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EDITORIAL

On World Kidney Day: from early detection to access to kidney disease treatment

A propósito del Día Mundial del Riñón: de la detección temprana al acceso al tratamiento de la enfermedad renal

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As every year, World Kidney Day will be celebrated on March 13th, prompting educational campaigns worldwide aimed at raising awareness among the general population about kidney care. Given that chronic kidney disease (CKD) has a significant impact on quality of life, morbidity, and mortality, it is crucial to use this opportunity to raise its visibility among the public. It is estimated that approximately 10% of the global population suffers from some form of CKD, with 78% residing in low- or middle-income countries. These regions also face challenges such as malnutrition, infection risks, low birth weight, environmental factors, and limited access to healthcare services[1-3].

CKD is an asymptomatic, slowly progressive, and often irreversible condition. However, early detection can modify factors that lead to its progression to advanced stages or prevent death from its complications, particularly cardiovascular ones. Late referral and lack of access to renal support therapies and transplantation are significant factors affecting the prognosis of individuals with CKD[1-3].

Globally, including in Latin America, diabetes mellitus remains the leading cause of CKD, followed by other cardiovascular and metabolic conditions. In addition, there is an epidemic of CKD of unknown etiology affecting certain regions of Central America[4,5].

Access to treatment in Latin America is heterogeneous and depends on each country's health care system, public health expenditure, and the existence of a national renal health policy and program that addresses the needs of the entire population. Some Latin American countries have national programs that include timely detection, prevention, access to medications, and renal support therapies, bolstered by renal health promotion programs, data registries, and organ donation promotion. However, these countries represent < 15% of Latin America, and in other cases, national renal health programs are either absent or limited to specific systems, such as social security, non-governmental organizations, or certain states or provinces.

Most Latin American nephrologists work in isolation, making significant efforts from their local settings to address

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this situation. However, even if physicians are well-versed in detection, prevention, and treatment concepts, their impact remains limited. It is essential to emphasize that CKD, in its entirety, must be addressed by a national renal health system under the guidance of the central government and implemented by each public health ministry, with the participation of various stakeholders, including medical societies, nutritionists, nurses, social workers, psychologists, researchers, and patient associations[1,4].

Proposal by the Latin American Society of Nephrology and Hypertension (SLANH)

Given the described context, SLANH, through its Renal Health Committee, is making a significant contribution by encouraging countries to move toward the creation of a "Renal Health Program"[6]. In their publication, the authors propose a comprehensive approach, ranging from early and timely detection of CKD, access to drugs and renal support therapies, to the integration of other elements, such as advanced CKD clinics and tele-nephrology. They also highlight the importance of CKD registries at all stages, including not only patients requiring dialysis and transplantation but also those with less advanced CKD. They recommend early detection and standardization of follow-up pathways based on each country's resources, targeting at-risk individuals (diabetics, hypertensives, and metabolic syndrome patients, those exposed to occupational heat stress) or healthy individuals seeking health care for various reasons[6].

Screening is recommended using an estimated glomerular filtration rate (eGFR) and the albumin-to-creatinine ratio in a random sample. For individuals with eGFR < 60 mL/min/1.73 m^2, evaluation by a primary care physician is recommended to assess renal health status and consider timely referral to a nephrologist. For this purpose, it is crucial to standardize diagnostic methodologies, suggesting the use of the CKD-EPI 2021 equation or the MDRD4 186-factor equation if serum creatinine is not standardized. Laboratories must report eGFR once a serum creatinine value is obtained, even if not explicitly requested by the physician[6].

It is also essential to establish a clear pathway for CKD patients. In Latin America, the number of nephrologists per country is limited, making it vital to train primary care physicians, who are often the first point of contact and diagnosis. They will evaluate the patient and determine if a nephrology referral is necessary (Fig. 1).

Interdisciplinary care for CKD patients is crucial. Instead of referring patients to multiple specialists (nephrologist, cardiologist, diabetologist, nutritionist, nurse), it is advisable to establish advanced renal care clinics where patients can be evaluated, treated, and informed by all specialists in a coordinated manner, providing better follow-up for their condition.

As is well known, Latin America is highly heterogeneous in terms of geography, culture, and languages. In many cases, patients cannot easily travel long distances to see a nephrologist. Therefore, tele-nephrology can be a valuable tool for the detection and follow-up of CKD patients. Experiences such as Chile's have shown that this technology is feasible for improving outcomes, reducing costs, and reaching more patients[6].

Ensuring access to nephroprotective medications is critical. In recent years, it has been demonstrated that, in addition to lifestyle changes, blood pressure control, and the use of renin-angiotensin-aldosterone system blockers, sodium-glucose cotransporter-2 inhibitors, the non-steroidal selective mineralocorticoid receptor antagonist finerenone, and semaglutide for overweight or obese patients with diabetic kidney disease, have a significant impact on CKD progression, complications, and mortality. A renal health program must focus on providing patients with access to these drugs, which will ultimately prove cost-effective, saving resources for healthcare systems to treat more patients[7-9].

On the other hand, registries are an essential tool for understanding the pathology and evaluating the program and its execution team. Therefore, a core component of a renal health program is the creation, maintenance, and strengthening of registries, not only for dialysis and transplantation but for all CKD patients.

None of this is possible without sustainability and governance. A renal health program must have a legal foundation, establishing it as a national public health policy with regulations for implementation, promotion, and patient care. It must be led by qualified individuals from nephrological, health care, and epidemiological perspectives, who can selflessly execute a renal health program that is accessible, cost-effective, and practical.

The "Resolution on Prioritizing Kidney Health," proposed by Guatemala to the World Health Organization, aims to reduce the epidemic of non-communicable diseases by promoting kidney health, and strengthening CKD prevention and control. It will be put to a vote by governments at the upcoming General Assembly in May of this year. If approved, kidney health will be elevated to a global priority, making the

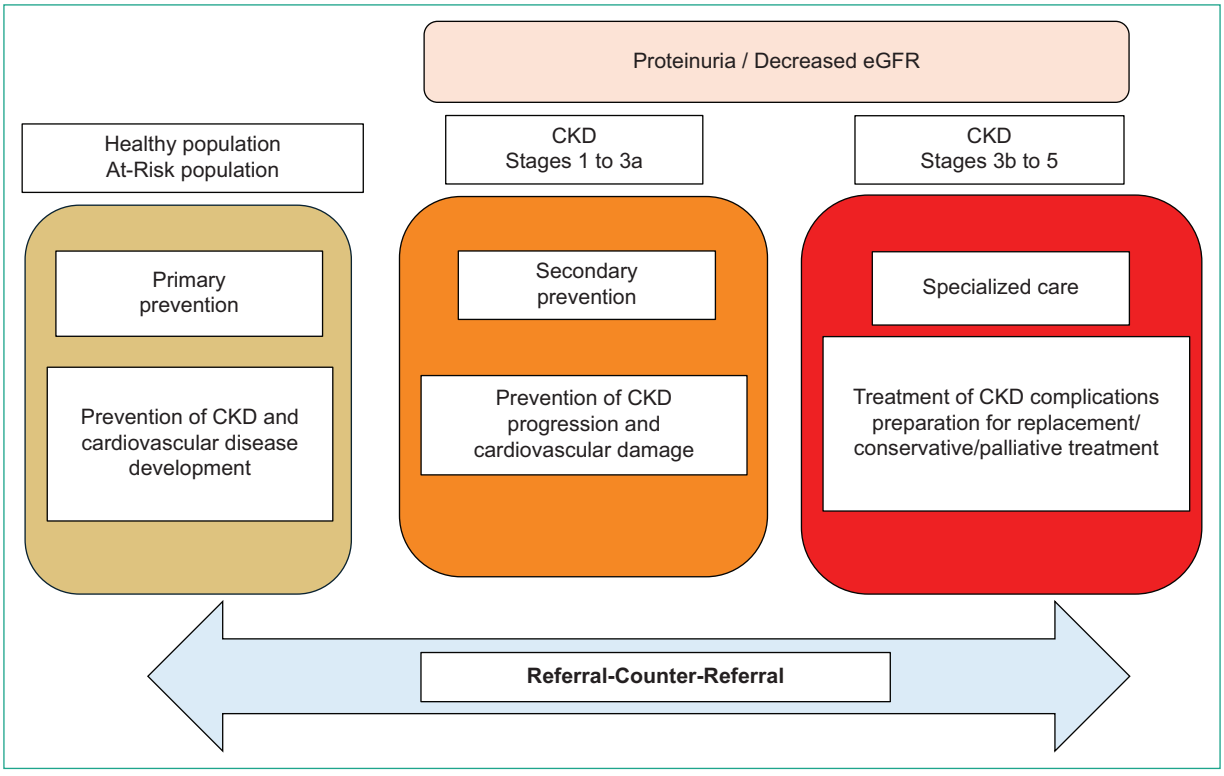

Figure 1. Renal health policy: from early detection to access to treatment (*adapted from ref.*[6]).

creation of national renal health programs more feasible and providing the general population with access to kidney health promotion, early detection, and treatment, while strengthening healthcare teams' capacities.

SLANH is committed to promoting and supporting the creation of these programs across the region. Through a dedicated renal health team composed of highly trained and prepared specialists, we pledge to support the various efforts countries may undertake and strengthen the capacities of those already taking steps in this important mission.

A major goal and challenge for us is that we are not only a scientific society with purely educational objectives but are also actively participating in influencing and collaborating on the planning and development of renal health policies, contributing our part to the dream of better kidney health in the region. SLANH works for kidney health for everyone, everywhere!

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

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

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SPECIAL ARTICLE

Health economics, a tool to assess the burden of chronic kidney disease in Latin America

Economía de la salud, una herramienta para evaluar la carga de la enfermedad renal crónica en Latinoamérica

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In Latin America (LA), as in other parts of the world, end-stage chronic kidney disease (ESCKD) constitutes a public health problem associated with high morbidity, mortality, significant costs, and a decreased quality of life. The prevalence of ESCKD under renal replacement therapies (RRT) in LA increased from 119 patients per million population (pmp) in 1991 to 669 pmp in 2013. The incidence shows a wide variation in the region, ranging from 462 pmp in Panama down to 20 pmp in Paraguay[1]. Hemodialysis continues to be the treatment of choice in the region (87%), with 45% of patients located in Brazil[2]. On the other hand, both incidence and prevalence correlate positively with the gross domestic product of each country, which may be one of the factors explaining the variability in the epidemiological behavior of ESCKD in the region[1,2]. It is not only extremely important to consider the number of patients with kidney disease but also to assess the health impact. Chronic kidney disease (CKD) accounts for 4.67% of total deaths worldwide and is responsible for 1.11% of years of life lost and 2.77% of years of life adjusted for disability[3]. When treatment costs, especially in terminal stages, are added, the problem takes on catastrophic dimensions.

In most LA countries, managing CKD is a very complex activity that faces a series of challenges, not only of a medical-scientific nature but also political-economic ones, including demographic, epidemiological, and cultural transitions; insufficient preventive programs; different social protection schemes; lack of effective access to RRT; large dispersed and marginalized population groups living with significant inequity and/or social inequality; the burden of other chronic-degenerative diseases; and the rising cost of services derived from medical care[4]. Furthermore, another series of problems associated with treatment have been identified, such as late diagnosis of CKD due to a lack of employment and availability of tools for the early detection of kidney damage; failure to apply timely nephroprotective and cardioprotective measures; and/or the systematic management protocols for early CKD, especially in high-risk groups.

Although LA made significant progress against poverty and extreme poverty, hunger, infant mortality –especially among children aged 1-5 years– and the reduction in the incidence of infectious or emerging diseases over the past 5 years, the region finds itself at a crossroads regarding its capacity to grow and distribute wealth in

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the future[5]. The deep disparities affecting our region regarding health are one of the main challenges to be faced. These health inequalities accumulate throughout the life course and prevent the full enjoyment of rights and full participation in all spheres of our society[5].

The fundamental objective of any health system is to maximize the health level of the population it covers[6]. However, no society can allocate sufficient resources to provide total and instantaneous health services to meet all health needs because "resources are finite and needs are infinite." This creates the need to seek methodological strategies that have progressed from assessing the costs and benefits of interventions to making better decisions in light of the evident limitation of available resources and the high complexity of CKD treatment.

In recent decades, health has become, in almost all contemporary societies, an activity with broad repercussions on critical variables for the economy, such as productivity, inflation, employment, and competitiveness. This issue draws the attention of all social actors involved in the debate on this topic: The government or decision-makers, clinical professionals, manufacturers or producers of health technology, and researchers. The interest stems from the definition of economics: "A social science that studies how economic agents –households, businesses, governments– use their scarce resources to specialize in production and exchange and consume goods and services"[7]. Consequently, health economics studies the production, distribution, and consumption related to the set of goods and services to obtain health[6].

Economic evaluation is an important tool of health economics. Its objective is to assess the costs and benefits of drugs, medical technologies, and health programs; that is, it compares the impact of an intervention on the health status of affected individuals (whether outcome or benefit) with the impact of the intervention on resource consumption[6,8]. This makes it necessary, in every decision made, to consider the benefit, diagnostic, or therapeutic that is forgone by choosing the best reasonably available alternative. The choice means that when one action is carried out, another must be sacrificed. Costs are measured by these sacrificed alternatives, and in economics, this is called "opportunity cost"[6-8].

Therefore, in the field of health, to position ourselves before a decision rationally and minimize the opportunity cost of decisions, we must compare various courses of action and study the relationship between the resources consumed (costs) and the outcomes obtained (consequences). This is what the economic evaluation of health interventions aims to achieve, which appears as a necessary methodology for both those making clinical decisions in direct care and for those responsible for planning[8]. However, despite the apparent benefits of the methodology of economic evaluation, its results are not routinely incorporated into clinical decision-making or health policies, especially in conditions with excessive global burdens such as CKD.

Within economic evaluation studies (cost-effectiveness, cost-utility, and cost-benefit), cost-effectiveness analysis has been defined as an important methodological tool for establishing the efficiency of health interventions and programs, guiding the establishment of priorities for the financing of health services, and assessing their impact in terms of clinical-health benefits and economic costs[8]. This analysis has the potential to significantly influence clinical practice and decision-making in the health sector.

Finally, the development of economic evaluation studies must be incorporated, as well as the transfer of their results into decision-making, to identify those alternatives that offer the greatest health benefit at the lowest possible cost (economic efficiency). Other strategies aimed at stopping the CKD epidemic in our region should continue to be strengthened, such as the implementation of prevention, diagnosis, and early treatment programs for CKD; promoting the development of research studies aimed at better understanding etiological factors, mechanisms of renal damage progression, and identifying new therapeutic agents; consolidating national CKD registries in the region; implementing interdisciplinary care models to limit and control risk factors for CKD; and supporting all these interventions with economic evaluations to determine their cost-effectiveness or cost-benefit.

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ORIGINAL ARTICLE

Plasma exchange by filtration as a therapeutic resource in nephrology: a 30-year historical sample

Intercambio plasmático por filtración como recurso terapéutico en nefrología: una muestra histórica de 30 años

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Abstract

Objective: *To evaluate the response to treatment using plasma exchange by filtration in an unpublished sample of 296 patients over a 30-year period, highlighting its consistent application and efficacy in various pathologies.* **Materials and methods:** *An observational, descriptive-analytical, retrospective, cross-sectional study was conducted, gathering data from 296 patients (325 cycles, 2252 sessions) with 23 treated pathologies between January 1993 and June 2023 across 8 healthcare entities.* **Results:** *About 55.7% of the patients were female and the global average age was 49.2 ± 18.9 years. Principal diagnoses included Guillain-Barré syndrome and related conditions (51.4%), myasthenia gravis (16.9%), thrombotic microangiopathies (11.1%), encephalitis/myelitis (9.1%), and others (11.5%). Kidney pathologies were present in 11.5% of patients. The study identified a medical discharge rate of 72.6%, with a 12.2% of the patients displaying partial treatment response, and 15.2% experiencing mortality due to inadequate response. Mortality correlated with fewer sessions (p = 0.001), use of fresh frozen plasma (p = 0.01), intensive care unit admission (p = 0.03), and mechanical respiratory assistance on admission (p = 0.001).* **Conclusions:** *The research underscores PE's efficacy in severe autoimmune diseases, especially neurological ones, advocating for interdisciplinary collaboration and recommending accessibility and safety enhancements for broader adoption.*

Keywords: *Therapeutic plasma exchange. Plasmapheresis. Autoimmune disorders. Nervous system diseases. Treatment outcome.*

Resumen

Objetivo: *Evaluar la respuesta al tratamiento mediante intercambio plasmático por filtración en una muestra inédita de 296 pacientes a lo largo de un período de 30 años, destacando su aplicación consistente y eficacia en diversas patologías.* **Materiales y métodos:** *Se realizó un estudio observacional, descriptivo-analítico, retrospectivo y transversal, recopilando datos de 296 pacientes (325 ciclos, 2252 sesiones) con 23 patologías tratadas entre enero de 1993 y junio de 2023 en 8 entidades de salud.* **Resultados:** *Aproximadamente el 55.7% de los pacientes eran mujeres, y la edad promedio global fue de 49.2 ± 18.9 años. Los principales diagnósticos incluyeron el síndrome de Guillain-Barré y condiciones relacionadas (51.4%), miastenia gravis (16.9%), microangiopatías trombóticas (11.1%), encefalitis/mielitis (9.1%) y otras (11.5%). Las patologías renales estuvieron presentes en el 11.5% de los pacientes. El estudio identificó una tasa de alta médica del 72.6%, con un 12.2% de los pacientes mostrando una respuesta parcial al tratamiento y un 15.2% de mortalidad debido a una respuesta inadecuada. La mortalidad se correlacionó con un menor número de sesiones (p = 0.001), uso de plasma fresco*

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congelado (p = 0.01), admisión en unidades de cuidados intensivos (p = 0.03) y asistencia respiratoria mecánica al ingreso (p = 0.001). **Conclusiones:** *La investigación subraya la eficacia del intercambio plasmático en enfermedades autoinmunes graves, especialmente las neurológicas, abogando por la colaboración interdisciplinaria y recomendando mejoras en la accesibilidad y seguridad para una adopción más amplia.*

Palabras clave: *Intercambio plasmático terapéutico. Plasmaféresis. Trastornos autoinmunes. Enfermedades del sistema nervioso. Resultado del tratamiento.*

Introduction

Plasma Exchange (PE) is a medical procedure that has been widely used, mainly in developed countries and for more than 60 years, for the treatment of various diseases, especially those of autoimmune origin. It consists of the extraction of a certain volume of blood plasma and its replacement with human plasma or albumin with the aim of removing pathogenic elements which are responsible for diseases or replacing deficient factors in the body. This treatment is included in the generic group of therapeutic apheresis (TA) and was developed by hemotherapists, who created the technique using centrifugation to separate plasma and other blood products, thus facilitating their subsequent transfusion. Furthermore, plasma separation is directly applied in autoimmune diseases. In the 1970s, a variant was introduced through filtration separation which at present is used by nephrologists from Hemodialysis (HD) units, due to its affinity as regard equipment, human resources, and supplies, and its availability in the intensive care units (ICU)[1,2].

