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ORIGINAL ARTICLE

Guayaquil consensus: financial neutrality in organ donation

Consenso de Guayaquil: neutralidad financiera en la donación de órganos

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Abstract

Objective: *In the context of projections for Latin America, the Guayaquil Document is expected to serve as a crucial reference framework for establishing policies that ensure financial neutrality in the region. As we move towards 2030, countries in the area will likely adopt stricter measures to ensure donors do not incur economic losses from their altruistic decisions. Considering the recent legislative proposal from the United States – the End Kidney Deaths Act (H.R. 9275, 118th Congress) – which proposes a $50,000 tax deduction for living kidney donors ($10,000 annually for five years), the signing societies express their deep ethical, legal, and social concerns.* **Materials and methods:** *This document has been consensually agreed upon and approved by all nephrology societies in Latin America that comprise SLANH during the XXI Congress of SLANH, held in Guayaquil, Ecuador, from August 27 to 30, 2025. It has also been subscribed, discussed, consensually agreed upon, and approved by the transplant societies of Latin America and the Caribbean that form STALYC during the XXVI Latin American and Caribbean Transplant Congress and the V Paraguayan Transplant Congress, held in Asunción, Paraguay, from October 1 to 3, 2025.* **Results/**

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Conclusion: *Although the project states its purpose of reducing mortality from chronic kidney disease (CKD), its implementation sets a precedent that contradicts the universal principles of altruistic donation and financial neutrality enshrined in the Istanbul Declaration (2018) and the WHO Guiding Principles (2010). This document alerts health authorities, legislators, ethics committees, medical societies, and international organizations in Latin America and the Caribbean to the risks that such initiatives may pose to more fragile systems, eroding public trust and compromising distributive justice and human dignity.*

Keywords: *Altruistic donation. Istanbul declaration. Transplant ethics. Distributive justice. Protection of living donors. Sustainability of the transplant system.*

Resumen

Objetivo: *En el contexto de las proyecciones de América Latina, se anticipa que el Documento de Guayaquil sirva como un marco de referencia crucial para establecer políticas que aseguren la neutralidad financiera en dicho ámbito. A medida que se avanza hacia el año 2030, se espera que los países de la región adopten medidas más estrictas para garantizar que los donantes vivos no enfrenten pérdidas económicas derivadas de su decisión altruista. Ante la reciente propuesta legislativa de los Estados Unidos – End Kidney Deaths Act (H.R. 9275, 118.º Congreso) – que plantea una deducción fiscal total de 50.000 USD para donantes vivos de riñón (10.000 USD anuales durante cinco años), las sociedades firmantes expresan su profunda preocupación ética, legal y social.* **Material y métodos:** *Este documento ha sido consensuado y aprobado por las sociedades de nefrología de América Latina que conforman la Sociedad Latinoamericana de Nefrología e Hipertensión (SLANH) durante el XXI Congreso de la SLANH, celebrado en Guayaquil (Ecuador) del 27 al 30 de agosto de 2025. Asimismo, ha sido suscrito, discutido, consensuado y aprobado por las sociedades de trasplante de América Latina y el Caribe que conforman STALYC) durante el XXVI Congreso Latinoamericano y del Caribe de Trasplante y el V Congreso Paraguayo de Trasplante, celebrados en Asunción, (Paraguay) del 1 al 3 de octubre de 2025.* **Resultados/Conclusión:** *Aunque el proyecto declara la finalidad de reducir la mortalidad por enfermedad renal crónica (ERC), su implementación establece un precedente que contradice los principios universales de la donación altruista y de la neutralidad financiera consagrados en la Declaración de Estambul (2018) y en los Principios Rectores de la Organización Mundial de la Salud (OMS) (2010). El presente documento alerta a las autoridades sanitarias, legisladores, comités de ética, sociedades científicas y organismos internacionales de América Latina y el Caribe sobre los riesgos que dichas iniciativas pueden generar en sistemas más frágiles, erosionando la confianza pública y comprometiendo la justicia distributiva y la dignidad humana.*

Palabras clave: *Donación altruista. Declaración de Estambul. Ética del trasplante. Justicia distributiva. Protección del donante vivo. Sostenibilidad del sistema de trasplantes.*

Purposes of the document

- To establish a unified position among Latin American countries regarding the *End Kidney Deaths Act* bill, promoting an ethical approach to organ donation.[1]
- To reinforce the principle of financial neutrality in organ donation and transplantation, preventing economic inequalities from influencing the decision to donate.[2]
- To warn about the risks of implementing fiscal incentive models in Latin America, where socioeconomic conditions may distort altruism in donation.[3]
- To reaffirm commitment to the principles of voluntary, altruistic, and equitable donation, in alignment with the Istanbul Declaration and WHO standards.[4]
- To urge governments in the region to maintain and strengthen their ethical frameworks for organ donation and transplantation.[5]

Definitions

- Financial neutrality: donors and their families must neither gain nor lose money as a result of donation. This principle entails reimbursement or strict compensation of reasonable, verifiable, and directly related costs (travel, accommodation, meals, loss of income, dependent care, drugs, and complications), without profit or economic gain.[1-4]
- Economic incentive: monetary transfer or material benefit exceeding reimbursement of actual costs and intended to stimulate donation (e.g., fixed payments, predetermined tax credits, scholarships, or patrimonial benefits unrelated to documented expenses).[5]
- Financial gain: any surplus over real and reasonable costs or benefits not causally linked to donation. This concept is central to bioethical debates criticizing commodification of the human body.[4-6]

– Economic disincentive: monetary cost that may discourage or prevent donation. The donor or their family expects their economic situation to worsen as a result of donation.[7,8]
– Altruistic donation: a free and voluntary act of organ donation without expectation of economic or material benefit.[6,7]
– Organ trafficking: the procurement, mediation, or transfer of organs through coercion, deception, or economic benefit.
– Transplant tourism: movement of recipients and donors to countries with weak regulations and/or that permit or tolerate commercial practices.[1]
– Exploitation of vulnerable persons: use of economic and social need, as well as educational deprivation, to obtain organs, in violation of autonomy and human dignity.[2,7-9]

These concepts derive from current international reference frameworks:

– Declaration of Istanbul (2018 edition): prohibits organ trafficking, transplant tourism, and financial gain. Permits and promotes financial neutrality through cost reimbursement.[1]
– WHO Guiding Principles (1991, reaffirmed 2010): prohibit any payment or compensation in exchange for organs, while allowing reimbursement of reasonable expenses to protect donors.[10]
– Regional instruments (Council of Europe/Oviedo Convention and its Bioethics Committee guidelines; TTS/ISN best practices and Council of Europe guidelines (1997-2014); United Nations and WHO Bioethics Committee guidelines; Aguascalientes Document): all promote non-profit neutrality, traceability, clinical self-regulation, and donor protection.[9]

Ethical-political analysis for Latin America

Convergences and divergences regarding financial neutrality

Financial neutrality is a complex and sensitive issue. Convergences include recognition of the economic barriers donors face and the need to prevent financial losses arising from donation. Divergences emerge when neutrality is abandoned by establishing incentives that confer material gain to donors.

Risks for Latin America and the Caribbean

Economic incentive proposals, although framed as fiscal or recognition mechanisms, generate multiple risks in the region. These risks justify the development of this position document due to their imminent impact on Latin American and Caribbean countries.

Normalization of payment for organs: modifying the ethical framework of organ donation by accepting direct payments or payments disguised as tax credits normalizes the buying and selling of organs and introduces commercialization of non-commercializable goods.[11]

Structural inequality and socioeconomic vulnerability: payments for organ donation (direct or via tax credits) may induce economically vulnerable individuals to donate kidneys motivated by financial need. In the absence of true autonomy, economic incentives become mechanisms of exploitation, and organ donation becomes a means of survival.

Erosion of public trust: the Council of Europe (2002) states that public trust in organ donation and transplantation rests on three pillars: transparency, absence of profit, and altruism. Monetary compensation for donation undermines these principles. By allowing organs to become market goods, gratuity and altruism are eliminated, creating a market system favoring those who can pay and jeopardizing public trust.[2,12]

Impact on international cooperation: accepting incentive payments represents a rupture with WHO, the Council of Europe, the Istanbul Declaration, and national legislations prohibiting organ commercialization through direct or indirect payments. Financial gain from donation establishes tacit inequality among human beings and violates the first 2 articles of the Universal Declaration of Human Rights, generating profound consequences for international cooperation in transplantation.[1,2,7,12]

Comprehensive donor protection and ethical strategies to promote organ donation

Protection of living donors is an essential ethical and public health duty. Transplant systems must ensure donors suffer no economic, social, or medical harm and that their rights are fully protected. Latin American countries must strengthen legal frameworks and support programs that reinforce public trust, eliminate economic disincentives, and ensure financial neutrality consistent with international standards.

Measures for the protection of living donors

– Definition and full reimbursement of donation-related expenses: donors must receive full reimbursement of all real, reasonable, and documented expenses:

travel, accommodation, meals, income loss, dependent care, drugs, and treatment of complications.
– Labor and social protection: legislation must guarantee job security, paid leave, reinstatement, and prohibition of any discrimination due to having donated an organ.
– Medical coverage and follow-up: national health systems must ensure cost-free care, clinical follow-up, and permanent coverage for potential donation-related complications.
– Independent ethical review: each donation process must be reviewed by an ethics committee that verifies voluntariness, absence of coercion, and full understanding of risks. Traceability, registration, and transparency must be mandatory.
– National registry of living donors: the creation of official registries integrating medical, social, and economic information is recommended to evaluate outcomes, design public policies, and prevent irregularities.
– Sanctions against profit or intermediation: any form of profit, advertising, or intermediation in organ donation must be subject to sanctions in full compliance with the criminal legislation in force in each country, preserving the altruistic nature of the act. In contexts where no specific regulations yet exist, legal frameworks should be promoted to define and sanction such practices, ensuring donor protection and system transparency.
– In countries with low rates of organ donation from deceased donors, the primary incentive policy should focus on strengthening and optimizing these programs.
– Paired exchange donation: the promotion and regulation of laws enabling paired exchange donation is encouraged in countries where this option is not yet available, always ensuring transparency, equity, and absence of economic incentives. This regulatory framework expands transplant opportunities among compatible living donors while preserving the ethical principles of altruism and financial neutrality.

Ethical strategies to promote the donation of organs, cells, and tissues

– Public education campaigns: sustained, evidence-based campaigns should be promoted to inform the general population about living and deceased donation and to dismantle common myths, using media channels such as television, radio, social networks, and schools. The impact of these campaigns may be evaluated by measuring increases in national transplant numbers before and after implementation, the number of living donor registrations, family consent rates, and changes in public awareness assessed through surveys, thereby determining the efficacy of these initiatives in fostering donation.
– Promotion of paired exchange donation: the development and regulation of legislation enabling paired exchange donation should be encouraged in countries lacking this option, ensuring transparency, equity, and the absence of economic incentives. This form of regulation expands transplant opportunities while preserving altruism and financial neutrality.
– Symbolic and honorary recognition: mechanisms of public recognition (certificates, commemorative events, national distinctions) should be established to acknowledge the donor's contribution without implying any economic benefit.
– Promotion of regional self-sufficiency in transplantation: programs for deceased donor organ donation should be strengthened, organ procurement optimized, single transparent national waiting lists established, and regional coordination among countries improved or created.
– Psychosocial support and family accompaniment: psychological, social, and family support must be guaranteed before, during, and after the donation process, including professional counseling and full coverage of associated costs.
– Regional cooperation (SLANH, STALYC, DICG): collaboration is recommended for the development of guidelines, audits, and educational programs; and for promoting continuous professional training through medical and nursing education programs incorporating ethics, communication with donors and families, and the principles of financial neutrality and human dignity.

Conclusions

This document seeks to reaffirm and ratify, with firmness and unanimous consensus, the position of the two Latin American societies composed of national societies from Latin America and the Caribbean: SLANH and STALYC.
– Reaffirm the principle of financial neutrality.
– Reject any form of financial or fiscal incentive for donors or their families.
– Harmonize national legal frameworks with the Istanbul Declaration and WHO Guiding Principles.
– Strengthen deceased donor organ donation.
– Protect human dignity as the central axis of donation and transplantation.

These measures, originally proposed in the Guayaquil Document (SLANH-STALYC, DICG), reaffirm that the only ethical form of compensation for donors is the

strict reimbursement of verifiable costs and reject any economic incentive, direct or indirect, including tax credits. Implementation of these recommendations will strengthen trust in donation and transplantation systems, increase social participation, and protect human dignity as the foundation of organ transplantation in Latin America and the Caribbean.

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The authors declare that this study was conducted with the authors' own resources.

Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

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

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

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

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ORIGINAL ARTICLE

Towards better control of hypertension: the value of a physiological approach guided by the renin-angiotensin-aldosterone axis

Hacia el mejor control de la hipertension arterial: el valor de un enfoque fisiológico guiado por el eje renina-aldosterona

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Abstract

Objective: *To propose a pathophysiological and personalized approach for the management of resistant hypertension, based on renin and aldosterone measurements, allowing classification of hormonal phenotypes and guiding antihypertensive therapy.* **Material and methods:** *A scoping review was conducted following the PRISMA-ScR guidelines, focusing on the hormonal classification of hypertension into four main phenotypes: primary hyperaldosteronism, low-renin hypertension, renovascular activation, and Liddle-like phenotype. Their pathophysiology, biochemical profile, and therapeutic response were analyzed, with emphasis on applicability in Latin American settings.* **Results:** *Each phenotype is associated with specific therapeutic strategies (mineralocorticoid receptor antagonists, renin-angiotensin system inhibitors, amiloride, or sodium restriction). Phenotypic identification improves blood pressure control, reduces polypharmacy, and guides the search for treatable secondary causes.* **Conclusion:** *Hormonal stratification based on renin and aldosterone is a practical and accessible tool to advance personalized medicine in resistant hypertension, particularly useful in regions with a high prevalence of low-renin phenotypes. Its implementation should be integrated into a comprehensive evaluation that considers other hormonal causes of hypertension.*

Keywords: *Hypertension. Renin. Aldosterone. Hormonal phenotypes. Personalized medicine.*

Resumen

Objetivo: *Proponer un enfoque fisiopatológico y personalizado para el manejo de la hipertensión arterial resistente, basado en la medición de renina y aldosterona, que permita clasificar fenotipos hormonales y orientar la terapia antihipertensiva.* **Material y métodos:** *Se realizó un scoping review siguiendo la guía PRISMA-ScR, sobre la clasificación hormonal de la hipertensión en cuatro fenotipos principales: hiperaldosteronismo primario, hiporreninemia, activación renovascular y fenotipo tipo Liddle. Se analizaron su fisiopatología, perfil bioquímico y respuesta terapéutica, con énfasis en su aplicabilidad en contextos latinoamericanos.* **Resultados:** *Cada fenotipo se asocia con estrategias terapéuticas específicas (antagonistas del*

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receptor mineralocorticoide, inhibidores del sistema renina-angiotensina, amilorida o restricción de sodio). La identificación fenotípica mejora el control tensional, reduce la polifarmacia y orienta la búsqueda de causas secundarias tratables. **Conclusión:** *La estratificación hormonal basada en renina y aldosterona es una herramienta práctica y accesible para avanzar hacia una medicina personalizada en hipertensión resistente, especialmente útil en regiones con alta prevalencia de fenotipos hiporreninémicos. Su aplicación debe integrarse a una evaluación integral que considere otras causas hormonales de hipertensión.*

Palabras clave: *Hipertensión. Renina. Aldosterona. Fenotipos hormonales. Medicina personalizada.*

Introduction

Hypertension is the leading modifiable risk factor for cardiovascular disease, significantly contributing to global morbidity and mortality rates. It is estimated that 1.280 billion adults aged 30 to 79 years worldwide have hypertension, predominantly in low- and middle-income countries.[1] In Latin America, hypertension is estimated to be responsible for more than two million deaths due to cardiovascular disease, of which one million occur before the age of 70 years.[2]

Despite the availability of multiple classes of antihypertensive drugs and advances in clinical guidelines, according to data from the World Health Organization (WHO), only 1 in 5 patients (21%) achieve adequate blood pressure control. Resistant hypertension is defined as uncontrolled blood pressure despite the use of at least three antihypertensive agents of different classes, administered at maximum doses and including a diuretic, a calcium channel blocker, and a renin-angiotensin system blocker.[3] Cohort studies and international meta-analyses report a prevalence of true resistant hypertension of approximately 10%.[4-6]

In the subgroup of patients with resistant hypertension, the use of a more personalized approach based on hormonal evaluation of the renin-angiotensin-aldosterone system (RAAS) represents a promising strategy. Measurement of plasma renin activity (PRA) and aldosterone levels allows identification of different physiological phenotypes of hypertension, thereby guiding more precise treatment. This strategy enables the selection of drugs aimed at correcting the predominant alteration in each patient, whether sodium retention, autonomous aldosterone secretion, or activation of the renin-angiotensin axis, and has shown promising results in blood pressure control.[7-9]

Ultimately, given the social, economic, and genetic context of Latin America, the adoption of more personalized and precise approaches is not only an opportunity but an urgent necessity to improve hypertension control and reduce cardiovascular burden in the region.

Methodology

We conducted a scoping review of the literature on arterial hypertension, with emphasis on pathophysiological classification based on renin and aldosterone measurements, identification of hormonal phenotypes, and targeted therapeutic strategies. The methodology was structured according to PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines.

A systematic search was performed in the PubMed, Scopus, Embase, and Google Scholar databases, without restrictions on publication date. Combinations of MeSH terms and free text in English and Spanish were used, including:

"Hypertension" AND "renin" OR "aldosterone" OR "RAAS"

"Renin-aldosterone ratio" AND "phenotype-guided therapy"

"Primary aldosteronism" AND "treatment" OR "mineralocorticoid receptor antagonist"

"Low-renin hypertension" OR "Liddle-like phenotype" AND "treatment"

Filters were applied to include only articles with full text available in English or Spanish. Letters to the editor without new data, opinion pieces, and conference abstracts without full publication were excluded.

Titles and abstracts were independently screened by two reviewers (MAEB and JDL). Articles addressing RAAS pathophysiology, hormonal phenotypes, clinical studies, or experimental models related to hypertension and therapy guided by renin and aldosterone were selected for full-text review. Discrepancies were resolved by consensus.

Inclusion criteria

- Basic, translational, or clinical studies exploring the role of renin and aldosterone in hypertension and hormonal phenotypes.
- Systematic or narrative reviews discussing pathophysiological and therapeutic mechanisms.

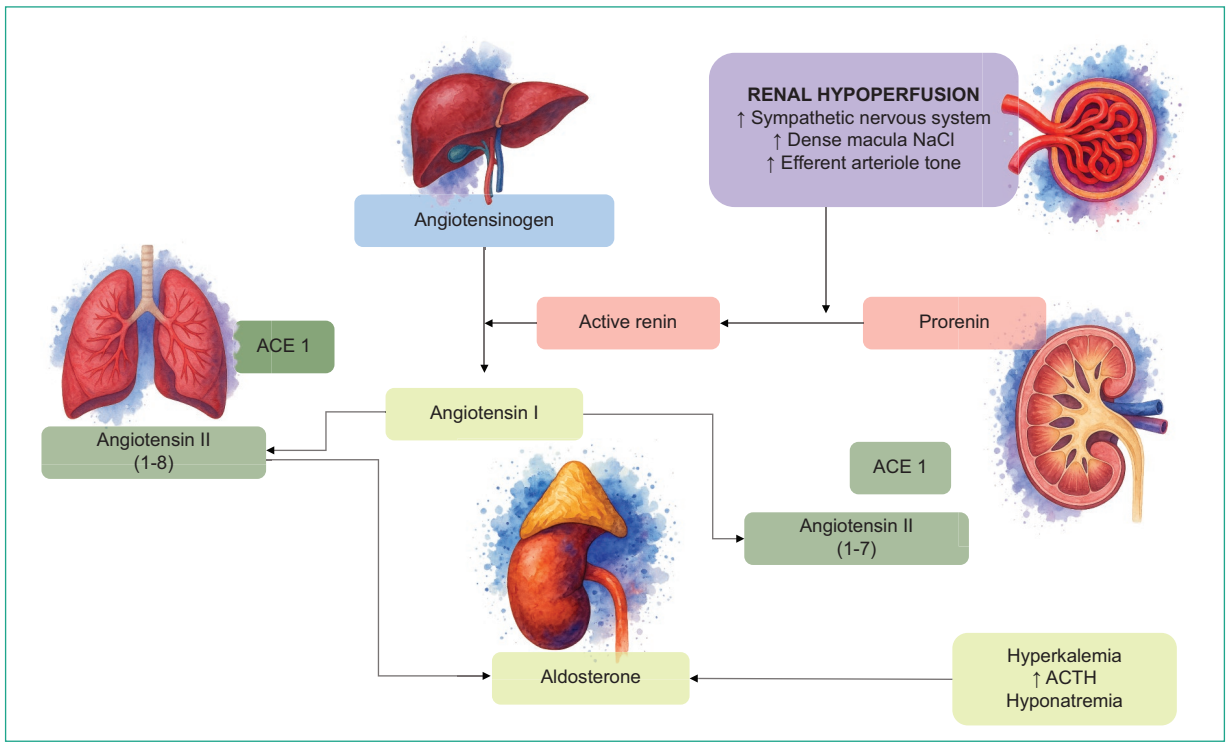


Figure 1. Interaction of the renin-angiotensin-aldosterone system. *Created with BioRender.*

– Clinical or preclinical trials on therapies guided by hormonal profile, including mineralocorticoid receptor antagonists, RAAS inhibitors, or amiloride.

Exclusion criteria

– Epidemiological studies without pathophysiological or hormonal analysis.
– Articles without full-text access or not peer-reviewed.

From each article, the following elements were extracted: study type, study population, methods for measuring renin and aldosterone, identified hormonal phenotype, treatment applied, and outcomes in blood pressure control. The information was synthesized narratively and grouped into the following thematic axes: hormonal phenotypes, associated pathophysiology, targeted therapeutic strategies, and clinical applicability in Latin American populations.

Physiology of the renin-angiotensin-aldosterone system (RAAS)

The renin-angiotensin-aldosterone system (RAAS) is a fundamental hormonal axis in the regulation of blood pressure, intravascular volume, and sodium and potassium balance. This regulatory system likely evolved in response to environmental pressures when early human ancestors faced low salt availability and, therefore, low dietary sodium intake. Under these conditions, activation of the RAAS promotes renal salt conservation and water retention, thereby maintaining adequate tissue perfusion in a low-salt environment.[10]

Its activation begins with the release of renin by the renal juxtaglomerular apparatus in response to renal hypoperfusion, reduced sodium delivery to the macula densa, or sympathetic stimulation. Renin converts angiotensinogen, produced in the liver, into angiotensin I, which is subsequently transformed into angiotensin II by angiotensin-converting enzyme (ACE), primarily in the pulmonary endothelium (Fig. 1).

Angiotensin II is a potent vasoconstrictor; it stimulates adrenal aldosterone secretion, increases sodium reabsorption in the proximal tubule, and contributes to vascular remodeling and endothelial dysfunction. Additionally, it is associated with fibrosis, inflammation, and target-organ damage, particularly affecting the kidneys and heart.

Aldosterone, synthesized in the zona glomerulosa of the adrenal cortex, is the final effector of the RAAS. Its synthesis is mediated by the enzyme aldosterone synthase (CYP11B2), whose expression is primarily regulated by angiotensin II, serum potassium, and to a lesser extent by adrenocorticotropic hormone (ACTH). Additional factors such as products derived from visceral adipose tissue, increased sympathetic activity, and high salt intake – particularly in hypertensive individuals – also play a role.

In addition to promoting sodium reabsorption in the distal tubule through activation of the mineralocorticoid receptor (MR) and expression of the epithelial sodium channel (ENaC), aldosterone exerts important non-epithelial effects, including promotion of vascular and myocardial fibrosis, inflammation, oxidative stress, and endothelial dysfunction.[10]

The mineralocorticoid receptor belongs to the nuclear steroid receptor family and is expressed mainly in epithelial tissues such as the distal renal tubule, distal colon, sweat glands, as well as in the heart, central nervous system, vasculature, and adipose tissue. In the kidney, MR regulates sodium reabsorption and potassium secretion through genomic and non-genomic effects. In its classical (genomic) form, aldosterone freely diffuses across the cell membrane, binds to the cytoplasmic MR, which subsequently translocates to the nucleus and activates transcription of key genes. Among the main effectors are ENaC, the Na^+/K^+ ATPase, and the thiazide-sensitive sodium-chloride cotransporter (NCC), as well as regulatory proteins such as serum and glucocorticoid-regulated kinase 1 (SGK1), which prolongs ENaC half-life at the apical membrane by inhibiting its degradation mediated by NEDD4-2 (neural precursor cell expressed developmentally downregulated protein 4-2).[10,11]

Non-genomic effects of aldosterone include activation of various kinases such as protein kinase C (PKC), mitogen-activated protein kinases (MAPK), and the epidermal growth factor receptor (EGFR), as well as intracellular calcium mobilization and rapid modulation of pre-existing ion channels. Additionally, aldosterone can modulate paracellular permeability through effects on tight junction proteins such as claudins, further expanding its role in sodium reabsorption control.[12]

Aldosterone enhances the expression of ACE and AT1 receptors, thereby amplifying the vasoconstrictive, inflammatory, and proliferative response of angiotensin II. This positive feedback is further promoted by oxidative stress, which stimulates the generation of reactive oxygen species (ROS), activation of NADPH oxidase, endothelial dysfunction, and vascular remodeling.[11,12]

Under conditions of high sodium intake, overexpression and activation of MR in target tissues may persist even in the presence of normal or low circulating aldosterone levels, either due to local synthesis or loss of function of 11β-HSD2, allowing MR activation by glucocorticoids. This inappropriate MR activation may contribute to smooth muscle hypertrophy, vascular fibrosis, arterial calcification, arterial stiffness, and increased salt sensitivity.[13-15]

In addition to the classical pressor arm of the RAAS described above, there is a “depressor” or protective branch, primarily mediated by ACE2, which converts angiotensin II into angiotensin 1-7. This peptide exerts vasodilatory, anti-inflammatory, and antifibrotic effects through activation of the Mas receptor and other intracellular pathways, counteracting many of the harmful actions of angiotensin II. This protective RAAS axis plays a key role in cardiovascular and renal homeostasis, and its dysfunction is also implicated in the pathophysiology of hypertension and its complications[16].

