT)–dialysis and transplantation–is anticipated to more than double to 5.4 million from 2010 to 2030[13,14]. KFRT, especially hemodialysis, is unavailable or unaffordable to many in LICs and LMICs, contributing to millions of deaths annually. LICs and LMICs comprise 48% of the global population but account for only 7% of the treated kidney failure population[15].

Who is at risk of kidney disease?

Testing people at high-risk for kidney disease (case-finding) limits potential harms and false-positive test results compared with general population screening that should only be considered in high income countries (HICs). Limiting testing to those at increased risk of CKD would still capture a large proportion of the global population. Moreover, targeted case-finding in patients at high risk of CKD is not optimally performed even in HICs. About one in three people worldwide have diabetes and/or hypertension. There is a bidirectional relationship between CVD and CKD, with each increasing the risk of the other. The American Heart Association and European Society of Cardiology call for testing those with CVD for CKD, as part of routine cardiovascular assessments[1,16].

Other CKD risk factors include family history of kidney disease (e.g., APOL1-mediated kidney disease common in people of West African ancestry), prior AKI, pregnancy-related kidney disease (e.g., pre-eclampsia), malignancy, autoimmune disorders (systemic lupus erythematosus, vasculitis), individuals born with low birth weight or pre-term, obstructive uropathy, recurrent kidney stones, and congenital anomalies of the kidney and urinary tract (CAKUT), as shown in figure 1[3]. The social determinants of health strongly affect CKD risk, both for individuals and at a country level. In LICs and LMICs, heat stress for agricultural workers is thought to cause CKD of unknown etiology, an increasingly

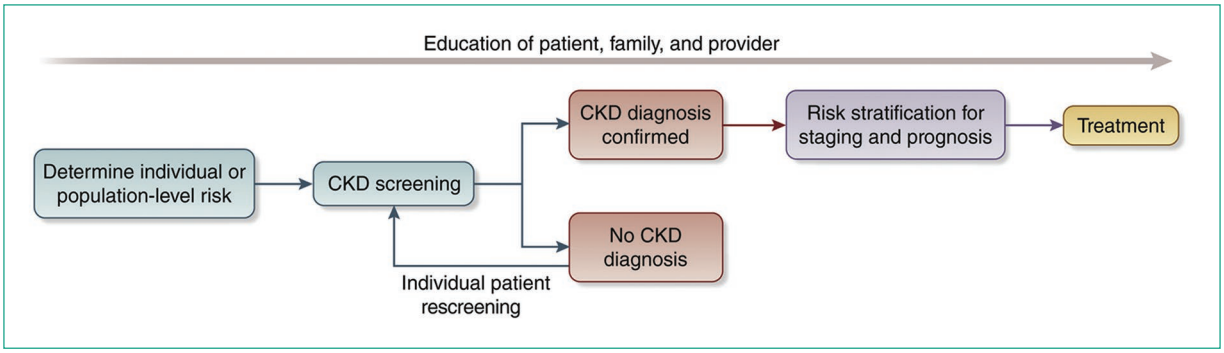

Figure 2. Conceptual framework of a chronic kidney disease testing, risk stratification, and treatment program, see reference[30].

recognized major global cause of CKD[17]. In addition, envenomations, environmental toxins, traditional medicines, and infections (viral hepatitis B or C, HIV, and parasites) deserve consideration as risk groups, especially in endemic areas[18,19].

How can we check kidney health?

Conceptually, there are three levels of CKD prevention. Primary prevention reduces the incidence of CKD by treating risk factors; secondary prevention reduces progression and complications in those with detected CKD; and, tertiary prevention improves outcomes in those with kidney failure by improving management, such as improved vaccination or optimal dialysis delivery[20]. Primary and secondary prevention strategies can utilize the eight golden rules for kidney health promotion; healthy diet, adequate hydration, physical activity, blood pressure monitoring and control, glycemic monitoring and control, avoidance of nicotine, avoidance of regular use of non-steroidal anti-inflammatory drugs, and targeted testing for those with risk factors[21]. Five of these are identical to "Life's Essential 8" rules for improving and maintaining cardiovascular health which also includes healthy weight, adequate sleep, and lipid management[22]. Early detection focuses on secondary CKD prevention that involves protecting kidney health and reducing cardiovascular risk.

Are your kidneys okay?

Globally, early detection of CKD is rare, haphazard and even less likely to occur in LICs or LMICs. At present, only three countries have a national program to actively test for CKD in at-risk populations and a further 17 countries actively test at-risk population during routine health encounters[23]. Even in HICs, albuminuria is not assessed in over half of people with T2DM and/or hypertension[24-26]. Startlingly, in those with documented reduced kidney function, a diagnosis of CKD is often missing. A study in HICs showed absence of CKD diagnosis among 62-96% of the population with laboratory evidence of CKD stage G3[27].

We recommend that healthcare professionals perform the following tests for all risk groups to assess kidney health, as shown in figure 2:

- Blood pressure measurements as hypertension is the most prevalent risk factor for kidney disease worldwide[3,28,29].
- Body mass index since obesity is epidemiologically associated with CKD risk indirectly through T2DM and hypertension and as an independent risk factor. Visceral adiposity contributes to monocyte microinflammation and cardiometabolic kidney risk[3,28,29].
- Testing for diabetes with glycosylated hemoglobin or fasting blood sugar or random glucose is part of kidney health assessment as T2DM is a common risk factor[3,28,29].
- Evaluating kidney function using serum creatinine to estimate GFR (eGFR) is recommended in all settings[3]. GFR should be estimated with a validated, race-free equation appropriate for the country, or region and age group[3]. In general, the eGFR < 60 mL/min/1.73 m^2 is the threshold for CKD in adults and children, although a threshold of < 90 mL/min/1.73 m^2 can be flagged as "low" in children and adolescents over the age of 2 years[3]. A limitation of creatinine-based eGFR is that creatinine is also a marker of nutrition and muscle mass. Therefore, states of malnutrition and frailty overestimate kidney function[3,30]. Thus, eGFR using the combination of serum creatinine and cystatin C is generally

more accurate than either biomarker alone in most clinical contexts. However, the feasibility of cystatin C use is mainly limited to HICs due to assay availability and cost relative to creatinine[3,30,31].

– Testing for kidney damage (albuminuria). In adults and children, a first morning sample is preferred for assessing albuminuria[3]. In adults, quantitative urinary albumin-creatinine ratio (uACR) is preferred as the most sensitive test[3]. Importantly, urinary albumin is in the process of being standardized analytically, which should ultimately facilitate worldwide uACR standardization[32]. In children, both urinary protein-creatinine ratio and uACR should be tested in order to assess tubular proteinuria[3]. Semiquantitative albuminuria testing allows for flexibility for point of care or home-based testing[33]. Semiquantitative or qualitative screening tests should be positive in > 85% of individuals with quantitative uACR 30 mg/g or more to be useful[34]. In resource-constrained settings, urine protein dipstick testing may be used with a threshold of +2 proteinuria or greater to reduce false positive results for repeat confirmatory testing[35].

In specific populations, the following can be considered:

– Testing for hematuria is notable as the forgotten risk factor in recent clinical practice guidelines. It is particularly important for those at risk for glomerular disease, particularly immunoglobulin A nephropathy[36].
– Baseline imaging in groups with signs or symptoms of structural abnormalities (e.g., pain and hematuria) to evaluate for kidney masses, cysts, stones, hydronephrosis, or urinary retention is important. Antenatal ultrasound can detect hydronephrosis and other CAKUT.
– With increasing availability of genetic testing, family cascade CKD testing is indicated when there is a known genetic risk of kidney disease[37].
– In those who have an occupational risk of developing kidney disease, kidney testing should be offered as part of occupational health programs.
– Those who donate kidneys should be included in a post-donation surveillance program to assess kidney health over the long-term[38].

Potential benefits of early detection

Screening for CKD fits with many of the World Health Organization's Wilson-Jungner principles. Early stage CKD is asymptomatic and effective treatments, including lifestyle modification, interdisciplinary care, and pharmacologic interventions, are established[2,3,30,35]. The World Health Organization (WHO) essential medicines that improve CKD outcomes should be widely available, including ACE inhibitors, angiotensin receptor blockers, statins, and sodium glucose co-transporter-2 inhibitors (SGLT2i)[2,39]. SGLT2i alone are estimated to decrease the risk of CKD progression by 37% in people with and without diabetes[40]. For a 50-year old person with albuminuria and non-diabetic CKD, this could extend their future period of healthy kidney function from 9.6 years to 17 years[41]. These essential medicines reduce progression to more advanced CKD stages and limit cardiovascular hospitalization to provide short-term cost-effectiveness, especially for LICs. Where available and affordable, the range of new paradigm-shifting medications to slow CKD progression also includes glucagon-like peptide-1 receptor antagonists, non-steroidal mineralocorticoid receptor antagonists, endothelin receptor antagonists, and specific disease-modifying drugs (e.g. complement-inhibitors) that herald an exciting new era for nephrology.

Considering the significant healthcare costs associated with CKD, particularly hospitalization and kidney failure, effective preventive measures offer clear economic benefits for both high- and LICs. CKD confers enormous costs to the individual, their families, healthcare systems, and governments worldwide. In the United States, CKD costs Medicare over US$85 billion annually[13]. In many high- and middle-income countries, 2-4% of the health budget is spent on kidney failure care alone. In Europe, healthcare costs associated with CKD are higher than those associated with cancer or diabetes[42]. Reducing the burden of kidney care worldwide will also have profound environmental effects, as it will save water and plastic waste, especially associated with dialysis[43]. On an individual level, CKD costs are frequently catastrophic, particularly in LICs and LMICs, where the individual largely bears the burden of payment. Only 13% of LICs and 19% of LMICs cover the costs of KFRT for adults[15]. CKD causes 188 million people in low and lower-middle-income countries annually to be faced with catastrophic healthcare expenditures[44].

The most widely cited and studied incremental cost effectiveness ratio (ICER) threshold to assess screening is < US$50,000 per quality-adjusted life year (QALY)[45]. If the prevalence of CKD is high, a population-wide screening strategy should be considered in HIC[33,46]. For example, in the United States, a recent Markov simulation model of population-wide screening for CKD, which included appropriate SGLT2i treatment added to standard of care ACE inhibitors or angiotensin receptor

blockers for adult's age 35-75 years old with albuminuria, concluded that screening to identify CKD would be cost-effective[46]. In addition, an analysis of a home-based general population semiquantitative albuminuria screening in Holland was also found to be cost effective[33]. Case finding to detect CKD in higher risk groups rather than mass or general population screening will reduce costs and other harms whilst increasing the true positive rate of the screening tests[3,35,45]. An alternate ICER threshold proposed by WHO is < 1-3 times that the ratio of the gross domestic product per capita income per QALY can be used to assess case finding approaches in LIC and LMIC[45]. The recommended tests for detecting kidney disease are low-cost and minimally invasive, facilitating their administration across diverse settings. Basic testing of eGFR and urinary ACR are widely available and using urine dipstick testing where quantitative proteinuria testing is unavailable or unaffordable will drastically reduce testing costs[31].

If coupled with effective intervention, early identification of people with kidney disease will benefit the individual, the health care system, governments, and the economy[44]. Health and quality of life benefits for the individual would lead to improved productivity, especially in the young with more working years ahead, and to developmental/educational improvements in children and young adults. Individuals would face less catastrophic health expenses, governments and healthcare systems will save money not only on CKD care but also on CVD costs, and economies will benefit from more worker participation. This is especially crucial for lower-income countries, where the greatest burden of CKD exists and is cruelly coupled with the lowest ability for governments and individuals to afford kidney care.

Challenges and solutions for implementation

Structural barriers to widespread identification and treatment of people with CKD include cost, reliability of testing and lack of health information systems to track CKD burden. These are underpinned by a lack of relevant government and healthcare policy, low healthcare professional knowledge and implementation, poor general population perceived kidney disease risk, and low patient CKD awareness. Solutions for implementing effective interventions include tying CKD identification to existing screening programs, educating the public and primary care professionals, and leveraging non-governmental organization joint advocacy programs to focus health policy agendas on kidney disease. Any solutions must balance the potential benefits and harms of screening and case-finding programs. Ethical implications for consideration include the availability of resources (such as health care workers and medicines), the affordability of testing and treatment, false positives or negatives, and anxiety for patients and their families[47].

Screening and case-finding programs require workforce capacity, health information systems, reliable testing equipment and equitable access to medical care, medicines, vaccines, and medical technologies. Primary care is at the front lines of the battle to protect kidney health, particularly in low and LMICs. The tiny nephrology workforce, with a median global prevalence of 11.8 nephrologists per million population and an 80-fold difference between LICs and HICs, is inadequate to detect and manage the vast majority of CKD[23]. As for other chronic diseases, primary care clinicians and other front-line health workers are foundational to early detection of CKD[48]. Testing must be affordable, simple and practical, with point-of-care creatinine testing and urine dipsticks useful in resource-limited settings[31]. Educational efforts directed at primary care clinicians are key to integrating CKD detection into routine care, despite constrained time and resources[49-51]. Automated clinical decision support could leverage electronic health records to identify people with CKD or at high-risk of CKD and recommend appropriate actions to clinicians (Fig. 2).

At present, few countries have CKD registries, limiting our ability to highlight the disease burden to governments. Knowledge of CKD burden assists in prioritizing kidney health needs, which should then progressively expand to encompass the full spectrum of kidney care[52]. A global survey revealed only a quarter of the countries (41/162) had a nation specific CKD strategy and fewer than a third (48/162) recognized CKD as a public health priority[23]. The WHO's recognition of CKD as a major driver of NCD mortality would be impactful in increasing awareness, improving local surveillance and monitoring to implement clinical practice guidelines and improving resource allocation[2].

Programs for the early detection of CKD will require extensive coordination and engagement of stakeholders, including governments, health systems and insurers. International and national kidney organizations, such as the International Society of Nephrology, already advocate to the WHO and individual governments for the prioritization of kidney disease. We must continue this work, collaborating to streamline early detection program planning and implementation. Connection to existing community interventions (e.g., CVD

Table 1. Are your kidneys okay? person perspectives on CKD awareness, detection and treatment from the literature, see references[4,57]

I actually didn't fully understand because nobody had actually given me the full information of what I had in a way that I could kind of go, "Well this is what I've got (CKD), and this is why I've got it."
[the clinicians] they can answer those [kidney health] questions,... but it's all very jargonistic.
I didn't know what it (CKD) meant so I couldn't really share it with other people.
I may not know what my [kidney health] numbers are, but I do know what the tests are, and I do know that I've had them done before.
Well, let me put this way: I'm now well aware now of the significance of the kidneys and about what the issues are here. And I would definitely consider. When I go to the doctor, I would say to him, "Now, listen. You did the blood tests. But how are my kidneys doing? What are the numbers?
I know that they have done urine tests in the past, and I know protein and sugar was in my urine.
I went from never taking a tablet to taking 22 tablets. What going on here? I didn't know what they were. But I just number them and that did help me a lot because I realized what was going on but some of them, every time I went there [to see the doctor], I'd get another tablet. I knew that I had to take it because they knew what they were doing, the doctors that I went to see.
This (CKD) is something new, so immediately I was like, just another thing to be concerned about. But then I felt kind of empowered, and like I really do want to get ahead of this thing. I feel like I do want to have a conversation with my primary care physician.
What I would be mostly interested in is what is happening, why is it happening, and what can I do to slow it (CKD) down?

CKD: chronic kidney disease.

prevention) in LMICs and HICs can decrease cost and maximize efficiencies by integrating into existing programs. Such programs will need to be adapted to the local context and can be held in a variety of settings, such as individual healthcare practices, hospitals, as well as regional or national healthcare facilities or as outreaches in rural communities. Depending on local regulations and resources, screening and case-finding can also take place outside of medical settings such as town halls, churches, or markets. Volunteers in the community can also assist with community-based screening and case-finding efforts.

In conjunction with reorienting the clinical practice of health care professionals to a greater focus on timely detection of CKD, we must focus on general population perceived risk education and health promotion activities, as well as education programs aimed at patient awareness and empowerment. General population awareness of kidney disease is poor, with nine out of ten people with CKD unaware they are affected[53]. Coverage of kidney disease is missing from the mainstream conversation, with an analysis of lay press showing kidney disease was 11-times under-represented in discussed compared to the actual cause of death[54]. A number of national and international organizations have developed public-facing quizzes on risk of kidney disease, supported by a regional study that showed socially vulnerable patients with hypertension do not understand their kidney risks[21,55-57]. Online and direct education for healthcare professionals can improve consumer health literacy. Patient activation, engagement, and shared decision-making are downstream impacts of awareness. Awareness education is nuanced for CKD, including detection and risk stratification to inform and empower rather than frighten regarding the timing and extent of interventions (Table 1)[4,27,57]. Getting the balance right will optimize self-efficacy and patient, family, and caregiver engagement.