The term PE is internationally used (Therapeutic PE, Scambio Plasmático, Échange de Plasma, among others) to distinguish it from plasmapheresis employed to obtain hemoderivatives. The main international registries include patients and pathologies treated using both methods and revealing similar results[3]. That is the case of the Canadian, French, Italian, Japanese, American, World Apheresis Association, and Spanish Groups among others.

Numerous diseases with mainly autoimmune, but also toxic and metabolic pathogenesis, have been treated with apheresis, and the obtained results have shown significant variability. However, PE continues to be the most used aphaeretic technique in the main registries. The first review work was a compilation of cases carried out in 1980 by the Canadian Group. Subsequently, emblematic work has been performed in the nephrological field using PE, such as the one conducted in Harvard in 1996; a study with more than 200 patients with nephrological diseases treated with PE. Moreover, in 2004, the National Association of HD Technicians presented “Therapeutic Plasmapheresis in HD Units” at the Italian Nephrology Congress. Over the years, numerous studies have been performed to demonstrate the benefits of PE in terms of recovery of clinical-laboratory parameters, bioimaging, time spent in the ICU, and assisted mechanical ventilation time[4,5].

Since the beginning of the 21st century, an exhaustive compilation of worldwide published works has been carried out which was classified according to their characteristics; ranging from controlled and randomized double-blind studies to those based only on expert opinion and observations. This review allowed to establish levels of evidence and recommendation. The development of guides, books, and manuals that include the evidence collected in these studies began in 2013.

The best “pattern” that governs the application of PE and all the apheresis techniques throughout the world is established by the American Society for Apheresis (A.S.F.A.) through its guides and updates carried out every 4-5 years based on the publications in The American Journal of Apheresis. These guidelines are organized in four categories: (1) precise indication as the main treatment; (2) precise indication, but as adjuvant treatment; (3) it has no precise indication, but it can be used as an adjuvant in severe cases with a lack of response to other treatments; and (4) there is no evidence to support its usefulness or, on the contrary, there is evidence that indicates a lack of response. These categories provide an essential framework for clinical practice and reveal the current state of scientific knowledge in the field of PE and TA in general. Each case must be treated following a structured scheme to guarantee an effective application of PE: confirm the diagnosis as well as the underlying pathogenesis (Dx); identify the most relevant pathogenic or deficient factors; verify the category on the basis of the guidelines of the A.S.F.A.; establish a therapeutic plan that includes the definition of the cycle to be carried out, the vascular access and replacement fluid among others following the A.S.F.A. Guidelines and also, define specific objectives to achieve and closely monitor the patient’s evolution. This systematic approach guarantees

a rigorous and personalized application of PE, aligned with best clinical practices and guidelines established by the A.S.F.A[6-8].

PE emerges as an efficient therapeutic strategy in various medical conditions playing a crucial role in the management of neuromuscular and systemic diseases.

In the case of Guillain-Barré (GB) syndrome and its Miller Fisher variant, demyelination of peripheral nerves and paralysis are triggered by different antibodies, such as antimyelin, antigangliosides, and immune complexes. PE has demonstrated its effectiveness in this context, accelerating the patients' recovery even in the absence of circulating auto-antibodies (CAA), using clinical symptoms, electromyography,and cerebrospinal fluid as a reference[9,10].

In the case of myasthenia gravis (MG), PE offers a direct response against the anti-acetylcholine receptor or anti-musk antibodies, thus depleting nicotinic and muscarinic muscle receptors. This approach has revealed positive results, especially in critical moments such as the myasthenic crisis, major perisurgical periods, or after thymectomy, contributing to improve the patients' quality of life in view of the chronic nature of the disease[11,12].

PE performs a significant role for the thrombotic thrombocytopenic purpura (TTP) when applied early and intensively. This procedure allows the elimination of CAA and the replacement of the ADAMTS13 enzyme, effectively reversing thrombocytopenia, hemolysis, and microcirculation thrombotic ischemia caused by the uncontrolled growth of Von Willebrand factor[13,14].

In the context of systemic lupus erythematosus, classic PE emerges as an effective alternative in those cases where the immunoadsorption (IA) is not possible to be carried out, especially when there are specific clinical and laboratory criteria (ASFA category 1). That is the case of cerebritis, pulmonary hemorrhage, TTP, pregnancy to avoid immunosuppressant, rapidly progressive primary glomerulonephritis with negative response to immnopresosants[15,16].

Finally, PE is an effective therapy in the treatment of RPGN, the diagnosis based on clinical criteria, renal biopsy, and the presence of anti-glomerular basement membrane antibodies (AC AMBG), alone or associated with ANCA. However, early and intensive intervention is essential due to the high rebound of antibodies that occurs after treatment. This approach highlights the importance of a careful and personalized application of PE in the management of RPGN[17,18]. Furthermore, in renal transplantation, the role of PE is perhaps the most important within nephrology, especially in cases of acute humoral rejection (AHR) and in the recurrence of focal and segmental sclerosis in the graft[17,18].

Leaving aside the examples mentioned above, classic PE continues to be the most widely used form of TA (more than 60% of the main registries) and has proven to be a highly effective therapeutic modality resolving various pathologies in different areas. The PE filtration variant, in particular, has shown a notable growth in popularity thanks to its practicality and lower cost compared to other similar therapies. Its implementation has been successful in many countries, contributing significantly to both saving lives in critical situations as well as improving the quality of life of patients who are affected by different types of chronic diseases[19-21].

PE by filtration has played a fundamental role in nephrology as a therapeutic resource to treat many diseases mainly autoimmune and other medical conditions[22]. This research project immerses itself in an unpublished sample, covering 30 years of work, involving 296 patients, 325 therapeutic cycles, and over 2000 sessions which provide a vision of these patients' response to the treatment, highlighting the use and consistent application of PE by filtration.

Materials and methods

A quantitative study with an observational, descriptive-analytical, retrospective, and cross-sectional design was carried out. Data were collected from 296 patients (325 cycles and 2252 sessions) with a total of 23 pathologies treated between January 1993 and June 2023 in eight health-care entities (two public and six private). The STROBE guide (https://www.equator-network.org/) was used for the self-assessment of this publication[23].

Information was gathered from patients' medical records, including year of medical care, age, sex, specific treated pathologies, cycles carried out with each patient, health care system where they were treated, number of sessions performed, type of vascular access, replacement fluids used during the procedure, need for admission in an ICU, use of MRA at the time of admission, and response to treatment.

PE treatments were carried out using HD equipment adapted to PE. A.S.F.A. guidelines were followed to determine the diagnosis and treatment guidelines and the therapeutic approaches were agreed on with different specialist involved with the patient care. In addition, TA manual guidelines authored by Dr. Anaya Fernando were used[8,24,25].

PE was based on each patient's specific clinical needs and following the current clinical recommendations. Single filtration (FS) treatments were chosen, and in the rare cases of double filtration (DF), a handmade configuration was implemented with a second pump in parallel manually synchronized at 30% of the blood flow of the first. The use of this adaptation carried out manually, was the result of the lack of availability of DF equipment in our country. This strategy was only used in the early years (1993-1994) due to the high costs associated with "cascade" filters. Despite this temporal limitation, the "coupling" allowed a more precise control of both, blood flow and exchange volume, improving the efficacy, and safety of the procedure.

The ideal vascular access was a double-lumen catheter, mainly in the femoral vein, due to the lower risk of short-term complications. However, in some cases, previous functional definitive accesses were used in cases of AHR of kidney transplants.

Different filters, such as Plasmaflo and Cascadeflo from Asahi and Plasmaflux from Fresenius MC were used in the procedure. A large number of patients were treated with hollow fiber membranes (made of biocompatible material) with a surface area of 0.5 m2, while in the case of pediatric patients, 0.25 m^2 membranes were used. The pores, in all cases, were of 0.5 microns in diameter, allowing the passage of all plasma components (including albumin, immunoglobulins, and coagulation factors, but not the cells). The membranes, generally Polysulfone, were used with a fiber diameter of 200 microns.

The cycles were established in five sessions (except in pathologies in which they were programmed according to objectives to be achieved, as in TTP). During the early years, the filter was reused (1 per cycle) until 2004 (only a few patients were treated per year), following the AAMI biosecurity standards for reprocessing and inter-session storage. During the period of the filters reuse, controls of the electrophoretic proteinogram of the plasma fluid were carried out in the uses 1, 3, and 5, confirming stable effectiveness. Simultaneously, during those controls, intra- and extra-hollow fiber bacteriological studies were performed, with negative results for the cultures. After 2004, the filter used in each session was discarded.

The frequency of PE sessions varied according to the individual needs of each patient. The initial cycle sessions were daily carried out and, but in cases where more than one cycle was required, a quarterly approach was performed from the sixth session onward. The main replacement fluid used was the fresh frozen plasma (FFP) administrated during each session until 2004. Then, human albumin was used as replacement fluid with 5% preparations in 500 ml bottles or 20% preparations in those of 50 ml, achieving replacement at a rate of 5%, considering the saline solution to complete a 1:1 exchange with the extracted plasma, while also taking into account the patient's albumin levels.

For cases of thrombotic microangiopathies (TMA), pulmonary hemorrhage, or other situations with coagulopathies, or after 2–3 daily sessions with abnormal coagulation profile, 1/2 or one plasma volume of FFP was replaced. The plasma calculation to be extracted under normal blood count conditions was done at a rate of 40 ml per kilogram of theoretical weight. If the patient was anemic, the plasma fraction was calculated on the basis of the hematocrit. Sodium heparin was used as anticoagulant in the majority of cases unless the patient had specific contraindications.

The duration of the sessions varied between 2 ½ and 3 ½ h depending on the volume to be extracted and the patient's hemodynamic tolerance. Vital parameters were monitored during the PE sessions and also laboratory tests were carried out before and after each session to evaluate the patient's stability and the response to treatment.

The statistical analysis was carried out with SPSS V28.0 software (IBM Inc. Armonk, NY, USA.) The qualitative variables are described with absolute frequency (n) and percentages (%). Normality contrasts were performed with the Kolmogorov–Smirnov test. Quantitative variables are described with mean ($\Re$) and standard deviation (SD) or with median (Me) and quartiles 1 (Q1) and quartile 3 (Q3) according to their distribution. The analysis of the relationship between qualitative variables was accomplished through the Pearson's Chi-square test or Fisher's exact test. Comparison between means or medians was performed with the independent samples T-test or the Mann-Whitney U test. The comparison of means among three groups was conducted using ANOVA or the Kruskal-Wallis test. The statistical significance level was set at an alpha value of 0.05.

Results

A sample of 296 patients was analyzed who performed 325 cycles and 2252 sessions. The majority of patients were female, comprising 55.7% of the sample, with a global average age of 49.2 ± 18.9 years, with a minimum of 6 years old and a maximum of 87. A total of 11 patients were less than 17 years old (Table 1). The number of patients who received treatment per year is displayed in figure 1.

Table 1. Demographic characteristics of the sample

Variable	Value (n)
Sex, n (%)	
Female	55.7 (165)
Male	44.3 (131)
Age (years) ℜ ± SD	
Total sample	49.2 ± 18.9
Female sample	48.4 ± 18.8
Male sample	50.2 ± 19.1
Pediatric patients, n (%)	
Yes	3.7 (11)

The pathologies diagnosed were Guillain-Barré syndrome and related ones (GB-S) with 51.4% (n = 152), MG with 16.9% (n = 50), TMA with 11.1% (n = 33), encephalitis/myelitis with 9.1% (n = 27) and others with 11.5% (n = 34) (see in order in Fig. 2). Kidney pathologies were present in 11.5% (n = 34) of patients in a primary or secondary way. On the basis of ASFA categorization, 79% of patients were Category 1, 13% Category 2, and 8% Category 3.

Considering the treatment characteristics, 98% (n = 290) of patients had temporary vascular access. Table 2 shows that 62.5% of patients were treated in private clinics and sanatoriums, the median number of sessions was a value of 5 and the most used replacement fluid was albumin in 89.9% of patients. Moreover, 86.8% of patients were admitted to ICU, 31.4% required MRA on admission and 72.6% received a medical discharge. It is important to highlight that complications during treatment were only present in a 3.7% (n = 38) of sessions being hypotension and reaction to plasma the most frequent. The study found a medical discharge rate of 72.6%, with 12.2% showing partial response to treatment, and 15.2% experiencing death due to lack of response.

Age, sex, and the health system did not show an association with death ($p > 0.05$). Death demonstrated association with a lower number of sessions ($H = 30.7$; d.f. = 2, $p = 0.001$) (Fig. 3), with the use of FFP as a replacement fluid ($X^2 = 8.72$; d.f. = 4; $p = 0.01$), with ICU admission ($X^2 = 7.27$; d.f. = 2; $p = 0.03$) and with MRA on admission ($X^2 = 59.6$; d.f. = 2; $p = 0.001$) (Fig. 4). The proportion of deaths was 18.8% in TMA, 13.2% in GBS-R, 10% in MG, and 7.4% in encephalitis/myelitis. GBS-R and TMA had a higher frequency of death than MG and encephalitis/myelitis ($X^2 = 18.5$; d.f. = 8; $p = 0.02$) (Fig. 5).

Table 2. Characteristics of the treatment received by patients

Variable	Value (n)
Health system, n (%)	
Public	37.5 (111)
Private	62.5 (185)
Number of sessions	
Me (Q1-Q3)	5 (5-9)
Replacement fluid, n (%)	
Albumin	66.6 (197)
Frozen Fresh Plasma	10.1 (30)
Albumin+Fresh Frozen Plasma (FFP)	23.3 (69)
ICU admission, n (%)	
Yes	86.8 (257)
MRA on admission, n (%)	
Yes	31.4 (93)
Evolution, n (%)	
Medical discharge	72.6 (215)
Partial response to treatment	12.2 (45)
Death due to lack of response	15.2 (30)

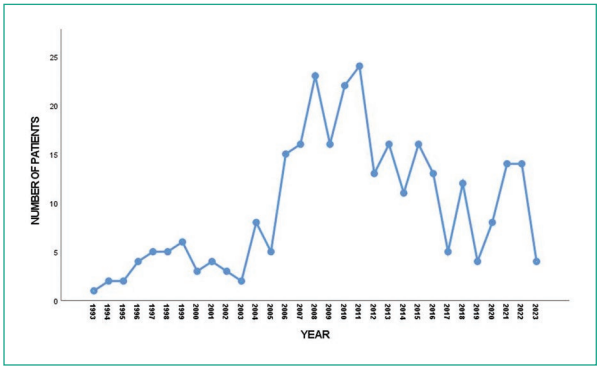

Figure 1. Patients under treatment according to year of study.

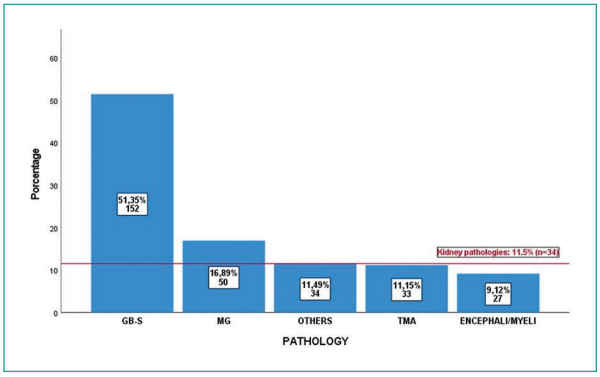

Figure 2. Frequency distribution of treated pathologies.

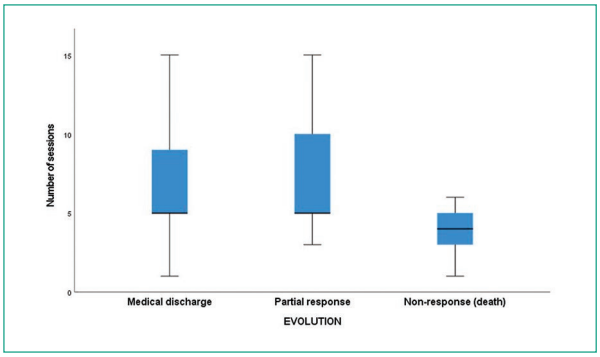

Figure 3. Box plot of sessions according to evolution.