Overall, the RAAS is a complex system with circulating, local, and intracellular components that interact to regulate blood pressure. Its imbalance – whether due to hyperactivity or dysregulation – is central to the pathophysiology of multiple forms of hypertension.

Hormonal evaluation of the RAAS: measurement of renin, aldosterone, and physiological phenotypes

A physiological approach to hypertension requires accurate measurement of two key components of the renin-angiotensin-aldosterone axis: plasma renin activity (PRA) or direct renin concentration (PRC), and plasma aldosterone concentration (PAC). These measurements allow identification of specific hormonal phenotypes with direct therapeutic implications.

Measurement methods

Renin can be measured in 2 ways: as plasma renin activity (PRA), which reflects its functional capacity to generate angiotensin I, or as plasma renin concentration (PRC) using immunoassays.[17,18] Aldosterone is typically quantified by immunoassay in serum. Both parameters should ideally be obtained under standardized conditions: in the morning, with the patient in an upright position for at least 2 hours, and without diuretics, ACE inhibitors, angiotensin receptor blockers,

Table 1. Effects of antihypertensive drugs on renin and aldosterone concentrations

Drug class	Effect on PAC	Effect on PRA	Effect on ARR
Beta-blockers	↓	↓↓	↑
MRA	↑	↑↑	↓
ACEi	↓	↑↑	↓
ARB	↓	↑↑	↓
DHP CCB	↓	↓	↓
Diuretics (loop, thiazides)	↓/↑	↑/↓	↓
Potassium-sparing diuretics	↓/↑	↑↑	↓
Hydralazine	↓	↑	↓

Arrows indicate the direction and magnitude of the change. ↑, increase; ↓, decrease; ↑↑, marked increase; ↓↓, marked decrease; ↓/↑, variable effect. PRA: plasma renin activity; PAC: plasma aldosterone concentration; ARR: aldosterone-renin ratio; MRA: mineralocorticoid receptor antagonists; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; DHP CCB: dihydropyridine calcium channel blockers.

Table 2. Cutoff values for renin, aldosterone, and the aldosterone-renin ratio

Parameter	Reference value	Recommended source
Low renin	PRA < 1.0 ng/mL/h; PRC < 10 mU/L	Buffolo et al., 2020[20] Funder et al., 2016[17]
Normal or high renin	PRA ≥ 1.0 ng/mL/h; PRC ≥ 10-20 mU/L	Buffolo et al., 2020[20]
Elevated aldosterone	PAC > 15-16 ng/dL	Doumas et al., 2017[21] Funder et al., 2016[17]
Normal aldosterone	PAC 5-15 ng/dL	Monticone et al., 2018[22]
Inappropriately normal aldosterone	PAC 5-15 ng/dL	Buffolo et al., 2020[20]
Low aldosterone	PAC < 5 ng/dL	Monticone et al., 2018[22]
Elevated ARR (suggestive of primary aldosteronism)	ARR ≥ 30 ng/dL per mU/L with PAC > 10 ng/dL	Funder et al., 2016[17]

PRA: plasma renin activity; PRC: direct renin concentration; PAC: plasma aldosterone concentration; ARR: aldosterone-renin ratio.

spironolactone, or beta-blockers – if possible – for at least 4 weeks prior to sampling, due to their interference with the ratio.[17,19]

Withdrawal of all interfering antihypertensive medications is feasible in patients with mild hypertension but may be problematic in others. In this context, several guidelines and studies have proposed "neutral" therapeutic alternatives that allow blood pressure control without significantly interfering with the interpretation of the aldosterone-renin ratio (ARR).[17] These include alpha-blockers such as doxazosin, non-dihydropyridine calcium channel blockers such as verapamil or diltiazem, and centrally acting sympatholytic agents such as clonidine. If all potentially interfering agents cannot be safely discontinued, results should be interpreted considering possible confounding factors. Table 1 summarizes the expected changes in measurements with each drug.

The aldosterone-renin ratio (ARR) is calculated as PAC/PRC and is essential for detecting primary aldosteronism (PA). Although there is no universally accepted cutoff, ARR values ≥ 30 (ng/dL per mUI/L) with PAC > 10 ng/dL are suggestive of autonomous aldosterone secretion (Table 2)[17,20-22].

The combined evaluation of PRA or PRC and aldosterone levels allows identification of distinct physiological phenotypes of hypertension. This classification not only helps elucidate the underlying mechanisms of blood pressure elevation but also enables rational and personalized therapeutic guidance (Fig. 2).

Among the most recognized phenotypes are:

– **Primary aldosteronism phenotype (low renin/high aldosterone)**
  Characterized by suppressed renin activity (PRA < 1.0 ng/mL/h), elevated plasma aldosterone (> 15-16 ng/dL), and an aldosterone-renin ratio (ARR) ≥ 30 ng/dL/mUI/L. This profile is suggestive of autonomous aldosterone secretion. It is associated with hypokalemia (although not always present) and is more prevalent in cases of resistant hypertension. Treatment includes mineralocorticoid receptor antagonists such as spironolactone or eplerenone. If ARR is elevated, a confirmatory test should be performed, such as the intravenous saline loading test or the fludrocortisone suppression test.[17]
– **Liddle phenotype or pseudohyperaldosteronism (low renin/low aldosterone)**
  This profile is characterized by simultaneous suppression of renin (PRA < 1.0 ng/mL/h) and plasma aldosterone (PAC < 5-6 ng/dL), in the context of hypertension, hypokalemia, and resistance to renin-angiotensin axis blockers. It is more frequent in individuals of African descent, younger patients, and those with a family history of early-onset hypertension.[20] It may correspond to classic Liddle syndrome, a monogenic disorder caused by activating mutations

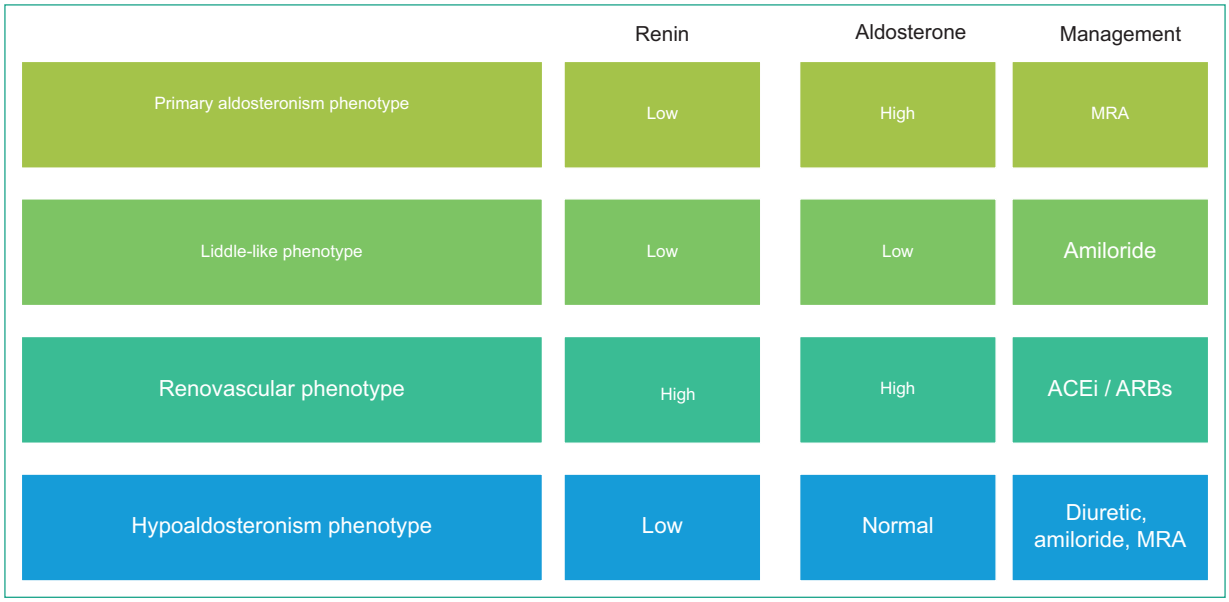


Figure 2. Hormonal phenotypes and associated therapeutic strategies in resistant hypertension.

in epithelial sodium channel (ENaC) subunits, which increase sodium reabsorption independently of aldosterone. The most frequent genetic mutations associated with Liddle syndrome affect the SCNN1B and SCNN1G genes, encoding the β and γ subunits of ENaC.[23]

Liddle-like phenotype: patients without identified mutations but with the same hormonal profile and clinical response.

Targeted treatment includes amiloride, which directly inhibits ENaC, thereby reducing sodium reabsorption and improving blood pressure.[24] Amiloride is more effective than mineralocorticoid receptor antagonists because the underlying mechanism is ENaC activation independent of aldosterone.[25]

– **Renovascular phenotype (high renin/high aldosterone)**

This phenotype is characterized by elevated plasma renin activity (PRA ≥ 1.0 ng/mL/h, with values > 6-10 ng/mL/h in severe cases) and elevated plasma aldosterone (PAC > 15-16 ng/dL). It reflects true activation of the renin-angiotensin-aldosterone system (RAAS), generally secondary to reduced renal perfusion, commonly seen in renovascular disease, renal artery stenosis, or chronic nephropathies. In this group, patients may respond to RAAS inhibitors (ACE inhibitors/ARBs) and careful volume control.[26] Bilateral renal artery stenosis or stenosis in a solitary kidney should be ruled out before initiating ACE inhibitors or ARBs.

Renovascular hypertension is typically associated with elevated renin and aldosterone levels; however, in bilateral or chronic forms, plasma renin activity may normalize or even decrease due to volume expansion or RAAS-blocking medications, explaining variability in renin/aldosterone patterns reported in the literature.[27,28]

– **Hyporeninemic phenotype (low renin/normal aldosterone)**

Characterized by suppressed renin levels (PRA < 1.0 ng/mL/h or PRC < 10 mUI/L) and aldosterone concentrations within the reference range (5-15 ng/dL), but inappropriately maintained in the context of a suppressed RAAS.

Several mechanisms have been proposed: the presence of aldosterone-producing cell clusters (APCCs) with somatic mutations (CACNA1D, ATP1A1), particularly in older individuals; micronodular adrenal hyperplasia not detectable by conventional imaging; and impaired feedback of aldosterone on renin secretion, especially in individuals of African descent, patients with obesity, or metabolic syndrome.[26,29]

This hormonal profile is common in patients with salt-sensitive hypertension, resistant hypertension without a clear secondary cause, or elderly hypertensive patients. It has been associated with increased arterial stiffness, target-organ damage, and

progression of kidney disease, even in the absence of overt primary aldosteronism.

The PATHWAY-2 study, designed to determine the best treatment strategy for resistant hypertension, showed that in patients with low renin, spironolactone was significantly more effective in reducing blood pressure than bisoprolol or doxazosin, highlighting the therapeutic value of hormonal phenotyping.[29]

More recently, Tsai et al. demonstrated that although the captopril test may help differentiate subclinical primary aldosteronism from other forms of hyporeninemic hypertension, aldosterone-targeted therapy was effective in both groups, regardless of test interpretation. This suggests that empiric initiation of mineralocorticoid-targeted therapy in patients with low renin may be a reasonable clinical strategy.[30]

Management of this phenotype is based on the use of thiazide or thiazide-like diuretics (e.g., indapamide) as first-line therapy, dietary sodium restriction, and, in cases with suspected ENaC overexpression, the use of amiloride. Low-dose spironolactone may also be effective, even if ARR is not elevated.[20]

Because these patients often exhibit sodium retention and volume expansion, they typically respond poorly to RAAS blockers; therefore, diuretics are the cornerstone of treatment, with thiazide diuretics such as hydrochlorothiazide or chlorthalidone being particularly effective.[31]

Recognition of these phenotypes not only facilitates the selection of more effective treatments and reduction of polypharmacy but also enables identification of secondary forms of hypertension and tailoring of interventions to each patient's genetic and environmental context.