Conclusion: a call to action

We call on all healthcare professionals to check the kidney health of their patients at risk of kidney disease. In tandem, we must work with public health organizations to improve the general population's perceived risk of kidney disease and empower people at risk to seek kidney health checks. To ensure this change can be delivered, we must work with healthcare systems, governments, and the WHO to prioritize kidney disease and create effective and efficient early detection programs for kidney disease. Only then will the paradigm-shifting benefits of lifestyle change and pharmacologic treatments translate to better kidney and overall health for people all around the world.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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ORIGINAL ARTICLE

Analyzing the process of training nephrologists in Uruguay. Forty years of program: analysis of curricular trajectories, time invested and success in the degree

Análisis del proceso de formación de nefrólogos en Uruguay. Cuarenta años de programa: análisis de la trayectoria curricular, tiempo invertido en la formación y éxito en la titulación

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Abstract

Objective: *The analysis of the process of training nephrologists in Uruguay is scarce. We assessed the curricular trajectories (CTs) time invested and success rate in obtaining the nephrologist specialty degree at the University of the Republic in Uruguay.* **Material and methods:** *Information (1979-2022) was obtained from University of the Republic databases. All possible CTs were identified, the success in obtaining the title and, the invested times in formation in the different CTs were evaluated.* **Results:** *Since the beginning of the specialty, the annual median interquartile range (IQR) number of students entering the nephrology training program was 7.5 (4.8-12.0) and the annual median (IQR) number obtaining the nephrologist degree was 6.0 (4.5-8.0). There was female predominance (65%); 12 possible CTs were identified and 76.3% entering students obtained the nephrologist degree. The median (IQR) of time until the degree was 6 years (4.5-8.4), without differences between sexes ($p > 0.05$) and with longer times ($p < 0.05$) for the graduated by out-of-run promotion.* **Conclusions:** *The formation of nephrologists in Uruguay has several possible CTs, female predominance and a good balance between student entry and graduates. This information allows longitudinal evaluation and identification of opportunities for improvement, in the only training program for nephrologists in Uruguay.*

Keywords: *Education professional. Nephrology. Educational measurement. Academic performance.*

Resumen

Objetivo: *Son escasos los análisis sobre la formación de nefrólogos en Uruguay. Analizar las trayectorias curriculares (TC), tiempo invertido en la etapa formativa y éxito en la obtención del título de nefrólogo en la Universidad de la República (UdelaR) en Uruguay.* **Material y métodos:** *Se obtuvo información (1979-2022) de diferentes fuentes de datos de la UdelaR. Se identificaron las TC posibles, se evaluaron los tiempos invertidos en formación y el éxito en la obtención del título en las diferentes TC.* **Resultados:** *Desde el inicio de la especialidad la mediana (intervalo intercuartílico [IIC]) de ingreso anual fue 7.0 (4.0-12.0) estudiantes/año y la de egreso anual 6.0 (4.0-8.0) nefrólogos/año. Predominaron las mujeres (65%); se identificaron 12 posibles TC y el 76.3% obtuvo el título. La mediana (IIC) de tiempo hasta la titulación fue de 6 años (4.5-8.4), sin*

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diferencias entre sexos (p > 0.05) y con tiempos más largos (p < 0.05) para los graduados por competencia notoria. **Conclusiones:** *La formación de nefrólogos en Uruguay tiene varias TC posibles, predominio femenino y un buen balance entre ingresos y egresos. Este análisis longitudinal permite identificar oportunidades de mejora en el único programa de formación de nefrólogos en Uruguay.*

Palabras clave: *Educación profesional. Nefrología. Evaluación educacional. Desempeño académico.*

Introduction

Nephrology is a medical specialty that focus on renal structure and function, diagnosis, and treatment of kidney diseases. It is integrated into the primary, secondary, and tertiary levels of health care[1-3]. It is a branch of medicine with a strong component of internal medicine[4]. However, the scope of nephrology extends into various disciplines and areas of knowledge. It has a critical care component and is involved in the treatment of patients with acute or chronic renal conditions, where kidney disease contributes to the patient's severity and dialysis treatment is often required[4-6]. Nephrology also extends into pediatrics, where the frequency and clinical presentation of renal diseases, as well as their treatment, have remarkable differences[7]. Nephrology care requieres interaction with other medical specialties. From the first level of care, with family doctors and through the Renal Health Program, to the secondary and tertiary levels, where it closely interacts with clinical laboratories, bacteriology, infectious diseases, imaging, and pathology among others[8]. In Uruguay, the interaction between nephrologists and these areas has been crucial in developing new diagnostic and therapeutic tools. More recently, nephrological practice demands the use of point of care ultrasound as a clinical extension to improve diagnostic precision, reduce procedural complications, and shorten treatment time[9]. In several instances, diagnostic or therapeutic techniques that involve invasive procedures are required, which has led to interventional nephrology[10]. Thus, the training of nephrology specialists, although complex, is essential to meet the needs of the health care system[11-13].

In Uruguay, there is a single nephrology training program (Nephrology Center at Hospital de Clínicas, School of Medicine, University of the Republic [UdelaR])[14], with different training providers organized into Associated Teaching Centers (CEDA acronym from spanish). This setup helps concentrate and maximize the efficiency of resources in training this complex specialty and contributes to standardizing nephrology practices across the country. The nephrology specialty in Uruguay has been recognized by the Posgraduate Educational Office of the School of Medicine, UdelaR, since 1979[4]. The Nephrology Department was established and the regular postgraduate nephrology program began, with the first course enrolling 16 students that same year. The title of specialist by out-of-run promotion was awarded to 10 physicians[15]. Since 1979, there have been different nephrology study programs (syllabus): 1979, 1988, and 2003. The most recent one, still in effect, establishes a training period of 3 years, during which the student is expected to complete their specialty thesis and take a clinical board exam. Since 1993, the national residency program included a nephrology residency during the final year of internal medicine residency, improving student dedication to training. Furthermore, a specific nephrology residency was later created, with the first cohort starting in 2004. Subsequently, several public and private teaching centers were accredited by the Posgraduate Educational Office of the Faculty of Medicine as associated units, allowing the nephrology residency training program to expand beyond Hospital de Clínicas. Recently, a new syllabus for the Posgraduate Educational Office was approved, awaiting validation by other UdelaR institutional authorities[16]. This new syllabus proposes a 4-year training period-consistent with other international programs-including an additional year for the completion of the thesis and defines the competencies that nephrologists will have on graduation.

Information about human resources (HR) training in the health care sector, particularly regarding syllabus the efficiency of academic programs, is a key input for strategic planning of new health care HR[17-19]. Due to multiple factors, this information is scattered and therefore unavailable for decision-making in Uruguay. In this study, we aimed to analyze the results of the nephrology specialist training program and the possible curricular paths that lead to graduation in this specialty. Finally, we emphasize the information that could potentially be considered for planning HR training in nephrology.

Material and methods

Data from 1979 to 2022 were obtained from the Administrative Teaching Management System (SGAE ,

acronym from spanish) and the database of the Nephrology Center, UdelaR.

A database was created with all students enrolled in the nephrology postgraduate program since its inception, excluding those who never started the courses but including graduates for whom the specific syllabus plan could not be identified.

Curricular trajectory (CT) was defined as the sequence of courses and academic achievements that could lead to the attainment of the degree of nephrology specialist during the analyzed period. All possible CTs from the beginning of the nephrology specialist training program up to the moment of this analysis were identified.

CTs, annual admissions and graduations, and time to graduation (TTG) were evaluated. The analyses were disaggregated by gender and syllabus. Finally, the results of the 2003 syllabus were analyzed, considering admissions from 2003 through 2018, allowing a 4-year period for the latest cohort to graduate. A specific analysis of the 2003 syllabus was conducted as it was in effect at the time of this analysis and to independently evaluate the impact of the nephrology residency program, which began in 2004.

The category "on-time graduates"[20] was defined based on the theoretical duration of the program according to the current syllabus (3 years) and the one pending approval (4 years). Students who had not graduated after the theoretical time frame of the program were considered delayed students.

"Terminal efficiency" was calculated as the ratio of "on-time graduates" to the total number of students who entered the 2003 plan by 2018, expressed as a percentage.

Statistical analysis: categorical variables were described using absolute frequencies and percentages, while quantitative variables were reported with medians, interquartile ranges (IQR, 25-75), and/or minimum and maximum values (min-max). To compare differences between groups of quantitative variables, a 95% confidence interval (95% CI) for the difference in medians was estimated.

Statistical analyses were performed using the statistical software and programming language R version 4.1.0[21].

Results

General characteristics

Since the registration of the nephrology specialty at the Posgraduate Educational Office of the School of Medicine (1979), a total of 476 students have enrolled to obtain the title of nephrology specialist (Fig. 1). Students who never started the courses (n = 84) were excluded from the analysis, leaving 392 students for analysis.

At the beginning of the specialty, the first students (n = 16), who graduated between 1979 and 1982, obtained their degrees out-of-run promotion documented performance, or validation, and therefore, do not formally belong to any syllabus. These graduates are presented separately in the analyses (Tables 1 and 2). Furthermore, considering that the current syllabus has a duration of 3 years plus an additional year for completing the monograph and preparing for the final board exam, it was assumed that students who entered during the last 4 years (2019-2022) are still in progress and are not expected to have graduated (Fig. 1). Therefore, out of the 392 students who began their CT, 54 students are still in progress at the time of this analysis. Of the remaining 338 students, 258 (76.4%) obtained the degree of specialist, while 80 (23.6%) did not (Fig. 1). Of these, 7 (8.7%) are in the process of obtaining their degree, 27 (33.8%) completed all the required courses but have not yet taken the final board exam, 11 (13.7%) dropped out in different semesters, and 35 (43.8%) have no available data.

Among the 392 students included in the analysis, 256 (65.3%) were women. The proportion of women was predominant across all plans and periods analyzed (Table 3).

Admissions from 1979 through 2022

Figure 2 shows the evolution of annual admissions and graduations from the start of the specialty in 1979 to 2022.

Up to 2018, admissions for the 1979, 1988, and 2003 plans were 79, 126, and 117 students, respectively (Table 2). In addition, there were 16 foundational admissions at the beginning of the specialty, which do not belong to any syllabus and another 54 admissions to the 2003 plan between 2019 and 2022, who are still in progress (Table 2).

Since the start of the nephrology specialty in Uruguay, the median (IQR) number of annual admissions was 7.0 (4.0-12.0) students per year. The number of annual admissions increased over time (median [IQR]): 6.0 (4.0-11.0), 7.0 (4.0-11.5), and 8.0 (5.0-12.0) students per year, in the successive 1979, 1988, and 2003 plans, respectively. In all syllabus plans, female admissions were predominant. Across all plans (1979-2022), female admissions accounted for 65% (Table 3).

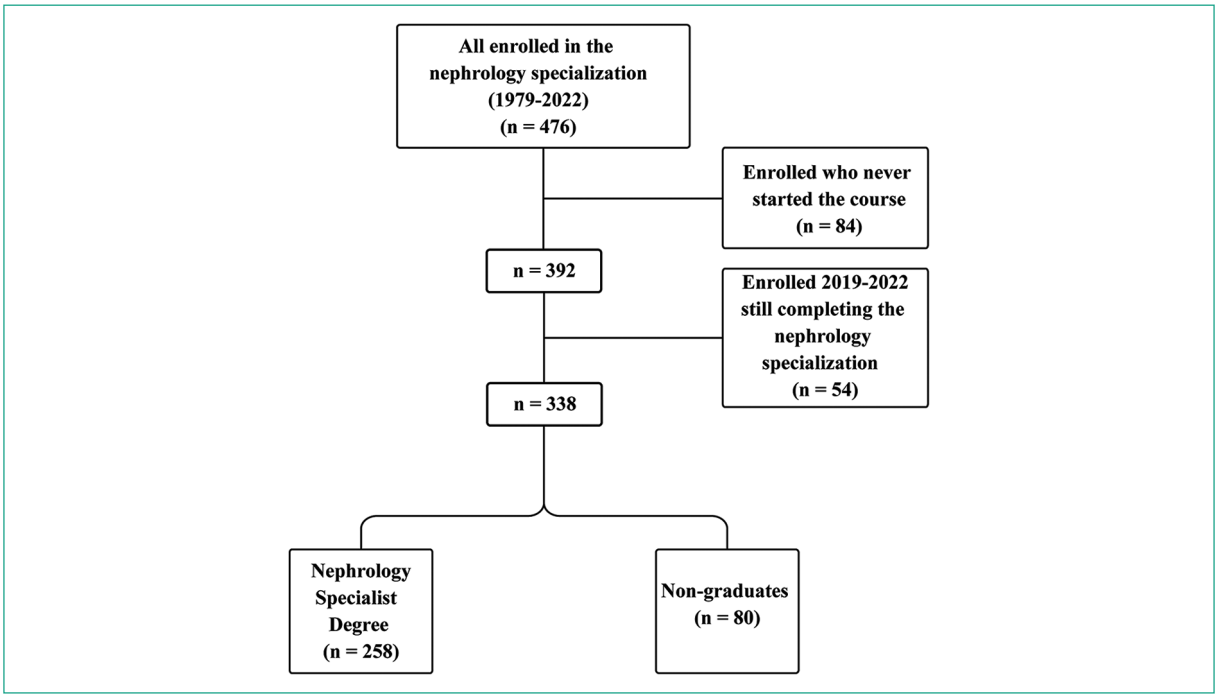

Figure 1. Selection and segmentation process of the population. The flowchart represents the process flow of students enrolled in the postgraduate specialization course from 1979 through 2022.

Graduations from 1979 through 2022

In the analysis of graduations (degree attainment) by syllabus (Table 2), foundational graduates (n = 16), who did not follow any specific plan, and students from the 2003 plan from 2019 through 2022 (n = 54) who are still in progress at the time of this analysis, are also differentiated. For the 1979, 1988, and 2003 plans, annual graduations were 73, 104, and 65, respectively, representing 92.4%, 82.5%, and 55.5% of the respective admissions (Table 2).

Since the start of the nephrology specialization courses in Uruguay, the median (IQR) annual graduation rate was 6.0 (4.0-8.0) nephrologists per year.

Table 1 summarizes the graduation data according to the possible final modalities of the CTs. Overall, most graduates (86.8%) completed their final exam, corresponding to trajectories 1, 2, 4, 5, 7, and 8 (Fig. 3), while a minority (13.2%) graduated through other possible modalities: out-of-run promotion documented performance, or validation.

Throughout the successive syllabus (1979, 1988, and 2003), the number (%) of graduates "by final exam" decreased: 73 (100%), 97 (93.3%), and 54 (83.1%). Conversely, the proportion of non-graduates increased: 6 (7.6%), 22 (17.5%), and 52 (44.4%), respectively.

TTG

All cases with available admission and graduation dates to the specialty (n = 242) were analyzed. The TTG was 6 years (IQR, 4.5-8.4) (Fig. 4). The TTG was shorter ($p > 0.05$) for women (5.8; IQR, 4.5-8.3 years) than for men (6.2; IQR, 4.7-8.6 years). The TTG was longer for those who graduated through the out-of-run promotion modality (n = 18) compared to those who graduated by final examination (n = 224), 7.4 (IQR, 5.8-10.3) versus 5.7 (IQR, 4.5-8.4) years.

Among those who obtained their degree through out-of-run promotion (n = 18), 10 (55.6%) were nephrology clinical instructors (grade 2 assistants); of these, five followed a residency path with a median training time of 6.1 years (min-max: 5.8-7.7), and five completed postgraduate studies, with nephrology being their 2nd specialty after internal medicine, with a median of 6.5 years (min-max: 3.8-9.8).

Curricular trajectories

A comprehensive analysis identified 12 CTs.

Figure 3 outlines each possible CT for obtaining the title of nephrology specialist and the frequency of these (n = 258). Students who completed postgraduate or

Table 1. Summary of graduation rates with details of the CT

CT for which the title was obtained	Graduated based on CT				Graduates*	Non-graduates†	Total (%)
	Documented performance	Out-of-run promotion	International degree revalidation	Final board exam	All CTs (%)	All CTs (%)	
1979-2018	1	32	1	224	258 (76.3)	80 (23.7)	338 (100)
2019-2022‡	-	-	-	-	-	54 (100)	54 (100)
Total					258 (65.8)	134 (34.2)	392 (100)

*Corresponds to the sum of "graduates" in all CTs.
†Corresponds to "non-graduates" regardless of the CT followed.
‡Includes students enrolled from 2019 through 2022 (n = 54) who, at the time of this analysis, are at various stages of progress but are not yet eligible for graduation because < 4 years have passed since enrollment.
CT: Curricular trajectories.