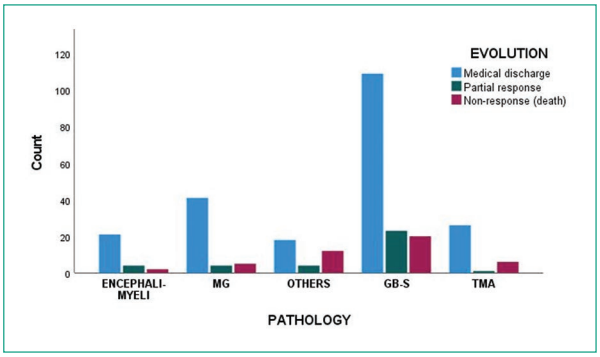

Figure 5. Grouped bars according to evolution and pathologies.

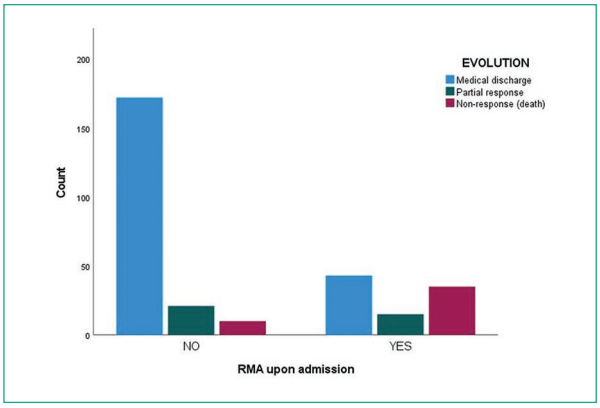

Figure 4. Grouped bars according to evolution and MRA on admission.

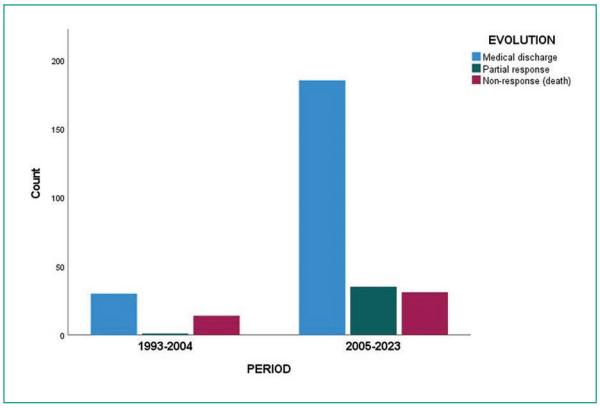

Figure 6. Grouped bars according to evolution and periods of years.

Although an analysis done considering temporal periods, it was observed that during 1993-2004 the rate of deaths was of 31.1% while between 2005 and 2023 deaths represented 12.4% of the evolutions; this difference is statistically significant (X^2 = 13.4; d.f. = 2; p = 0.001) (Fig. 6).

Discussion

First, when analyzing this study, it is crucial to highlight the historical evolution of PE in the first 11 years which were marked by the handmade configuration of HD equipment to perform the procedure. The initial stage was characterized by the filters reuse and the manual conduct of sessions in the three cases of DF; these limitations were overcome with the standardization of the filter provision and the transition to an automated approach starting in 2005. Despite the challenges, especially the lack of specialized machines and the high costs of filters, the results, especially in pathologies such as GB and MG, proved to be highly satisfactory with medical discharge in more than 70% of the treated patients. This value agrees with other authors' reports (Kumar et al. 2005 and Kaya et al. 2013)[26,27].

Regarding the overall mortality rate found of 15%, with no intra-treatment deaths, it coincides with a value of 16% observed by another author in a series of 96 patients (Ersan et al., 2018)[28]. Furthermore, it was observed a clear association with the presence of patients in MRA at the beginning of treatment, highlighting the importance of a timely and early referral from less complex centers as well as the need to recognize the practice of PE in less serious conditions on the side of paying entities, a discussion that has yielded positive outcomes since 2005. When these aspects were addressed and corrected, a meaningful improvement in the results was observed.

In addition, the selection of the replacement fluid was a critical factor, highlighting the effectiveness of the use of 5% human albumin despite the eventual return to the

FFP in specific cases. Two studies on PE carried out in Latin America (Cordoba et al. 2005 and Palma-García et al. 2018) reported, on a series of 68 and 230 cases, respectively, the use of albumin 5% in the range of 60–66% of treatments, which coincides with the value of 66.6% reported in the present research[29,30]. The limited availability of specific TA equipment in many centers should not be an insurmountable obstacle; adapted HD machines proved to be valuable resources, highlighting the versatility and accessibility of PE by filtration in various HD units.

It is important to highlight the interdisciplinary collaboration with hematologists, hemotherapists, therapists, and neurologists which strengthen the comprehensive approach of PE. Even though the availability of DF equipment presents a challenge, its limitation should not put in the shade the success of the treatment in pathologies such as LDL-TFA and other specific conditions. Close collaboration among specialties and the recognition of the network of HD units throughout the country are key elements to optimize the use of PE as a therapeutic resource.

Conclusions

In this research, the high rate of medical discharges emphasizes the usefulness and effectiveness of PE in patients severely affected by various autoimmune diseases, as long as the indication comes in terms with the ASFA guidelines. The majority of the cases studied belong to neurological diseases, highlighting the crucial role of PE in this area. This intervention not only broadens the scientific spectrum but also the professional one, especially for nephrologists, who are natural experts in extracorporeal filtering therapies. Interdisciplinary collaboration between nephrologists, neurologists, hematologists, rheumatologists, and intensivists, among others, enriches clinical practice.

To optimize the safety of the procedure, the availability of 5% human albumin in 500 mL presentations is suggested, eliminating the need to complete the volume with parenteral solutions in large quantities. It is essential to look for solutions to make the equipment that allows PE and DF, currently predominant in public hospitals and certain provinces, accessible to more private centers. This expansion would not only benefit patients with various pathologies but also those of a metabolic and toxic nature.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

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

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

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

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

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ORIGINAL ARTICLE

BK virus assessment in lupus nephritis: is this a potential trigger for disease activity?

Evaluación de virus BK en la nefritis lúpica: ¿es un potencial desencadenante de actividad de la enfermedad?

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Abstract

Objective: *The BK virus (BKV) is a human polyomavirus widely distributed in the population. In deeply immunosuppressed patients, such as those undergoing renal transplantation, the virus can be reactivated, leading to BKV nephropathy; the main risk factor is the degree of immunosuppression. Limited literature analyzes BKV infection in lupus nephritis (LN). Our objective was to study the BKV in LN.* **Material and methods:** *Patients over 18 years with LN confirmed by histology were prospectively studied for 1 year at the University Hospital. BKV viremia was detected and quantified using real-time-polymerase chain reaction.* **Results:** *Twenty-seven patients were included, 85% were women. About 100% were perceived as Caucasians. The 77.8% had proliferative LN at the debut, and the median evolution time was 11.5 years (IQR: 4.0-16.8). At enrollment, all patients received immunosuppressive treatment with prednisone (62%), mycophenolate (85%), and/or hydroxychloroquine (89%). We did not obtain positive viremia in any patient. At the time of blood sampling, 100% were in remission, and of them, 89% were in complete remission.* **Conclusions***: We did not detect any patients with positive BKV viremia. The absence of viremia could be due to the high degree of remission and low immunosuppressive burden in this population.*

Keywords: *Lupus erythematosus systemic. Kidney diseases. Lupus nephritis. Immunosuppressive agents. BK virus.*

Resumen

Objetivo: *El virus BK (VBK) es un poliomavirus humano ampliamente distribuido en la población. En situaciones de inmunosupresión, como el trasplante renal, puede reactivarse y generar nefropatía; su principal factor de riesgo es el grado de inmunosupresión. Hay escasa literatura que analice la infección por VBK en la nefritis lúpica. Nuestro objetivo fue estudiar el VBK en la nefritis lúpica.* **Material y métodos:** *Estudio prospectivo en pacientes con nefritis lúpica confirmada por histología, mayores de 18 años, asistidos en el Hospital Universitario, durante 1 año. Se utilizó RT-PCR para detectar y cuantificar la viremia del VBK.* **Resultados:** *Se incluyeron 27 pacientes, el 85% mujeres. El 100% se autopercibían caucásicos. El 77.8% tenían nefritis lúpica proliferativa al debut y la mediana de evolución fue de 11.5 años (RIC: 4.0-16.8). En el momento de la evaluación todos los pacientes recibían tratamiento inmunosupresor de mantenimiento con prednisona (62%), micofenolato (85%) o hidroxicloroquina (89%). No se obtuvo viremia positiva en ningún paciente. Al realizar la determinación, el 100% estaban en remisión y el 89% en remisión completa.* **Conclusiones:** *No encontramos pacientes con viremia por VBK positiva. El alto grado de remisión y la baja carga inmunosupresora de esta población podrían explicar los hallazgos.*

Palabras clave: *Lupus eritematoso sistémico. Enfermedad renal. Nefritis lúpica. Inmunosupresores. Virus BK.*

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, systemic, inflammatory, and immune-mediated disease. It presents with a wide spectrum of clinical manifestations, resulting from the interaction of genetic and environmental factors. Lupus nephritis (LN) is a common sign of SLE, with a prevalence of 50% according to various series. It usually presents within 5 years after the diagnosis of SLE[1]. The rate of progression to end-stage renal disease is 4.3% up to 10.1%[2]. In the Uruguayan Registry of Glomerulopathies, LN constitutes the third leading cause of kidney biopsy in individuals older than 14 years (7.81/million population/year) and is the most common among systemic diseases, along with vasculitis related to anti-neutrophil cytoplasmic antibodies[3]. In a Uruguayan cohort of patients with LN, survival (considering combined endpoints of the need for permanent dialysis and death) was 80% at 5 years and 77% at 10 years[3,4]. Kidney failure, along with infections, cancer, and cardiovascular events, are the most common causes of death in patients with SLE[5]. These complications are favored by immunosuppressive treatment, making it a challenge to minimize immunosuppression in the management of LN[6,7].

BK virus (BKV) is a human polyomavirus that is acquired in early childhood and is widely distributed in the population (60% up to 80% in adults). After the primary infection, it persists in the genitourinary tract[8] and can reactivate in situations of immunosuppression[9]. Approximately 80% of kidney transplant recipients develop BKV viruria, of which one-third will present viremia. Of these, up to 10% develop BKV-associated nephropathy (BKVN) in the following year[9-11], with graft loss in up to 50% of cases[12]. Furthermore, BKV replication has been reported across different conditions associated with immunosuppression, such as solid organ transplant recipients (lung, heart, liver, and pancreas) and hematopoietic stem cell recipients[13]. In all these cases, the main risk factor for BKVN is the degree of immunosuppression. However, the significance of BKV infection in patients with SLE on immunosuppressive treatment remains unknown. Although BKV viremia is reported in up to 15% of patients with SLE, there is great heterogeneity in the viral load level of BKV that is established as positive[14].

In this study, we aimed to evaluate the prevalence of BKV infection in patients with LN confirmed by histological study during follow-up at the general nephrology outpatient clinic of the Hospital de Clínicas, and to assess the degree of association between BKV infection and the level of immunosuppressive treatment.

Material and methods

Study population

We conducted a prospective cohort study on patients with histological diagnosis of LN older than18 years and monitored at the nephrology outpatient clinic of the Hospital de Clínicas in Montevideo, Uruguay from February 2020 through February 2021.

Inclusion criteria were patients under follow-up at the nephrology outpatient clinic of Hospital de Clínicas with a diagnosis of LN confirmed by kidney biopsy and who provided signed consent to participate in the study.

Blood sample collection

Blood samples were obtained from all patients with LN. The extraction was performed together with the routine request for control tests required. Between 3 and 5 mL of blood were drawn into a single tube with ethylenediaminetetraacetic acid. A quantitative analysis of real-time polymerase chain reaction (RT-PCR) for BKV was performed.

Clinical characteristics at the time of kidney biopsy and blood collection for BKV determination were reviewed, including age, sex, race, creatinine levels, albumin levels, daily proteinuria, presence of microhematuria, blood pressure, and positivity for immunological markers (antinuclear antibodies, anti-double-stranded DNA, anti-Smith, complement levels, anticardiolipin antibodies, anti-beta-2-microglobulin, lupus anticoagulant, and cryoglobulinemia). The type and dosage of immunosuppressive medication received at diagnosis and subsequently during follow-up at the outpatient clinic were also recorded. The occurrence of infectious complications during the course, leukopenia, lymphopenia, neoplasms, and metabolic complications was evaluated.

DNA extraction and purification from plasma

Plasma fraction was drawn from the blood by low-speed centrifugation. About 200 μL of plasma per patient was used to isolate total DNA. The DNA Blood Mini kit (Qiagen) was used to isolate the DNA following the manufacturer's instructions. Samples can be frozen at −80°C after collection for later analysis as a batch. A single determination was made at the time of the interview in the outpatient clinic.

RT-PCR

RT-PCR was used to detect and quantify BKV. Primers were designed to amplify the viral capsid protein (VP-1) of BKV with forward primer 5' GCA GCT CCC AAA AAG CCA AA 3' and reverse primer 5' CTG GGT TTA GGA AGC ATT CTA 3'. The BKV Dunlop strain plasmid was obtained from American Type Culture. This collection was used as a positive control. PCR amplifications were performed using iTaq Universal SybrGreen Supermix (Bio-Rad) with the following PCR conditions: the thermal cycle started with a denaturation step at 95°C for 10 min, followed by 40 cycles of 95°C for 10 s and 60°C for 10 s. Quantitative RT-PCR assays were conducted using the Bio-Rad CFX96 detection system. RT-PCR amplification data were analyzed with software provided by the manufacturer (ABI 7500). The samples were run in duplicates. Data were expressed as copies of viral DNA per milliliter of plasma. Control lanes were also included for each run[8].

Operational definitions

Hypertension was defined as ≥ 140/90 mmHg in, at least, two determinations in the office and in, at least, two consecutive visits separated by 15 days. Serum creatinine was measured by the Jaffe method in the central laboratory of the institution. Renal failure was defined as an estimated glomerular filtration rate chronic kidney disease (EPI) < 60 mL/min/1.73 m^2.

Active sediment was defined as the finding in urine examination of at least five erythrocytes per field, leukocyturia, or cellular casts that could not be explained by other causes.

LN was defined as renal involvement due to SLE. The categorization of lupus nephropathy (ISN/RPS 2003) was used, considering proliferative nephropathies: LN class III and VI, and associations of III + V and IV + V. For the evaluation of clinical activity of SLE, the SLE Disease Activity Index (SLEDAI) stratification system was used. Complete remission was defined as a glomerular filtration rate > 60 mL/min/1.73 m^2 (or decrease to baseline creatinine values) associated with proteinuria < 0.5 g/day; presence of inactive sediment < 5 erythrocytes/field, < 5 leukocytes/field, and no blood casts per field; and serum albumin > 3 g/sL. Partial remission was defined as stabilization (±25%) or improvement of glomerular filtration rate versus baseline values, along with a decrease in proteinuria levels: in patients with baseline proteinuria > 3.5 g/day, a decrease to < 3.5 g/day or PrU/CrU < 3.3 g/g, and in patients with baseline proteinuria < 3.5 g/day or PrU/CrU < 3.3 g/g, a reduction > 50% compared to baseline. Treatment resistance was considered when neither of the two previous definitions applied. Relapse was defined as the reappearance of proteinuria with active sediment in patients who had previously achieved partial or complete remission.

Statistical analysis

The results of continuous variables were expressed as mean and standard deviation or as median and interquartile range (IQR), as appropriate based on the results of the normality study. Clinical and paraclinical characteristics were compared using t-tests or analysis of variance for continuous variables and Chi-square tests for categorical variables. The SPSS statistical package (Chicago, IL, United States) was used. $p < 0.05$ was considered significant.

Ethical aspects

The project was approved by Hospital de Clínicas Medical School Ethics Committee. Researchers analyzed data without identifiable patronymic information of the patient and committed to respecting the current personal data protection law (Law No. 18.331).

The study did not involve any blood extraction beyond what was necessary for monitoring and following up on the nephropathy, nor was it designed to carry out any type of intervention.

Results

A total of 27 patients with a histological diagnosis of LN were included, being followed at the nephrology outpatient clinic of Hospital de Clínicas from February 2020 through February 2021. A total of 85% were women, and 78% identified themselves as Caucasian. The median (IQR) age at diagnosis of SLE was 27.0 (18.5-32.0) years. At the time of the study, the median (IQR) duration of SLE was 12.5 (4.3-18.0) years, and the median duration since the diagnosis of LN was 11.5 (4.0-16.8) years. Regarding nephrological syndrome, at the time of kidney biopsy (taken as the onset of lupus nephropathy), 48% had asymptomatic urinary alterations, 41% had nephrotic syndrome, and 11% rapidly progressive glomerulonephritis. At the time of the diagnosis of LN, the median (IQR) of serum creatinine was 0.68 (0.63-0.80) mg/dL, and the median of proteinuria was 1.13 (0.43-5.5) g/day; 77% of the patients had

hematuria, and 18% had casts in the sediment. In addition, 41.7% had hypertension. The rest of the patient characteristics at the time of LN diagnosis are shown in table 1.