Clinical evidence of PRA/aldosterone-guided therapy

The clinical utility of phenotyping hypertensive patients through renin and aldosterone measurement has been supported by multiple observational studies and clinical trials, demonstrating benefits in blood pressure control, treatment rationalization, and identification of treatable secondary causes.

In a randomized trial, Egan et al.[32] compared a therapeutic algorithm guided by plasma renin activity in 77 patients with treated but uncontrolled hypertension versus usual care by specialists without access to renin levels. The algorithm classified patients with low PRA (< 0.65 ng/mL/h) as volume-dependent hypertension (V), treated with natriuretic agents (diuretics, aldosterone antagonists, calcium channel blockers, or alpha-blockers), and patients with high PRA (≥ 0.65 ng/mL/h) as renin-dependent (R), treated with RAAS blockers (ACE inhibitors, ARBs, or beta-blockers).

After follow-up, systolic blood pressure decreased significantly more in the renin-guided group (–29 ± 3 mmHg) than in the control group (–19 ± 3 mmHg; p = 0.03), and the blood pressure control rate (< 140/90 mmHg) was 74% versus 59%, respectively. The total number of drugs used was similar (~3 per patient), but with more rational use: inappropriate use of RAAS blockers in low-PRA patients was reduced by 60%.

These results demonstrated that renin-guided therapy improved blood pressure control without increasing pharmacologic burden by aligning treatment with the predominant pathophysiological mechanism.

In Africa, the study by Akintunde et al.,[33] a multicenter randomized trial including 105 patients with uncontrolled hypertension, compared usual care versus a physiologically individualized treatment strategy based on renin and aldosterone measurement. At 12 months, blood pressure control (< 140/90 mmHg) was achieved in 50% of patients in the hormonal-guided group versus 11.1% in the control group (p = 0.0001). Mean systolic blood pressure dropped from 170 ± 18 to 139 ± 17 mmHg, without differences in the number of medications or frequency of medical visits. The benefit was particularly pronounced in Nigeria and South Africa, where systolic control reached 78.6% vs 15% (p < 0.0001).

Furthermore, the study revealed a high prevalence of hyporeninemic and Liddle-like phenotypes, as well as primary aldosteronism, confirming the clinical relevance of using amiloride or aldosterone antagonists according to individual hormonal profiles.

In Latin America, the study by Durán et al.[34] in Afro-Colombian patients with resistant hypertension provided local evidence. Through measurement of direct renin and aldosterone, patients were classified into physiological phenotypes, identifying a high frequency of Liddle-like and hyporeninemic profiles. Using different cutoffs for the aldosterone-direct renin ratio (ADRR), the prevalence of suspected primary aldosteronism ranged from 4.5% to 23%.[34]

Overall, these studies confirm that a physiological approach guided by renin and aldosterone enables effective personalization of antihypertensive therapy, particularly useful in patients with resistant or poorly controlled hypertension, and especially relevant in Afro-descendant and mixed populations in Latin America.

Clinical applicability and limitations

The personalized hormonal approach to hypertension has a strong pathophysiological basis and promising clinical evidence. However, its implementation in clinical practice faces technical, logistical, and knowledge-related limitations.

Although this approach focuses on the measurement of renin and aldosterone, it is important to recognize that other hormonal alterations may contribute to hypertension. These include dysfunction of the sympathetic axis, non-classical adrenal disorders, thyroid disease, and other endocrine conditions. A comprehensive evaluation of the patient should consider these potential etiologies to achieve complete and personalized management.

In many Latin American countries, plasma renin activity (PRA) and aldosterone concentration are not routinely available. Barriers include test costs, lack of inter-laboratory standardization, the need for specific sampling conditions, and general lack of familiarity with interpretation. Furthermore, renin and aldosterone are dynamic hormones sensitive to multiple factors: body position, timing, salt intake, stress, prior medications, and pharmacological stimulation. Measurements should ideally be performed under controlled conditions, taking these variables into account to ensure reliable phenotypic classification.

Although guidelines for evaluating primary aldosteronism recommend discontinuing medications that interfere with RAAS measurements, this may not be feasible in patients with severe hypertension or comorbidities. In such cases, phenotyping should be interpreted with caution but can still provide valuable therapeutic guidance.

Latin America has a high burden of resistant hypertension, often affecting populations with African, Indigenous, or mixed ancestry, in whom sodium retention mechanisms and low renin levels predominate. This suggests that a physiological approach may have an even greater impact in our region by identifying patients who would benefit from amiloride or spironolactone, rather than multiple ineffective empirical drug combinations.

However, other strategies for managing resistant hypertension should not be overlooked. For example, bioimpedance-based assessment of volume status, cardiac function, and peripheral resistance offers an alternative approach that may also guide drug selection effectively. These strategies are not mutually exclusive and may, in fact, be complementary, improving therapeutic outcomes in this subgroup of patients.[35,36]

Conclusions

Knowledge and evaluation of the renin-angiotensin-aldosterone axis enable a physiological and personalized approach to hypertension management, particularly useful in resistant cases. Identification of hormonal phenotypes through measurement of renin and aldosterone allows more precise treatment selection, improved blood pressure control, and reduction of unnecessary polypharmacy.

Studies in African and Latin American populations demonstrate that this approach is not only feasible but particularly relevant in settings where non-classical hormonal profiles predominate, such as salt-sensitive hypertension and the Liddle-like phenotype.

Despite its advantages, implementation faces practical barriers, mainly limited access to hormonal testing and lack of inclusion in local clinical guidelines. Progressive incorporation of this strategy into diagnostic and therapeutic algorithms for resistant hypertension may contribute to more precise, equitable, and effective medicine in Latin America.

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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 human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that an artificial intelligence tool, ChatGPT, was used to support the preparation of the manuscript and to assist in the generation of illustrative figures.

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ORIGINAL ARTICLE

Type 2 diabetes mellitus and clinical outcomes in peritoneal dialysis: a retrospective cohort study in a Peruvian public Hospital

Diabetes mellitus tipo 2 y desenlaces clínicos en diálisis peritoneal: estudio de cohorte retrospectiva en un hospital público peruano

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Abstract

Objective: *To examine whether type 2 diabetes mellitus (T2DM) is associated with all-cause mortality in peritoneal dialysis (PD), and to assess technique failure and first peritonitis.* **Material and methods:** *Retrospective cohort in a public Peruvian hospital (2020–2024). Mortality was analyzed with Cox models (crude, age/sex-adjusted) and a prespecified clinical Cox model additionally adjusting for cardiovascular disease and peritoneal transport status (PET; PET0 as "not available") using complete cases. Technique failure was assessed with Fine-Gray (death as competing event), and peritonitis with Poisson regression (log person-time offset).* **Results:** *Among 123 patients (61% with T2DM), 39 deaths occurred (29/75 vs 10/48). Cox estimates were imprecise (HR 1.49, 95% CI 0.72–3.08 crude; HR 1.59, 0.71–3.53 age/sex-adjusted). In the clinical model (n = 114; 36 deaths), the HR was 0.86 (0.37–2.00; p = 0.729). No clear differences were observed for technique failure (SHR 0.71, 0.28–1.79 crude; 0.86, 0.26–2.84 adjusted) or peritonitis (RR 0.91, 0.50–1.73).* **Conclusions:** *Crude mortality was higher in T2DM, but adjusted estimates were imprecise; clinically relevant effects in either direction cannot be excluded.*

Keywords: *Peritoneal dialysis. Diabetes mellitus type 2. Mortality. Kidney failure chronic. Proportional hazards models. Competing risks.*

Resumen

Objetivo: *Evaluar si la diabetes mellitus tipo 2 (DM2) se asocia con mortalidad por todas las causas en diálisis peritoneal (DP), y analizar falla de técnica y primer episodio de peritonitis.* **Material y métodos:** *Cohorte retrospectiva en hospital público peruano (2020–2024). La mortalidad se analizó con Cox (crudo, ajustado por edad y sexo) y un modelo clínico preespecificado que además ajustó por enfermedad cardiovascular y transporte peritoneal (PET; PET0 como "no disponible") en análisis complete-case. La falla de técnica se evaluó con Fine-Gray (muerte como evento competitivo) y la peritonitis con Poisson (offset de años-paciente).* **Resultados:** *Se incluyeron 123 pacientes (61% con DM2) y ocurrieron 39 muertes (29/75 vs 10/48). Las estimaciones de Cox fueron imprecisas (HR 1,49; IC 95%: 0,72–3,08 crudo; HR 1,59; 0,71–3,53 ajustado).*

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En el modelo clínico (n = 114; 36 muertes), HR 0,86 (0,37–2,00; p = 0,729). No se observaron diferencias claras en falla de técnica (SHR 0,71; 0,28–1,79 y 0,86; 0,26–2,84) ni en peritonitis (RR 0,91; 0,50–1,73). **Conclusión:** *La mortalidad cruda fue mayor en DM2, pero las estimaciones ajustadas fueron imprecisas; no se descartan efectos clínicamente relevantes en cualquiera de los sentidos.*

Palabras clave: *Diálisis peritoneal. Diabetes mellitus tipo 2. Mortalidad. Insuficiencia renal crónica. Modelos de riesgos proporcionales. Riesgos competitivos.*

Introduction

Diabetes mellitus is currently the most frequent cause of end-stage renal disease in many countries, and its prevalence continues to rise.[1] In some healthcare systems, nearly 60% of patients initiating renal replacement therapy have a diagnosis of diabetes, and this proportion has shown sustained growth over the past two decades.[2] In Latin America, the situation is similar, although limitations in access to home-based modalities such as peritoneal dialysis persist.[3]

Peritoneal dialysis (PD) offers relevant advantages for many patients, including greater autonomy, reduced hospital dependence, and better preservation of residual renal function during the first years of treatment[3]. However, evidence regarding clinical outcomes in diabetic patients treated with PD remains contradictory. Some meta-analyses have reported higher mortality in older individuals with diabetes or multiple comorbidities, particularly when treatment extends beyond three years[2,4]. In contrast, analyses adjusted for confounding factors using propensity score matching have found similar survival rates between patients on PD and those on hemodialysis[5].

Glycemic control in PD poses particular challenges. Continuous glucose absorption from the dialysate, which may reach between 100 and 200 g daily, makes it difficult to maintain stable glycemia and may worsen insulin resistance[6,7]. In addition, glycated hemoglobin loses reliability as a marker of metabolic control in advanced kidney disease due to alterations in erythrocyte lifespan and hemoglobin metabolism[1]. There are no clinical trials defining specific glycemic targets for this population, and most clinical studies on medications exclude patients undergoing dialysis.

Several studies have documented that diabetic patients on PD have a higher risk of cardiovascular mortality, peritonitis, and technique failure compared to non-diabetic patients[4,8]. Nevertheless, programs that include intensive training and structured follow-up have shown comparable outcomes between both groups[9]. In Latin America, information remains limited, and PD programs face logistical challenges such as geographic distances, scarcity of human resources, and variability in training protocols[10-12].

Based on these considerations, the primary objective of this study was to evaluate the association between diabetes mellitus and all-cause mortality in patients treated with peritoneal dialysis in a Peruvian public hospital. Secondary objectives included analyzing the relationship between diabetes and technique failure using competing risk models, comparing prescription and dialysis adequacy between groups, studying residual renal function as an effect modifier of outcomes, and determining the incidence of peritonitis. Finally, the potential modifying effect of sex on the association between diabetes and clinical outcomes was explored.

Methods

Study design and setting

We conducted a retrospective cohort study at *Hospital II-2 Tarapoto*, a 200-bed public referral center located in the San Martín region, in the Peruvian Amazon. The hospital has a peritoneal dialysis program that applies standardized protocols for catheter placement, patient training, and monthly follow-up. The cohort included all patients who initiated chronic PD between January 1, 2020, and December 31, 2024.

Participants

All patients > 18 years who initiated chronic PD during the study period and had at least 1 documented follow-up visit were included. Those with fewer than 30 days of observation were excluded, except for individuals who died or experienced technique failure within that period. Patients transferred from other dialysis programs and those with insufficient information to classify the primary exposure were also excluded.

Definition of exposure

The primary exposure was a diagnosis of diabetes mellitus prior to the initiation of PD, defined according

to the criteria of the American Diabetes Association: glycated hemoglobin ≥ 6.5%, fasting glucose ≥ 126 mg/dL on two occasions, 2-hour glucose ≥ 200 mg/dL during an oral glucose tolerance test, or random glucose ≥ 200 mg/dL with typical symptoms[1]. Diabetes was considered present in any patient with a prior medical diagnosis or receiving treatment with hypoglycemic agents.

Endpoints

The primary endpoint was all-cause mortality during follow-up, verified through death certificates or hospital records.

Secondary endpoints included:

- Technique failure: defined as permanent transfer to hemodialysis for any cause other than transplantation or recovery of renal function.
- Peritonitis: diagnosed according to the criteria of the International Society for Peritoneal Dialysis (ISPD), which require abdominal pain, cloudy effluent, and/or a cell count > 100 leukocytes/μL with at least 50% neutrophils[13].
- Dialysis prescription and adequacy: number of daily exchanges, infused volume, use of icodextrin-containing solutions, and weekly Kt/V values and creatinine clearance.
- Residual renal function: measured by urea and creatinine clearance in 24-hour urine.