Table 2. Summary of graduation rates with details of the CT classified according to the curriculum followed

Curriculum	Graduated based on CT				Graduates*	Non-Graduates†	Total (%)
	Documented performance	Out-of-run promotion	International degree revalidation	Final board exam	All CTs (%)	All CTs (%)	
No curriculum	1	14	1	0	16 (100)	0 (0)	16 (100)
1979	0	0	0	73	73 (92.4)	6 (7.6)	79 (100)
1988	0	7	0	97	104 (82.5)	22 (17.5)	126 (100)
2003‡	0	11	0	54	65 (55.5)	52 (44.4)	117 (100)
2003§	0	0	0	0	0 (0)	54 (100)	54 (100)
Total	1	32	1	224	258 (65.8)	134 (34.2)	392 (100)

*Corresponds to the sum of "graduates" in all CTs in each curriculum.
†Corresponds to "non-graduates" regardless of the CT followed.
‡Includes 115 cases that belonged to the 2003 curriculum who enrolled from 2003 through 2018, and two cases in the 2003 curriculum with enrollment dates prior to 2003.
§Includes students enrolled from 2019 through 2022 (n = 54), who, at the time of this analysis, are at various stages of progress but are not yet eligible for graduation because < 4 years have passed since enrollment.
CT: curricular trajectories.

Table 3. Distribution by gender according to curriculum

Curriculum	Women (%)	Men (%)	Total (%)
No curriculum	5 (31.2)	11 (68.8)	16 (100)
1979	49 (62.0)	30 (38.0)	79 (100)
1988	92 (73.0)	34 (27.0)	126 (100)
2003	110 (64.3)	61 (35.7)	171 (100)
Total	256 (65.3)	136 (34.7)	392 (100)

residency programs, as stipulated in the respective syllabus and took the final examination (trajectories 1 and 4) accounted for 60% of the cases.

The next most frequent paths are those who pursued a nephrology postgraduate degree after having previously completed another specialty (paths 6, 7, and 9) and obtained their qualification either through a final examination after completing the postgraduate program (paths 6 and 7: 20.5%) or through out-of-run promotion (path 9: 5.8%). Together, these paths represent 86.3% of the cases.

Analysis of CTs for the 2003 study plan

Overall (n = 392), 117 completed the 2003 syllabus-plan up to December 31, 2018, with 70 (59.8%) being female. The median age at graduation was 32 years (IQR, 32-36). Women graduated at a younger median age (33 years; IQR, 32-34 years) than men (34 years; IQR, 32-38 years).

Table 4 analyzes the 2003 plan graduates (2003-2018 period) by the modality in which they completed their

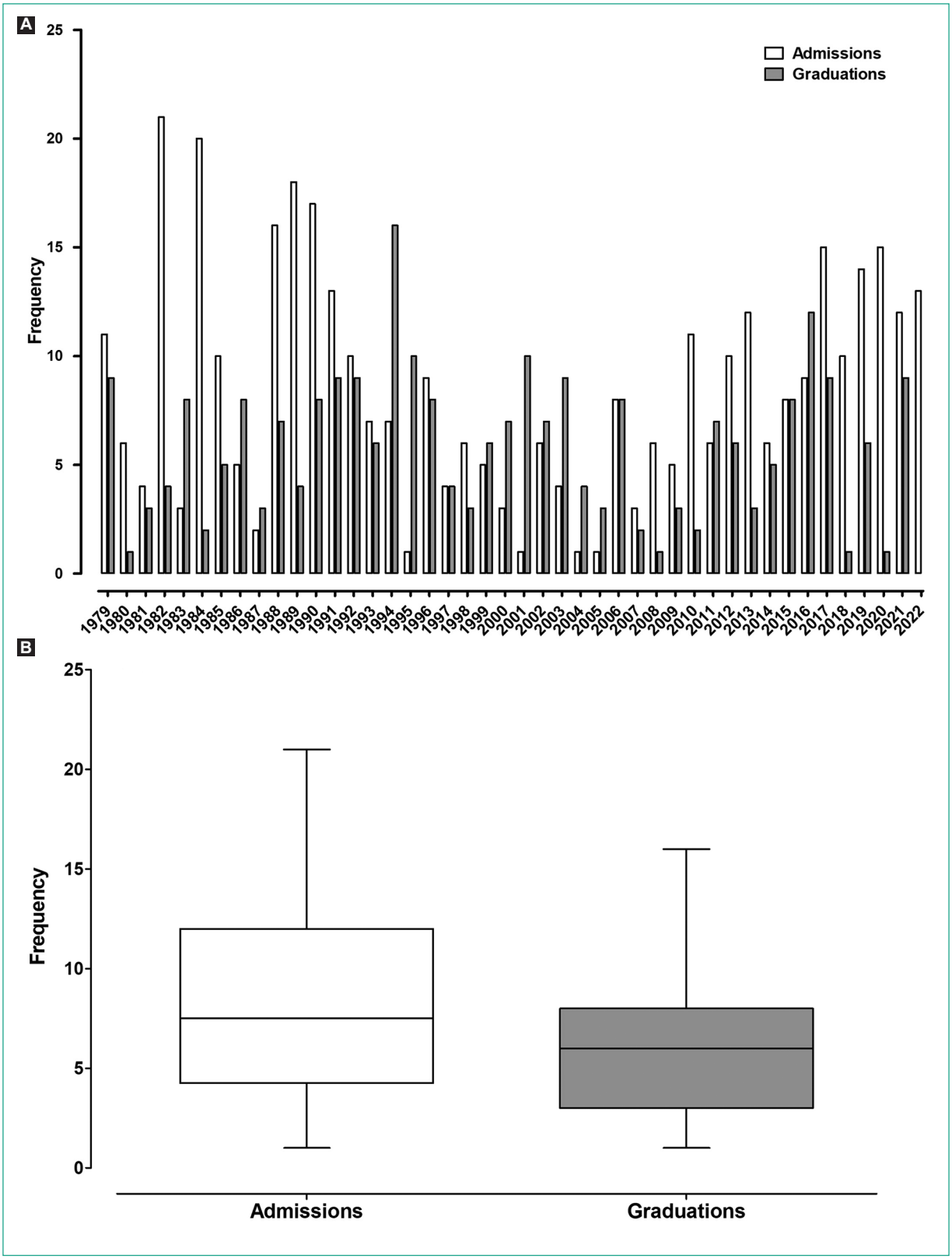

Figure 2. Admissions and graduations from 1979 through 2022. **A:** absolute frequencies per year from the start of the postgraduate course until 2022. **B:** the box plots represent the median and interquartile range of admissions and graduations in the nephrology specialization from the start of the courses until 2022.

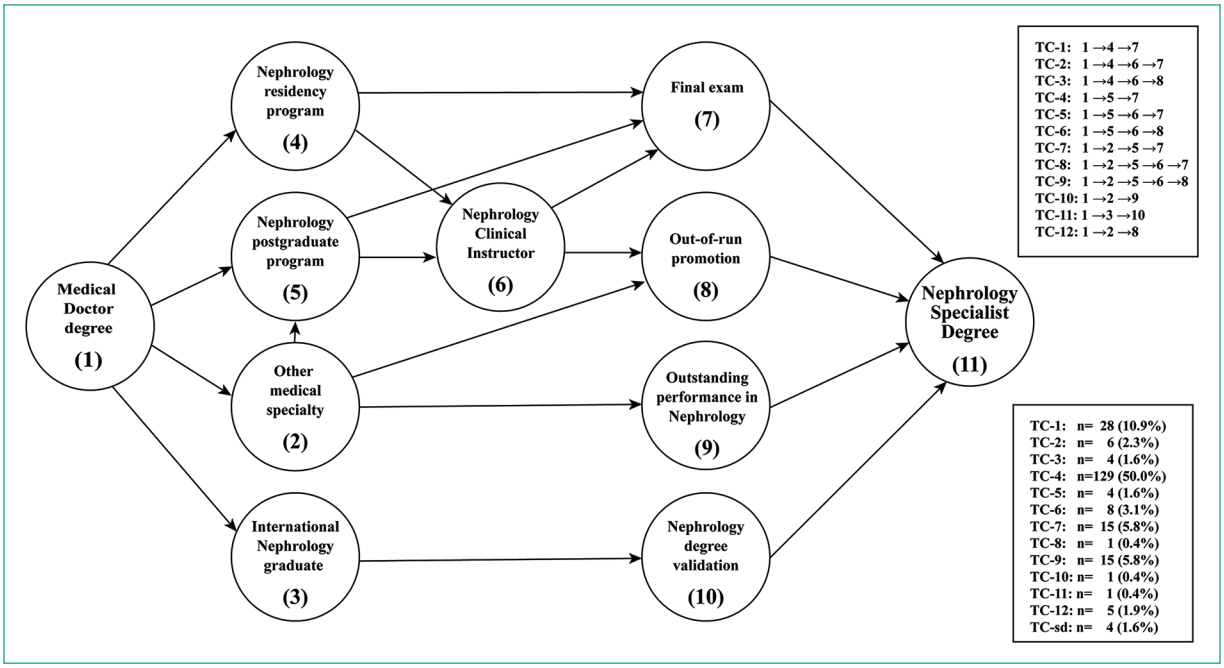

Figure 3. Possible curricular paths to obtain the title of nephrology specialist. Diagram shows all the identified curricular paths (upper box) and their frequency (lower box) from the start of the postgraduate course in 1979 until 2022.
CT: curricular trajectories; ND: no data.

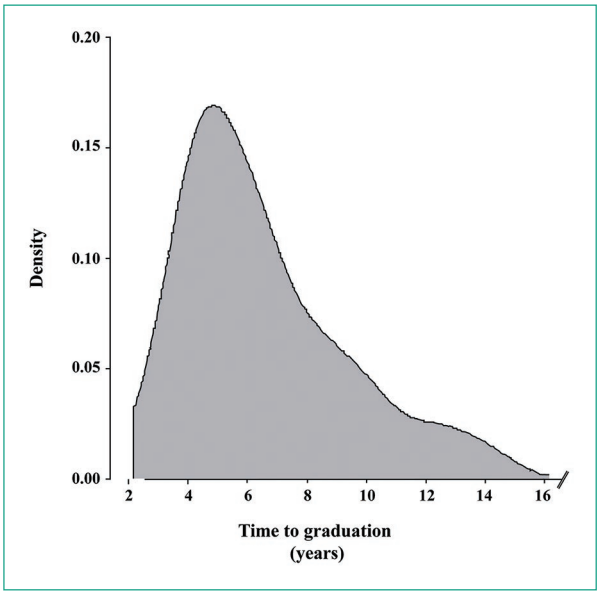

Figure 4. Distribution of time to qualification times to graduation in years. Histogram of the time to qualification for all graduates from the start of the nephrology specialization in 1979 until 2022.

CT. Overall, the TTG was 5.0 years (min-max: 4.0-6.3). The median TTG for graduates by final examination (n = 53) was 4.8 years (min-max: 3.4-14.4). Those who followed a residency CT (n = 27) had a shorter TTG with less variation than those who followed a postgraduate CT (n = 22); 4.6 years (min-max: 3.4-6.1) versus 4.9 years (min-max: 3.4-14.4), median difference –0.3 years (95% CI, –1.39-0.5). For those who graduated through out-of-run promotion (n = 11), the median TTG was longer at 6.1 years (IQR, 5.7-7.7). Among these, there was no difference between those whose CT included residency (n = 5), 6.1 years (IQR, 5.9-7.7), and those who followed postgraduate studies (n = 6), 6.1 years (IQR, 4.9-7.3).

Efficiency evaluation

Considering a stipulated training time of 3 years in the 2003 plan, a terminal efficiency of (11/104) × 100 = 10.6% is estimated. However, if a TTG of around 3.4-4.4 years is considered, the terminal efficiency increases to (20/104) × 100 = 19.2%.

Discussion

The training of nephrologists at the only institution (UdelaR) responsible for training these specialists in Uruguay was analyzed. We found that during this period, three out of every four students who pursued the

Table 4. Graduation by final curricular path of the 2003 curriculum

Final status	Final trajectory through which the degree was obtained			Total (%)
	Out-of-run promotion (%)	Graduation (final exam) (%)	Not graduated (%)	
Enrolled and graduated	11 (17.2)	53 (82.8)	0 (0)	64 (100)
Only enrolled	0 (0)	0 (0)	51 (100)	51 (100)
Total	11 (9.6)	53 (46.1)	51 (44.3)	115 (100)

specialization graduated (76.3%). There was a predominance of women at both admission and graduation (65% and 70%, respectively), and they also achieved graduation in shorter TTG. We found an acceptable balance between the median number of admissions and graduations, 7.5 (4.8-12.0) and 6.0 (4.5-8.0), respectively. The median TTG (6 years; CI, 4.5-8.4 years) exceeded the stipulated time frames (3-4 of courses and a final thesis) across the different syllabus. Only 1 in 5 students (19.2%) managed to graduate as a nephrologist in < 4.5 years.

Planning for future nephrology specialist training remains a global concern[17-19,22]. In 2022, in response to the institutions responsible for accrediting postgraduate medical education in the U.S., the American Society of Nephrology (ASN) promoted the formation of a task force to consider whether the current training and certification requirements in nephrology should be expanded[22]. This group has been given the challenging task of considering all aspects of the future of the specialty to ensure that new generations of nephrologists are prepared to provide high-quality nephrology care[22]. This task force made 10 recommendations that would help redefine the strategic lines for the training of future nephrology specialists[22]. One of them is to "establish individualized paths to meet professional goals"[22]. In other words, the diversity of the 12 possible CTs that the specialist training in Uruguay allows should be seen as a strength of the program.

On the other hand, our analysis reveals a median TTG that exceeds the stipulated time, resulting in a higher median age at graduation. Addressing this issue requires considering the difficulties faced in planning and implementing a nephrology training syllabus in the context of a resource-limited country[23], where nephrology training is exclusively centered at the public university.

The shortage of resources for specialist training prevents filling all postgraduate training positions with residency placements. Therefore, many postgraduates who do not secure a residency position have lower academic performance, with longer TTGs. Furthermore, during the 2nd year of the UdelaR nephrology postgraduate program, dialysis techniques are taught. From then on, clinics providing dialysis services offer jobs to postgraduate students, confronting them with the decision to reduce their academic studies and maintain a dual position of work and academic study. If the balance tips in favor of paid work to the detriment of academic study, the situation becomes exhausting for students, leading them to postpone their courses and exams, or even, after several attempts, abandon their goal of obtaining the degree in nephrology. Although current legislation requires that doctors working in dialysis centers be nephrologists[24], the inability to fill positions with graduated nephrologists has led to a relaxation of oversight by the governing authorities. These factors can therefore lead to a very low terminal efficiency in the stipulated training times. The new UdelaR nephrology specialist training program, still under evaluation, will incorporate competency-based training and add a fourth curricular year for the development of the postgraduate thesis[25]. Originally (2004), the residency program had 1 spot for nephrology, which gradually increased, mainly due to the addition of CEDAs (clinical education centers) from different nephrological clinics in the public and private sectors. In 2023, most available spots (10 out of 17) were for residents. The mid-term challenge is to add new CEDAs, particularly in regions geographically distant from Montevideo, Uruguay to encourage newly trained nephrologists to settle in the regions that need them the most.

The nephrologist training program in Uruguay has several strengths: (a) the Nephrology Center at UdelaR has a level of clinical development that serves as a national reference for key areas of nephrology (general nephrology, nephrology for acute and critical patients, chronic dialysis techniques [hemodialysis, online hemodiafiltration, and peritoneal dialysis], and kidney transplants); (b) regardless of training times, three out of four students (76.3%) graduate, and the ratio of median

annual admissions to graduations is acceptable; and (c) access to postgraduate education is free and through a resident examination for Uruguayan students (currently 15 spots/year), but foreign students who pass the prior examination to validate their medical degree may also access it by paying a tuition fee (2 spots/year). The number of spots remains full, with an excess of applicants unable to secure a place. This reality contrasts with the U.S. and other countries where aspirations fail to fill the available spots[26,27].