A total of 77.8% of patients had proliferative LN. Regarding the treatment received at the time of LN diagnosis, it is noteworthy that 100% of patients received immunosuppressors. None of those with non-proliferative nephropathy received methylprednisolone or cyclophosphamide. A total of 33% of patients received mycophenolate, and 50% azathioprine. Among patients with proliferative nephropathy, 38.1% initially received methylprednisolone, 42.9% cyclophosphamide, 47.6% mycophenolate, and 14.3% azathioprine. The clinical and paraclinical characteristics and the therapy received at the time of LN diagnosis are shown in table 2.

In all patients with LN under follow-up, viremias for BKV tested negative. At the time of viremia determination, 4 of the 6 (66%) patients with non-proliferative nephropathy and 20 of the 21 (95%) patients with proliferative nephropathies were in complete remission. Regarding the activity of SLE evaluated by SLEDAI, 0 had severe activity (score < 11), 4 had moderate activity (score 6-10), and the rest mild or no activity whatsoever.

Regarding therapy at the time of sampling for viremia due to BKV, five out of the six patients with non-proliferative nephropathy were on hydroxychloroquine, three on prednisone, four on mycophenolate, and two on azathioprine. A total of 19 out of the 21 patients with proliferative nephropathy were on hydroxychloroquine, 14 on prednisone, and 19 on mycophenolate, while 0 patients were on azathioprine.

Table 3 shows the clinical characteristics of the patients and the treatment instituted at the time of the determination of viremia by BKV.

Table 4 shows the clinical situation of the patients regarding the activity of SLE determined by SLEDAI and the immunosuppressive treatment at the time of the determination of viremia by BKV.

Table 1. Characteristics of patients at the onset of lupus nephritis (n = 27)

General characteristics	
Age, years (median)	27
Female sex, n (%)	85
Caucasian ethnicity, n (%)	78
Duration of SLE, years (median, IQR)	12.5 (4.3-18.0)
Duration of LN, years (median, IQR)	11.5 (4.0-16.8)
Characteristics of LN at disease onset	
AUA, n (%)	48
Nephrotic syndrome, n (%)	41
RPRF, n (%)	11
Serum creatinine, mg/dL, median (IQR)	0.68 (0.63-0.80)
Hypertension, n (%)	41.7
Proteinuria, g/day, median (IQR)	1.1 (0.4-5.5)
Hematuria, n (%)	77.3
Cylindrical casts, n (%)	17.6
Non-proliferative, n (%)	22.2
Proliferative, n (%)	77.8

AUA: asymptomatic urinary alterations; SD: standard deviation; RPRF: rapidly progressive renal failure; SLE: systemic lupus erythematosus; LN: lupus nephritis; IQR: interquartile range.
This table summarizes the main clinical and paraclinical characteristics of the patients at the time of renal biopsy, considered as the onset of LN.

Discussion

In this study, we systematically sought the presence of viremia by BKV in all patients diagnosed with LN being monitored at the nephrology outpatient clinic of a university hospital. The main result is that we found no positive viremias, with all patients under some form of maintenance immunosuppressive treatment and 89% in complete remission.

A systematic review on the prevalence of BKV in recipients of solid non-renal organ transplants found 17 cases of nephropathy associated with BKV (NVBK) in recipients of lung, heart, liver, and pancreas[15]. Infection by BKV has been studied in kidney transplant recipients, and the deleterious effect it exerts on the graft is well documented. In this group of patients, it is important to achieve a diagnosis, not only because it constitutes an infectious complication, minimizing the impact and loss of the graft but also because it constitutes a differential diagnosis of acute graft rejection, with opposing treatments for both conditions. There is no effective antiviral therapy versus NVBK, and standard therapy consists of reducing the immunosuppression load. While viremia occurs in 10% up to 30% of kidney transplant recipients, NVBK only occurs in 2% of cases. The presumptive diagnosis of NVBK is established with a BKV DNA load > 10^4 copies/mL, even when histology does not show virus replication[12]. NVBK is more common when the degree of immunosuppression is at its peak. Most patients are asymptomatic. Kidney transplant recipients affected by NVBK are at greater risk of graft loss[16].

We found few studies that evaluate BKV infection in SLE. Colla et al.[14] investigated viremia and viruria for BKV in 40 patients with LN and found positive viremia in 15% and positive viruria in 13.8%. In this study, there were no significant differences in renal function, urine sediment, SLE activity as measured by the SLEDAI, the presence of anti-DNA antibodies, or type of immunosuppressive therapy used. Viremia was determined by PCR with a sensitivity of the study of ≥10^2 copies/mL of BKV DNA[14].

Table 2. Characteristics of lupus nephritis, proliferative and non-proliferative at the time of diagnosis

Characteristic	Non-proliferative (n = 6)	Proliferative (n = 21)
Age at PRB (years)	24	29
Clinical presentation		
AUA, n (%)	50	48
Nephrotic syndrome, n (%)	50	38
RPRF, n (%)	0	14
Serum creatinine, mg/dL, median (IQR)	0.64 (0.49-0.66)	0.70 (0.65-0.80)
Hypertension, n (%)	40	33
Proteinuria, g/day, median (IQR)	1.2 (0.2-7.7)	1.1 (0.4-4.5)
Active sediment, n (%)	50	62
Serology		
Positive ANA, n (%)	83	94
Anti-DNA positive, n (%)	80	62
C3, mg/dL, median (IQR)	69.5 (58.0-101.0)	62.0 (43.0-88.0)
C4, mg/dL, median (IQR)	9.0 (6.8-24.8)	8.0 (6.0-15.0)
Treatment at diagnosis		
Methylprednisolone, n (%)	-	38.1
Cyclophosphamide, n (%)	-	42.9
Mycophenolate, n (%)	33.3	47.6
Azathioprine, n (%)	50.0	14.3

ANA: antinuclear antibodies; AUA: asymptomatic urinary alterations; RPRF: rapidly progressive renal failure; PRB: percutaneous renal biopsy; IQR: interquartile range. This table contrasts the characteristics of clinical presentation and treatment of patients with proliferative versus non-proliferative LN

Table 3. Characteristics at the time of viremia determination for VBK in patients with lupus nephritis, proliferative and non-proliferative

Characteristic	Non-proliferative (n = 6)	Proliferative (n = 21)
Serum creatinine, mg/dL, median (IQR)	0.66 (0.54-1.49)	0.87 (0.65-1.17)
Hypertension, n (%)	16	19
PrU, g/day, median (IQR)	0.20 (0.01-0.35)	0.25 (0.05-0.30)
Active sediment, n (%)	16	33
Serology		
Anti-DNA positive, n (%)	67	62
C3, mg/dL, median (IQR)	91.0 (61.5-135.5)	95.5 (72.2-111.2)
C4, mg/dL, median (IQR)	22.5 (9.7-31.0)	16 (9.5-24.2)
Leukopenia, n (%)	16.7	90
Lymphopenia, n (%)	33.3	
Renal response		
Complete remission, n (%)	66.7	95
Partial remission, n (%)	33.3	5
SLEDAI, n (%)		
≤ 5	66.7	57.2
> 6	33.3	42.8
Treatment		
ACEi/ARA II (n)	5/6	18/21
Hydroxychloroquine (n)	5/6	19/21
Prednisone (n)	3/6	14/21
Mycophenolate (n)	4/6	19/21
Azathioprine (n)	2/6	0/21
Viremia VBK by PCR, n (%)		
Negative	100	100
Positive	0	0

ACEi: angiotensin-converting enzyme inhibitor; ARA II: angiotensin II receptor antagonist; PCR: polymerase chain reaction; PrU: proteinuria; IQR: interquartile range. This table shows the clinical characteristics at the time of sampling for determining VBK viremia, contrasting patients with proliferative forms (who may be assumed to have higher immunosuppressive burden) with patients with non-proliferative forms of lupus nephritis.

Table 4. Doses of immunosuppressants at the time of VBK viremia determination

Patient	Time PRB (years)	SLEDAI	PDN (mg)	HCQ (mg)	Aza (mg)	MMF (mg)
1	3	1	5	200	-	1500
2	13	0	0	200	-	1500
3	16	0	5	200	-	500
4	16	4	5	400	125	0
5	5	8	10	200	-	2000
6	4	0	5	200	-	1000
7	22	4	10	200	-	0
8	20	6	10	200	-	720
9	12	0	0	100	-	720
10	7	2	0	200	-	2000
11	7	4	5	200	-	720
12	0	8	5	400	-	1500
13	1	4	20	400	-	0
14	2	0	0	200	-	2000
15	16	8	0	200	-	2000
16	10	0	0	200	-	1000
17	1	0	20	0	-	1440
18	24	2	5	200	-	1080
19	2	10	30	200	-	2000
20	14	2	0	0	-	540
21	9	0	5	200	-	2000
22	24	4	0	200	-	1000
23	1	4	5	200	-	3000
24	3	2	0	200	-	1440
25	1	2	2.5	400	-	2000
26	22	0	10	0	100	0
27	5	2	0	200	-	2000

Aza: azathioprine; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; PRB: percutaneous renal biopsy; PDN: prednisone, SLEDAI: systemic lupus erythematosus disease activity index.
A total of 100% of the patients were in the maintenance phase.

Gupta et al.[8] conducted a 1-year prospective follow-up of a pediatric cohort of 32 patients with SLE and serial determinations of viremia and viruria. Positive viremia and viruria were found in 22% and 28% of the patients, respectively A cutoff for positive viremia was established as any PCR determination > 0 copies/mL. It is also noteworthy that in the monitored population, biological drugs were used: most were on rituximab (anti-CD20 monoclonal antibody) and to a lesser extent belimumab (anti-B cell stimulator), abatacept (anti-cytotoxic T lymphocyte-associated antigen-4-immunoglobulin), infliximab (anti-tumor necrosis factor alpha), and tocilizumab (anti- interleukin-6 receptor). The use of steroids and cyclophosphamide was not shown to influence the presence of BKV[8].

The Norwegian study by Sundsfjord et al.[17] on the presence of BKV and JC virus in the urine of patients with SLE did not find positive viremias. Viruria was found in 16% of patients with SLE. No correlation was ever found between periodic or persistent viruria and the intensity of immunosuppression in that population.

In the studies cited with patients with SLE, there is great heterogeneity regarding the viral load value of BKV established as positive versus the studies mentioned with kidney transplant recipients, which complicates the comparison of results[12].

In our study, we evaluated the presence of viremia by BKV in patients with LN being monitored in the nephrology outpatient clinic of a university hospital in Uruguay. We recruited a total of 27 patients with a median (IQR) duration of their nephropathy of 11.5 (4.0-16.8) years. In this population, we did not obtain positive viremias. While we performed a single determination, which is a limitation, we highlight that it was performed at different stages of immunosuppressive therapy. It is noteworthy that a study conducted in the same hospital, which evaluated the presence of viremia by BKV in kidney transplant recipients, found positive viremia in 20% of patients with suspected NVBK. The laboratory responsible for performing the viremia determinations was the same as that in our study[18].

LN is a disease with a wide spectrum of histological presentations that differ in both the severity of clinical presentation and the requirement for immunosuppressive treatment and renal prognosis. For these reasons, we decided to divide the population into two groups: proliferative and non-proliferative LN.

Various causes could explain why the viremias of the entire studied population tested negative. Most patients (89%) were in complete remission. A low percentage presented leukopenia and lymphopenia (both 11%), suggesting a state of greater susceptibility to infections, especially viral ones, where cellular immunity plays a fundamental role. It is impressive that the initial severity effect of SLE could have been diluted by the response to treatment and the close follow-up conducted in this population.

In this study, a single determination of viremia was made. For the diagnosis of viral diseases, repeated determinations, and fundamentally viral kinetics, are relevant diagnostic elements, as viremias can be transient. Conducting serial determinations of viremia for BKV could increase the likelihood of finding positive viremias, as patients with SLE go through different stages in their progression regarding clinical and paraclinical activity of the disease, as well as in terms of the intensity of immunosuppressive therapy. These factors can determine variations in susceptibility to BKV infection[19]. It is likely that, compared to other populations of immunocompromised patients, such as kidney transplant recipients, our patients with LN being monitored were on a lower immunosuppression load.

Therefore, the main limitations of this study are the low number of patients recruited and having taken a single sample for viremia determination.

Conclusions

We can conclude that performing a single determination of viremia for BKV has limited yield in patients under outpatient follow-up for LN, with low clinical activity of LN evaluated by SLEDAI and with maintenance immunosuppressive treatment. There is a need to complete the study of patients with LN by performing serial determinations of viremia for BKV and correlating the results over time with the progression of nephropathy.

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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 the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

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.

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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PERMANYER

ORIGINAL ARTICLE

Humoral response to SARS-CoV-2 vaccination in lupus nephritis

Respuesta a la vacunación contra SARS-CoC-2 en la nefritis lúpica

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Abstract

Objective: *The development of vaccines has been the most effective control measure for the pandemic caused by SARS-CoV-2. Studies testing the efficacy of vaccines in patients with lupus nephropathy (LN) have not been conducted and to assess antibodies (Ab) generation against SARS-CoV-2 after vaccination in patients with LN under immunosuppressive treatment, followed at the Hospital de Clínicas, Montevideo, Uruguay.* **Material and methods:** *We conducted a prospective study on patients with LN. Blood samples were drawn 1 month after the second dose of the SARS-CoV-2 vaccine. We used an enzyme-linked immunosorbent assay test to check for the presence of Ab, which were sensitized with the Receptor Binding Domain fragment of the SARS-CoV-2 spike protein. We also recorded any adverse effects and variations in the SLEDAI score after vaccination.* **Results:** *We enrolled 19 patients, median age 35.5 years, 89% were female. The overall rate of seroconversion was 63% (p = 0.11). Patients in complete remission (CR) showed a significantly higher Ab response. Among those vaccinated with Pfizer-BioNTech, 83% generated Ab (p = 0.03), while among those vaccinated with Sinovac, 54% did so (p = 0.69). Patients initially treated with cyclophosphamide showed a significant difference in Ab generation (p = 0.009).* **Conclusions:** *LN patients who were vaccinated with Pfizer or who were in CR showed a higher level of anti-SARS-CoV-2 seroconversion.*

Keywords: *Lupus nephropathy. Vaccination. SARS-CoV-2. Antibodies. Immunosuppressants. Seroconversion.*

Resumen

Objetivo: *La mejor medida de control lograda para la pandemia por SARS-CoV-2 ha sido el desarrollo de vacunas. Los pacientes con nefritis lúpica (NL) no han sido incluidos en estudios que comprueben la eficacia de estas en dicha población. Analizar la capacidad de generar anticuerpos (Ac) frente a la vacunación contra SARS-CoV-2 en pacientes con NL bajo tratamiento inmunosupresor, seguidos en el Hospital de Clínicas, Montevideo, Uruguay.* **Material y métodos:** *Se realizó un estudio prospectivo, en pacientes con NL a quienes se extrajo sangre periférica al mes de la segunda vacuna para SARS- CoV-2. Se buscó la presencia de Ac por test de ELISA, sensibilizado con el fragmento Receptor Binding Domain de la proteína de la espícula del SARS-CoV-2. Se registraron efectos adversos y variaciones en el score SLEDAI luego de administrada la vacuna.* **Resultados:** *Se incluyeron 19 pacientes con NL, la mediana de edad fue de 35.5 años, el 89% era de sexo femenino. La tasa global de seroconversión fue del 63% (p = 0.11). Los pacientes en remisión completa (RC) generaron*

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una respuesta de Ac significativamente mayor. Los vacunados con Pfizer-BioNTech generaron Ac en un 83% (p = 0.03), mientras que los vacunados con Sinovac en un 54% (p = 0.69). Aquellos tratados inicialmente con ciclofosfamida presentaron una diferencia significativa a favor de la generación de Ac (p = 0.009). **Conclusiones:** *Se logra mayor seroconversión anti-SARS-CoV-2 en pacientes vacunados con Pfizer-BioNTech o en RC.*

Palabras clave: *Nefritis lúpica. Vacunación. SARS-CoV-2. Anticuerpos. Inmunosupresores. Seroconversión.*

Introduction

Coronavirus disease 2019 (COVID-19) is a multisystemic condition caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. In March 2020, the World Health Organization classified the COVID-19 situation as a pandemic[2]. Since then, its spread had devastating implications, becoming one of the leading causes of death globally in the subsequent 2 years.

In this context, the need arose to implement health measures to control the pandemic. Among these, vaccination against the virus proved to be the most effective strategy.

In Uruguay, the use of three vaccines was approved: Pfizer-BioNTech (BNT162b2), Sinovac (CoronaVac®), and Oxford-AstraZeneca (AZD1222). Vaccination was organized in stages, initially prioritizing the most vulnerable and exposed groups: healthcare personnel, patients with chronic kidney disease on hemodialysis, institutionalized individuals in nursing homes, incarcerated individuals, essential workers, and immunocompromised patients. Vaccination then proceeded by age groups[3]. This vaccination scheme was implemented with the knowledge that both age and certain comorbidities contributed to worse disease outcomes[4].

Vaccination of patients with systemic lupus erythematosus (SLE) was controversial due to the theoretical possibility of reactivation or worsening of their underlying condition, especially in those undergoing treatment with corticosteroids, mycophenolate (MF), rituximab, or who presented a very aggressive clinical form[5]. National and international recommendations and guidelines for active SARS-CoV-2 immunization were based on the experience with other vaccines, such as influenza and pneumococcal vaccines. General preventive measures such as social distancing, mask-wearing, and handwashing to prevent contagion were also emphasized[6,7], as well as close monitoring of symptoms when they occurred. At the time of this study, Uruguay's recommendations for patients with autoimmune diseases indicated that if the patient had received a primary regimen with the Sinovac vaccine, they should receive two additional doses of Pfizer-BioNTech vaccine, 28 days apart. If the primary regimen was with the Pfizer-BioNTech or Oxford-AstraZeneca vaccine, a single dose of Pfizer-BioNTech was recommended at least 1 month after the last dose of the primary regimen[8].