Data sources and measurements

Information was obtained from electronic and paper medical records using a standardized form. Sociodemographic, anthropometric, and clinical variables were collected, including age, sex, body mass index, primary kidney disease, prior hemodialysis, cardiovascular comorbidities, and laboratory results (hemoglobin, albumin, creatinine, blood urea nitrogen, calcium, phosphorus, and parathyroid hormone).

Prescription data were obtained from monthly medical orders, and adequacy measurements were performed quarterly according to international guidelines.

Bias

The possibility of confounding by indication was assessed, considering that diabetic patients might have been more frequently referred to HD based on clinical judgment. When available, the reason for modality selection was recorded.

Misclassification bias of diabetes was reduced through cross-verification of recorded diagnoses and treatments.

To avoid bias in peritonitis detection, uniform diagnostic criteria and standard education on warning signs were applied.

Loss to follow-up was documented, and attempts were made to contact absent patients by telephone to verify their vital status.

Sample size

The cohort was considered a complete census of patients treated during the study period; therefore, no sample size calculation was performed.

Adjustment variables

Multivariable models included variables selected based on biological plausibility: age, sex, body mass index, primary kidney disease, history and duration of hemodialysis, cardiovascular disease, albumin, hemoglobin, peritoneal transport (when available), residual renal function, and mean Kt/V[4,14].

Statistical analysis

Continuous variables were described as mean (SD,) or median (IQR,) according to distribution; categorical variables as frequencies and percentages. Comparisons between patients with and without type 2 diabetes mellitus were performed using Student's *t* test or Mann-Whitney test, and chi-square or Fisher's exact test, as appropriate.

All-cause mortality was analyzed using Cox proportional hazards models with 2 specifications: crude model and model adjusted for age and sex. Additionally, to address relevant clinical confounding, a primary clinical model (S_PET1) for mortality was defined a priori, adjusting for age (continuous), sex, cardiovascular disease (yes/no), and peritoneal transport (categorical PET: PET_0_not_available, PET_2, PET_3, PET_4). This model was estimated using complete-case analysis, reporting N and the number of included events. Any convergence warnings related to PET categories with a low number of events were documented.

The proportional hazards assumption was evaluated using Schoenfeld residuals and log-log plots.

Technique failure was evaluated within a competing risks framework, considering death as a competing event, using Fine-Gray models in crude and age- and

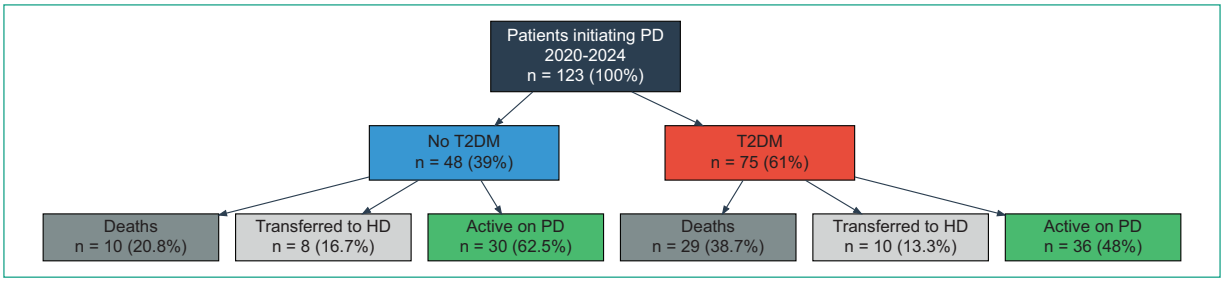


Figure 1. Participant flow diagram. Flow from the total number of patients who initiated peritoneal dialysis (n = 123) to the final distribution according to diabetic status, including outcomes (deceased, transferred to hemodialysis, active on peritoneal dialysis at the end of follow-up).

sex-adjusted versions; cumulative incidence functions are presented.

Peritonitis (first episode) was modeled using Poisson regression including a log(patient-years) offset. Overdispersion was assessed; if identified, a quasi-Poisson specification was used (the final choice is reported in the results).

Analyses were performed using R version 4.3.3[15]. The significance level was set at 0.05 (2-tailed).

Ethical considerations

The study was approved by the Research Ethics Committee of *Hospital II-2 Tarapoto*. A waiver of informed consent was granted due to the retrospective nature of the study and the exclusive use of anonymized data. The study was conducted in accordance with the Declaration of Helsinki (2013) and current Peruvian regulations on health research[16].

Results

Participant flow and baseline characteristics

The cohort included 123 patients who met the inclusion criteria (Fig. 1). Of these, 75 (61%) had type 2 diabetes mellitus and 48 (39%) did not. Baseline characteristics are summarized in table 1. For the primary clinical mortality model (S_PET1), 114 patients with complete covariates were available; 9 were excluded from the multivariable analysis due to missing data. In this subset, 36 deaths occurred.

Diabetic patients were older (mean, 55.9 years [SD, 8.6] vs. 48.0 years [SD, 16.8]; *p = *0.001). No significant differences were observed between groups in terms of sex, body mass index, serum albumin, or residual renal function at the initiation of peritoneal dialysis (Fig. 1) (Table 1).

Table 1. Baseline characteristics according to diabetic status

Characteristic	Global (n = 123)	Without T2DM (n = 48)	With T2DM (n = 75)	p
Age, years, mean (SD)	52.8 (12.9)	48.0 (16.8)	55.9 (8.6)	0.001
Female sex, n (%)	72 (58.5)	26 (54.2)	46 (61.3)	0.549
BMI, kg/m², mean (SD)	24.5 (4.7)	24.9 (4.1)	24.2 (5.1)	0.657
Serum albumin, g/dL, mean (SD)	2.8 (1.1)	3.0 (1.1)	2.6 (1.0)	0.113
Weekly Kt/V, mean (SD)	1.77 (0.55)	1.89 (0.53)	1.69 (0.56)	0.196
RRF, mL/min/1.73 m², mean (SD)	3.4 (4.4)	4.2 (4.3)	2.9 (4.4)	0.300

SD: standard deviation; T2DM: type 2 diabetes mellitus; RRF: residual renal function; BMI: body mass index; Kt/V: dialysis adequacy index. Comparisons were performed using Student's *t* test or Mann-Whitney *U* test according to distribution.

Follow-up and events

Total follow-up time was 153.2 patient-years (median follow-up 10.2 months; IQR, 4.1-18.6 months). A total of 39 deaths were recorded (32%): 29 in the diabetes group (39% of the group) and 10 in the non-diabetes group (21% of the group). Eighteen permanent transfers to hemodialysis (technique failure) were documented: 10 in diabetic patients (13%) and 8 in non-diabetic patients (17%). (Table 2).

Mortality

The mortality rate was higher in the diabetic group (28.8 per 100 patient-years; 95% CI, 19.3-41.4) than in the non-diabetic group (19.0 per 100 patient-years; 95%

Table 2. Incidence of outcomes according to diabetic status

Outcome	Group	Episodes (n)	Patient-years	Rate per 100 PY (95% CI)
All-cause mortality	Without T2DM	10	52.6	19.0 (9.1-35.0)
	With T2DM	29	100.6	28.8 (19.3-41.4)
Technique failure (transfer to HD)	Without T2DM	8	52.6	15.2 (6.6-30.0)
	With T2DM	10	100.6	9.9 (4.8-18.3)
Peritonitis (first episode)	Without T2DM	16	52.6	30.4 (17.4-49.4)
	With T2DM	28	100.6	27.8 (18.5-40.2)

Rates and confidence intervals were calculated using a Poisson distribution.
PY: patient-years; T2DM: type 2 diabetes mellitus; HD: hemodialysis; CI: confidence interval.

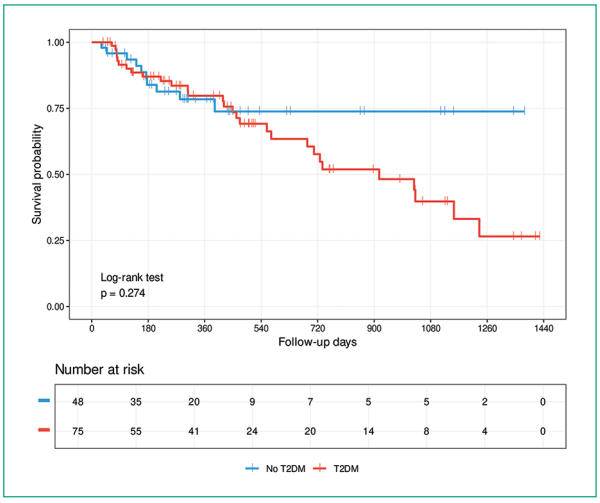


Figure 2. Kaplan-Meier survival according to diabetic status. Unadjusted curves for patients with and without diabetes.

Table 3. Cox regression models for all-cause mortality

Model	HR	95% CI	p
Crude (T2DM vs without T2DM)	1.49	0.72-3.08	0.280
Adjusted for age and sex	1.59	0.71-3.53	0.256
Main clinical model (age, sex, CVD, and PET)	0.86	0.37-2.00	0.729

The adjusted model includes age (continuous variable) and sex (male as reference). Proportional hazards assumptions were verified using Schoenfeld residuals. The main clinical model was estimated using complete-case analysis (n = 114; 36 events) and included CVD (yes/no) and categorical PET (PET_0_not_available, PET_2, PET_3, PET_4).
T2DM: type 2 diabetes mellitus; HR: hazard ratio; CI: confidence interval.

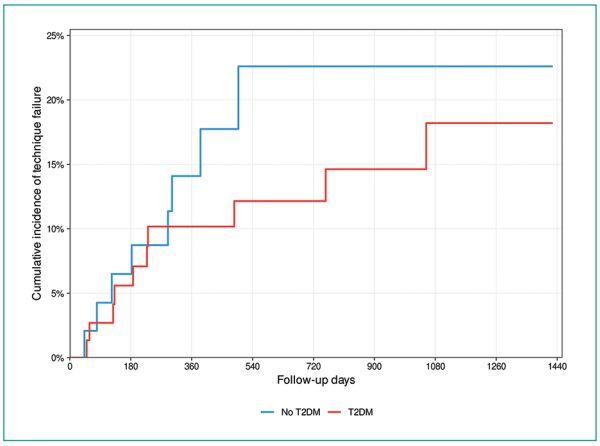


Figure 3. Cumulative incidence of technique failure (competing risks analysis). Fine-Gray cumulative incidence functions (transfer to hemodialysis as the event), considering death as a competing event.

CI, 9.1-35.0). In Cox models, diabetes was not statistically significantly associated with mortality (crude model HR, 1.49; 95% CI, 0.72-3.08; adjusted for age and sex HR, 1.59; 95% CI, 0.71-3.53) (Fig. 2).

In the Cox proportional hazards analysis (Table 3), the crude model showed a hazard ratio (HR) of 1.49 (95% CI, 0.72-3.08; p = 0.280) for diabetes versus no diabetes. After adjustment for age and sex, the HR was 1.59 (95% CI, 0.71-3.53; p = 0.256). Proportional hazards assumptions were verified using Schoenfeld residuals (p > 0.05 for all covariates).

In the prespecified clinical model incorporating cardiovascular disease and PET (S_PET1), diabetes was not associated with mortality (HR, 0.86; 95% CI, 0.37-1.996; p = 0.729; n = 114; 36 deaths). A convergence warning was observed for the PET_2 category, consistent with a low number of events; the estimate of the main effect of diabetes was stable.

Technique failure (competing risks)

In the analysis considering death as a competing event, technique failure rates were 15.2 per 100 patient-years (95% CI, 6.6-30.0) in the non-diabetic group and 9.9 per 100 patient-years (95% CI, 4.8-18.3) in the diabetic group (Table 2). Cumulative incidence functions showed overlap between groups (Fig. 3).

Table 4. Fine-Gray competing risk regression models for technique failure

Model	SHR	95% CI	p
Crude (T2DM vs without T2DM)	0.71	0.28-1.79	0.470
Adjusted for age and sex	0.86	0.26-2.84	0.810

Death was treated as a competing event. The adjusted model includes age (continuous variable) and sex (male as reference).
T2DM: type 2 diabetes mellitus; CI: confidence interval; SHR: subdistribution hazard ratio.

In Fine-Gray models (Table 4), the crude subdistribution hazard ratio (SHR) was 0.71 (95% CI, 0.28-1.79; p = 0.47) for diabetes versus no diabetes. After adjustment for age and sex, the SHR was 0.86 (95% CI, 0.26-2.84; p = 0.81).