The overall results of our analysis show a balanced median number of admissions and graduations across various plans. This could be seen as a disconnect between the fixed number of trained specialists and the growing needs of the health care system due to the sustained increase in the prevalence of kidney disease and better access to new technologies and treatments[28]. However, from 2010 through 2022, there was a rising trend in admissions to the nephrology specialty, remaining above 10 admissions per year, except for 4 years. Recent estimates show that Uruguay has one nephrologist per 18,584 inhabitants[29], approximately 50.5 nephrologists per million population[12]. These figures position Uruguay as one of the countries with the highest number of nephrologists relative to its population[17,18]. At present, there is a real difficulty in covering some hemodialysis shifts in nephrology; however, health system-wide projections, under various scenarios, indicate a surplus of specialists, even considering different assumptions[13]. This warrants continued active and dynamic work to maintain the balance in specialist training, with a broad approach that considers contextual issues related to health system organization and working conditions, among others.

While this analysis allows for important conclusions, it is not without limitations. First, the information was scattered, and there was no single source with all the available data. However, it was possible to compile a robust and reliable database by consulting formal and informal sources that allowed data verification for the analysis. Second, the Posgraduate Educational Office which oversees all medical specializations, did not have available all the semester progress reports for all students, preventing a more detailed analysis of the progress of delayed students.

This could be addressed in future research by completing the available paper sources and corroborating them with interviews and informal sources. Finally, we cannot address efficiency and quality by separately evaluating the areas in which nephrologists work, such as general nephrology (including outpatient clinical consultation), acute nephrology (including critical care), chronic nephrology (including hemodialysis and peritoneal dialysis), and finally transplantation. The new syllabus incorporates several of the ASN recommendations and will allow competency-based evaluations among other virtues. The current knowledge landscape suggests that challenges lie ahead that will lead to defining dynamic nephrologist training programs enriched with new disciplines.

Conclusions

Nephrologist training in Uruguay has accumulated over 40 years of experience. There are several possible CTs to achieve nephrology specialist graduation. This aligns with the ASN recommendations and allows a profession with such a broad scope to benefit from specialists in training coming from different trajectories. In all plans, there was a predominance of women, who achieved graduation in shorter times than men. Considering the entire analyzed period, there is a good balance between admissions and graduations, which is slightly lost in recent years as admissions have significantly increased. As far as we know, this is the first analysis of nephrology specialist training with a historical perspective of over 40 years. This analysis will help improve future programs, how information is stored, and identify opportunities for improvement in Uruguay's only nephrologist training program.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

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ORIGINAL ARTICLE

Training of adult nephrologists in Argentina: open doors and empty chairs

Formación de nefrólogos de adultos en Argentina: puertas abiertas y sillas vacías

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Abstract

Objective: *To identify the motivations of graduates for choosing nephrology as a specialty and explore possible reasons for the loss of interest in it, to characterize nephrology specialization programs in the country, and to compare the interest of Argentine and foreign graduates in the available positions. In Argentina, there are fewer residents in nephrology and more positions in training programs remain vacant.* **Material and methods:** *A qualitative-quantitative study (2018-2023) involving nephrology residents, training educators and training centers. The study investigated participants' perceptions, types of programs, number of residents and nationality, as well as available and filled positions.* **Results:** *A total of 122 residents, 51 trainers, and 44 centers participated. Reasons for choosing nephrology included its clinical component, breadth and complexity, and attraction to a specific area. The main reasons for disinterest were the lengthy training period, work overload, uncertain job prospects, and low professional remuneration. At the time of the study, there were 17 basic residencies, 11 post-basic residencies, and 16 specialization careers in operation. There 208 residents in total (43% of them foreign). Between 2017 and 2021, 422 positions were available, of which 341 (81%) were filled.* **Conclusions:** *The vacant positions reflect a lack of interest in nephrology among Argentine graduates, which is not seen among foreign graduates. This may impact the nephrology workforce in the coming years.*

Keywords: *Medical education. Postgraduate. Specialization. Residencies.*

Resumen

Objetivo: *Identificar en los graduados motivaciones para elegir la especialidad de nefrología y posibles razones de pérdida de interés por la misma, caracterizar los programas de especialización en nefrología del país, y distinguir el interés de los graduados argentinos y extranjeros por las plazas disponibles en Argentina. Hay cada vez menos médicos residentes en nefrología y más plazas vacantes en los programas de formación.* **Materiales y métodos:** *Estudio cuali-cuantitativo (2018-2023) con residentes de nefrología, docentes formadores y centros formadores. Se indagaron las percepciones de los actores, los tipos de programas, el número de residentes y su nacionalidad, así como las plazas disponibles y cubiertas.* **Resultados:** *Participaron 122 residentes, 51 formadores y 44 centros. Los motivos para elegir nefrología fueron el componente clínico, su amplitud y complejidad, y la atracción por alguna área específica. Las principales razones de desinterés fueron*

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el tiempo de formación muy largo, la sobrecarga de trabajo, el futuro laboral incierto y la baja remuneración profesional. Al cierre del estudio funcionaban 17 residencias básicas de nefrología, 11 posbásicas y 16 carreras de especialización; había en total 208 residentes (el 43% extranjeros). Las plazas disponibles entre 2017 y 2021 fueron 422, de las cuales se cubrieron 341 (81%). **Conclusiones:** *Las plazas vacantes reflejan el desinterés de los graduados argentinos por la nefrología, que no se observa en los extranjeros. Esto podría afectar el capital humano nefrológico en los próximos años.*

Palabras clave: *Educación médica. Posgrado. Especialización. Residencias.*

Introduction

Nephrology education in Argentina has grown since the 1960s, strongly linked to the development of nephrology as a specialty and the creation of more than 40 training centers (TCs) with residency and fellowship programs, university specialization degrees, scholarships, and internships[1,2], which for many years have been very attractive and of great interest to young Argentine and other Latin American graduates as training and specialization programs in nephrology. However, some indicators of nephrology training in Argentina suggest, in the last 15 years, a progressive loss of interest among graduates in the specialty, which could jeopardize the clinical nephrology workforce needed to meet the demands generated by the increasing number of patients with kidney disease.

This hypothesis arises from the records kept by the Evaluation, Accreditation, and Certification Committee (CEAC) of the Argentine Society of Nephrology (SAN) with data on TCs, nephrologists in training (NTs), and nephrology specialists (NSs), where a progressive decrease in the number of residents and fellows in nephrology is observed, which in the past 15 years fell by 33% (from 310 in 2008 down to 208 in 2022), coinciding with a small increase in the number of active nephrologists in Argentina, which went up by only 6% (from 1370 in 2008 to 1450 in 2022) (Fig. 1).

This flattening of the growth curve of NSs is concerning when compared to the global prevalence of patients on chronic dialysis[3], which in the same period increased by 21% (from 24,778 in 2008 to 29,921 in 2022), demanding greater human capital, adequate in number and capacity to provide care to these patients, and to interact with networks and providers at the first level of care to address the increasing incidence and prevalence of chronic kidney disease (CKD). Another worrying aspect is the divergence between the slopes of the prevalence curves of chronic dialysis and the number of NSs, which in its progressive trend has generated a growing gap between the demands of nephrological care and the available human capital, which today is being filled by non-nephrologist professionals in many centers across the country (Fig. 1).

Faced with this reality of the specialty, the SAN incorporated nephrology education among its priority lines of action. Through the CEAC, research projects focused on the training quality of NT[4-7] and different scientific-academic activities (congresses, forums, symposia) have been conducted, which, added to the regular control procedures (recognition of residencies, accreditation of TCs, certification of NSs), have made it possible to identify and understand the reasons that may explain the growing disinterest of graduates in the nephrology specialty.

The objectives of this study are to identify in NTs the motivations that led them to choose nephrology as a specialty and the possible reasons that may explain the loss of interest of graduates in it, to characterize the nephrology specialization programs in Argentina, and to distinguish the interest of Argentine and foreign graduates in the training positions available in the TCs.

Method

This research was conducted in the period 2018-2023 with a mixed methodological approach of qualitative-quantitative complementation, with a non-experimental, multiple cross-sectional (three samples) research design and exploratory scope. Three non-probabilistic and self-selected (voluntary participation) samples were used, consisting of NTs (residents and fellows in nephrology specialization programs), training teachers and instructors of NTs, and centers and programs for training in the specialty.

The following categories of analysis were defined:

– The perceptions of NTs about the specialty and their training: motivations that led them to choose the specialty, factors that hinder learning and their training, and reasons to which they attribute the decrease in the number of those interested in pursuing this specialization.
– The factors perceived by teachers that hinder the training of NTs: those that have «negative» effects on

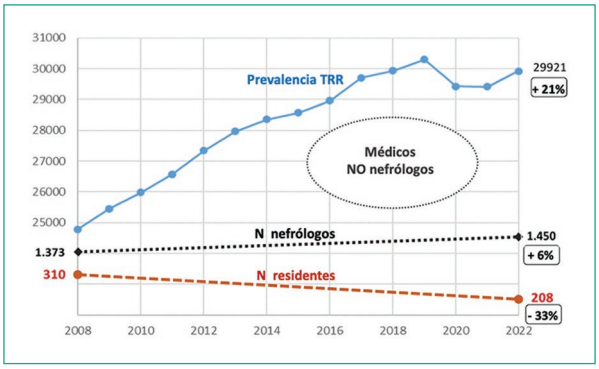

Figure 1. Trends in chronic kidney disease and number of nephrologists in Argentina (2008–2022).

their performance and training, related to their undergraduate education, English proficiency, information seeking, time management, teacher support, possible conflicts within the service, and personal or family problems.

– The characteristics of the TCs and nephrology training programs: regional location of each TC, type and duration of the program, certification or degree awarded, current number of NTs and their nationality. The training programs were grouped into three types, according to the regulations of the National Ministries of Health and Education[8,9]:
  - Basic Residencies (BR)[8], which are accessed with a bachelor's degree, without the need for prior training in another specialty, where all training takes place in a nephrology service (minimum 3 years) or articulated with 1 year of prior clinical training (total 4 years). Programmatic fellowships approved as BR were also included in this group.
  - Post-Basic Residencies (PBR)[8], which require a complete prior BR (internal medicine or analogous specialty) for admission. Programs that required at least 2 years of basic clinical training and post-basic «programmatic» fellowships were also included in this category.
  - University Specialization Careers (USC)[9], which are medical-assistance postgraduate university programs, basic and post-basic, lasting 3 years, and include careers independent of residencies and residencies that operate within the context of a USC.
  - Residency or specialization positions offered and awarded, considering the number of positions available in the period 2017-2021, offered by all TCs in the country, and the number and proportion of positions filled (awarded) and vacant in the same period.

To facilitate the recording and analysis of data, the country was divided into four geographical areas: Autonomous City of Buenos Aires (CABA), Province of Buenos Aires (PBA), Provinces of Córdoba and Santa Fe (CBA-SF), and other provinces (Table 1).

Information collection instruments

Self-administered questionnaires were used to investigate the perceptions of NTs and teachers, with open-ended and multiple-choice pre-coded questions, which were applied in 2018 in 2 national online surveys: one for NTs and the other for instructors and training teachers. The survey links were e-mailed to the 161 NTs registered with the SAN (2018 cut-off) and to the heads of the 39 TCs registered with the SAN (2018 cut-off) to disseminate it among their teachers.

Information on active programs and available and filled positions between 2017 and 2021 was collected through self-reporting by the TCs. The form was sent in 2022 to the heads of all TCs (47).

Data analysis

Qualitative information from the questionnaires was analyzed manually, coding the open-ended responses to organize them into key conceptual areas or themes. The quantitative information was analyzed by TC, by program, and by region. Data are expressed as absolute values, percentages, and fractions, as appropriate. Central tendency and dispersion values were calculated as summary measures. Double-entry tables were used to present the summarized data, and box plots and column charts were used for the graphical representation of variables. For statistical analysis, Student's z and t tests were used, applying XLSTAT 2022 software (AddinsoftTM). A significance level of $p < 0.05$ was adopted.

Results

Perceptions of residents, fellows, and trainees

The national survey was answered by 122 NTs (76% of those registered), 64% women, with a mean age of 31.9 ± 3 years (range, 25-40) and 61% of Argentine nationality.

Table 1. Population, area, number, and rates of nephrologists in the 4 Argentine geographic areas defined for this research study

Jurisdiction	Population	Area (km²)	Nephrologists (n)	Nephrologists per million population*
CABA	3,075,646	205.9	363	118
PBA	17,541,141	305,907.4	335	19.1
CBA–SF	7,296,868	297,956.9	245	33.5
Other provinces	11,228,282	1,127,828.1	202	18
National total	45,377,046	3,669,710.7	1,284	28.3

*Per million population.
CABA: Autonomous City of Buenos Aires; CBA-SF: Córdoba-Santa Fe; PBA: Province of Buenos Aires.
Source: National Geographic Institute. Ministry of Defense, 2022 Census. Health Workforce Map, Ministry of Health, 2020.

Regarding the reasons that led them to choose nephrology as a specialty, some based their attraction on the connection that nephrology has with internal medicine: «...it is the most complete clinical subspecialty...»; «It is a dynamic specialty, combining internal medicine with interesting procedures such as dialysis and transplantation...»; «Being an internist, I was interested in completing my training with a more specific and complex clinical specialty»; «I like it because for internal medicine it is like an integrating specialty»; «... what attracts me most is that it remains a clinical specialty in all its situations»; «I chose it because during my internal medicine residency I liked treating renal patients more than others»; «I like nephrology because it has a lot of clinical practice and it is a difficult specialty that intrigued me a lot.»

Other NTs highlighted the value of nephrology as an independent specialty: «It is a challenging specialty both from a medical and intellectual point of view...»; «I like it for its relationship with other systems and pathologies...»; «...it is very rewarding because it allows maintaining long-lasting doctor-patient relationships...»; «...the kidney seems fascinating to me for all that it does, and I like to play a bit at replacing it and seeking the perfect balance...»; «For the social and personal impact of kidney disease and the possibility of preventing its progression...»; «For the breadth of possibilities (clinical nephrology, dialysis, transplantation) and that it works with all specialties»; «...it is a complex specialty, studying the internal environment, the management of chronic and acute renal failure, arterial hypertension, and glomerulopathies led me to choose it.»

Finally, others expressed their attraction to a specific area of nephrology: «...I chose it because there is a lot of contact with critical care medicine»; «I am very passionate about kidney transplantation»; «The internal environment and the kidney's relationship with the systems...»; «I am very interested in patients with glomerulopathies and their forms of presentation»; «Interventional nephrology and providing a lifeline to patients»; «I always liked renal physiology and the management of the internal environment»; «Acute cases and instrumentation delight me»; «...the world of glomerulopathies seems fascinating to me…»

On the other hand, when asked about the reasons to which they attributed the decrease in the number of graduates interested in specializing in nephrology, some questioned the prolonged time required for training: «When we graduate, we need to work, and nephrology is too long a specialty...»; «...the training time is very long and the coursework very intense»; «When we are in our 5th year, there are already colleagues from other specialties who are working»; «superior courses (careers) where you specialize without the need for such a long residency are preferable.»

Others raised weaknesses in the training programs: «In the residency there is a lot of clinical work and little training»; «There is little teaching organization and a lack of a unified program...»; «There are no opportunities for interesting procedures, such as renal biopsy and catheters...»; «...the workloads are excessive and the scholarships (salaries) are not always adequate»; «...public conditions are devastated, and the possibility of learning is limited by daily work and lack of resources»; «we earn almost half of what a staff physician earns and work twice as much «… we have to look for jobs outside to survive»; «...many on-call duties, complex patients, and poor remuneration...»; «There are no nephrology residencies in the interior; you have to settle in Buenos Aires.»

Others argued issues related to an uncertain job future: «It is a complex and very poorly paid specialty»; «...the job market is very limited and the remuneration is very low»; «Job placement is very difficult» if it is not in a high-complexity hospital»; «You only get a job in a dependent relationship with a multinational...»; «It is one of the worst-paid specialties, and there are no job opportunities»; «Despite the number of nephrology patients there are, the payment to the nephrologist is very low»; «Doing such a long residency to work in a dialysis center covering shifts like other doctors with little training» makes no sense»; «...interventional nephrology procedures are now done by other specialties...»; «To practice the specialty, you have to compete with non-nephrologist doctors.»

Finally, others objected to the lack of information in the undergraduate program: «There is little knowledge about the specialty due to the scarcity of dissemination in the faculty»; «Many think that nephrology is only equal to hemodialysis»; «There is a lack of promotion of the specialty in the careers»; «There is a lot of ignorance among graduates about kidney diseases…»; «It is not a specialty that is talked about much in the faculty»; «They do not know the vast field that the specialty implies."

Regarding the factors that hinder learning and their training as specialists, the opinions of the NTs are presented in table 2, in comparative form with the opinions of the trainers.

Perceptions of instructors and training teachers of specialists

The national survey was answered by 51 trainers from the 39 registered TCs, 59% were men, the mean age was 52 ± 9.4 years (range, 32-68), and 63% had no (formal) training or education in university or postgraduate teaching.