In this study, we analyzed the capacity to generate a humoral immune response to SARS-CoV-2 vaccination in patients with lupus nephritis (LN) being monitored in our outpatient clinic.

Population and methods

We conducted a prospective study with patients with LN followed at the Nephrology Outpatient Clinic of Hospital de Clínicas, Montevideo, Uruguay, between May and November 2021. The research protocol was approved by the Institutional Ethics Committee and registered as a human research project with the Ministry of Public Health (MSP).

Patients

The study was approved by the Ethics Committee of Hospital de Clínicas Dr. Manuel Quintela and registered with the MSP. Participant confidentiality was maintained.

Included were patients with LN who had received or were receiving immunosuppressive treatment, were under follow-up at the Nephrology Outpatient Clinic of Hospital de Clínicas, and had received the second dose of the SARS-CoV-2 vaccine at least 30 days prior. Excluded patients were as follows: patients with a history of respiratory infection due to SARS-CoV-2; patients under 18 years of age; patients with HIV; and pregnant individuals. No serology testing was conducted before vaccination. Health directives prioritized vaccination for immunosuppressed patients, so study participants were vaccinated early and had completed the proposed vaccination schedule. SARS-CoV-2 detection was only performed in symptomatic patients, per health directives.

Variables studied included age, sex, occupation, and origin, date of SLE diagnosis, clinical form of LN at diagnosis, current immunosuppressive treatment, disease status using the SLEDAI score (https://qxmd.com/

calculate/calculator_335/sledai-2k), presence of comorbidities, history of SARS-CoV-2 infection, vaccine administered, vaccination dates, adverse effects, vaccine impact on the underlying disease (through SLEDAI score), and presence of antibodies (Abs) 30 days after the second vaccine dose.

Detection of the immune response: serological tests

At the time of this study, various antigenic substrates were used, which were developed in each laboratory. These included nucleocapsid protein (N), a combination of N protein plus spike protein (S), and others that used only S protein. Protein quantification methods included enzyme-linked immunosorbent assays (ELISA), immunochromatography, and automated chemiluminescence assays[9].

For our study, we used an ELISA test developed by the University of the Republic and the Institut Pasteur in Montevideo.

Sample extraction protocol

One month after the second dose of the SARS-CoV-2 vaccine, patients were scheduled for blood sample collection. Eight milliliters of peripheral venous blood were extracted to obtain serum for subsequent analysis of anti-SARS-CoV-2 Abs using the ELISA test developed by the University of the Republic and the Institut Pasteur in Montevideo. The plates in these kits are sensitized with the Receptor Binding Domain (RBD) fragment of the SARS-CoV-2 spike protein, allowing for the detection of RBD-specific immunoglobulin (Ig) G Abs in serum samples. Using the technique controls included in the kit, a threshold value of 10 BAU/mL was established for interpreting results. Results were classified as positive (≥ 10 BAU/mL), negative (< 10 BAU/mL), or indeterminate, in which case the procedure was repeated.

Statistical analysis

The analyses were performed using SPSS (IBM SPSS, Version 19, Chicago). Continuous variables were expressed as mean or median and interquartile ranges (IQR), depending on whether they followed a normal distribution. Patient characteristics were expressed as proportions. The variables of interest were compared using the t-test or proportion contrasts, with a 95% confidence interval (CI 95%). Chi-squared tests were used to evaluate variable associations $p < 0.05$ was considered statistically significant.

Results

Demographic characteristics

A total of 21 patients were recruited, of whom two were excluded due to a recent history of COVID-19. The analysis included 19 patients with LN who met the inclusion criteria and had available antibody measurements. The median age was 35.5 (34-36) years, and 89% were women. Regarding residence, 63% lived in Montevideo, and 42% were employed. Among the enrolled patients, 8 (42%) had hypertension, one had diabetes mellitus, and two were obese (Table 1).

Baseline disease characteristics

The overall seroconversion rate was 63% ($p = 0.11$). The median (IQR) age at the time of SLE diagnosis was 25 (20.0-31.0) years. The median (IQR) duration since LN diagnosis was 7 (4.5-14.5) years. Patients with different types of LN were included, categorized as proliferative and non-proliferative. Notably, 79% of the patients had proliferative LN, and among them, only 60% ($p = 0.28$) developed anti-SARS-CoV-2 Abs. Among patients with non-proliferative LN, 75% ($p = 0.18$) developed Abs, showing a higher seroconversion rate but without statistical significance.

When analyzing SLE and LN activity, patients with complete remission had a significantly higher ($p = 0.01$) seroconversion rate for anti-SARS-CoV-2 Abs (Table 1 and Fig. 1A).

Immunosuppressive drugs

Regarding initial treatment, 11% of patients received methylprednisolone, 37% cyclophosphamide (CF), 74% prednisone (PDN), 37% hydroxychloroquine (HCQ), 37% MF, and 19% azathioprine. For current immunosuppressive treatment, 84% of patients were treated with MF mofetil (MMF), 58% with PDN, and 95% with HCQ. Among patients currently receiving MMF, 63% had positive antibody (Ab) levels ($p = 0.11$), while 55% of those treated with PDN ($p = 0.65$) and 61% of those treated with HCQ ($p = 0.19$) showed positive antibody results.

When comparing antibody levels by type of drug received, it was found that patients initially treated with

Table 1. General characteristics of patients with LN included in the study, discriminated by immune response (antibody titers)

Characteristic	All (n = 19)	Antibody titles < 10 (n = 7)	Antibody titles ≥ 10 (n = 12)	p
Age at T0, median (IQR)	25.0 (20.0-31.0)	30.0 (24.0-31.0)	23.5 (16.8-30.0)	0.13
Age at T1, median (IQR)	35.5 (31.0-52.5)	34.0 (31.0-59.0)	36 (29.5-45.3)	0.67
Women, n (%)	17 (89.5)	7 (0.41)	10 (0.59)	0.3
Montevideo residents, n (%)	12 (63.2)	3 (0.25)	9 (0.75)	0.01
Working, n (%)	8 (42.1)	1 (0.13)	7 (0.87)	0.004
Hypertension, n (%)	8 (42.1)	3 (0.38)	5 (0.62)	0.35
Diabetes, n (%)	1 (5.3)	0	1 (1.00)	0.32
Obesity, n (%)	2 (10.5)	0	2 (1.00)	0.08
Proliferative LN, n (%)	15 (78.9)	6 (0.40)	9 (0.60)	0.28
Non-proliferative LN, n (%)	4 (21.1)	1 (0.25	3 (0.75)	0.18
Complete remission, n (%)	15 (78.9)	4 (0.27)	11 (0.73)	0.01
Partial remission/activity, n (%)	4 (21.1)	3 (0.75)	1 (0.25)	0.18
Years since LN diagnosis, median (IQR)	7 (4.5-14.5)	6 (4.0-15.0)	8.5 (4.8-13.8)	0.76

LN: lupus nephritis; IQR: interquartile range.

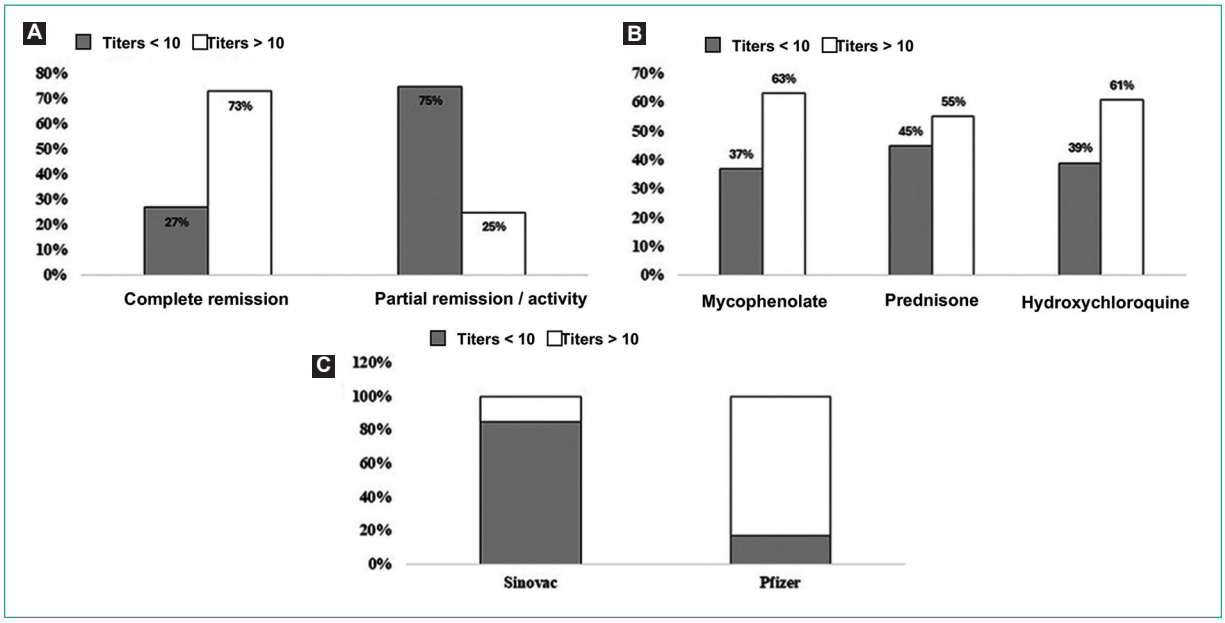

Figure 1. Immune response to anti-SARS-CoV-2 vaccination in 19 LN patients, categorized by disease activity **(A)**, treatment types **(B)**, and vaccine received **(C)**.
LN: lupus nephritis; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

CF had a significant difference (p = 0.009), with higher seroconversion rates. These findings are summarized in table 2 and figure. 1B. No significant relationship was found between having received CF as initial therapy and the current status of SLE and LN activity in terms of complete remission.

Table 2. Pharmacological treatment of LN received at the start and at the time of anti-Sars-CoV-2 antibody determination, discriminated by immune response (antibody titers)

Characteristic	All (n = 19)	Antibody titles < 10 (n = 7)	Antibody titles ≥ 10 (n = 12)	p
Treatment for LN at onset				
Methylprednisolone, n (%)	2 (10.5)	0	2 (1.00)	0.08
Cyclophosphamide, n (%)	7 (36.8)	1 (0.14)	6 (0.86)	0.009
Prednisone, n (%)	14 (73.7)	5 (0.36)	9 (0.64)	0.14
Hydroxychloroquine, n (%)	7 (36.8)	3 (0.42)	4 (0.58)	0.56
Mycophenolate, n (%)	11 (57.9)	4 (0.36)	7 (0.64)	0.20
Azathioprine, n (%)	4 (21.1)	1 (0.25)	3 (0.75)	0.19
Treatment for LN at the time of anti-SARS-CoV-2 antibody determination				
Mycophenolate, n (%)	19 (1.00)	7 (0.37)	12 (0.63)	0.11
Prednisone, n (%)	11 (57.9)	5 (0.45)	6 (0.55)	0.65
Hydroxychloroquine, n (%)	18 (94.7)	7 (0.39)	11 (0.61)	0.19

LN: lupus nephritis; SARS-CoV-2: coronavirus 2 of severe acute respiratory syndrome.

Abs developed by vaccine type and comparison by seroconversion

Of all the study participants, 68% were vaccinated with Sinovac, while 32% received Pfizer-BioNTech. Among patients vaccinated with Sinovac, 54% (p = 0.69) developed Abs against the vaccine. On the other hand, among patients vaccinated with Pfizer-BioNTech, 83% showed positive serology, with a significant difference (p = 0.03) compared to those who did not develop Abs after vaccination (Table 3 and Fig. 1C).

In addition, when considering only the group that failed to generate Abs, 85% (p = 0.011) belonged to those vaccinated with Sinovac (Table 3).

Adverse effects of the vaccine and changes in disease activity

Twelve patients reported adverse effects following vaccination, including pain, erythema, edema, fever, fatigue, headache, diarrhea, pruritus, and myalgias. Pain was the most prevalent, reported by 10 patients – six vaccinated with Sinovac and four with Pfizer-BioNTech. Erythema, edema, pruritus, and myalgias were observed only in those vaccinated with Pfizer-BioNTech, with pruritus being statistically significant (p = 0.02). Conversely, fever (p = 0.31) and diarrhea (p = 0.08) were observed exclusively in patients vaccinated with Sinovac (Table 3). No patient reported rash. When comparing disease activity before and after vaccination, no changes in SLE activity were observed, as evaluated using the SLEDAI score.

Table 4 shows each patient's year of SLE and LN diagnosis and the respective antibody levels following the two vaccine doses.

Discussion

The main result of our work is that greater anti-SARS-CoV-2 seroconversion is achieved in patients vaccinated with Pfizer-BioNTech or in complete remission.

Patients with autoimmune diseases were excluded from phase III clinical trials due to the potential risk of adverse effects and disruption of the underlying disease. In this sense, our study is innovative in evaluating the quality of the vaccination response in patients with LN.

In our study, the overall rate of seroconversion after the administration of two doses of the anti-SARS-CoV-2 vaccine was 63% in patients with LN. A systematic review[10] included patients with different autoimmune diseases vaccinated with mRNA vaccines. In studies that assessed the seroconversion rate after two doses, rates reached 83.1% (p = 0.01), increasing to 90.7% (p = 0.01) when only the SLE population was considered[10]. These results show a higher seroconversion rate than in our study. This difference could be explained by two factors. First, the review does not account for

Table 3. Immune response (seroconversion, antibody titers) and adverse effects for each type of vaccine. Sinovac vaccine CoronaVac® and Pfizer vaccine Pfizer-BioNTech

Characteristic	All (n = 19)	Sinovac (n = 13)	Pfizer-BioNTech (n = 6)	p
Anti-SARS-CoV-2 antibody titles				
Titles < 10, n (%)	7 (36.8)	6 (0.85)	1 (0.14)	0.011
Titles ≥ 10, n (%)	12 (63.2)	7 (0.58)	5 (0.42)	0.44
Adverse effects				
Pain, n (%)	10 (52.6)	6 (0.60)	4 (0.40)	0.38
Erythema, n (%)	1 (5.3)	-	1 (1.00)	0.31
Edema, n (%)	2 (10.5)	-	2 (1.00)	0.08
Fever, n (%)	1 (5.3)	1 (1.0)	-	0.31
Fatigue, n (%)	4 (21.1	2 (0.5)	2 (0.50)	1.00
Headache, n (%)	4 (21.1)	3 (0.75)	1 (0.25)	0.19
Diarrhea, n (%)	2 (10.5	2 (1.00)	-	0.08
Itching, n (%)	3 (15.8)	-	3 (1.00)	0.02
Myalgia, n (%)	2 (10.5)	-	2 (1.00)	0.08

SARS-CoV-2: coronavirus 2 of severe acute respiratory syndrome.

the severity of SLE, and thus, the magnitude of immunosuppressive treatment required. Second, among the vaccines received by our patients, 68% were Sinovac, which has a lower global seroconversion rate compared to mRNA vaccines.

Izmirly et al.[11] evaluated the immune response and SLEDAI status changes in 90 SLE patients after immunization with mRNA anti-SARS-CoV-2 vaccines. Compared to a control group of 20 healthy patients, the seroconversion rate after one or two doses was lower in lupus patients. Specifically, 28.8% of lupus patients had IgG immune responses below the lowest response in controls (p = 0.01). The seroconversion rate in our LN sample was lower than in the general population.

In a study by Ammitzbøll et al.[12] conducted in Denmark, they investigated a sample of SLE and rheumatoid arthritis patients treated with immunosuppressive agents similar to those used by our patients. Among 134 patients, 103 (77%) showed seroconversion 8 days after the second Pfizer-BioNTech vaccine dose. In SLE patients alone, the seroconversion rate rose to 89%. This trend aligns with our findings, where the seroconversion rate for patients vaccinated with Pfizer-BioNTech was 83% (p = 0.03).

International guidelines recommend anti-SARS-CoV-2 vaccination for patients with chronic inflammatory diseases regardless of disease activity or immunosuppressive treatment[13]. A 1998 study related to influenza immunization showed that SLE patients with active disease had a lower immunogenic response compared to inactive patients and healthy controls[14]. Our definitions of complete or partial remission were based exclusively on nephrological parameters specific to LN remission. Nonetheless, the SLEDAI score also takes some of these into account, which is why we consider it representative.

Anuraag et al.[10] also evaluated the seroconversion rate based on treatment plans. Among pharmacological therapies, seroconversion rates were as follows: 78.2% for corticosteroids, 70.4% for MF, 80.3% for methotrexate, and 89.5% for hydroxychloroquine (HCQ). In our study, the seroconversion rate was 63% for MF and 61% for HCQ. However, we analyzed each drug individually without considering polytherapy.

In Izmirly et al.[11], patients treated with MF, prednisone (PDN), or polytherapy had lower seroconversion rates than controls and lupus patients treated with HCQ alone. Among lupus patients, 46% of those on PDN had low seroconversion rates, similar to our findings of 45%.