Prescription and dialysis adequacy

Prescription and dialysis adequacy parameters are summarized in table 5. No significant differences were observed between diabetic and non-diabetic groups in the number of daily exchanges, infused volume, total weekly Kt/V, peritoneal fluid-derived Kt/V, or residual Kt/V. Residual diuresis was numerically higher in the non-diabetic group (median 280 mL vs 20 mL in diabetics), although with wide variability. Peritoneal ultrafiltration was similar between groups (median 1455.5 mL in non-diabetics vs 1510.5 mL in diabetics) (Table 5).

Peritonitis incidence

A total of 44 first episodes of peritonitis were documented during follow-up: 16 in patients without diabetes (30.4 per 100 patient-years; 95% CI, 17.4-49.4) and 28 in patients with diabetes (27.8 per 100 patient-years; 95% CI, 18.5-40.2) (Table 2). In the adjusted analysis using Poisson regression (Table 6), the rate ratio (RR) for diabetes versus no diabetes was 0.91 (95% CI, 0.50-1.73; p = 0.78).

Discussion

This study evaluated the association between type 2 diabetes mellitus and clinical outcomes in patients treated with peritoneal dialysis in a Peruvian public hospital. Crude mortality was higher in the diabetes group (28.8 vs 19.0 per 100 patient-years), but Cox models did not show a conclusive association after adjustment. In the model adjusted for age and sex, the estimate was imprecise (HR, 1.59; 95% CI, 0.71-3.53),

Table 5. Dialysis prescription and adequacy according to diabetic status

Variable	Without T2DM (n = 25)	With T2DM (n = 39)
D/Pcr, median (IQR)	0.77 (0.66-0.84)	0.76 (0.69-0.88)
Diuresis, mL, median (IQR)	280 (0-650)	20 (0-212.5)
CAPD dose, L, median (IQR)	86 (75-103)	83 (68.5-98.5)
Kt/V CAPD fluid, median (IQR)	1.65 (1.51-1.92)	1.55 (1.34-1.88)
Residual Kt/V, median (IQR)	0.07 (0-0.36)	0 (0-0.13)
Total Kt/V, median (IQR)	1.80 (1.60-2.08)	1.68 (1.39-2.01)
Peritoneal ultrafiltration, mL, median (IQR)	1455.5 (1071-1789.3)	1510.5 (1287.5-1812.5)

Available n values per variable are indicated in parentheses. Comparisons between groups were not statistically significant (p > 0.05 for all variables).
D/Pcr: dialysate/plasma creatinine ratio; T2DM: type 2 diabetes mellitus; CAPD: continuous ambulatory peritoneal dialysis; Kt/V: dialysis adequacy index; IQR: interquartile range.

Table 6. Poisson regression model for peritonitis incidence

Variable	RR	95% CI	p
T2DM (vs without T2DM)	0.91	0.50-1.73	0.775

The model shows no significant association between diabetic status and peritonitis incidence.
T2DM: type 2 diabetes mellitus; CI: confidence interval; RR: rate ratio.

and in the pre-specified clinical model that incorporated cardiovascular disease and peritoneal transport (PET), the association remained non-significant (HR, 0.86; 95% CI, 0.37-2.00). Overall, these findings suggest that the crude difference may be influenced by clinical confounding, and that the sample size limits precision to rule out clinically relevant effects in either direction. No differences were observed in technique failure, peritonitis, or dialysis adequacy parameters between groups.

The relationship between diabetes and mortality in peritoneal dialysis has generated contradictory results in the literature. A recent meta-analysis by Cheng et al.[2] showed that peritoneal dialysis was associated with higher mortality than hemodialysis in older adults with diabetes (HR, 1.17; 95% CI, 1.10-1.25), particularly when treatment duration exceeded three years. In our

cohort, crude mortality was also higher in diabetes, but adjusted estimates were imprecise and did not allow a conclusive association to be established. The width of the confidence intervals suggests limited precision due to sample size and follow-up duration (median 10.2 months), so clinically relevant effects in either direction cannot be ruled out.

In contrast, recent studies using propensity score matching have shown more favorable results. Xu et al.[5] reported similar survival rates between diabetic patients treated with peritoneal dialysis and hemodialysis in China, suggesting that modality choice should be individualized according to patient characteristics. Similarly, Liu et al.[17] found that peritoneal dialysis was associated with better survival in diabetic patients when compared with hemodialysis using competing risk analyses. A very recent meta-analysis by Nardelli et al.[18] concluded that both modalities offer equivalent survival benefits in the general population, although differences according to age and geographic location were identified.

The mean age of our diabetic patients (55.9 years) was lower than that reported in series from developed countries, where patients older than 65 years predominate. This demographic difference could partially explain the lower mortality in our cohort, as the deleterious effect of diabetes on survival appears to be magnified with advanced age and the presence of multiple comorbidities, as reported by Zhang et al.[4] in their meta-analysis of risk factors in peritoneal dialysis.

A relevant finding was the absence of an association between diabetes and technique failure when death was considered a competing event (SHR, 0.86; 95% CI, 0.26-2.84; p = *0.81). This result contrasts with the traditional clinical perception that diabetic patients are at higher risk of discontinuing peritoneal dialysis. Chen et al.[14] used Fine-Gray models in a Taiwanese cohort and found that diabetes was not an independent predictor of technique failure after adjusting for confounders, supporting our findings.

The high proportion of patients with a past medical history of hemodialysis in our cohort (76%) deserves special consideration. Sun et al.[19] demonstrated in a meta-analysis that prior hemodialysis does not increase peritoneal dialysis dropout rates, although it may influence mortality. This phenomenon may reflect a selection bias, where patients who successfully transition to peritoneal dialysis after hemodialysis represent a group with better adaptive capacity and lower comorbidity burden.

The peritonitis rate was similar between diabetic and non-diabetic patients (27.8 vs 30.4 per 100 patient-years; RR, 0.91; 95% CI, 0.50-1.73). This finding is consistent with recent multicenter studies. Meng et al.[8] reported in China that, although diabetic patients had slightly different microbiological profiles (higher frequency of coagulase-negative *Staphylococcus*), the overall incidence of peritonitis was comparable between groups. Our results support this observation, suggesting that standardized training and follow-up protocols may mitigate the risk traditionally attributed to diabetes.

The study by Cotovio et al.[9] in Portugal showed that peritoneal dialysis programs with intensive training achieved satisfactory outcomes in diabetic patients despite the risk of loss of autonomy. This finding underscores the importance of program organization and training quality as key determinants of outcomes, beyond individual patient characteristics.

A recent meta-analysis by Zhao et al.[20] on risk prediction models for peritonitis identified diabetes as a significant predictor (OR, 3.55; 95% CI, 1.27-5.83), along with low albumin, elevated C-reactive protein, and neutrophil-to-lymphocyte ratio. The absence of association in our study may be due to differences in design (retrospective observational study versus prospective prediction models) or to variations in clinical management practices across centers.

Wijewickrama et al.[21] highlight in their narrative review the complexities of glycemic management in peritoneal dialysis, including the continuous absorption of glucose from the dialysate (100-200 g daily), which complicates metabolic control. In our study, residual renal function was numerically higher in the non-diabetic group (4.2 vs 2.9 mL/min/1.73 m^2), although this did not reach statistical significance. Preservation of residual renal function is an important determinant of survival in peritoneal dialysis, and its more rapid decline in diabetic patients may contribute to the excess mortality observed in longer-term studies.

A recent study by Xu et al.[22] identified a significant interaction between fasting glucose and LDL cholesterol on mortality in peritoneal dialysis, demonstrating that elevated glucose levels (≥ 7.0 mmol/L) were associated with higher mortality only in patients with LDL-C ≥ 3.37 mmol/L. This finding suggests that glycemic and lipid control should be addressed jointly in the diabetic peritoneal dialysis population. Wijewickrama et al.[21] documented in a multicenter clinical audit that 15% of diabetic patients on peritoneal dialysis had impaired hypoglycemia awareness and 21% reported at least one monthly hypoglycemic event, highlighting the complexity of glycemic management in this population.

The strengths of this study include the use of appropriate statistical models for the analysis of outcomes in peritoneal dialysis, specifically Fine-Gray models that consider death as a competing event for technique failure. This methodological approach, similar to that used by Chen et al.,[14] allows for more accurate estimation of the true incidence of transfer to hemodialysis without overestimating risk. In addition, the study provides valuable information from a Latin American setting with limited resources, where evidence on peritoneal dialysis in diabetic patients is scarce.

The main limitations include the retrospective design with its inherent biases, the limited sample size reducing statistical power to detect smaller differences, and the relatively short follow-up. The absence of information on longitudinal glycemic control, specific use of hypoglycemic agents, and hypoglycemic events prevents assessment of the impact of metabolic management on outcomes. Additionally, the main clinical model required a complete-case approach due to missing data in covariates (114/123 patients), which may introduce bias if data are not missing at random and reduces the effective number of analyzed events. In the PET component, the PET_2 category showed instability due to a low number of events; therefore, category-specific results should be interpreted with caution. Finally, the single-center nature limits generalizability to other peritoneal dialysis programs in the region.

The results of this study suggest that in programs with structured training and monthly follow-up, diabetes alone does not determine worse survival or higher technique dropout during the observed period. Modality selection may therefore focus on patient preference, social support, and home feasibility, accompanied by an individualized metabolic plan and standardized measures for the prevention and management of peritonitis.[3,8]

Future research should focus on prospective multicenter studies with longer follow-up evaluating specific strategies for glycemic management, preservation of residual renal function, and prevention of cardiovascular complications in diabetic patients undergoing peritoneal dialysis. Additionally, there is a need to develop risk prediction models adapted to Latin American contexts that incorporate socioeconomic variables and health system organization.

The findings of this study are applicable to public peritoneal dialysis services with structured training protocols, access to antibiotics, and catheter replacement capability. Their transfer to settings with different infrastructure, greater use of icodextrin, or different thresholds for modality switching requires cautious interpretation.

Conclusions

In this retrospective cohort study conducted in a Peruvian public hospital, type 2 diabetes mellitus showed higher crude mortality, but adjusted estimates were imprecise and did not allow a conclusive association with mortality, technique failure, or peritonitis in patients treated with peritoneal dialysis.

Dialysis prescription and adequacy parameters were similar between diabetic and non-diabetic patients. These findings suggest that peritoneal dialysis may be an appropriate alternative for selected diabetic patients when standardized training and follow-up protocols are implemented.

Multicenter studies with larger sample sizes and longer follow-up are required to confirm these results and to evaluate the impact of specific interventions on glycemic control and preservation of residual renal function in this population.

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Conflicts of interest

The authors declare that IS works for Vantive. The remaining authors declare that there are no financial or personal conflicts of interest that could have inappropriately influenced the conduct, analysis, or presentation of this study.

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Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected

and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

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

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ORIGINAL ARTICLE

Influence of body weight on biochemical alterations in patients with kidney stones

Influencia del peso corporal sobre las alteraciones bioquímicas en pacientes con litiasis renal

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Abstract

Objective: *To determine the prevalence of metabolic disorders in patients with kidney stones, to analyze sex-specific differences in anthropometric and biochemical parameters according to body weight, and to evaluate the association between body mass index (BMI) and key biomarkers, including creatinine, uric acid, urea, vitamin D, and parathyroid hormone (PTH).* **Material and methods:** *A retrospective observational study was conducted in adult patients with confirmed kidney stones. Participants were classified according to BMI as normal weight, overweight, or obese. Demographic, anthropometric, and biochemical data were obtained from medical records. Serum parameters included creatinine, calcium, phosphorus, uric acid, urea, sodium, potassium, vitamin D, and PTH. Urinary parameters included 24-hour urine volume, pH, creatinine, calcium, citrate, oxalate, magnesium, uric acid, sodium, and potassium.* **Results:** *Excess body weight was associated with a progressive increase in urinary uric acid excretion in both sexes. In obese men, significantly lower vitamin D levels, a more acidic urinary pH, increased urinary excretion of calcium, uric acid, and electrolytes, and a higher prevalence of diabetes and multiple metabolic disorders were observed. Overweight and obese women showed higher serum uric acid and urea levels, lower vitamin D concentrations, more acidic urinary pH, and increased urinary excretion of creatinine, phosphorus, uric acid, sodium, and potassium.* **Conclusions:** *Obesity is associated with pro-lithogenic metabolic and urinary alterations, including hyperuricemia, acidic urinary pH, and increased electrolyte excretion, which may contribute to an increased risk of kidney stone formation and recurrence.*

Keywords: *Kidney stones. Obesity. Metabolic profile. Body mass index.*

Resumen

Objetivo: *Determinar la prevalencia de trastornos metabólicos en pacientes con litiasis renal; analizar diferencias en parámetros antropométricos y bioquímicos según el peso; y evaluar la relación entre IMC y niveles de biomarcadores clave (creatinina, ácido úrico, urea, vitamina D, PTH).* **Materiales y métodos:** *Estudio observacional retrospectivo en pacientes con*