Regarding the factors that «negatively» influence the overall performance and training of NTs, trainers pointed to lack of time due to clinical overload and deficiencies in undergraduate training as the main problems (Table 2).

Both groups agreed that the overload of clinical tasks in the service is the factor that most negatively impacts the training of NTs as specialists. However, trainers underestimated the perceptions of NTs regarding the magnitude of the impact generated by factors such as clinical overload, lack of encouragement and support from the nephrologists of the service, conflicts generated within the TC, and personal and family problems of the NTs.

Characteristics of the centers and training programs

The requested information was completed by 44 TCs, representing 94% of those registered in the country in 2022, where different training programs are developed: 17 BR (39%), 11 PBR (25%), and 16 USC (36%).

Most TCs are concentrated in the most populous provinces of the country: CABA (27%), PBA (20%), and CBA-SF (25%). In the other provinces, the TCs are distributed in Chaco (1), Entre Ríos (2), Formosa (1), Mendoza (1), Misiones (2), Neuquén (1), Salta (1), San Juan (1), Santiago del Estero (1), and Tucumán (1); they are BR and PBR in regional high-complexity health care centers. The rest of the Argentine provinces do not have nephrology TCs (Fig. 2 and Table 1).

The training time in the specialty varies according to the type of program: BRs, which are developed over 4 years, have a total workload of around 9000 hours; PBRs, which in their two training stages (3-4 years of internal medicine plus 3 years of nephrology) span 6-7 years and have a workload exceeding 20,000 hours; and USCs, lasting 3 years, according to established standards, have a (minimum) workload of 5280 hours.

Residents and fellows of the specialty

In 2022, 208 NTs were undergoing training throughout the country, 123 of whom (59%) were doing so in a TC in CABA, 35 (17%) in PBA, 25 (12%) in CBA-SF, and 25 (12%) in other provinces (Fig. 2).

A total of 119 of the 208 NTs (57%) were of Argentine nationality and 89 (43%) of foreign origin (Ecuador, Bolivia, Colombia, Mexico, and Paraguay). Almost all foreigners (99%) were training in TCs in CABA and PBA. No significant differences were found in the choice of programs according to nationality, since when comparing the percentage distribution of Argentines vs foreigners in each program, 34% vs. 31% ($p = 0.857$) was observed in BR, 21% vs. 26% ($p = 0.514$) in PBR, and 45% vs. 43% ($p = 0.807$) in USC.

Regarding the regional distribution of NTs, most (59%) were training in CABA, which marks a significant difference with the other regions when comparing the means of NTs per TC (Fig. 3). Therefore, the high number of NTs in the capital city depends on the number of available positions and not on the number of TCs, as the number of TCs (Fig. 2) is similar in the 4 regions: 12 in CABA, 9 in PBA, 11 in CBA-SF, and 12 in other provinces.

Another variable that may influence the differences observed in figure 3 is the strong concentration (99%)

Table 2. Factors that hinder the learning and training of nephrologists in training: percentage of opinions from trainees and trainers, and statistical comparison of factors perceived as having a high negative impact

Rank*	Factors affecting NF training	Trainees (n = 122)	Trainers (n = 51)	p
1	Lack of time due to care workload	66%	39%	0.0017
2	Lack of support or encouragement from the team	56%	12%	0.0000
3	Conflicts within the TC	52%	20%	0.0002
4	Poor reading comprehension in English	37%	24%	0.1268
5	Personal or family problems	36%	10%	0.0009
6	Difficulty searching for scientific literature	32%	24%	0.3539
7	Deficiencies in undergraduate education	22%	31%	0.2759

TC: training centers; NF: nephrologists in training.
*Rank based on responses from trainees.

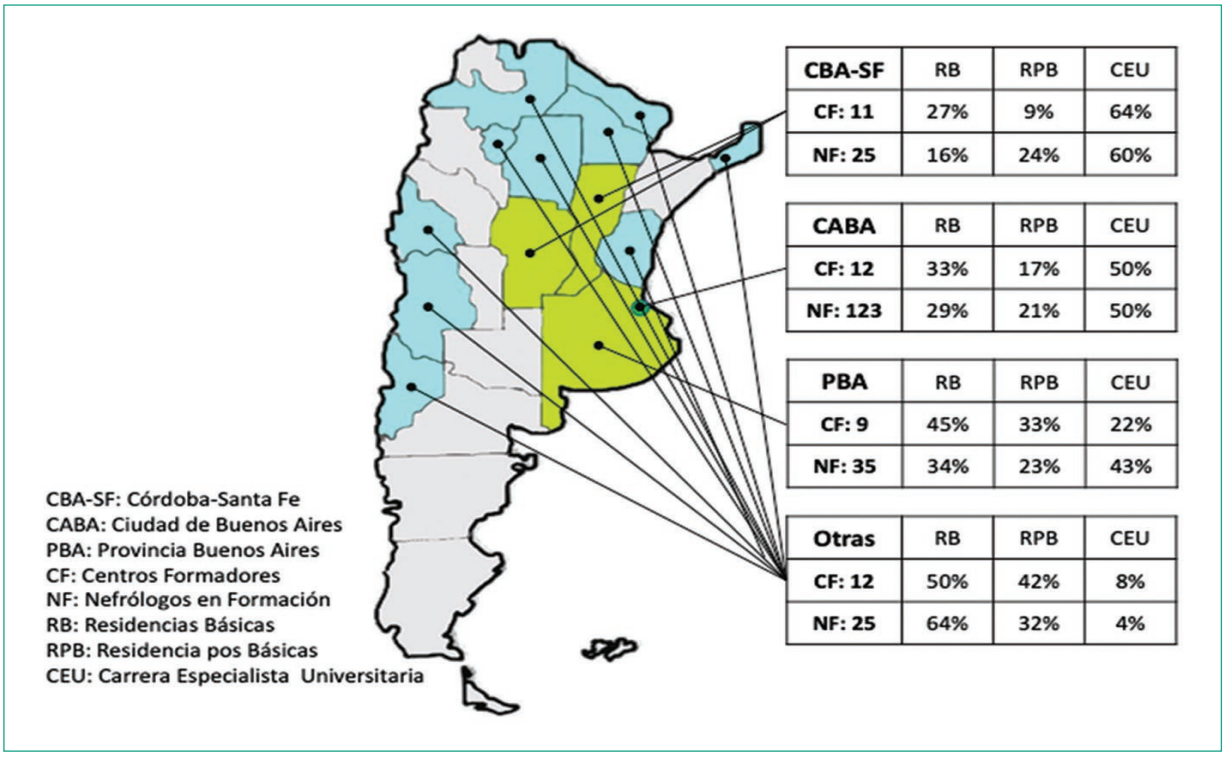

Figure 2. Regional distribution of training centers and nephrology fellows according to program type (BR, PBR, or CEU).

of foreign NTs in CABA and PBA. To analyze this possibility, the data were recalculated by subtracting the number of foreigners. When considering only Argentine NTs, the disparities between the regions are less marked, but significant differences persist between CABA: 4.2 ± 1.7 vs. PBA: 2.2 ± 1.5 (p = 0.011); vs. CBA-SF: 2.2 ± 1.6 (p = 0.009); and vs. other provinces: 2.5 ± 1.2 (p = 0.009). There are no differences between PBA, CBA-SF, and the other provinces.

Specialization positions offered and awarded

Between 2017 and 2021, a total of 422 positions were offered nationwide for entry into the first year of

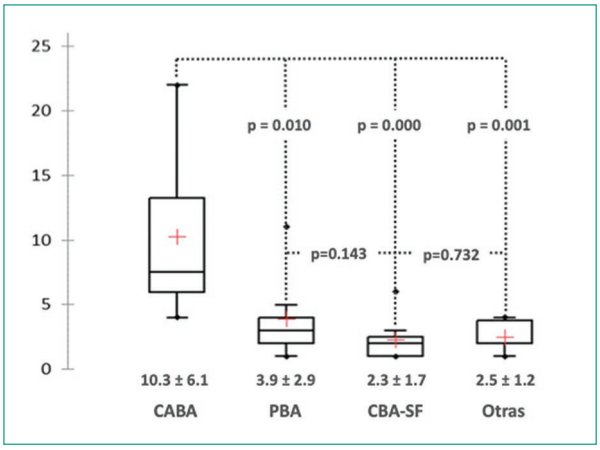

Figure 3. Box plots and means (± standard deviation) of nephrology fellows per training center by region. CABA: Autonomous City of Buenos Aires; CBA-SF: Córdoba-Santa Fe; PBA: Province of Buenos Aires.

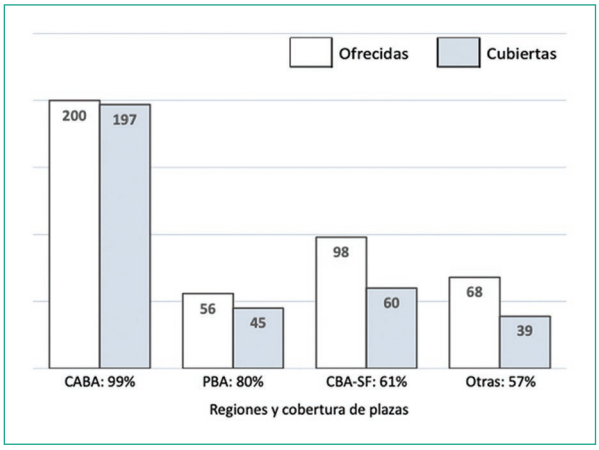

Figure 4. Available and filled training positions by region (2017–2021). CABA: Autonomous City of Buenos Aires; CBA-SF: Córdoba-Santa Fe; PBA: Province of Buenos Aires.

nephrology residencies and USCs: 83 in 2017, 83 in 2018, 86 in 2019, 89 in 2020, and 81 in 2021. Of the total, 341 positions were filled: 68 in 2017, 64 in 2018, 70 in 2019, 73 in 2020, and 66 in 2021; thus, 81 (19%) remained vacant. The slot coverage rate was similar across all programs. The ratio of filled positions to offered positions was as follows: in BR 101/121 (83%), in PBR 84/104 (81%), and in USC 156/197 (79%). There were no significant differences in the comparison of proportions between BR vs. PBR (p = 0.724), BR vs. USC (p = 0.427), and PBR vs. USC (p = 0.862).

Significant differences in the slot coverage rates were observed across the different regions (Fig. 4). When comparing the percentages of slot coverage rates across regions, significant differences were found among CABA (99%) and PBA (80%; p = 0.000), CBA-SF (61%; p = 0.000), and other provinces (57%; p = 0.000). There were also differences between PBA and CBA-SF (p = 0.023) and other provinces (p = 0.011). No significant differences were found between CBA-SF and other provinces (p = 0.734).

Discussion

Motivations for choosing nephrology as a specialty

Nephrology specialization programs in Argentina have, for many years, been of great interest to Argentine and other Latin American graduates for their nephrology training. This interest in the specialty is mainly motivated by each graduate's perception of nephrology: for some, its appeal lies in the clinical component, viewing it as a subspecialty of internal medicine; others perceive it as a broad and complex specialty with its own identity; and some are attracted to specific areas of nephrology, highlighting the internal environment, glomerulopathies, and transplantation.

Strikingly, none of the NTs surveyed mentioned employment aspects as a reason for choosing the specialty, unlike what emerged in interviews conducted in 2008[10], in which there were expressions such as: «I like nephrology as a practice and it seems like a good job opportunity»; «it is the part of our medical practice with the best job prospects»; «I like the specialty as a work option»; «there is demand for professionals»; «it presents different job options.» On the contrary, 15 years after these expressions, the working conditions of nephrology were considered among the factors that generate disinterest in the specialty.

Reasons explaining graduates' disinterest in the specialty

In the last 20 years, many authors have warned about a global and progressive disinterest of graduates in the nephrology specialty, a phenomenon that has been extensively studied in the United States of America[11-23] and reported by other countries such as Canada[24], the United Kingdom[25], Australia[26], and some in Latin America[27-29].

Several authors, through surveys, interviews, and focus groups, have studied the reasons for this loss of interest and have related it to various factors, such as distorted perceptions of the specialty (loss of prestige)[19,20,26]; a very complex specialty with few opportunities for professional development[20-22]; programs with a lack of exposure to nephrology, low quality of instruction, and lack of innovation[18,19,26,30]; lack of mentors and few procedural practices in nephrology[15,19,20,22]; burnout due to imbalances between residents' work and personal life[17,23,24]; care of highly complex and demanding patients[18,19,22]; limited opportunities in the job market[20,21]; and relatively low remuneration compared to other subspecialties of internal medicine[19,22,23,26,30].

In Argentina, the reasons for this disinterest in the specialty were investigated in the 2018 National Survey, in which 122 NTs perceived the main reasons to be the graduates' work urgency (very long training time); the intensity of work in the residency (a lot of clinical work and little training); the scarcity of residencies in the interior of the country; the reduction of the clinical component of the specialty (predominance of the dialysis profile); the loss of procedures and practices of the specialty (outsourced); the job future in a dependent relationship (dialysis companies); low professional remuneration (modulated market); and the little information provided by undergraduate programs about the specialty, among others.

The prolonged training time, due to the graduates' «work urgency» was one of the main reasons for disinterest in the specialty expressed by NTs in 2018. In the same vein, other authors have linked the prolonged training time with imbalances between residents' work and personal life, which for some[23,24] was a reason for disinterest in the specialty and for others[15] was the reason for resigning from the training program.

The training time for nephrologists in Argentina is very diverse and depends on the chosen program, as it can range from 3 years (5280 hours) in a USC to 6-7 years (> 20,000 hours) in a PBR. If the time required for graduation in a medical career, which varies between 6 and 8 years[31], is added to this training period, the complete training of a nephrology specialist in Argentina can require between 12 and 15 years, a time that exceeds the average range of 9 to 13 years calculated in the joint work carried out by ASN-ERA-EDTA-ISN on 106 countries[32].

The intensity and overload of clinical work in the service or TC were also pointed out by NTs as a cause of disinterest in the specialty, as they reduce time for formative academic activities and limit independent study hours.

In addition, both NTs and training teachers recognized the overload of clinical tasks as the factor with the greatest negative impact on the learning and performance of NTs. This situation of the training context can be aggravated by the work tasks outside the service that some NTs perform to improve their income, according to their own expressions.

Another reason for disinterest in the specialty, pointed out by NTs, is the scarcity of training programs in the interior of the country. This situation is related to the heterogeneous geographical distribution of TCs, which are mostly (73%) located in the most populous jurisdictions of Argentina (CABA, PBA, CBA, and SF), which house almost all USCs (94%). The strong concentration of TCs in this central region of the country coincides with the distribution of medical careers, which are mostly located in the same region[31].

Nephrology specialization programs in Argentina

The training of NSs in Argentina is linked to three types of training programs: BRs, which focus on nephrology as a basic specialty (equivalent to cardiology, intensive care, and others); PBRs, which address nephrology as a clinical subspecialty; and USCs, which offer nephrology as another option for postgraduate training. The first two endorse training with a certificate (of approval or specialist) and the USCs with a specialist degree. These differences do not influence the practice of the specialty, as all three programs are recognized by all jurisdictions of the country as valid for advertising and practicing as a nephrology specialist, given that, in Argentina, the recognition of specialties and their certification modalities is exercised by the provincial states (Ministries of Health or Medical Colleges by law), and the nephrology specialty has the same denomination in all jurisdictions of the country[33].

Perhaps for these reasons, no differences were observed in terms of program preference, either among graduates in Argentina or abroad.

Regarding the NT population, the regional distribution of the 208 NTs is also very heterogeneous, with most training in CABA (59%) and PBA (17%). This distribution is not related to the number of TCs or the types of programs offered, but rather to the strong concentration of foreigners, who show a high preference (99%) for TCs in CABA and PBA.

Interest of Argentine and foreign graduates in offered specialization positions

Between 2017 and 2021, only 81% (341/422) of the available positions nationwide for entry into a nephrology training program were filled. This slot coverage rate is 20 points higher than the national average recorded: 60.36%[34] in the period 2010-2022, with 21,232 positions offered and 12,815 awarded in all health specialties with national funding (national, provincial, and university TCs). A similar situation was reported in the United States, starting in 2010, when a sharp decline in applications for nephrology residency fellowships was recorded, which between 2015 and 2020 maintained a proportion of 60-70% of applicants compared to the fellowships offered[19,30].

Slot coverage rate in nephrology was similar across the different programs but showed significant differences between different regions: CABA, 99%; PBA, 80%; CBA-SF, 61%, and other provinces 57%. These regional differences were also recorded in all medical specialties (in 2010-2022)[34], indicating that they are not exclusive to nephrology.