A positive association was observed between initial CF administration and antibody development (p = 0.009). Although statistically significant, this result cannot be compared with previous studies since they consider

Table 4. Year of diagnosis of SLE/NL, start of treatment, and antibody titer

Patient	Year of SLE diagnosis	Year of LN diagnosis	Induction treatment start (LN)	Titles Ab
1	2000	2000	2000	70
2	1987	1995	1995	38
3	2015	2016	2016	349
4	2018	2018	2018	48
5	2016	2016	2016	12
6	2005	2007	2007	17
7	2008	2008	2008	380
8	2007	2011	2011	39
9	2014	2014	2014	85
10	2008	2008	2008	89
11	2017	2017	2017	3,452
12	2017	2017	2017	569
13	1993	1993	1993	4
14	2015	2015	2015	0
15	2016	2016	2016	1
16	2018	2018	2018	4
17	2011	2011	2011	2
18	1992	2001	2001	1
19	2007	2020	2020	1

Ab: antibodies; SLE: systemic lupus erythematosus; LN: lupus nephritis.

current CF treatment rather than initial administration. We found no significant association between the current disease activity (complete remission, CR) and having received CF.

In Geisen et al.[15], mRNA vaccines were given to 26 patients with chronic inflammatory diseases. Only mild side effects were reported, with no fever, severe adverse effects, or disease reactivation. However, Muñoz et al. reported LN relapses after SARS-CoV-2 vaccination with Sputnik V and Sinopharm[16]. Our sample included only LN patients, with six receiving an mRNA vaccine. The results showed similar trends. In our study, the most common symptoms were as follows: local pain (67%), edema (33%), fatigue (33%), myalgias (33%), and headache (17%). No severe renal or extra-renal manifestations or changes in SLEDAI were observed after the second vaccine dose[15].

These data are consistent with the accumulated evidence up to this point that patients with autoimmune diseases under immunosuppressive therapy are capable of developing a satisfactory immune response after receiving the anti-SARS-CoV-2 vaccination, without significant side effects or flare-ups of their underlying disease[7,11]. While this result was expected, it supports the recommendations established by health authorities when vaccinating patients with NL[17].

The results of our research should be interpreted in the context of certain limitations. First, the results are based on a small sample size, and some results may not reach statistical significance for this reason. It should be noted that NL is a low-prevalence disease. Second, although the immunosuppressive drugs the patients were receiving at the time of the anti-SARS-CoV-2 antibody serological evaluation were recorded, the doses of these drugs were not considered. Third, the measurement of the vaccine response was solely humoral, without considering the cellular component of the immune response, which is more difficult to assess. Fourth, the study design only considers the temporal dimension from vaccination to a single antibody determination, making it

impossible to assess the duration of this humoral response. Finally, contrasting with a healthy population where the seroconversion rate is not influenced by immunosuppressive treatment would have allowed for a control group to compare the seroconversion rate and post-vaccination adverse effects.

Conclusions

After anti-SARS-CoV-2 vaccination of patients with NL, a global seroconversion rate of 63% is achieved. The anti-SARS-CoV-2 seroconversion rate is significantly higher when patients are vaccinated with Pfizer-BioNTech and/or are in complete remission of their disease. After vaccination, with either vaccine, there were no severe adverse effects or variations in the disease activity score (SLEDAI). Achieving complete remission of NL has another prognostic advantage in the context of the COVID-19 pandemic. It appears to be advisable to administer the Pfizer-BioNTech vaccine over Sinovac.

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The authors declare that this work was carried out using their own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the Institutional Ethics Committee.

Confidentiality of data. The authors declare that no patient data are included in this article. In addition, the authors have acknowledged and followed the recommendations according to the SAGER guidelines, depending on the type and nature of the study.

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

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REVIEW ARTICLE

Situation of chronic kidney disease in Latin America, with emphasis on diabetic kidney disease: difficulties and challenges

Situación de la enfermedad renal crónica en América Latina, con énfasis en la enfermedad renal diabética: dificultades y desafíos

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Abstract

Chronic kidney disease (CKD) is a serious public health problem worldwide, with a high prevalence in the adult population and often lately diagnosed. A meeting of experts in nephrology, with participants from Argentina, Brazil, Chile, Colombia, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, and the Dominican Republic, was held with the aim of generating proposals and a call to action on how to deal with CKD and cardio-renal-metabolic syndrome. Based on a review of the best available evidence and from the perspective of experience in daily practice about the difficulties and opportunities for optimizing early diagnosis and treatment of CKD, with emphasis on diabetic kidney disease, a description of the current scenario, the challenges and proposals for improving this situation in the region are presented.

Keywords: *Chronic kidney disease. Diabetes. Diabetic kidney disease. Obesity. Epidemiology. Implementation. Kidney health policy.*

Resumen

La enfermedad renal crónica (ERC) es un grave problema de salud pública en todo el mundo, con elevada prevalencia en la población adulta y cuyo diagnóstico con frecuencia ocurre tardíamente. Con el objetivo de un cambio de visión para generar propuestas y un llamado a la acción acerca de la forma de afrontar a la ERC y el síndrome cardio-reno-metabólico, se llevó a cabo un encuentro de expertos en nefrología, con participantes de Argentina, Brasil, Chile, Colombia, Ecuador, El Salvador, Guatemala, México, Nicaragua y República Dominicana. A partir de la revisión de la mejor evidencia disponible y

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bajo la óptica de la experiencia en la práctica diaria acerca de las dificultades y las oportunidades para optimizar el diagnóstico precoz y el tratamiento de la ERC, con énfasis en la enfermedad renal diabética, se presenta una descripción del escenario actual, los retos y las propuestas para mejorar esta situación en la región.

Palabras clave: *Enfermedad renal crónica. Diabetes. Enfermedad renal diabética. Obesidad. Epidemiología. Implementación. Políticas de salud renal.*

Introduction

Chronic kidney disease (CKD) is a serious public health problem worldwide, with a high prevalence in the adult population. Its diagnosis often occurs late, typically in stage ≥ 3 of the kidney disease improving global outcomes (KDIGO) classification. CKD is projected to become the fifth leading cause of death globally by 2040, with an increasing impact on morbidity and mortality[1]. Similarly, CKD presents a challenge in Latin America, with an average prevalence of 9.9% in the adult population across all stages (Table 1)[2,3].

In this context, aiming to shift perspectives and generate proposals, as well as to call for action in addressing CKD and the cardio-renal-metabolic syndrome, a meeting of nephrology experts was held. The participants were from Argentina, Brazil, Chile, Colombia, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, and the Dominican Republic. We conducted a review of the best available evidence, combined with daily practice experiences. This focused on the challenges and opportunities for optimizing early diagnosis and treatment of CKD, with an emphasis on diabetic kidney disease (DKD) in Latin America.

Burden of disease in the region

CKD imposes a significant burden on patients, their families, and health-care systems, especially in low- and middle-income countries. This is due to the high costs of treating the disease itself and its complications, including both advanced renal and cardiovascular issues, which manifest from intermediate stages of CKD[4,5]. Consequently, mirroring global findings, regional experts highlight the importance of appropriate screening for at-risk populations to enable early diagnosis and slow progression from the initial stages of CKD. Equally, there is a recognized need to involve health-care teams at the primary care level.

The working group identified shared barriers across the region and outlined potential solutions summarized in table 2. It is crucial to note that diabetes mellitus (DM), a major global public health issue, is one of the primary risk factors for CKD. The age-standardized prevalence of type 2 DM (T2DM) is projected to average 11.3% in Latin America and the Caribbean by 2050, underscoring its significant regional impact[6].

The importance of early CKD diagnosis becomes evident when considering the high incidence and prevalence rates of renal replacement therapy in Latin America (Table 3)[7].

CKD associated with DM: Renal function assessment

The lack of resources and low awareness of CKD associated with T2DM in Latin America, both in the general population and among health-care teams, hinders early diagnosis and timely treatment. Renal health programs aimed at improving the health of individuals at risk or with CKD associated with T2DM have proven useful[8]. To this end, in alignment with global recommendations, the Latin American working group advocates the use of an estimated glomerular filtration rate (eGFR), primarily based on serum creatinine. In specific cases, and under nephrology guidance, cystatin C determination may be added.

Ideally, each country should adopt a standardized and widely recognized methodology (mass spectrometry with isotope dilution) for serum creatinine determination to improve eGFR calculation accuracy. It is proposed to determine eGFR from the first consultation in individuals with T2DM and repeat it according to current guideline recommendations[9] and individual patient needs. A similar approach was previously applied to 24-h albuminuria measurement. However, due to logistical difficulties and the potential for false positives or negatives, the current recommendation is to calculate the albumin/creatinine ratio (ACR) in a single urine sample.

Although current guidelines[9] recommend referring patients to a specialist when eGFR is ≤ 30 mL/min/1.73 m², the working group suggests, wherever possible, referral of T2DM patients with values ≤ 45 mL/min/1.73 m² in the region to ensure timely specialist care. In addition, referral to a nephrologist is recommended for patients with an ACR > 300 mg/g, as per current guidelines[9]. An alternative for defining nephrology referrals that have already been evaluated in some countries in the region

Table 1. The burden of chronic kidney disease and its risk factors in Latin America (excluding diabetes *mellitus*)

Country	CKD prevalence % (95%CI)	CKD attributable mortality % (95%CI)	DALYs lost to CKD (n) (95%CI)	Obesity % (95%CI)	Elevated blood pressure % (95%CI)	Smoking % (95%CI)
Argentina	8.64 (8.09-9.23)	4.49 (4.09-4.88)	2.55 (2.29-2.83)	28.5 (23.7-33.7)	22.6 (17.0-28.9)	17.7 (15.5-19.9)
Bolivia	6.16 (5.75-6.56)	5.83 (4.91-6.82)	3.08 (2.54-3.67)	18.7 (14.2-23.7)	17.9 (12.5-24.1)	19.6 (16.5-23.1)
Brazil	8.35 (7.81-8.85)	3 (2.77-3.15)	1.81 (1.65-1.97)	22.3 (18.9-25.9)	23.3 (18.1-28.8)	10.6 (9.8-11.5)
Chile	10.15 (9.48-10.83)	4.45 (4-4.83)	2.26 (1.99-2.53)	28.8 (24.2-33.7)	20.9 (15.8-26.8)	25.6 (22.7-28.4)
Colombia	11.47 (10.67-12.29)	3.85 (3.35-4.22)	2.26 (1.96-2.53)	22.1 (18.3-26.2)	19.2 (14.2-24.7)	10.4 (8.1-13.0)
Costa Rica	14.75 (14.07-15.52)	5.62 (5.03-6.1)	3.62 (3.12-4.08)	25.7 (21.2-30.6)	18.7 (14.0-24.3)	7.8 (6.0-9.9)
Cuba	12.31 (11.48-13.16)	2.57 (2.35-2.79)	2.28 (2.02-2.54)	26.7 (21.9-31.7)	19.0 (13.8-25.3)	16.2 (13.1-19.6)
Ecuador	8.27 (7.73-8.82)	7.47 (6.84-7.95)	3.88 (3.34-4.42)	19.3 (14.9-24.3)	17.9 (12.6-23.7)	5.0 (4.2-6.0)
El Salvador	11.87 (11.08-12.63)	10.15 (9.2-10.89)	6.47 (5.58-7.32)	22.7 (18.0-27.7)	18.7 (13.3-24.7)	6.1 (4.6-8.0)
Guatemala	8.90 (8.29-9.50)	6.35 (5.91-6.74)	3.7 (3.34-4.04)	18.8 (14.9-23.2)	21.2 (15.3-27.7)	7.2 (5.5-9.2)
Haiti	5.80 (5.34-6.22)	2.37 (1.87-3.39)	1.57 (1.29-2.05)	20.5 (16.0-25.6)	24.5 (17.8-31.9)	5.2 (4.1-6.7)
Honduras	8.03 (7.45-8.61)	6.02 (5.09-7.49)	3.62 (3.11-4.31)	19.4 (15.1-24.1)	21.4 (15.6-27.9)	9.0 (7.3-10.9)
Mexico	13.81 (12.95-14.65)	9.82 (9.29-10.22)	6.32 (5.64-6.98)	28.4 (24.7-32.3)	19.7 (14.8-25.1)	9.5 (9.1-10.1)
Nicaragua	10.79 (10.10-11.50)	11.89 (11.08-12.64)	7.07 (6.13-7.98)	21.8 (17.3-26.7)	20.8 (15.1-27.3)	8.8 (6.6-11.4)
Panama	11.72 (10.96-12.51)	5.82 (5.19-6.29)	3.41 (2.97-3.84)	22.5 (18.0-27.4)	19.9 (14.8-25.8)	3.5 (2.8-4.3)
Paraguay	7.55 (7.04-8.03)	5.51 (4.95-5.96)	3.07 (2.64-3.51)	19.0 (13.9-24.6)	24.6 (17.9-31.8)	9.9 (7.6-12.7)
Peru	10.00 (8.27-12.26)	5.28 (4.59-5.8)	2.63 (2.24-3.01)	19.1 (16.0-22.4)	13.7 (10.5-17.4)	8.1 (6.5-10.0)
Puerto Rico	16.82 (15.64-18.08)	6.25 (5.47-6.87)	4.33 (3.76-4.92)	-	-	8.8 (7.2-10.8)
Dominican Republic	7.60 (7.07-8.12)	3.23 (2.65-3.97)	2.28 (1.9-2.76)	26.9 (22.0-32.2)	21.5 (15.4-28.4)	6.7 (5.2-8.5)
Uruguay	9.76 (9.12-10.36)	2.92 (2.59-3.22)	1.7 (1.51-1.87)	28.9 (23.7-34.4)	20.7 (15.3-26.6)	18.6 (16.4-20.9)
Venezuela	12.28 (11.44-13.04)	5.56 (5.03-6.05)	3.62 (3.17-4.02)	25.2 (20.9-29.8)	18.6 (13.7-24.1)	13.3 (10.6-16.5)

CKD: chronic kidney disease; DALYs: disability-adjusted life years; 95% CI: 95% confidence interval.
Adapted and modified from the data of the Global Burden of Disease and the World Health Organization – Global Health Observatory[2,3].

is telemedicine (tele-nephrology), either synchronously or asynchronously. This approach optimizes the limited number of specialists available in the region and meets interconsultation demands with adequate quality[10]. Tele-nephrology aims to improve communication between specialists and primary care physicians, providing support, case discussion, and collaborative decision-making.

Other supplementary studies recommended for all patients from the first contact include general urine examination and, in some cases, renal ultrasound. The frequency of these tests will depend on the initial diagnosis. The working group proposes conducting them at least annually.

Cardiovascular risk and T2DM

Hypertension and T2DM are the primary risk factors for CKD in Latin America[1]. Most individuals with T2DM are considered to be at high or very high cardiovascular risk[11], regardless of their renal function. The risk factors associated with CKD are summarized in table 4. The working group emphasizes that both eGFR and ACR are essential for the diagnosis and monitoring of these patients and are also adequate for estimating cardiovascular risk[12].

Regarding treatment, and in alignment with recently updated international clinical practice guidelines (KDIGO, American Diabetes Association, European Society of

Table 2. Barriers and proposed facilitators to halt the progression of chronic kidney disease in Latin America

Barriers
– Lack of diagnosis or late diagnosis of CKD
– Insufficient public awareness of CKD, particularly among individuals with DM
– Absence or inefficiency of specific health policies for CKD (programs are either unimplemented or inadequate)
– Limited number or poor distribution of nephrologists and other specialists needed for optimal management of patients with DM and CKD
– Therapeutic inertia among healthcare teams and affected populations
– Insufficient or inappropriate medical education for primary and secondary healthcare professionals
– Delay in the introduction of innovative therapies for managing CKD in individuals with type 2 diabetes into clinical practice guidelines and local/regional regulations
– Lack of access to modern, first-line treatments not included in essential health service packages
– Unhealthy lifestyles, including increasing sedentary behavior and inadequate nutritional education starting from childhood
– Inadequate implementation and reporting of standardized serum creatinine-based glomerular filtration rate estimation and albumin-to-creatinine ratio measurement from isolated urine samples
– Insufficient financial resources in some countries and regions
Proposals
– Educate the general medical community and the public, empowering patients to adhere to their treatments
– Update and train nephrologists and other specialists involved in the care of CKD patients with DM
– Provide training to physicians and the broader renal health and primary care teams
– Develop and update simplified protocols, local or regional clinical practice guidelines, and algorithms to facilitate their use
– Improve access to evidence-based first-line therapies that demonstrate cardiovascular protection or slow the progression of kidney damage
– Holistically treat individuals with type 2 DM and CKD, involving primary care physicians, other healthcare team members, and specialists as needed (e.g., endocrinology, cardiology, nephrology, psychology, social work, and nutrition)
– Collaborate between scientific societies and health ministries in the region, aligning with local regulations where possible
– Establish health programs with monitoring requirements and regulations to evaluate their implementation

CKD: chronic kidney disease; DM: diabetes mellitus.

Hypertension, European Society of Cardiology), it is deemed fundamental to begin with clear lifestyle recommendations. These should include a suitable dietary plan, physical activity, and the cessation or avoidance of smoking[13]. Furthermore, in individuals with T2DM, the early inclusion of renin-angiotensin-aldosterone system (RAAS) blockers, metformin (for those with eGFR > 30/mL/min/1.73 m^2), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and statins are also recommended. The suggested treatment targets for these patients are summarized in table 5.