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litiasis renal. Se agruparon en bajo peso, normopeso, sobrepeso y obesidad. Se registraron datos antropométricos y bioquímicos en sangre y orina incluyendo vitamina D, pH urinario, calcio, ácido úrico, creatinina, fósforo, sodio, potasio y electrolitos. **Resultados:** *El exceso de peso se asoció con un aumento progresivo de ácido úrico urinario en ambos sexos. En hombres obesos, se halló vitamina D significativamente reducida, pH urinario más ácido, mayor excreción de calcio, ácido úrico y electrolitos, y una prevalencia más elevada de diabetes y trastornos metabólicos. En mujeres con sobrepeso y obesidad, se observaron niveles sanguíneos elevados de ácido úrico y urea, disminución de vitamina D, pH más ácido y excreción urinaria aumentada de creatinina, fósforo, ácido úrico, sodio y potasio.* **Conclusiones:** *La obesidad se vincula con alteraciones bioquímicas y urinarias pro-litogénicas (ácido úrico elevado, pH bajo, excreción aumentada de electrolitos), aumentando el riesgo de cálculos renales.*

Palabras claves: *Litiasis renal. Obesidad. Perfil bioquímico. Peso corporal.*

Introduction

Renal lithiasis (RL) is a complex systemic condition whose etiology involves both intrinsic factors, such as genetic predisposition, race, age, and sex, as well as extrinsic factors, including geographic location, climate, diet, and occupational conditions.[1] This disease presents a high prevalence, incidence, and recurrence rate, and carries a considerable risk of irreversible renal damage. In industrialized countries, it is estimated that up to 12% of men and 7% of women will develop kidney stones throughout their lifetime.[2]

In Argentina, the increase in overweight and obesity rates among adults in recent years adds an additional concern.[3-5] According to the 4th National Survey of Risk Factors, more than 66% of Argentine adults are overweight.[6] Furthermore, RL has been locally associated with an increased cardiovascular risk, highlighting its nature as a sign of a systemic disorder.[7]

This phenomenon is relevant, as studies such as the National Health and Nutrition Examination Survey (NHANES) in the United States (2007-2010) have demonstrated a higher prevalence of kidney stones in individuals with obesity (11.2%) and overweight (9.1%) compared to those with normal weight (6.1%).[8,9] In men, the relative increase in stone formation between the periods 1988-1994 and 2007-2010 was 63%, rising from 6.3% to 10.3%.[9,10]

Several studies have confirmed an association between body mass index (BMI) and the frequency of RL, with a high prevalence of obesity in these patients, ranging from 10% to 35%.[11-14] The risk of developing renal lithiasis is considerably higher in individuals with a BMI ≥ 30 vs those with a BMI of 21 to 22.9 kg/m^2. In particular, the relative risk of kidney stones in individuals with a BMI > 30 kg/m^2 has been estimated at 2.09 in young women, 1.90 in older women, and 1.33 in men.[15]

Excess weight contributes to metabolic imbalances and alterations in urinary composition, predisposing to kidney stone formation.[3-5] Over the past two decades, various mechanisms have been explored to explain the relationship between obesity and nephrolithiasis. These include dietary factors such as increased caloric and refined sugar intake, low fluid intake, consumption of purine-rich foods, and lifestyle changes.[16,17] Additionally, associated renal alterations have been described, such as acid–base imbalances and chemical modifications in urine composition, which further increase the risk of lithiasis.[18]

This research arises from the need to more precisely characterize the biochemical profile of patients with renal lithiasis according to body weight, as few studies have explored the underlying biochemical mechanisms in depth. While studies in Argentina have provided valuable data on the general etiology of RL.[19] or its relationship with cardiovascular risk.[7] there remains a gap in the detailed evaluation of specific metabolic alterations (such as insulin resistance, vitamin D-PTH axis alterations, and acid-base balance) in lithiasic patients stratified by BMI and sex. A recent local report has also highlighted obesity as an independent risk factor for RL.[20]

Therefore, the objectives of this study are to determine the prevalence of obesity, diabetes, and metabolic disorders in a population diagnosed with renal lithiasis, differentiating between men and women; to analyze differences in anthropometric and biochemical parameters between men and women according to body weight (normal weight, overweight, and obesity); and to evaluate the relationship between body weight and levels of key biomarkers (creatinine, uric acid, urea, vitamin D, and parathyroid hormone) in men and women. This will allow for a better understanding of the pathophysiology of renal lithiasis in the context of obesity and may contribute to the identification of useful clinical biomarkers in these patients.

Table 1. Baseline characteristics of the population by sex

Parameter	Men (n = 616)	Women (n = 695)	p
BMI (kg/m^2)	27.52 ± 4.32 (95% CI, 27.18-27.86)	24.95 ± 4.89 (95% CI, 24.58-25.32)	< 0.01
Cr (mg/dL)	1.02 ± 0.19 (95% CI, 1.00-1.04)	0.75 ± 0.14 (95% CI, 0.74-0.76)	< 0.01
Vitamin D (ng/mL) (n = 668)	25.85 ± 9.51 (95% CI, 25.13-26.57)	30.56 ± 11.47 (95% CI, 29.72-31.40)	< 0.01
Obesity, n (%)	23% (144) 95% CI, 20-26	15% (105) 95% CI, 13-18	< 0.01
Diabetes, n (%)	9% (54) 95% CI, 7-12	5% (35) 95% CI, 4-7	< 0.01

BMI: body mass index; Cr: creatinine.

Materials and methods

Study design

We conducted a quantitative observational, analytical study in a sample of patients older than 18 years with a confirmed diagnosis of renal lithiasis treated at a reference healthcare institution between January 2010 and December 2020. The study was approved by the institutional ethics committee, and all procedures were carried out in accordance with the principles of the Declaration of Helsinki.

Population and sample

The study population included patients diagnosed with nephrolithiasis by ultrasound, computed tomography, or stone analysis after spontaneous passage. To be eligible, participants had to have a complete biochemical profile and be classified into one of three body weight groups: normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), and obesity (BMI ≥ 30 kg/m^2). Patients with advanced chronic diseases, such as chronic kidney disease or neoplasms that could affect the biochemical profile, were excluded.

Data collection

Data were collected from medical records, including demographic (age, sex), anthropometric (weight, height, BMI), and clinical information. Biochemical analysis results were also retrieved for all patients, including:

Serum: creatinine (Cr), calcium (Ca), phosphorus (P), uric acid (UA), urea, sodium (Na), and potassium (K).

Urinary: 24-hour urine volume, pH, creatinine, calcium (CaU), citrate (Cit), oxalate (Ox), magnesium (Mg), uric acid, sodium, and potassium.

Additionally, the presence of diabetes mellitus and the diagnosis of multiple metabolic disorders were evaluated, defined as the coexistence of 2 or more of the following conditions: obesity (BMI ≥ 30 kg/m^2), diabetes mellitus (previous diagnosis or fasting glucose ≥ 126 mg/dL), dyslipidemia (LDL cholesterol ≥ 160 mg/dL or triglycerides ≥ 150 mg/dL or use of lipid-lowering agents), and hypertension (previous diagnosis or blood pressure ≥ 140/90 mmHg).[21]

Statistical analysis

Quantitative variables were expressed as mean ± SD, while categorical variables were expressed as frequency and percentage. For comparisons among the three weight groups (normal weight, overweight, and obesity), ANOVA was used for continuous variables and the chi-square test for categorical variables. Correlations between biochemical variables and BMI were evaluated using Pearson or Spearman tests, depending on data distribution. The level of statistical significance was set at $p \leq 0.05$, and the analysis was performed using SPSS software v.29.

Results

The analysis of baseline characteristics by sex (Table 1) included 616 men and 695 women diagnosed with renal lithiasis. Statistically significant differences were identified in anthropometric and biochemical parameters relevant to the metabolic profile.

Determination of the prevalence of obesity, diabetes, and metabolic disorders in a population with renal lithiasis, differentiating between men and women

Baseline characteristics by sex

The prevalence of obesity was greater in men, reaching 23% (95% CI, 20%-26%), while in women it was

Table 2. Laboratory parameters in men according to body weight

Parameter	Normal weight (n = 185/30%)	Overweight (n = 287/47%)	Obese (n = 144/23%)	p
Cr (mg/dL)	0.97 ± 0.15 (95% CI, 0.95-0.99)	1.04 ± 0.18 (95% CI, 1.02-1.06)	1.05 ± 0.24 (95% CI, 1.01-1.09)	< 0.01
Uric acid (mg/dL)	5.43 ± 1.09 (95% CI, 5.28-5.58)	5.96 ± 1.27 (95% CI, 5.81-6.11)	6.29 ± 1.53 (95% CI, 6.04-6.54)	< 0.01
Urea (mg/dL)	35.05 ± 7.80 (95% CI, 33.93-36.17)	37.60 ± 9.29 (95% CI, 36.53-38.67)	37.44 ± 9.48 (95% CI, 35.90-38.98)	< 0.01
PTH (ng/dL) (n = 735)	43.15 ± 16.66 (95% CI, 40.75-45.55)	48.16 ± 16.54 (95% CI, 46.24-50.08)	49.34 ± 25.01 (95% CI, 45.25-53.43)	< 0.05
Vitamin D (ng/mL) (n = 668)	26.72 ± 9.21 (95% CI, 25.41-28.03)	26.66 ± 9.43 (95% CI, 25.58-27.74)	22.95 ± 9.65 (95% CI, 21.30-24.60)	< 0.05

Cr: creatinine; PTH: parathyroid hormone; 95% CI: 95% confidence interval.

Table 3. Laboratory parameters in women according to body weight

Parameter	Normal weight (n = 403/58%)	Overweight (n = 185/27%)	Obese (n = 107/15%)	p
Uric acid (mg/dL)	4.06 ± 0.98 (95% CI, 3.97-4.15)	4.46 ± 1.13 (95% CI, 4.30-4.62)	5.06 ± 1.23 (95% CI, 4.83-5.29)	< 0.01
Urea (mg/dL)	31.20 ± 9.28 (95% CI, 30.29-32.11)	34.28 ± 10.73 (95% CI, 32.74-35.82)	34.53 ± 9.98 (95% CI, 32.64-36.42)	< 0.01
Vitamin D (ng/mL)	31.61 ± 11.85 (95% CI, 30.44-32.78)	30.00 ± 11.35 (95% CI, 28.37-31.63)	27.24 ± 9.33 (95% CI, 25.47-29.01)	< 0.05
Urine pH	5.89 ± 0.57 (95% CI, 5.83-5.95)	5.81 ± 0.60 (95% CI, 5.72-5.90)	5.67 ± 0.52 (95% CI, 5.57-5.77)	< 0.01

BMI: body mass index; Cr: creatinine; Ca: calcium; K: potassium; P: phosphorus; PTH: parathyroid hormone; Na: sodium; Mg: magnesium; Cit.: citrate; Ox: oxalate.

15% (95% CI, 13%-18%), a statistically significant difference ($p < 0.01$). Similarly, the prevalence of diabetes was higher in men, at 9% (95% CI, 7%-12%) vs 5% in women (95% CI, 4%-7%).

The mean body mass index in men was 27.52 kg/m^2, with a 95% CI, of approximately 27.18 to 27.86, significantly higher than that observed in women, whose average BMI was 24.95 kg/m^2 (95% CI, approximately 24.58-25.32). Regarding biochemical parameters, men had mean creatinine levels of 1.02 mg/dL (95% CI, approximately 1.00-1.04), higher than those of women, who had 0.75 mg/dL (95% CI, approximately 0.74-0.76). In contrast, vitamin D levels were significantly lower in men, with a mean of 25.85 ng/mL (95% CI, approximately 25.13-26.57), compared to 30.56 ng/mL in women (95% CI, approximately 29.72-31.40).

Metabolic disorders and diabetes

The diagnosis of multiple metabolic disorders (≥2 alterations) showed a high frequency in the obesity group, affecting 72% of obese men (95% CI, 65%-79%) and 82% of obese women (95% CI, 74%-89%), demonstrating a marked accumulation of metabolic alterations in individuals with higher body weight.

Evaluation of the relationship between body weight and levels of key biomarkers (creatinine, uric acid, urea, vitamin D, PTH) in men (Table 2)

In men, a direct relationship was observed between increasing body weight and several renal and metabolic biomarkers. Creatinine levels increased progressively from normal weight to obesity, reaching a mean of 1.05 mg/dL in the obese group (95% CI, approximately 1.01-1.09) vs 0.97 mg/dL in the normal-weight group (95% CI, approximately 0.95-0.99).

Similarly, uric acid levels were higher in obese men, with a mean of 6.29 mg/dL (95% CI, approximately 6.04-6.54) vs normal-weight men, who had mean values of 5.43 mg/dL (95% CI, approximately 5.28-5.58). Urea also showed an increase associated with higher body weight, with statistically significant differences between groups.

Parathyroid hormone levels showed an upward trend as body weight increased, reaching 49.34 ng/dL in the

obese group (95% CI, approximately 45.25-53.43), compared with 43.15 ng/dL in the normal-weight group (95% CI, approximately 40.75-45.55). At the same time, obese men had lower vitamin D levels, with a mean of 22.95 ng/mL (95% CI, approximately 21.30-24.60) vs the other weight groups.