Regarding NTs of foreign nationality, 43% (89/208) of all NTs is very high vs the 18% of foreigners registered in the national residency system of the health team in the period 2018-2021[35], whose ranking of nationalities (average) was 82% for Argentina, 7% for Bolivia, 3.8% for Colombia, 2.4% for Ecuador, and others. This difference between nephrology and other specialties indicates a great interest of foreign graduates in the nephrology specialty and in the TCs of our country, which is very gratifying for Argentine nephrology education. However, it is also a cause for concern, considering our country's need for human capital in nephrology and the fact that we cannot count on all current NTs, as many foreigners may return to their country upon completion of their training.

Possible health and educational consequences

The disinterest in nephrology shown by Argentine graduates, which is not perceived in foreign graduates, manifests itself in the training positions that remain vacant each year, the progressive decrease in the number of NTs, and the flattening of the growth curve of the number of nephrologists in Argentina (Fig. 1). This situation is worrying given the high prevalence of CKD in our country, which, according to the 4th National Survey of Risk Factors, conducted in 2018-2019[36], reaches 12.7% among those older than 18 years (1 in 8 Argentines has CKD), making early detection and early treatment essential to avoid complications in more advanced stages of the disease.

Another very alarming issue is the uncertainty of having, in the near future, an adequate number of nephrology specialists to meet the needs of patients with advanced CKD, since according to data from the Ministry of Health-Health Workforce[37], 19% (approximately 275) of NSs are in the 60 to 65 age group and are those who could retire from clinical practice within the next 5 years. On the other hand, around 68 new nephrologists enter the workforce each year, 43% of whom are foreigners who will mostly return to their country of origin, and the remaining 57% (approximately 38 nephrologists) are Argentines who will join the workforce (adding approximately 190 in 5 years), an insufficient number to replace those who retire due to age, which could lead to a decrease in the total number of nephrologists in the coming years, accentuating the divergence between the prevalence curve of chronic dialysis and that of the number of nephrologists (Fig. 1). This growing gap between the demands of nephrological care and the available human capital is being filled by non-nephrologist professionals (internists, general practitioners, family doctors, intensivists, etc.) in many centers across the country[2].

This situation, in addition to jeopardizing the quality of clinical care and nephrological procedures, could also deviate the appropriate path for nephrology training, distort the professional profile of the specialist, weaken the prestige of nephrology as a specialty, affect working conditions, and deteriorate professional fees; all of these are factors linked to the disinterest of graduates in the specialty and, consequently, could generate a vicious cycle that would affect the training of nephrology specialists in Argentina.

Strengths and weaknesses of the research

The main strengths of this study lie in its qualitative-quantitative approach, which provides depth and breadth to the analysis, and in its wide national coverage, which offers a representative view of nephrology training in Argentina. Among its weaknesses are the absence of a more precise longitudinal analysis of the variables studied and a possible bias in the analyzed sample of trainers, which does not ensure the representativeness of all TCs.

Conclusions

The training of nephrologists in Argentina is linked to various programs and training times, distributed in 13 of the 23 provinces, with a high concentration in CABA. All these programs are equally valid for practicing the specialty in the different regions of the country.

There are currently 208 nephrology fellows (NFs), 43% of whom are international graduates. The NF population has decreased by more than 30% over the past 15 years, a decline consistent with an increase in unfilled residency positions, reflecting a loss of interest in the specialty among Argentine graduates—a phenomenon not observed among international candidates.

This drop in the training of new nephrologists is particularly concerning in a context where the demand for human resources is increasing due to the rising number of cases of CKD. The situation could worsen further given the high proportion of international NFs who may return to their home countries after completing their training[1]. This poses significant challenges to the sustainability of nephrology care in Argentina and highlights the urgency of reviewing and strengthening training and retention strategies for nephrology specialists within the country.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

SGLT2 inhibitors in lupus nephritis: a multicentric study in Latin America

Inhibidores de SGLT2 en la nefritis lúpica: un estudio multicéntrico en América

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Abstract

Objective: *The objective of the study is to examine the effect of sodium-glucose transporter 2 inhibitors (SGLT2) on proteinuria and renal function progression over 12 months in patients with proliferative lupus nephritis (LN).* **Material and methods:** *A retrospective observational analysis was conducted on patients with LN in Argentina and Colombia. Patients diagnosed with class III or IV + V LN were followed for 12 months. Out of 95 biopsies of focal or diffuse proliferative LN, 74 histological samples met the inclusion criteria. These were divided into two groups: Group A included 35 patients who received conventional treatment plus SGLT2 inhibitors (empagliflozin 10 mg daily) and Group B included 39 patients who received only conventional treatment. Both groups received the same dose of cyclophosphamide and maintenance with mycophenolic acid. Laboratory findings, proteinuria behavior, and renal function progression were evaluated over 12 months.* **Results***: Among the 74 patients, 64 were women (86.4%), with a mean age of 34 ± 12 years. Group A showed a reduction in proteinuria at 12 months to 0.48 (0.38-0.71) compared to Group B, which did not receive SGLT2 inhibitors, with proteinuria at 0.8 (0.42-1.3) (p = 0.02).* **Conclusions:** *Patients who received conventional immunosuppressive treatment and added SGLT2 inhibitors showed a reduction in proteinuria over a 12-month follow-up period.*

Keywords: *Lupus nephritis. Sodium-glucose cotransporter 2 inhibitors. Antinuclear antibodies. Systemic lupus erythematosus.*

Resumen

Objetivo: *Examinar el efecto de los inhibidores del cotransportador sodio-glucosa tipo 2 (iSGLT2) sobre la proteinuria y la progresión de la función renal durante 12 meses en pacientes con nefritis lúpica proliferativa (NL).* **Material y métodos:** *Se realizó un análisis observacional retrospectivo en pacientes con NL en Argentina y Colombia. Se siguió durante 12 meses a pacientes diagnosticados con NL clase III o IV + V. De 95 biopsias de NL proliferativa focal o difusa, 74 muestras histológicas cumplieron con los criterios de inclusión. Estas se dividieron en dos grupos: el Grupo A incluyó 35 pacientes que recibieron tratamiento convencional más inhibidores de SGLT2 (empagliflozina 10 mg diarios), y el Grupo B incluyó 39 pacientes que recibieron solo tratamiento convencional. Ambos grupos recibieron la misma dosis de ciclofosfamida y mantenimiento con ácido micofenólico. Se evaluaron los hallazgos de laboratorio, el comportamiento de la proteinuria y la progresión de la función renal durante 12 meses.* **Resultados:** *Entre los 74 pacientes, 64 eran mujeres (86.4%), con una edad media de 34 ± 12 años. El Grupo A mostró una reducción en la proteinuria a los 12 meses a 0.48 (0.38-0.71) en comparación*

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con el Grupo B, que no recibió inhibidores de SGLT2, con proteinuria de 0.8 (0.42-1.3) (p = 0.02). **Conclusiones:** *Los pacientes que recibieron tratamiento inmunosupresor convencional y añadieron inhibidores de SGLT2 mostraron una reducción en la proteinuria durante un seguimiento de 12 meses.*

Palabras clave: *Nefritis lúpica. Inhibidores del cotransportador sodio-glucosa tipo 2. Anticuerpos antinucleares. Lupus eritematoso sistémico.*

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multisystem involvement and heterogeneous clinical features. Immunological alterations, especially the production of various autoantibodies such as antinuclear antibodies (ANA), are characteristic of the disease. Approximately 50% of patients with SLE may develop kidney involvement during the course of the disease[1].

Lupus nephritis (LN) most often develops early in the course of the disease, and up to 10% of these patients progress to end-stage chronic kidney disease (CKD)[2]. Although LN is considered a classic form of immune-complex-mediated glomerulonephritis, the pathogenesis of this condition is complex. It may involve gene expression, both in the peripheral circulation and at the renal level, leading to neutrophil activation, increased interferon expression, and upregulation of myeloid cells and pro-inflammatory transcriptomes. Controlling the hyperreactive immune system is a key point in the management of lower esophageal sphincter[3], as is the control of secondary proteinuria.

Proteinuria is considered a risk factor for cardiovascular morbidity and mortality in patients with LN who present with CKD. A high incidence of cardiovascular events has been found in the literature among patients with persistent proteinuria[4]. Therefore, patients who have proteinuric CKD (with or without diabetes) may benefit from treatment with sodium-glucose transporter-2 (SGLT2) inhibitors by also decreasing the risk of secondary cardiovascular events.

SGLT2 inhibitors (iSGLT2) work by blocking the reabsorption of glucose into the proximal tubule through SGLT2, thereby lowering the renal glucose threshold and leading to substantial glycosuria. SGLT2 inhibitors have additional effects on the kidney that is likely independent of glycemic control. By blocking the cotransporter, they reduce sodium reabsorption. The resulting natriuresis reduces intravascular volume and blood pressure but also increases sodium supply to the macula densa. Increasing sodium supply to the macula dense normalizes tubuloglomerular feedback and thus reduces intraglomerular pressure (i.e., reduces glomerular hyperfiltration) through constriction of the abnormally dilated afferent arteriole. This and other mechanisms may explain the benefits of SGLT2 inhibitors in the progression of kidney disease[5]. Most studies demonstrating the renal protective benefits of these agents have been conducted in patients with diabetic kidney disease. However, several large trials suggest that SGLT2 inhibitors are beneficial in proteinuric patients with non-diabetic kidney disease[6].

The nephroprotective efficacy of iSGLT2 extended to non-diabetic CKD, such as immunoglobulin A nephropathy[7]. The net gain of SGLT2 inhibition is to reduce renal workload (intraglomerular pressure) and modulate weight loss and blood pressure. The paradigm for CKD and the management of congestive heart failure have been changed accordingly. It has been reported that iSGLT2s could block lipopolysaccharide-induced inflammatory responses mediated by the inflammasome NLRP3 and regulate macrophage polarization through the interaction of mammalian rapamycin (mTOR) and AMP-activated protein kinase pathways[8]. Therefore, iSGLT2 could further contribute to reducing inflammation, modulating endothelial dysfunction, and decelerating atherosclerosis, which is all relevant to the pathophysiology of SLE[9].

This study aims to evaluate the efficacy of iSGLT2 in patients with LN in terms of reducing proteinuria at 12 months of treatment and to verify the behavior of the glomerular filtration rate in this population.

Materials and methods

We conducted a retrospective observational analysis of patients with LN in two countries in Latin America (Argentina-Colombia) who were diagnosed with NL class III or IV + V and followed for 12 months. A total of 95 focal or diffuse proliferative LN biopsies were analyzed; a total of 21 patients were excluded because they did not have follow-up until 12 months or because they had heterogeneity in induction and maintenance treatment. A total of 74 histological samples were analyzed, and the clinical and pathological characteristics that met the inclusion criteria were analyzed (Table 1 and Fig. 1). The normality of the variables was

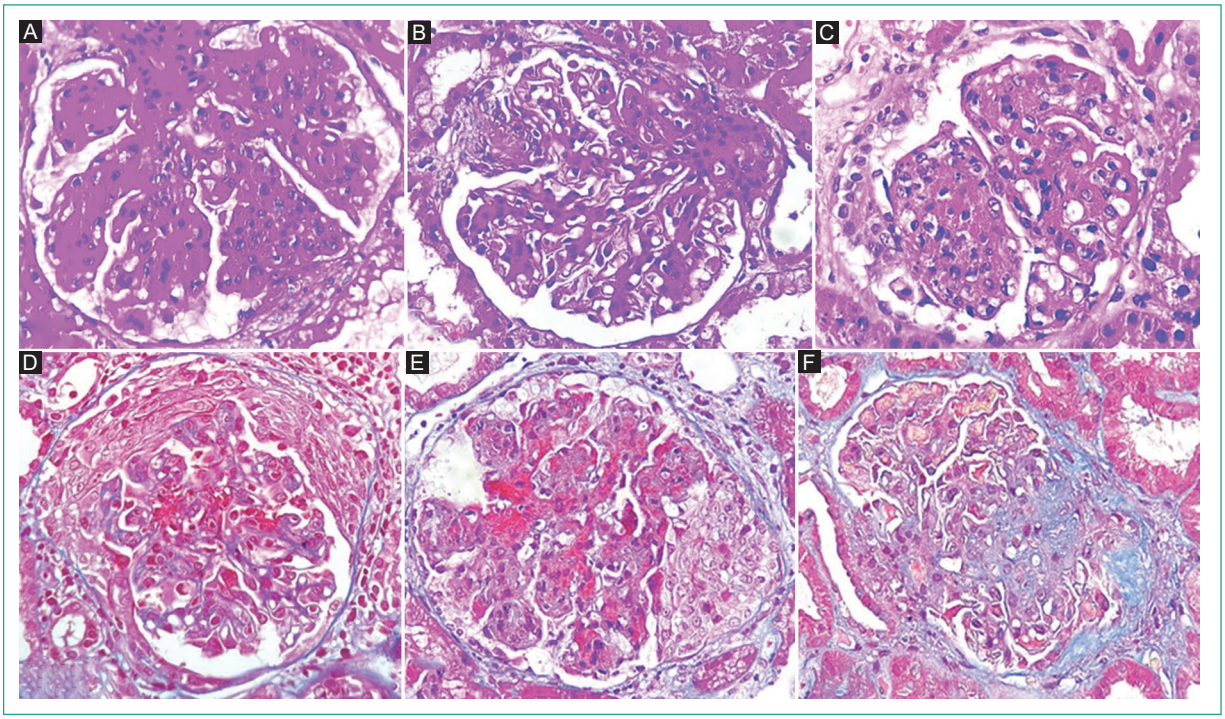

Figure 1. Glomerular lesions: PAS staining. **A:** endocapillary hypercellularity. **B:** mesangial hypercellularity and segmental sclerosis. **C:** kariorrhexis (HE staining), masson trichrome staining. **D:** cellular crescent). **E:** fibrinoid necrosis and cellular crescent. **F:** segmental sclerosis.

Table 1. Selection criteria

Inclusion criteria
Diagnosis of systemic lupus erythematosus, according to the American College of Rheumatology criteria of 1982. Renal biopsies of focal class III and diffuse class IV lupus nephritis, according to the 2003 classification of the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) Similar induction and maintenance treatment.
Exclusion criteria
Heterogeneity in treatments. Follow-up at < 12 months. Renal biopsy not processed by nephropathologists type 1 and 2 diabetes mellitus.
Renal pathology
Patients underwent renal biopsy at the time of diagnosis of lupus nephritis (LN) and were classified according to the 2003 ISN-RPS of LN. Activity indices and chronicity indices were calculated according to the Austin criteria.

determined using the Kolmogorov-Smirnov test. The X^2 test was used for categorical variables. The results of the study were to evaluate the decrease in proteinuria at 6 months and 12 months in both groups and the behavior of the estimated glomerular filtration rate (eGFR).

Results

Of the total of 74 histological samples, 86.4% were from female patients, with a mean age of 34 ± 12. They were subdivided into two groups (with and without Empagliflozin), and both cohorts received doses of cyclophosphamide 1 g intravenously monthly for 6 months and maintenance with mycophenolic acid dose 3000 mg (conventional treatment). Follow-up was performed for 12 months, evaluating clinical variables, such as 24-h proteinuria and urinary sediment. Complete remission was considered when the proteinuria of 24 was < 500 mg/day, soft urinary sediment was performed by a nephrologist (red blood cells < 5 red blood cells per field), and anti-DNA immunoserology (Table 2).

Regarding Group "A," 35 patients with LN received conventional treatment plus iSGLT2 (empagliflozin 10 mg daily) whereas in Group "B," 39 patients with proliferative LN were treated with conventional treatment but without iSGLT2. The cohort that SGLT2 inhibitors were added to the conventional treatment was called Group A, in which there was a decrease in proteinuria at 12 months compared to Group B which did not take SGLT2 inhibitors with a statistically significant difference; Group B: 0.8 (0.42-1.3) and Group A:

Table 2. Sociodemographic characteristics and laboratory findings

(n = 74)	Without empagliflozin (n = 39) (%)	With empagliflozin (n = 35) (%)	p
Age (SD)	34 ± 12	34 ± 11	0.828
Female sex, n (%)	33 (84.6)	31 (88.6)	0.619[a]
LN type, n (%)			
III	0 (0)	4 (11.4)	0.03[a]
IV	39 (100)	31 (88.6)	0.41
GFR mL/min (CKD EPI)	58ml ± /min	57 mL ± /min	0.21
Creatinine mg/day M (IQR)	1.2 (0.9-1.73)	0.91 (0.89-1.27)	0.137[b]
Proteinuria, g/day M (IQR)	2.2 (1.39-2.35)	1.9 (1.2-2.35)	0.198[b]
Hypertension, n (%)	12 (30.8)	12 (34.3)	0.747[a]

[a]Pearson's X^2 test.
[b]Kruskal-Wallis rank sum test, glomerular filtration rate (GFR) by CKD-EPI expressed milliliter minute (mL/min) expressed as mean (M) and standard deviation (SD), creatinine expressed in milligrams per deciliter (mg/dL), proteinuria expressed grams per day (g/day).
CKD: chronic kidney disease. Expressed as absolute number and percentage, mean, and standard deviation.