Kidney, T2DM, and obesity

The prevalence of obesity and metabolic syndrome is rising globally. Excess dysfunctional adipose tissue creates a “cross-talk” between various organs and systems, resulting in cardio-renal-metabolic dysfunction and clinical consequences such as an increased prevalence of DM, CKD, and cardiovascular disease. The main mediators of these alterations are inflammation, oxidative stress, endothelial dysfunction, and insulin resistance[14]. In this model, metabolic syndrome and DM form a continuum that represents the leading cause of CKD. Consequently, metabolic disturbances play a prominent pathophysiological role, with bidirectional interactions between the cardiovascular system and the kidney[15]. Specifically, hyperinsulinemia and insulin resistance contribute early to glomerular hyperfiltration, albuminuria, increased vascular permeability, and podocytopathy – clearly associated with the potential progressive loss of renal function. Simultaneously, endothelial dysfunction, oxidative stress, and increased synthesis of transforming growth factor-β contribute to inflammation and functional decline[16].

Given these factors, a strong interconnection among cardio-renal-metabolic conditions (T2DM, CKD, and cardiovascular disease) becomes evident, explaining the significant increase in their global prevalence. In this context, the rising prevalence of DM and CKD is also observed in Latin America, driven by sociocultural changes influenced by several factors: lack of awareness of risk factors among the population, changes in dietary behavior linked to industrialization and urban living, growing sedentarism, low motivation among health-care professionals to address these diseases, and absence of public policies and insufficient state resources for early diagnosis of at-risk individuals. Implementing appropriate programs could modify behaviors and establish proper treatment. Another contributing factor to the increased prevalence of CKD due to T2DM and other causes is the rise in life expectancy over the

Table 3. Prevalence and incidence rates of renal replacement therapy (dialysis and transplant) in Latin America (2019 data)

Country	Population	Prevalence rate (HD)	Prevalence rate (PD)	Dialysis (total)	Functional renal graft	Total	Dialysis (total)	In PD (%)	Rate of renal transplantation (pmp)
Argentina	44,938,712	674	46	720	243	963	163	6.4	35
Bolivia	11,513,102	452	2†	454†	3†	457†	114	0.0	2
Brazil	211,049,519	618	47	665	299	963	218	7.1	30
Chile	18,952,035	1236	81	1317	233	1550	204	10.0	22
Colombia	50,339,443	516	185	702	157	858	103	40.6	19
Costa Rica	5,047,561	40	209	249	318	567	38	NA	15
Cuba	11,333,484	293	6	299	131	430	108	0.0	15
Ecuador	17,373,657	735	21	756	12	768	6	2.7	13
El Salvador	6,453,550	297†	380†	677†	99†	776†	217†	0.0†	6†
Guatemala	16,604,026	304	221	525	51	575	140	19.9	6
Honduras	9,746,115	370‡	22‡	392‡	13‡	405‡	96‡	0.6‡	0‡
Mexico⁋	8,281,714/1,415,421	611	483	1094	729	1823	530	0.0	62
Nicaragua	6,545,503	35	65	100	11	111	31	73.7	2
Panama	4,246,440	488	113	601	100	701	181	21.5	8
Paraguay	7,044,639	317	16	333	54	387	36	6.0	4
Peru	32,510,462	515	57	572	46	618	62	6.5	3
Puerto Rico	3,193,694	1607†	130†	1737†	392†	2129†	419†	1.1†	18†
Dominican Republic	10,738,957	340	98	438	47	485	221	NA	5
Uruguay	3,461,731	734	62	796	398	1194	185	10.1	42
Venezuela	28,515,829	310	10	320	0	320	96	NA	1
Total	627,183,988	570	80	650	216	866	168	12	22

HD: Hemodialysis; PD: Peritoneal Dialysis; pmp: per million people; NA: not unavailable. Number of renal transplants performed in 2019.
†Data from 2018.
‡Data from 2020.
⁋Data from Jalisco and Aguascalientes due to lack of national data.
Adapted and modified from ref[9].

last five to seven decades. While this effect is positive, it has led to a greater incidence of chronic degenerative diseases such as those discussed in this document.

The working group highlights the importance of early screening for populations at risk. Generalized screening of the entire adult population is not feasible, so efforts should focus on individuals with key conditions associated with CKD development: visceral obesity, hypertension, glucose abnormalities, and a family history of CKD. Once affected individuals are identified, cultural changes related to these risk factors (non-pharmacological options) should be encouraged, alongside offering the best therapeutic options. Drugs targeting the pathophysiological mechanisms underlying renal damage are proposed, focusing on: blocking maladaptive mechanisms (particularly the RAAS and sympathetic system), reducing inflammation, improving hemodynamics, and optimizing metabolic control. To this end, RAAS blockers, SGLT2i, glucagon-like peptide-1 receptor agonists (GLP-1 RA), and non-steroidal mineralocorticoid receptor antagonists (MRAs) are included. To date, these four drug classes have demonstrated slowing of CKD progression and cardio-renal protection.

Table 4. Risk factors to consider for early detection of chronic kidney disease

T2DM
Hypertension or established cardiovascular disease
Age*
Chronic inflammation states
Family history of CKD (first degree)
Obesity

T2DM: type 2 diabetes mellitus; CKD: chronic kidney disease.
*Age of onset of DM2 should be prioritized; younger onset tends to have a worse prognosis. In some countries, such as Mexico, type 2 diabetes and chronic kidney disease are commonly observed at younger ages.

Therapeutic approach

Residual risk in T2DM treatment with CKD

DKD is a serious complication affecting 30-40% of patients with T2DM[17]. However, treatments to prevent the progression of DKD were unavailable until the early 1990s, when the role of the RAAS in the hemodynamic and structural changes of this disease was documented[18].

At least three pathophysiological mechanisms or axes are implicated in the onset and progression of DKD: Hemodynamic, metabolic, and inflammatory[19]. At present, there is no single intervention that completely addresses all three pathophysiological axes, making the idea of combination therapy attractive.

For RAAS blockade, in a meta-analysis, both angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) demonstrated a 13% reduction in the risk of kidney failure and a 29% reduction in the doubling of serum creatinine levels[20]. Nevertheless, as observed in the RENNAL[21] and IDNT[22] studies, patients treated with RAAS blockade still face a high residual risk of disease progression.

In 2015, SGLT2i was added to the therapeutic arsenal, with robust indirect or secondary evidence from cardiovascular safety studies and subsequent trials with primary renal outcomes. These studies demonstrated clear benefits, including a 37% reduction in the risk of renal disease progression[23]. However, in registry studies and renal-focused trials in CKD patients (CREDENCE, DAPA-CKD, and EMPA-KIDNEY)[24-26], the residual risk of disease progression persisted.

In patients on ACEi or ARBs, an "aldosterone escape" phenomenon has been recognized, potentially linked to mineralocorticoid receptor overactivity, proteinuria, and renal disease progression[27]. Finerenone, a non-steroidal MRA, and other drugs such as aldosterone synthase inhibitors[28] emerged to address safety concerns (induction of hyperkalemia) associated with classic steroidal MRAs (spironolactone and eplerenone) in reducing the progression of renal damage. Despite the clear benefit of finerenone in both cardiovascular and renal endpoints, the incidence of the composite renal variable (kidney failure, sustained reduction in eGFR > 40%, or renal-cause mortality) was reduced by 13% in participants in the FIDELIO-DKD study, similar to findings from previous studies, yet the residual risk of DKD progression remains uneliminated[29].

These observations raise questions about new pharmacological alternatives to manage residual risk. ACEi, ARBs, and finerenone do not affect glucose levels, whereas SGLT2i have reduced metabolic control efficacy when eGFR is < 60 mL/min/1.73 m^2. Despite the cardiovascular and renal benefits of these strategies, DKD patients frequently require additional pharmacological interventions.

Table 5. Treatment goals in patients with cardiovascular risk factors

Risk factor	Suggested goals
Hypertension	Normalization (blood pressure < 130/80 mmHg)
Low-density lipoprotein cholesterol	Every patient should be evaluated based on cardiovascular risk to set the therapeutic target: – Very high risk: LDL goal < 55 mg/dL – High risk: LDL goal < 70 mg/dL – Intermediate risk: LDL goal < 100 mg/dL KDIGO 2024 recommendations do not specify goals but apply the "statin intensity" guidelines from KDIGO 2013 for dyslipidemia. 100% of patients should use statins (ezetimibe is added when monotherapy with statins is insufficient). Glycated hemoglobin is around 7% (this goal will be less ambitious in older adults and frail patients). Use of GLP-1 receptor agonists is highlighted, as they are associated with greater effects on metabolic control in patients with chronic kidney disease.
Diabetes mellitus	Metformin is recommended by both KDIGO and the American Diabetes Association guidelines due to its significant benefits in controlling blood sugar. In Latin America, given resource constraints, its combined use can be an effective strategy to improve health outcomes and optimize costs associated with treating Type 2 diabetes, as long as the patient has an estimated glomerular filtration rate ≥ 30 mL/min 1.73/m^2.

The role of GLP-1 receptor agonists (GLP-1 RAs)

GLP-1-RAs are incretin-based drugs with potent effects on glycemia and weight, demonstrated cardiovascular benefits, and a 21% reduction in renal outcomes[30]. The underlying mechanisms associated with these benefits are not fully understood but appear to include both indirect actions (weight reduction, improved blood pressure, and, of course, metabolic control) and direct intrarenal mechanisms (anti-inflammatory effects, natriuresis, hemodynamic modulation, and among others)[9]. Initial evidence of nephroprotection originated from secondary endpoints in cardiovascular safety studies, primarily softer outcomes such as proteinuria, without initial evidence of benefits in hard clinical outcomes[30]. This scenario changed with the results of the randomized controlled FLOW trial, which had a composite renal and cardiovascular mortality outcome as its primary endpoint. The trial included adults with CKD and T2DM, with an eGFR of 50-75 mL/min/1.73 m^2 and an ACR of 300-5000 mg/g, or an eGFR of 25-50 mL/min/1.73 m^2 and an ACR of 100-5000 mg/g. Patients were randomized to receive 1 mg of subcutaneous semaglutide weekly or placebo in addition to standard therapy. This intervention reduced the primary composite endpoint (including major renal events such as dialysis, transplantation, or eGFR < 15 mL/min/1.73 m^2, renal-cause mortality, and cardiovascular-cause mortality) by 24%, in addition to showing other cardiovascular benefits[31].

GLP-1-RAs are considered first-line therapy for patients with diabetes and cardiovascular risk factors or established cardiovascular disease, regardless of glycated hemoglobin (HbA1c) levels[32]. In CKD guidelines, they are reserved as second-line therapy for patients not meeting individual targets for weight, HbA1c, and albuminuria, or those requiring better control of cardiovascular risk factors[9] (Table 6). However, the results of the FLOW trial could once again revolutionize treatment recommendations for CKD in the context of diabetes. The chronology of therapeutic advances is summarized in figure 1.

Actions to facilitate clinical application

Notable among the actions aimed at promoting the adoption of guideline recommendations in clinical practice is the proposal to conduct continuing medical education sessions to provide clear knowledge and messages to physicians at all levels of care. This strategy includes a national intervention through in-person events such as congresses, update seminars, or workshops to present the available scientific evidence on disease-modifying therapies with appropriate guidance for prescription. In addition, regional or local interventions, conducted either in person or virtually, are suggested to present clinical cases of interest and validate the benefits of these medications in daily practice.

A second suggested action involves collaboration with the pharmaceutical industry, which plays a significant role by supporting various academic activities that facilitate knowledge dissemination across all levels of health care.

A third strategy proposed for guideline adoption involves the engagement of medical societies at the national level to enhance the collection, evaluation, editing, and distribution of information through authorized channels (e.g., digital media and scientific journals). Similarly, presenting cost-effectiveness analyses to insurers and governments, emphasizing the utility of disease-modifying therapies as powerful tools to reduce health complications and lower health-care system costs, is essential.

Fourth, the development of national CKD registries and the application of tools to predict CKD and DKD progression can enable the screening of at-risk patient groups for targeted interventions.

A variety of factors must be addressed to ensure the appropriate implementation of new treatment modalities. These include: overcoming therapeutic inertia (from both physicians and patients), addressing the availability and cost of therapies, ensuring consistent and adequate screening for at-risk populations, increasing the involvement of primary care providers, and establishing health policies and allocating sufficient human and financial resources by ministries and governments in all countries.

Conclusion

CKD remains a major public health issue in our region, with diabetes being the most prevalent cause. A key challenge is the delayed diagnosis of CKD, both diabetic and non-diabetic, especially in the early stages, as it is often a painless and asymptomatic condition initially. Limited CKD screening, relying solely on albuminuria measurement, may miss a significant proportion of patients with eGFR > 60 mL/min who meet diagnostic criteria –particularly relevant in patients with diabetes-associated CKD–. Similarly, screening based only on serum creatinine could overlook many CKD cases. Therefore, a program measuring both indicators

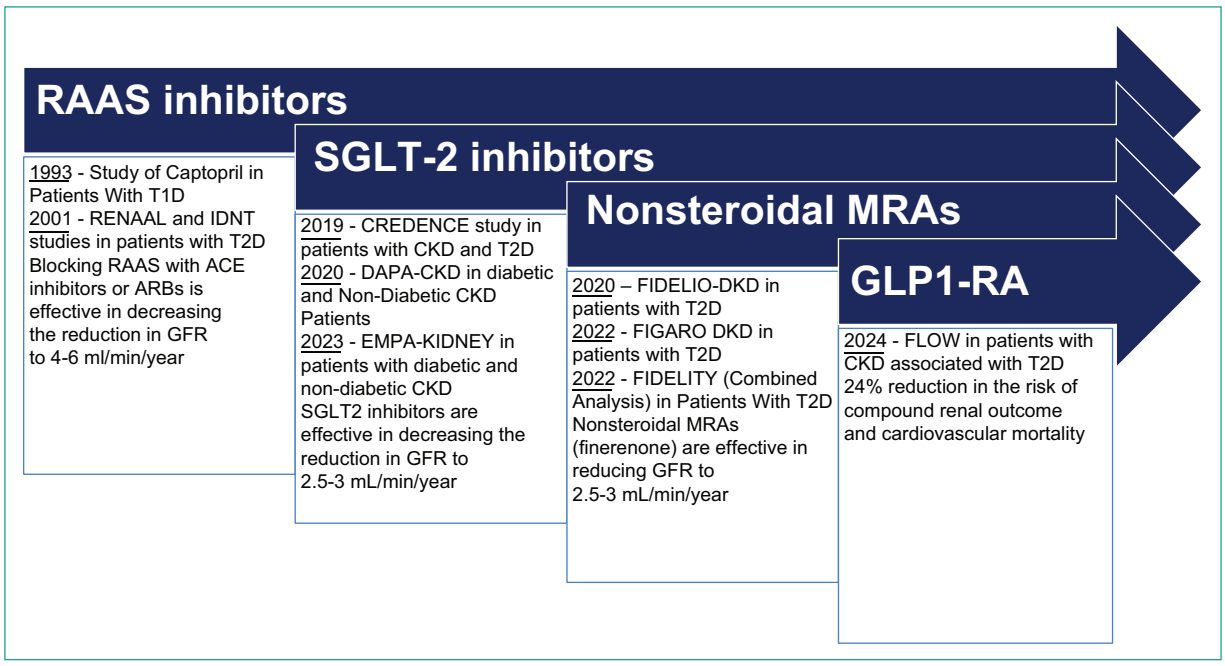

Figure 1. Timeline of the development of nephroprotection strategies. ARA: angiotensin receptor antagonists; GLP1-RA: glucagon-like peptide-1 receptor agonists; MRA: mineralocorticoid receptor antagonists; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; CKD: chronic kidney disease; ACEI: angiotensin-converting enzyme inhibitors; SGLT2: sodium-glucose cotransporter-2; RAAS: renin-angiotensin-aldosterone system; GFR: glomerular filtration rate *(adapted from Obrador et al.[7]).*

is necessary to strengthen early diagnosis in high-risk populations. To address this, efforts should focus on developing and enhancing: (1) structured, multidisciplinary nephroprotection programs, (2) health system registries in each country that include patients in renal replacement therapy as well as those with CKD at earlier stages, (3) collaborative teams representing patients, health-care professionals, and government agencies to integrate CKD into public health policies, and (4) programs with increased financial allocation from governments to achieve equitable distribution and reduce disparities in gender, race, social status, or geographic location. Negotiations with insurers, governments, and the pharmaceutical industry to regulate prices and include innovative therapies in coverage policies are also proposed.

Regarding the treatment of patients with CKD, whether associated with DM or other causes, significant progress has been made in recent years, particularly in pharmacological interventions for DKD. For all patients with DM and CKD, it is essential to focus on three primary treatment objectives: (1) optimize metabolic control, (2) slow the progression of kidney disease, and (3) reduce cardiovascular risk.

Table 6. Therapies for diabetic kidney disease according to phenotype

RAAS blockade	1. T2DM and hypertension 2. T2DM and moderate to severe albuminuria (ACR > 30 mg/g), with or without hypertension
SGLT2i	T2DM and DKD with eGFR > 20 mL/min/1.73 m², regardless of ACR value
Finerenone	T2DM, DKD with eGFR > 25 mL/min/1.73 m², ACR > 30 mg/g, and potassium < 5 mEq/L, in patients on the maximum tolerated dose of SRAA blockers
GLP-1 Receptor Agonists (GLP1-RA)	1. T2DM and DKD with overweight or obesity 2. T2DM and DKD with HbA1c above individual target, despite first-line treatment according to clinical practice guidelines 3. T2DM and DKD with ACR > 30 mg/g, despite first-line treatment according to clinical practice guidelines

GLP1-RA: GLP-1 receptor agonists; T2DM: type 2 diabetes mellitus; DKD: diabetic kidney disease; SGLT2i: sodium-glucose co-transporter 2 inhibitors; ACR: albumin-to-creatinine ratio; RAAS: renin-angiotensin-aldosterone system; eGFR: estimated glomerular filtration rate.

Finally, despite the availability of guidelines and their dissemination through various channels, there remains a low level of implementation of these recommendations in routine clinical practice. The barriers to achieving this

are related to healthcare professionals, patients, and the health-care systems specific to each country in the region.

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Conflicts of interest

J. Rico Fontalvo has received honoraria for lectures from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Merck, Novartis, Novo Nordisk, and Sanofi; and participated in advisory boards for AstraZeneca, Bayer, Lilly, Boehringer Ingelheim, and Novo Nordisk. A. Elberg has received honoraria for speaking and consulting from AstraZeneca, Bagó, Baliarda, Bayer, Boehringer Ingelheim, Novo Nordisk, Raffo, Sanofi, and Servier. E. Lorca has received honoraria for speaking and consulting from AstraZeneca, Axon Pharma, Baxter, Bayer, Boehringer-Ingelheim, Eli Lilly, Fresenius Kabi, Fresenius Medical Care, Merck, Novartis, and Novo Nordisk. R. Daza has received honoraria for lectures from AstraZeneca, Bayer, Boehringer Ingelheim, and Novo Nordisk. C. Castellaro has received honoraria for speaking and consulting from AstraZeneca, Bagó, Baliarda, Bayer, Boehringer Ingelheim, Elea, MSD, Novo Nordisk, and Raffo; and has served as an advisor for AstraZeneca, Bagó, Boehringer Ingelheim, Elea, Novo Nordisk, and Raffo. V. Villavicencio has received honoraria from AstraZeneca and Boehringer Ingelheim. V. Sánchez Polo has received honoraria for lectures from AbbVie, Asofarma, AstraZeneca, Iclos, Janssen, and Novartis; and is a researcher for Astellas, Aurinia, Novartis, and Sanofi. C. Bonanno has received honoraria for lectures from AstraZeneca, Bayer, and Boehringer Ingelheim. G. Rosa Diez has received honoraria as a speaker and advisory board member for AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. R. Correa-Rotter is a member of the executive committee for the DAPA-CKD, SONAR, and FINE-REAL studies, and national leader for the FLOW study; and has received honoraria for consulting or lectures from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and Sanofi.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments have been conducted on humans or animals for this research.

Confidentiality of data. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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

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PERMANYER

CLINICAL CASE

Euglycemic ketoacidosis in a non-diabetic patient: a rare adverse effect of sodium-glucose co-transporter type-2 inhibitors. A review based on a case report

Cetoacidosis euglucémica en un paciente no diabético: un efecto adverso poco frecuente de los inhibidores del cotransportador de sodio y glucosa de tipo 2 (SGLT-2). Revisión de la literatura basada en un caso clínico

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Abstract

Sodium-glucose co-transporter type-2 (SGLT-2) inhibitors (SGLT2i) are increasingly used in clinical practice, with proven benefits in chronic conditions such as diabetes mellitus, heart failure (HF), and chronic kidney disease. Prescription of SGLT2i is a common practice among healthcare providers. It is imperative that clinicians can identify and prevent adverse effects of these drugs. Euglycemic ketoacidosis (eKA) is a rare and potentially serious adverse effect of SGLT2i in patients with diabetes; recent reports indicate that this can also occur in non-diabetic patients. We present the case of an elderly non-diabetic female patient who was treated with SGLT2i for HF and developed eKA.

Keywords: *Sodium-glucose co-transporter type-2 inhibitors. Euglycemic ketoacidosis. Heart failure. Diabetes mellitus.*

Resumen

Los inhibidores de SGLT-2 (SGLT2i) se utilizan cada vez más en la práctica clínica, con beneficios en la diabetes mellitus, insuficiencia cardiaca (IC) y enfermedad renal crónica (ERC). La prescripción de SGLT2i es una práctica habitual entre los médicos. Es imprescindible que los clínicos sepan identificar y prevenir sus efectos adversos. La cetoacidosis euglucémica (eKA) es un efecto adverso raro, pero potencialmente grave de los SGLT-2i en pacientes con diabetes. Informes recientes indican que también puede producirse en pacientes no diabéticos. Presentamos el caso de una paciente anciana no diabética que recibió tratamiento con SGLT-2i para la IC y desarrolló eKA.

Palabras clave: *Inhibidores de SGLT-2. Cetoacidosis euglucémica. Insuficiencia cardiaca. Diabetes mellitus.*

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Introduction

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are currently recommended as second-line medications for the treatment of T2D mellitus. The consensus guidelines recommend the early use of SGLT2i to reduce the progression of cardiovascular and renal diseases[1,2].

Their use is increasing significantly, particularly following recent clinical trials demonstrating favorable cardiovascular and renal protective effects in both diabetic and non-diabetic patients[3,4].

Although most patients respond favorably to these drugs, there is a notable risk of developing ketoacidosis, frequently with normal or minimally elevated plasma glucose concentrations. An increasing number of reports indicate that SGLT2i may induce euglycemic diabetic ketoacidosis (eKA) in certain circumstances, including acute illness, decreased carbohydrate intake, or discontinuation of insulin[5-8]. eKA is defined by euglycemia (blood glucose ≤ 250 mg/dL), severe metabolic acidosis (arterial pH < 7.3, serum bicarbonate < 18 mEq/L), and ketonemia, which should not be confused with an isolated increase in circulating ketone levels induced by SGLT-2 inhibitors.

The incidence of eKA has grown with the broad use of SGLT2i, presenting a diagnostic challenge due to the variety of etiologies and the presence of normal blood glucose levels. Approximately 2.6-3.2% of DKA admissions are euglycemic[9,10]. DKA associated with SGLT2i has rates ranging from 0.16 to 0.76 events/1000 patient-years in patients with T2D, and SGLT2i increases the risk of DKA in T2D patients by sevenfold[5]. The estimated overall incidence of DKA associated with SGLT2i is approximately 0.1%[11]. Data on patients with type 1 diabetes who present with DKA associated with SGLT2 inhibitors show rates varying from 5% to 12%; however, euglycemia was not present in all cases[12]. SGLT2i is not approved for use in patients with type 1 diabetes, and data associated with other causes of eKA are scarce.

Importantly, DKA was not detected in initial randomized controlled trials of SGLT2i therapy in diabetes[13,14]. The phenomenon was first identified through case reports on off-label use of SGLT2i in type 1 diabetes and later on-label use in T2D[1,2,15,16].

It was previously assumed that DKA in the absence of diabetes could not occur as a consequence of SGLT2i therapy. An analysis of 73 cases conducted by the US Food and Drug Administration Adverse Event Reporting System between March 2013 and May 2015 revealed that 70 of the cases had a probable history of diabetes mellitus[17]. Multiple mechanisms have been proposed to explain the pathogenesis of SGLT2i-mediated eKA, including hyperglucagonemia, insulinopenia, and reduced renal β-hydroxybutyrate clearance; however, these are predominantly in diabetic patients[18]. It has been postulated that individuals without diabetes will not develop this complication due to adequate insulin secretory capacity, which protects against significant ketone formation. Reduced carbohydrate supply, compounded by continued SGLT2i-associated glucosuria, may create a switch to fatty acid metabolism and ketone production.

Here, we present a case description of severe eKA in patients without diabetes after treatment with SGLT2i for heart failure (HF) with double diuretic therapy.

Case presentation

A 70-year-old female patient was admitted to the hospital with a 3-day history of progressive dyspnea. Her medical history included HF with reduced ejection fraction (44%), hypertension, atrial fibrillation, chronic kidney disease (CKD) stage III (baseline serum creatinine [SCr] 1.73 mg/dL etiology cardiorenal syndrome), and obesity with gastric bypass surgery 12 years prior. The patient was a current smoker and she was taking a number of medications, including esomeprazole 20 mg once a day, megestrol 160 mg once a day, bisoprolol 2.5 mg once a day, furosemide 40 mg 3 times a day, spironolactone 12.5 mg once a day, sacubitril/valsartan 24/26mg once a day, dapagliflozin 10 mg once a day, alprazolam 0.25 mg once a day, quetiapine 25 mg once a day, and bisacodyl 0.5 mg once a day. It is noteworthy that diuretics and sacubitril/valsartan were initiated 2 weeks before admission and SGLT2i 1 month prior.

Upon admission, the patient exhibited normal blood pressure (109/80 mmHg), tachycardia (100-130 bpm), tachypnea, pulmonary subcrepitant rales, and anuria. The laboratory results demonstrated the following: the ABG demonstrated an oxygen saturation of 4 L/min, a pH of 6.963, a high unquantifiable pCO_2, a pO_2 of 175 mmHg, an unmeasured bicarbonate, and a lactate concentration of 1.3 mmoL/L. The serum glucose concentration was 80 mg/dL, and the ketonemia was 4.6 mmoL/L. The patient exhibited leukocytosis with neutrophilia and a C-reactive protein level of 13.35 mg/dL. The patient was diagnosed with acute kidney injury (AKI) stage 3, with a SCr level of 5.78 mg/dL, urea of 253 mg/dL, sodium of 132 mmoL/L, and potassium of 7.1 mmoL/L.

The diagnosis of severe AKI in CKD with severe eKA was done.

Renal replacement therapy (hemodialysis) was initiated, along with glucose and insulin perfusion. Blood and urine cultures were performed, and empiric antibiotic therapy was started. Ketonemia resolved in < 12 h, and insulin infusion was discontinued.

Metabolic acidemia persisted for 7 days, requiring intravenous bicarbonate supplementation, which was subsequently switched to an oral formulation and finally discontinued. The patient remained euglycemic throughout her hospitalization. Renal recovery was rapid, requiring only one dialysis session. She achieved full recovery after 14 days of hospitalization, and her SCr at discharge was 1.57 mg/dL. Culture results came out later and were negative.

Table 1 summarizes the patients' laboratory results according to the days of hospitalization.

At discharge, dapagliflozin was withdrawn.

Discussion

SGLT2i reduces renal tubular glucose reabsorption decreasing blood glucose levels without stimulating insulin release and increasing glycosuria. Then, these drugs decrease plasma insulin levels and increase plasma glucagon levels. Inhibition of SGLT2 in the proximal tubule alters kidney ATP turnover, leading to the preferential excretion of filtered ketoacids as Na+ or K+ salts. This results in an indirect loss of bicarbonate from the body and systemic acidosis under conditions of increased ketogenesis. These effects, associated with a reduction in liver fat, tissue inflammation, and increased β-cell activity, contribute to the delay in insulin requirement[18].

In DKA, absolute insulin deficiency leads to reduced glucose utilization and enhanced lipolysis. Increased free fatty acids (FFAs) in the liver, coupled with high glucagon levels, promote FFA oxidation and ketone body production. DKA typically presents with hyperglycemia, glycosuria, and hyperketonemia. eKa involves a different mechanism. SGLT2i induces a rapid increase in urinary glucose excretion lowering blood glucose, leading to decreased plasma insulin levels and a compensatory increase in glucagon levels, releasing inhibition of gluconeogenesis in the liver, and augmenting endogenous glucose production in both fasting and fed states. Of note, kidney glucose clearance is doubled in eKa compared to DKA. Thus, in DKA under SGLT2i, the lower insulin-to-glucagon ratio stimulates lipolysis, increasing FFA delivery to the liver and resulting in mild stimulation of ketogenesis. Therefore, eKA is pathophysiologically similar to DKA except for the SGLT2i-induced glycosuria, which artificially lowers plasma glucose levels and predisposes to increased ketogenesis. These lower glucose levels make early detection of eKA difficult and may lead to delayed treatment[16,19].

The fact that non-diabetic individuals can develop SGLT2i-associated ketoacidosis has significant implications for managing these patients in high-risk ketogenic situations. Fasting periods for surgery, colonoscopy, or hospitalization have been identified as high-risk times for SGLT2i-associated ketoacidosis[15,20,21]. In individuals with diabetes, guidelines suggest discontinuing SGLT2i 3 days before high-risk situations; however, this recommendation does not extend to non-diabetic individuals[22].

In the EMPA-KIDNEY trial conducted in patients with CKD, a single case of eKA was described (out of 3304 patients in the interventional arm). In another study, DAPA-CKD, no cases of diabetic ketoacidosis were reported (out of 2152 patients in the interventional arm)[23,24].

Recently, it was reported that eKA, though rare, is a potentially serious complication of SGLT2i treatment in non-diabetic patients[18,25]. To the best of our knowledge, only four case reports of eKA in non-diabetic patients have been published to date; these and the present case suggest that SGLT2i-associated ketoacidosis can be driven by a reduction in blood glucose and subsequent reduction in the stimulus for insulin secretion, rather than an absolute insulin deficit or resistance[12,16,20]. This ketosis appears to be related to carbohydrate loss, increased ketone body resorption, and a switch to fatty acid metabolism and ketosis to generate energy in the context of fasting, surgery, or acute illness[26,27].

In addition, in the clinical case described here, the recent introduction of two classes of diuretics with concomitant use of the SGLT-2i in an elderly CKD patient may have contributed to a state of increased dehydration, which is well known as a potential risk factor for ketosis. This was further compounded by a reduction in glucose availability resulting from dietary restrictions in an elderly patient, which was then exacerbated by a lack of insulin secretion due to an acute illness. A high C-peptide-to-insulin ratio is suggestive of enhanced SGLT2i-induced insulin clearance, which also may have contributed to relatively lower circulating insulin and subsequent ketoacidosis[28].

Known precipitants for ketoacidosis with SGLT2i use include infection or fasting, but in the current case, the sudden onset of acute and severe illness and lack of a clear diagnosis highlight that risk factors for eKA are not always evident. The temporal gap between the

Table 1. Patient laboratory tests

Hospitalization (Days)	Admission	1*	2	3	6	8	10	Discharge
Blood glucose (mg/dL)	127	119	128	135	83	108	-	94
pH	6.963	7.14	7.37	7.36	-	7.43	7.52	7.50
CO_2 (mmHg)	< 12.0	10	25	–	-	21	23	28
HCO_3-(mmoL/L)	-	3.4	14.5	12.04	-	13.9	18.8	21.8
K+(mmoL/L)	6.8	6.6	4.0	3.8	3.4	3.2	2.8	3.8
Lactate (mmoL/L)	1.3	1.6	0.8	1.8	–	1.6	1.3	1.8
Blood ketones (mmoL/L)	4.6	5	0	-	-	-	-	-
C-reactive protein (mg/dL)	13.35	-	-	-	15.06	12.04	-	5.81
Creatinine (mg/dL)	5.78	-	-	-	3.61	2.61	-	1.57
Urea (mg/dL)	253	-	-	-	140.1	106.1	-	72.6

introduction of novel pharmaceuticals and the manifestation of severe adverse effects may result in a delayed diagnosis.

Guidelines from the American Association of Clinical Endocrinologists and the American College of Endocrinology recommend discontinuing SGLT-2i in the presence of a low-carbohydrate diet, excessive alcohol consumption, before surgery, or strenuous physical activity[18]. These guidelines were written when these drugs were used only as oral antidiabetic agents, so they do not address recommendations for non-diabetic patients. The 2024 KDIGO Guidelines for the Assessment and Management of CKD state that it is reasonable to suspend SGLT-2 inhibitors when there is an increased risk of ketosis[18].

Conclusion

It is of the utmost importance to provide comprehensive education and awareness to both patients and physicians regarding this potential adverse event associated with SGLT2i treatment. In addition, there is a real need for future research to document the incidence of SGLT2i-associated eKA in patients without diabetes, regardless of how frequent this pathology could be because the widespread use of these agents for HF and kidney dysfunction, as advocated by recent guidelines, suggests that this complication may become more common[29,30].

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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 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.

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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Renal implications of chronic liver disease: focus on urinary crystals

Implicaciones renales de la enfermedad hepática crónica: cristales urinarios

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Case report

A 69-year-old male, with a past medical history of liver transplant due to alcoholic cirrhosis, was admitted for graft failure, confirmed by liver biopsy. He also presented worsening renal function with serum creatinine rising from 1.2 to 5 mg/dL, necessitating dialysis. Renal ultrasound, cyclosporine levels, and autoimmune evaluation were normal. Urine sediment microscopy revealed leucine crystal casts, as illustrated in figure 1.

These crystals, rarely found outside severe liver disease, may contribute to kidney injury, but their nephrotoxicity remains uncertain[1].

This case highlights the complex interplay between liver and kidney dysfunction, with leucine crystals serving as a potential marker of severe liver impairment impacting renal function[2,3].

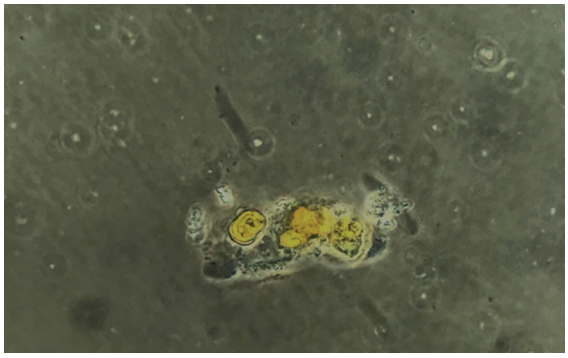

Figure 1. Detection of leucine crystal casts in fresh, unstained urine sediment is observed under phase-contrast microscopy at an original magnification of 400×. These crystals appear as yellow-brown spheres with an oil drop-like appearance and concentric striations.

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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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