Table 3. Results and laboratory findings

Assessment metrics	Without empagliflozin (n = 39) (%)	With empagliflozin (n = 35) (%)	p
Proteinuria at 6 months, M (IQR)	1.2 (0.76-2.35)	0.98 (0.71-1.37)	0.24[b]
Proteinuria at 12 months, M (IQR)	0.8 (0.42-1.3)	0.48 (0.38-0.71)	0.02[b]
Cr at 6 months, M (IQR)	0.96 (0.8-1.15)	0.9 (0.8-1)	0.19[b]
Cr at 12 months, M (IQR)	0.9 (0.8-1.2)	0.81 (0.79-0.93)	0.04[b]
TFG CKD EPI M/DS	59 ± 6 mL/min	61 ± 8 mL/min	0.10
Complete remission at 6 months, n (%)	10 (25.6)	9 (25.7)	0.99[a]
Complete remission at 12 months, n (%)	29 (74.3)	30 (85.7)	0.24[a]
US at 6 months, n (%)	11 (28.2)	10 (28.6)	0.97[a]
US at 12 months, n (%)	20 (51.3)	23 (65.7)	0.31[a]
Urinary infections	6 (15.3)	5 (14.3)	0.21
Other infections	5 (12.8)	4 (11.4)	0.32
Glycemic level before treatment	89 ± 2	88 ± 2	0.96
Glycemic level 12 months after treatment	90 ± 3	89 ± 4	0.94
RAAS inhibitors	39 (100)	35 (100)	1.03
Induction treatment, n (%)	39 (100)	35 (100)	0.64[a]
Maintenance treatment n (%)	13 (33.3)	6 (17.1)	0.11[a]
anti-dsDNA at 6 months, n (%)	20 (51.3)	15 (42.9)	0.47[a]
anti-dsDNA at 12 months, n (%)	29 (74.4)	33 (94.3)	0.02[a]
Activity index, M (IQR)	10 (8-12)	9 (7.5-10)	0.11[c]
Chronicity index, M (IQR)	2 (1.5-2)	2 (1-2)	0.75[c]

[a]Pearson's X^2 test.
[b]Kruskal-Wallis rank sum test.
[c]Median test. Proteinuria was expressed in g/24 h, creatinine (Cr) was expressed in mg/dL, median (M), and interquartile range (IQR). Glomerular filtration rate (GFR) estimated formula CKD EPI Mean and Standard Deviation (SD), Urinary sediment (US).
RAAS: renin-angiotensin-aldosterone system.

0.48 (0.38-0.71), p = 0.02 (Table 3). Both groups did not achieve complete remission due to the persistence of microhematuria (Table 2).

Discussion

This observational study evaluates the effect of empagliflozin on protein excretion in urine, preservation of renal function, urinary sediment, autoantibody immunoserology, and complete remission at 6 and 12 months defined according to the standards of the KDIGO 2021 guidelines in patients with focal or diffuse proliferative LN in two Latin American countries. Patients with diabetes mellitus were excluded, and all patients received renin-angiotensin-aldosterone system inhibitors and immunosuppression. There was no complete remission at 12 months, in both groups due to the persistence of microhematuria, but there was a marked decrease in the proteinuria value significantly, while in the glomerular filtration rate, there was no difference at follow-up at 12 months in both groups. No cases of genital infections related to the use of empagliflozin were reported in this cohort. The presence of urinary tract infections and other infections such as pneumonia and herpes zoster were evidenced in both groups, however, without a statistically significant difference, which is consistent with what has been previously described in the literature, where studies have shown a prevalence of urinary tract infections in patients treated with empagliflozin not higher than the control group[10,11].

Regarding other adverse events reported in the literature, no episodes of hypoglycemia were reported in this study. The mean blood glucose level in the group treated with empagliflozin was 88 ± 2 before and after receiving the treatment 89 ± 4 with no statistically significant difference (p = 0.94). In the literature, preclinical studies are reported where the use of empagliflozin in mice demonstrated a marked decrease in the levels of specific antibodies IgG anti-dsDNA, proteinuria, and serum creatinine levels. It is also evident that glomerular damage such as interstitial tubular damage decreased with the administration of empagliflozin[12]. In the study conducted by Zhao et al., it is described that in nine patients with LN treated with SGLT2 inhibitors for more than 2 months, a significant decrease in proteinuria from 29.6% to 96.3% was evidenced in the group exposed to empagliflozin, in addition, the eGFR remained relatively stable during treatment[12]. This is consistent with the results of the present study, which provides a greater number of participants with similar results. The decrease in proteinuria in this population not only reflects a nephroprotective effect but also its possible role in reducing the risk of associated cardiovascular events can be elucidated.

Limitations

The study design is observational and retrospective; this study only evaluated complete remission and did not analyze the different degrees of partial remission, which may provide more information and elucidate the role of isglt2 in disease progression.

Other limitations of this study are that most of the biopsies performed did not use electron microscopy due to availability, and although the presence of a thin basement membrane may coexist in LN, taking into account that this association is of very low probability, this could invalidate microhematuria as a criterion to determine renal lupus activity.

Conclusion

Accumulating evidence suggests that iSGLT2 has pleiotropic effects acting on different renal compartments with specific and varied molecular, cellular, and effects. It is postulated as a possible mechanism of action that empagliflozin could alleviate podocyte lesions by attenuating inflammation and enhancing autophagy by reducing the activity of mTORC112; however, more studies are still needed to elucidate the mechanism of action. This study showed that patients with proliferative LN had a marked decrease in the value of statistically significant proteinuria when empagliflozin was added; however, it was not possible to observe complete remission. Further prospective studies are essential to validate and expand this finding, which could potentially lead to more effective therapeutic approaches for patients with LN.

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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 considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CLINICAL CASE

Emphysematous pyelonephritis and orchiepididymitis due to Mycobacterium tuberculosis in a kidney transplant recipient

Pielonefritis enfisematosa y orquiepididimitis por Mycobacterium tuberculosis en un receptor de trasplante renal

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Abstract

Tuberculosis may present with extrapulmonary manifestations, 30-40% of which involve the genitourinary tract. The incidence of tuberculosis in kidney recipients is 20-74 times higher than in the general population. We present the case of a patient with a renal graft transplanted 10 years prior, who developed emphysematous pyelonephritis, treated with conservative management, associated with chronic orchiepididymitis due to Mycobacterium tuberculosis, resolved with radical orchiectomy.

Keywords: *Radical orchiectomy. Mycobacterium tuberculosis. Extrapulmonary tuberculosis. Renal transplantation. Emphysematous pyelonephritis.*

Resumen

La tuberculosis puede presentarse con manifestaciones extrapulmonares, de las cuales el 30-40% afectan el tracto urogenital. En la población receptora de riñón, la incidencia de tuberculosis es 20-74 veces mayor que en la población general. Se presenta el caso de un paciente con injerto renal trasplantado 10 años antes que desarrolló pielonefritis enfisematosa, tratada con manejo conservador, asociada a orquiepididimitis crónica por Mycobacterium tuberculosis, resuelta con orquiectomía radical.

Palabras clave: *Orquiectomía radical. Mycobacterium tuberculosis. Tuberculosis extrapulmonar. Trasplante renal. Pielonefritis enfisematosa.*

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Introduction

Tuberculosis (TB) is classified as the thirteenth leading cause of death worldwide and the most frequent infectious disease, causing approximately 1.3 million annual deaths according to the World Health Organization. A total of 5-45% of TB cases present with extrapulmonary signs, 30-40% of which affect the urogenital tract[1].

A meta-analysis including 60 studies analyzed the prevalence of active TB in solid organ transplant recipients, showing a pooled prevalence of 3% (95% confidence interval, 2-3)[2]. Specifically addressing the kidney transplant recipient population, a 2018 study by Arreola-Guerra et al.[3] found that 50% of patients were diagnosed with latent TB. Only 1 patient developed active TB prior to transplantation, representing a preoperative active TB prevalence of 0.43%, which is much higher than the average rate in the general population. The prevalence of active TB in kidney transplant recipients in this study was significantly low, and there are no further experiences in this group in Mexico[3]. The relevance of this disease lies in the fact that its diagnosis is often delayed, which can trigger complications such as urethral or ureteral stenosis, renal graft failure, chronic kidney disease, and infertility, among others[1]. Granulomatous inflammation and disease progression can lead to chronic tubulointerstitial nephritis, papillary necrosis, ulcers, fibrosis with extensive caseous destruction of the renal parenchyma,[1] and the formation of lobes, dilated calyces, and cavities[4,5].

In this article, we present a case of emphysematous pyelonephritis caused by *Mycobacterium tuberculosis* in a kidney transplant recipient, treated conservatively with subsequent recovery of graft function.

Case report

A 27-year-old male with a past medical history of chronic kidney disease diagnosed at age 14 of undetermined etiology. He received intermittent hemodialysis for 2 years and 6 months before a kidney transplant at age 16, with his 27-year-old sister, who shared one haplotype, as the donor. Induction was performed with basiliximab at a total dose of 40 mg. Intermediate risk for cytomegalovirus was assigned with D+ and R+, and universal prophylaxis with valganciclovir was administered for 3 months. The pre-transplant PPD result was non-reactive, and the chest X-ray was unremarkable. Twelve months post-transplant, he presented with borderline rejection, treated with IV corticosteroid boluses. The current immunosuppressive regimen is standard triple therapy (tacrolimus, mycophenolic acid, and prednisone) with optimal pre-admission levels (7 ng/mL).

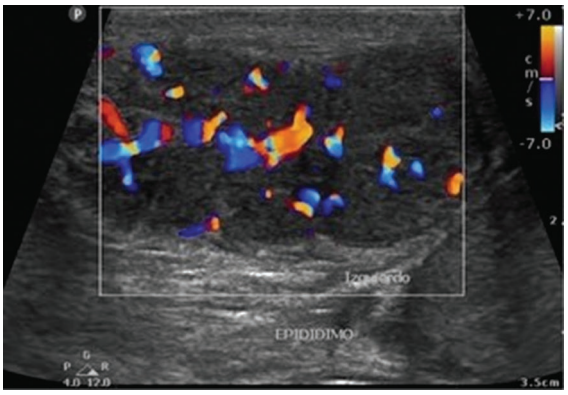

Figure 1. Testicular Doppler ultrasound showing data compatible with acute left orchiepididymitis.

In July 2022, he presented with dysuria, pollakiuria, bladder tenesmus, chills, and fever. A urinary tract infection was diagnosed and treated with nitrofurantoin for 7 days. Due to lack of improvement, the antibiotic was switched to a third-generation cephalosporin. However, he progressed into hypotension and acute graft dysfunction, requiring hospitalization.

During hospitalization, he developed acute left orchiepididymitis, confirmed by testicular Doppler ultrasound (Fig. 1). Therapy with a carbapenem and a fluoroquinolone was initiated without success. An abdominal computed tomography scan showed acute pyelonephritis of the renal graft, classified as grade 4 according to Huang-Tseng[6] (Fig. 2). Despite the initial indication for transplantectomy, treatment with piperacillin-tazobactam was chosen, leading to clinical improvement and subsequent discharge.

Two weeks later, he persisted with fever, night sweats, and testicular pain. In the absence of microorganisms in cultures and the presence of sterile pyuria, urology was consulted, and a radical left orchiectomy was performed. Cytomegalovirus syndrome was not suspected due to the absence of typical findings (leukocytopenia, thrombocytopenia, atypical lymphocytes, liver abnormalities) and the sole presence of fever. An epididymal abscess with non-fetid greenish secretion was identified. Histopathology concluded chronic epididymitis with granulomatous reaction and caseous necrosis in the tail of the

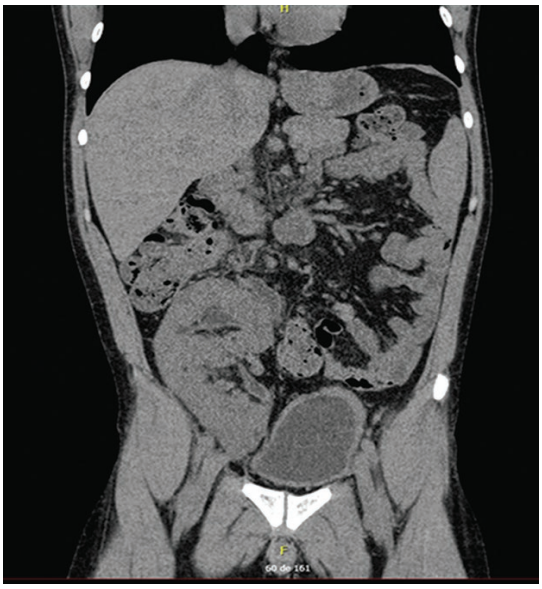

Figure 2. Simple computed tomography showing gas in the renal graft parenchyma, grade 2 according to the Huang-Tseng classification.

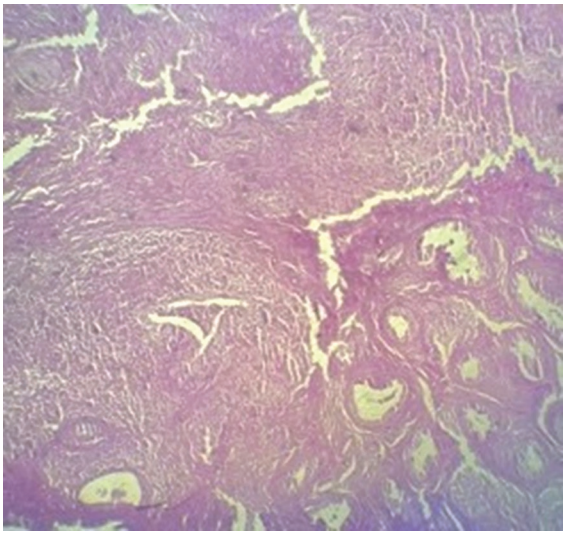

Figure 3. Histopathological section resulting from left orchiectomy with evidence of abundant inflammatory infiltrate and areas of caseous necrosis.

epididymis and the vas deferens (Fig. 3). The presence of *M. tuberculosis* was confirmed by Ziehl-Neelsen staining and molecular biology testing for *M. tuberculosis* (Xpert® MTB/RIF) in urine. Antituberculous treatment was initiated, leading to improvement within 72 hours and subsequent discharge.

The patient completed 12 months of treatment with isoniazid, rifampicin, pyrazinamide, ethambutol, and B complex, supervised by infectious disease specialists. Recent examinations showed a serum creatinine of 1.61, normal urine and blood counts, and a urine culture negative for *M. tuberculosis*. He will continue follow-up with nephrology and urology.

Discussion

Emphysematous pyelonephritis, described in 1898[7], is a necrotizing infection caused by gas-forming microorganisms that affect the collecting system, renal parenchyma, and extrarenal tissue[8]. *Escherichia coli* is the most common causative agent, followed by *Klebsiella, Aerobacter,* and other gram-negative bacilli[7].

Genitourinary TB, although uncommon, represents 8%-15% of extrapulmonary TB cases[9]. According to Sasi et al.[10], post-transplant TB manifests in 50% of cases as pulmonary, 30% as disseminated, 5% as lymph node, 4% as genitourinary, and, to a lesser extent, in the intestine, central nervous system, and bones. In our region, Parra-Michel et al.[11] report a TB prevalence of 1.4% in kidney transplant recipients, with extrapulmonary being the most common.

TB infection is usually a reactivation due to immunosuppression. Bacilli can remain latent in the urogenital tract and reactivate during immunosuppression, especially in transplant recipients[10]. Sorohan et al.[12] found that active TB usually manifests within the first post-transplant year, with a mean of 11.5 months. However, our case is atypical, presenting extrapulmonary TB 11 years after transplantation without a history of reactive PPD.

Several risk factors exist for TB, including recipient, donor, and transplant characteristics, induction therapy, and endemic factors[11]. Our patient presented several of these factors: prior hemodialysis, male sex, previous rejection, and use of immunosuppressants.

Urogenital TB, especially with scrotal and epididymal involvement, is poorly documented. Muneer et al.[13] reported that it usually manifests unilaterally in 66% of cases with non-specific symptoms. Diagnosis is based on *M. tuberculosis* culture or DNA identification, supported by imaging modalities[13,14]. However, detection in urine is rare[9], and invasive studies are often required to confirm diagnosis.

There is no consensus on the optimal therapy for emphysematous pyelonephritis in transplant recipients. In the general population, conservative therapy has a mortality rate of 75%[7]. Despite its rarity, this disease is serious in transplant recipients, with a risk of graft loss. Treatment of urogenital TB includes

antituberculous drugs[13]. Surgery is an option in case of pharmacological failure[9]. In our case, orchiectomy was selected due to the epididymal abscess and no response to antimicrobial therapies. Renal graft was successfully preserved after antituberculous therapy.

Conclusions

In kidney transplant recipients, urogenital TB is a rare infection but with potentially unfavorable outcomes, which is why identified cases have epidemiological relevance. It is essential to identify associated risk factors, make a timely diagnosis, and apply appropriate treatment to preserve graft function.

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CLINICAL CASE

Bacteremia in hemodialysis due to Ralstonia Pickettii, an inusual cause: case report

Bacteriemia en hemodiálisis por Ralstonia pickettii, una causa inusual: reporte de caso

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Abstract

The establishment of functional vascular access is critical for effective hemodialysis, with arteriovenous fistulas preferred over central venous catheters (CVCs) when feasible. CVCs, while essential in many cases, are associated with complications, including catheter-related bloodstream infections (CRBSIs). Ralstonia pickettii, a gram-negative, non-fermentative bacillus, is increasingly recognized as a nosocomial pathogen, which is associated with contamination of medical supplies and affects particularly in immunocompromised patients. This report presents a case of a 35-year-old male on hemodialysis that developed a CRBSI caused by Ralstonia pickettii with good evolution after antibiotic treatment. This case highlights the importance of considering Ralstonia pickettii in CRBSIs and consider epidemiological investigation to identify potential sources of contamination in healthcare settings.

Keywords: *Hemodialysis. Infection. Vascular access. Ralstonia picketti.*

Resumen

El establecimiento de un acceso vascular funcional es fundamental para una hemodiálisis efectiva, siendo las fístulas arteriovenosas preferidas sobre los catéteres venosos centrales (CVC) cuando es posible. Los CVC, aunque esenciales en muchos casos, están asociados con complicaciones, incluidas las infecciones del torrente sanguíneo relacionadas con el catéter (CRBSI). Ralstonia pickettii, un bacilo gramnegativo no fermentador, es cada vez más reconocido como un patógeno nosocomial, asociado con la contaminación de suministros médicos y que afecta particularmente a pacientes inmunocomprometidos. Este informe presenta el caso de un hombre de 35 años en hemodiálisis que desarrolló una CRBSI causada por Ralstonia pickettii, con buena evolución tras el tratamiento antibiótico. Este caso resalta la importancia de considerar Ralstonia pickettii en las CRBSI y de llevar a cabo investigaciones epidemiológicas para identificar posibles fuentes de contaminación en entornos de atención médica.

Palabras clave: *Hemodiálisis. Infección. Acceso vascular. Ralstonia pickettii.*

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Introduction

It is essential to plan the establishment of a functional vascular access that adequately delivers the prescribed dialysis, requires few interventions, and has few complications. According to data from the United States Renal Data System, in 2021 more than 85% of individuals who started hemodialysis did so with a catheter[1]. There are risks associated with the use of a central venous catheter, including acute procedural issues and chronic complications, especially infections. Catheter-related bloodstream infections (CRBSIs) have an incidence rate of 1.1 to 5.5 episodes per 1,000 catheter days and are associated with increased morbidity, hospitalization, and mortality[2]. Gram-positive bacteria are the most common etiology, with *Staphylococcus aureus* and coagulase-negative staphylococci responsible for 40% to 80% of CRBSIs, while Gram-negative organisms account for 20% to 40%[3]. *Ralstonia* species, particularly *Ralstonia pickettii*, are increasingly recognized as nosocomial pathogens, especially in immunocompromised patients, including those with human immunodeficiency virus and cystic fibrosis. Infections are often caused by contaminated medical solutions, leading to meningitis, endocarditis, pneumonia, and central bloodstream infections. Due to varying antibiotic susceptibilities, treatment of *Ralstonia* infections is not yet clearly established[4].

We present a case of catheter-related bloodstream infection caused by *Ralstonia pickettii* and how it was managed.

Case report

A 35-year-old man with chronic kidney disease of unknown etiology since 2014, currently on hemodialysis via a tunneled right jugular catheter, with no other relevant past medical history. The previously asymptomatic patient developed general malaise, chills, and fever > 38°C while on dialysis. He was referred from an external hemodialysis unit to our hospital. Based on clinical presentation, CRBSI was suspected[5]; peripheral and catheter blood cultures were obtained, and empirical treatment with vancomycin and ceftazidime was started. After 48 hours of antibiotic therapy, the patient presented to the emergency department conscious, febrile, tachypneic, tachycardic, with a blood pressure of 70/40 mmHg, clinically delayed capillary refill, and normal cardiovascular, respiratory, and abdominal exams. Upon admission, hemodynamic resuscitation was initiated, and the patient was admitted to intensive care. Antibiotic therapy with vancomycin and ceftazidime was continued. Lab test results showed severe metabolic acidosis, lactate 9 meq/L, hemoglobin 6.1 g/dL, and leukocytosis of 17,000/mL (Table 1). HIV infection was ruled out. A transthoracic echocardiogram was performed to rule out endocarditis and/or vegetations (Fig. 1), revealing left atrial dilation, concentric left ventricular hypertrophy, left ventricular ejection fraction of 48%, moderate-to-severe mitral regurgitation, mild pericardial effusion without right atrial collapse, and no evidence of vegetations or other findings suggestive of endocarditis.

Table 1. Patient lab test results in study

Test	Admission	Hospital discharge
Hemoglobin	6.1 g/dL	9 g/dL
Hematocrit	19.7%	28%
Total Leukocytes	17,000/mL	7,500/mL
Neutrophils	90.5%	60%
Platelets	193 x 10^9/L	220 x 10^9/L
Lactate	9 mmol/L	0.5 mmol/L
pH	7.09	7.31
pCO_2	30 mmol/L	42 mmol/L
PO_2	28 mm Hg	32 mm Hg
CO_2	14.1 mmol/L	mmol/L
HCO_3	13.1 mmol/L	-
Total Bilirubin	0.78 mg/dL	-
Direct Bilirubin	0.68 mg/dL	-
Indirect Bilirubin	0.1 mg/dL	-
Creatinine	11 mg/dL	9 mg/dL
BUN (Blood Urea Nitrogen)	88 mg/dL	54 mg/dL
Sodium	138 mmol/l	136 mmol/l
Potassium	5.9 mmol/l	5 mmol/l

On hospitalization day 3, results from the blood cultures obtained at the hemodialysis unit were received (Table 2), revealing the presence of *Ralstonia pickettii* growth. Empirical antibiotic treatment with vancomycin-ceftazidime was discontinued, and meropenem was initiated for 14 days. The catheter was also removed. Additionally, the patient received 3 units of packed red blood cells and continued to improve clinically, being discharged on hospitalization day 10[6].

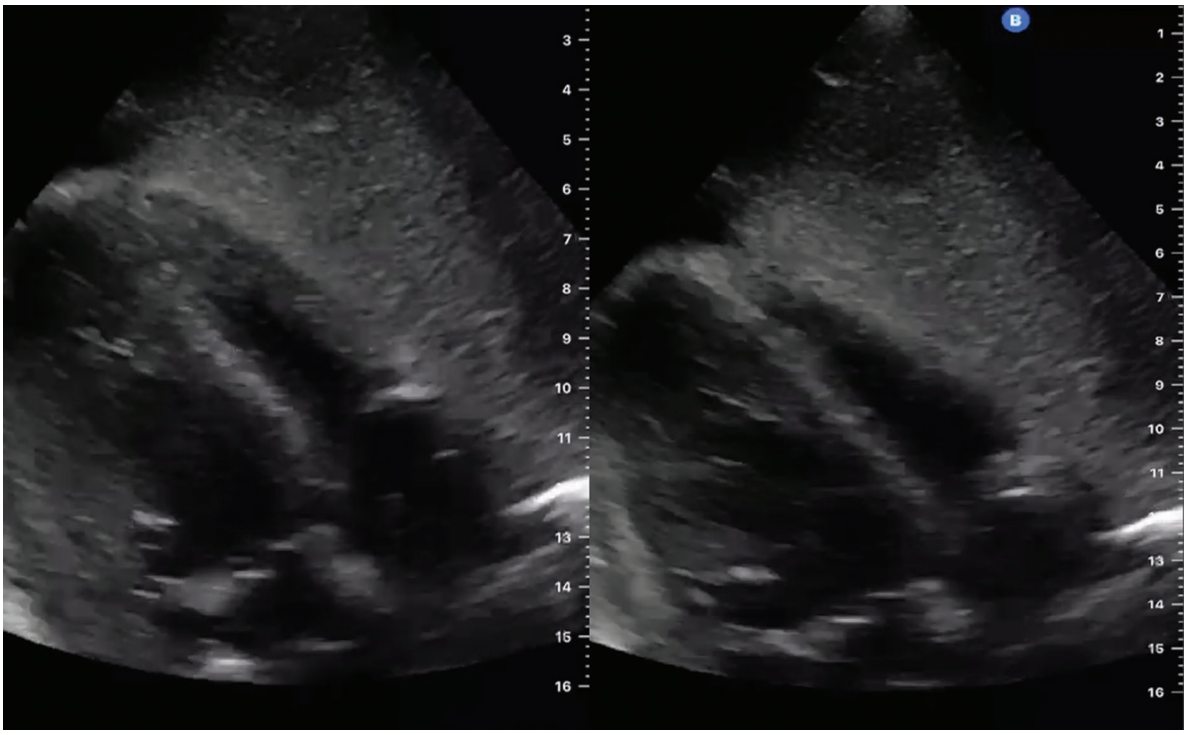

Figure 1. Transthoracic echocardiogram, apical 4-chamber view.

Table 2. Antibiogram of *Ralstonia pickettii* isolates in blood cultures

Antimicrobial	MIC µg/mL))	Interpretation
Amikacin	> 32	R
Aztreonam	< = 4	S
Ceftriaxone	< = 2	S
Ciprofloxacin	> 2	R
Cefepime	< = 2	S
Gentamicin	> 8	R
Levofloxacin	< = 2	S
Piperacillin Tazobactam	< = 16	S
Trimethoprim-Sulfamethoxazole	> 2/38	R
Tetracycline	< = 4	S
Tobramycin	> 8	R

MIC: minimum inhibitory concentration; S: susceptible; R: resistant.

Discussion

Ralstonia species are aerobic, Gram-negative, non-fermenting bacilli found in soil, wastewater, and plants. Although they have low virulence, they can cause sepsis, meningitis, pneumonia, and catheter-related bacteremia, particularly in immunocompromised patients, such as transplant recipients or those on hemodialysis[5]. They have also been responsible for serious nosocomial outbreaks, mainly through contaminated drugs, antiseptics, IV fluids, distilled water, dialysis machines, central venous catheters, and heparin solutions[6]. Furthermore, they are resistant to disinfectants such as chlorhexidine, which is widely used in clinical settings to clean vascular access in dialysis patients. The most common species are *Ralstonia pickettii, Ralstonia insidiosa,* and *Ralstonia mannitolilytica*[7].

Ralstonia pickettii is a non-fermenting aerobic Gram-negative bacillus found in soil and water. It can grow over a wide temperature range and in nutrient-poor liquids. It can form biofilms and pass through 0.2 µm filters used for sterilizing drugs and producing ultrapure water. It can also persist in hospital disinfectants such as chlorhexidine, which is used for skin antisepsis before inserting venous catheters or handling vascular access in hemodialysis[8].

Various studies have documented isolated cases and outbreaks of *R. pickettii* bacteremia in dialysis patients around the world (Table 3). No universal guidelines exist

Table 3. Case reports and series of *Ralstonia pickettii* bacteremia worldwide

Condition	Country	No. of Patients	Outbreak origin	Treatment	Mortality/ Outcome	Days on therapy	Reference
Bloodstream infection	Brazil	4	Injectable water	Ciprofloxacin Gentamicin	Not reported	Not Reported	Moreira et al.[7]
Bloodstream infection/ Pyelonephritis	Pakistan	3	Not recognized	Meropenem Colistin Levofloxacin	1 Recovered 2 Deceased	14 days	Nasir et al.[5]
Bloodstream infection	Philippines	3	Hemodialysis reprocessing machine tap	Cotrimoxazole Cefepime	Recovered	7 days	Aranas et al.[6]
Bloodstream infection	Uruguay	2	Contaminated Hemodialysis Water	Piperacillin/ Tazobactam, Meropenem	Recovered	14-21 days	Tejera et al.[8]
Bloodstream infection	Brunei	4	Contaminated Hemodialysis Water	Ceftazidime Meropenem, Catheter removal, Amoxicillin/ Clavulanic acid	Recovered	Not reported	Teth et al.[9]
Bloodstream infection	Colombia	124	Contaminated geparin	Ciprofloxacin	0.8% Mortality	Not reported	Saldarriega et al.[10]
Bloodstream infection	Italy	4	Plastic loading tubes connecting hemodialysis consoles	Ciprofloxacin Meropenem	Recovered		

regarding antibiotic choice or treatment duration for *Ralstonia pickettii* infections. Empirical antibiotic selection is typically based on syndrome diagnosis or susceptibility results from cultures[9-11]. However, most reported cases have been successfully treated with piperacillin-tazobactam, meropenem, ciprofloxacin, amikacin, or combinations of cephalosporins and aminoglycosides, as shown in table 3. In our case, the patient was on a 15-day regimen of meropenem with favorable disease progression.

Lastly, Saldarriaga-Quintero et al. described in detail the identification and control of the largest reported outbreak caused by *Ralstonia* spp. in a dialysis unit. The authors identified that water contamination used in the dialysis process played a crucial role in the outbreak, underscoring the need for rigorous water quality controls and effective preventive measures. Additionally, the clinical responses to various antibiotic regimens were analyzed, revealing considerable heterogeneity in treatment approaches and highlighting the lack of standardized empirical therapeutic clinical practice guidelines, as seen in other studies in the literature[12].

Currently, no specific cases of *Ralstonia pickettii* bacteremia in dialysis patients have been reported in Mexico, suggesting that the case presented here may be the first documented in the country.

Although *Ralstonia pickettii* is minimally virulent, it is known to cause a variety of potentially serious infections. When *Ralstonia pickettii* is isolated in blood cultures, contamination of medical products should be suspected and an epidemiological investigation initiated. This should include microbiological analysis of supplied fluids, medications, and dialysis water, as well as strict water quality control to eliminate potential sources of contamination if identified. This experience highlights the importance of developing uniform protocols and continuous monitoring systems to ensure safety in dialysis environments, including *Ralstonia pickettii* in their follow-up. Since the patient in this case was transferred from another unit, a detailed investigation into the source was not conducted; however, the dialysis unit from which the patient originated was notified to allow further investigation.

Conclusions

Whenever bacteremia or other isolations of *Ralstonia pickettii* occur, contamination of medical products such

as antiseptics, IV solutions, drugs, or even dialysis water should be suspected. Because *Ralstonia pickettii* is not perceived as a relevant pathogen due to its low virulence, it is often excluded from standard hospital analyses. Whenever this bacterium is isolated, a thorough investigation is necessary to identify the source and prevent large-scale outbreaks.

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An unexpected geological find. Intrauterine device within urolithiasis

Un hallazgo geológico inesperado. Dispositivo intrauterino dentro de una urolitiasis

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Introduction

Migration of intrauterine devices (IUDs) is rare but can cause urolithiasis and urinary tract infections (UTIs)[1-3].

Case

A 47-year-old woman with a history of an IUD inserted 22 years prior (with no history of problems during or after insertion) and lower UTIs due to *Escherichia coli* for the past 3 years presented to the Nephrology laboratory for analysis of a 6 cm diameter bladder stone (Fig. 1) that had been surgically removed. A × 10 stereoscopic examination (Fig. 2) revealed a copper T fragment in the stone.

Figure 1. Photograph of lithiasis with regular edges, ovoid in appearance, measuring 6 × 5 cm, whitish in color, and having a stony consistency.

Figure 2. Stereoscopy (× 10) of fractured lithiasis. A copper T fragment is observed at its upper end.

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Conclusion

In women with bladder stones and a history of an IUD, migration should be suspected as a source of bladder stones and UTIs. Migration is usually secondary to an unnoticed uterine perforation.

Funding

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Conflicts of interest

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

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