Evaluation of the relationship between body weight and levels of key biomarkers in women (Table 3)

In women, a consistent pattern of increasing uric acid and urea levels was identified as body weight increased. Obese women had mean uric acid levels of 5.06 mg/dL (95% CI, approximately 4.83-5.29), compared with 4.06 mg/dL in the normal-weight group (95% CI, approximately 3.97-4.15).

Urea levels were also higher in the obese group, with a mean of 34.53 mg/dL (95% CI, approximately 32.64-36.42) vs 31.20 mg/dL in normal-weight women (95% CI, approximately 30.29-32.11). Additionally, women with obesity showed lower vitamin D levels and a more acidic urinary pH, with a mean pH value of 5.67 (95% CI, approximately 5.57-5.77), suggesting a urinary environment potentially more favorable for stone formation.

Discussion

The analysis of the prevalence of obesity, diabetes, and metabolic disorders in patients with renal lithiasis, differentiated by sex, highlights a close interaction between excess weight and metabolic alterations that extends beyond the purely renal domain. The higher prevalence of diabetes in obese patients vs those who are overweight or normal weight confirms that obesity acts as an amplifier of metabolic risk in this population, supporting the perspective proposed by local studies linking RL with cardiovascular risk.,[7] consistent with what has been described by Trinchieri et al.[22].

This pattern suggests that renal lithiasis in obese individuals is not an isolated phenomenon but rather part of a systemic metabolic disorder characterized by insulin resistance, chronic low-grade inflammation, and multiple metabolic dysfunction, as reflected by the high frequency of multiple metabolic diagnoses (≥ 2 alterations) observed in patients with obesity (72% in men and 82% in women). From a pathophysiological perspective, insulin resistance plays a central role by altering peripheral glucose utilization, promoting lipotoxicity, and generating an inflammatory environment that progressively affects renal and tubular function, favoring changes in urinary metabolism, acid-base homeostasis, and renal function.

Within the context of local evidence, this study provides specific data that complement and deepen the available Argentine literature. While studies such as that by Fares et al.[19] have described the general etiology of RL in a cohort from Mar del Plata, and Abib et al.[7] have explored its association with cardiovascular risk factors, this analysis focuses on serum and urinary biochemical alterations associated with BMI and differentiated by sex, offering a mechanistic perspective that links obesity with specific lithogenic risk parameters. These findings are consistent with the recognized association between obesity and RL reported in national literature.[20]

When analyzing sex differences, in women there was a sustained increase in uric acid and urea levels as body weight increased. This finding is consistent with that reported by Ahmed et al.[22]. This may be interpreted as a reflection of a higher metabolic burden and alterations in purine metabolism, exacerbated by insulin resistance. These changes are also associated with a more acidic urinary environment, a condition that favors crystal precipitation, particularly uric acid, and may explain a greater susceptibility to certain types of lithiasis in obese women.

In men, the progressive increase in creatinine, uric acid, and urea as BMI rises suggests subclinical deterioration of renal function. This pattern, also described by Ahmed et al.[22], cannot be attributed solely to greater body mass or functional renal overload, but rather appears to reflect the convergence of multiple mechanisms: chronic low-grade inflammation, activation of the renin-angiotensin-aldosterone system, intrarenal hemodynamic alterations, and coexistence of comorbidities such as hypertension and insulin resistance. These findings highlight the need for preventive and therapeutic approaches that consider these gender differences, adding a level of detail not always present in general etiological studies.[19]

A relevant finding of this study is the progressive increase in parathyroid hormone levels as body weight increases, accompanied by a significant decrease in vitamin D levels in obese patients. This imbalance in the vitamin D-PTH axis suggests the presence of functional secondary hyperparathyroidism, possibly related to vitamin D sequestration in adipose tissue and its reduced systemic bioavailability. Modica et al.[23] have indicated that these alterations are associated with a higher prevalence of obesity, diabetes, and dyslipidemia, while Khodabakhshi, Mahmoudabadi, and Vahid[24] support the relationship between obesity and vitamin D

deficiency. From a renal perspective, this imbalance may favor hypercalciuria and modify the risk of calcium stone formation. The analysis of urinary pH provides an additional relevant pathophysiological element. The observation of a more acidic urinary environment in obese patients is consistent with the findings of Carbone et al.[25] and is particularly significant in the context of uric acid lithiasis. This urinary acidity may be explained, at least in part, by decreased renal ammoniagenesis secondary to insulin resistance, which reduces the kidney's buffering capacity and promotes urine acidification. In addition, there is increased urinary excretion of sodium, creatinine, phosphorus, calcium, and uric acid, as described by Trinchieri, Croppi, and Montanari,[26] increasing urinary supersaturation and lithogenic risk.

The differences observed in serum potassium and phosphorus levels between weight groups, as well as variations in urinary excretion patterns according to sex, suggest that the regulatory mechanisms of hydroelectrolytic and mineral balance may be modulated by both nutritional status and hormonal and metabolic factors specific to each sex. In women, the higher proportion of multiple metabolic diagnoses in the obesity group is consistent with the findings of Sonmez et al.[27] and Dong et al.,[28] who highlight greater female metabolic vulnerability in certain contexts, with potential implications for the recurrence of renal lithiasis.

The findings of this study suggest that renal lithiasis associated with obesity should be approached as a manifestation of a broader systemic metabolic disorder rather than solely as an isolated urological event. The identification of insulin resistance, urinary acidosis, and sex-specific biochemical alterations supports the need for prevention and follow-up strategies focused on: 1) weight control through dietary and physical activity interventions; 2) improvement of insulin sensitivity; 3) correction of the metabolic profile; 4) adequate hydration; and 5) periodic metabolic evaluation with 24-hour urine studies. The selective use of pharmacological therapies (urinary alkalinizing agents, thiazides, or agents that modulate uric acid metabolism) should be considered according to the patient's biochemical profile. Overall, these results position renal lithiasis as a relevant clinical marker of metabolic and cardiovascular risk, reinforcing the need for a comprehensive and personalized approach coordinated with the management of comorbidities such as diabetes, hypertension, and dyslipidemia.[19]

Among the limitations of the study, it is necessary to highlight, first, those inherent to the retrospective design based on medical record review. Although it allowed the analysis of a large and representative cohort over an extended period, it did not permit control or systematic measurement of key potential confounding variables: dietary intake (sodium, animal protein, oxalates, purines), degree of hydration, concomitant drugs (diuretics, allopurinol, vitamin D or calcium supplements, antacids), or level of physical activity. The absence of these data limits the ability to discriminate the specific effect of BMI on the observed biochemical parameters and may introduce bias in the identified associations. Additionally, the lack of information on kidney stone composition restricts the possibility of establishing more precise correlations between metabolic profiles and different types of lithiasis (especially uric acid versus calcium stones), whose pathophysiological mechanisms differ substantially. These limitations require that the results be interpreted as descriptive and exploratory associations that generate hypotheses needing confirmation through prospective and longitudinal studies with standardized data collection on dietary, environmental, and pharmacological factors, compositional analysis of stones, and rigorous control of confounding variables.

Conclusions

This study demonstrates a significant association between obesity and renal lithiasis, particularly in obese men, who show greater alterations in the biochemical profile, lower vitamin D levels, higher prevalence of diabetes, and abnormalities in urinary composition. In overweight or obese women, relevant changes were also observed, such as a more acidic urinary pH and alterations in electrolyte excretion, supporting the hypothesis of insulin resistance and vitamin D-PTH imbalance as underlying pathophysiological mechanisms.

These findings suggest that body weight control may play an important role in the prevention and management of renal lithiasis. However, prospective studies integrating analysis of diet, physical activity, and stone composition are required, as well as mechanistic research to further explore the interaction between obesity, insulin, and urinary metabolism.

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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 human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

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

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ORIGINAL ARTICLE

Clinical and biological profile and factors associated with high blood lead levels in chronic hemodialysis patients in a western French Guiana Hospital Center

Perfil clínico y biológico y factores asociados con niveles elevados de plomo en sangre en pacientes con hemodiálisis crónica en un Centro Hospitalario del oeste de Guayana Francesa

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Abstract

Objective: *The objective of this study is to describe the clinical and biological profile and identify factors associated with elevated blood lead levels (BLLs) in chronic hemodialysis (HD) patients in western French Guiana.* **Materials and methods:** *A cross-sectional analytical study was conducted in December 2022 among 65 chronic HD patients. BLLs were measured, and hyperleademia was defined as a BLL > 85 μg/L. Clinical, biological, and dialysis-related parameters were collected. Multivariate logistic regression was used to identify factors independently associated with elevated BLLs ($p < 0.05$).* **Results:** *Elevated BLLs were observed in 35 patients (54%), with a median BLL of 120 μg/L. Patients with high BLL were older and had lower residual urine output. In multivariate analysis, older age, higher serum albumin, lower total protein, and lower phosphate levels were independently associated with elevated BLL, while female sex was inversely associated. Vintage dialysis, dialysis adequacy, and erythropoiesis-stimulating agent dose were not independently associated with elevated BLL.* **Conclusions:** *Elevated BLLs are common in chronic HD patients in western French Guiana and are associated with older age, altered nutritional markers, and reduced residual renal function (RRF), whereas female sex appears to be protective. These findings support the need for routine BLL screening in at-risk dialysis populations, careful monitoring of nutritional status, and strategies aimed at preserving RRF.*

Keywords: *Lead poisoning. Hemodialysis. Malnutrition. Iron deficiency. Residual renal function.*

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Resumen

Objetivo: *Describir el perfil clínico y biológico e identificar los factores asociados con niveles elevados de plomo en sangre (NPS) en pacientes con hemodiálisis crónica en el oeste de Guayana Francesa.* **Materiales y métodos:** *Se realizó un estudio transversal analítico en diciembre de 2022 con 65 pacientes en hemodiálisis crónica. Se Se recolectaron parámetros clínicos, biológicos relacionados con la diálisis. Se utilizó regresión logística multivariante para identificar factores asociados de manera independiente con NPS elevado ($p < 0.05$).* **Resultados:** *Se observó NPS elevado en 35 pacientes (54%), con una mediana de 120 μg/L. Los pacientes con NPS alto eran mayores y presentaban menor diuresis residual. En el análisis multivariante, la edad avanzada, mayor albúmina sérica, menores proteínas totales y menores niveles de fósforo se asociaron de manera independiente con NPS elevado, mientras que el sexo femenino se asoció de manera inversa. La duración en diálisis, la adecuación de la diálisis y la dosis de agentes estimulantes de la eritropoyesis no se asociaron de manera independiente con NPS elevado.* **Conclusión:** *Los niveles elevados de plomo en sangre son frecuentes en pacientes con hemodiálisis crónica en el oeste de Guayana Francesa y se asocian con edad avanzada, alteraciones nutricionales, y disminución de la función renal residual, mientras que el sexo femenino parece tener un efecto protector. Estos hallazgos respaldan la necesidad de un cribado rutinario de NPS en poblaciones de riesgo, un seguimiento cuidadoso del estado nutricional, y estrategias destinadas a preservar la función renal residual.*

Palabras clave: *Intoxicación por plomo. Hemodiálisis. Malnutrición. Deficiencia de hierro. Función renal residual.*

Introduction

Lead (Pb) is a highly toxic heavy metal with well-established adverse effects on multiple organ systems, including the nervous, cardiovascular, hematopoietic, and renal systems.[1] Chronic Pb exposure remains a major public health concern worldwide, accounting for a substantial burden of morbidity and mortality. The World Health Organization estimates that exposure to Pb and other toxic chemicals contributes significantly to disability-adjusted life years, including cardiovascular disease and chronic kidney disease (CKD).[2]

In the general adult population, the prevalence of elevated blood lead levels (BLLs) has declined in many high-income countries, largely due to regulatory measures; however, important geographical disparities persist. In mainland France, the prevalence of elevated BLLs in adults has been estimated at 1.7%.[3] In contrast, French Guiana represents a specific epidemiological setting, with a markedly higher incidence of Pb exposure, mainly related to environmental and dietary factors rather than occupational exposure.[4] Socioeconomic vulnerability exacerbates this situation, with a significant portion of the population living below the poverty threshold.[5] Patients with CKD, particularly those undergoing chronic hemodialysis (HD), may be at increased risk of Pb accumulation. Reduced renal excretion, prolonged exposure time, and environmental factors may contribute to higher BLLs compared with the general population, as reported in several previous studies.[6-9] For example, a cohort of patients on maintenance HD in India reported significantly elevated blood Pb concentrations, highlighting the vulnerability of this population.[10]

Elevated BLLs in HD patients have been associated with inflammation, malnutrition, erythropoietin (EPO) resistance, secondary hyperparathyroidism, and increased cardiovascular and all-cause mortality, although the strength of these associations varies across populations and dialysis settings.[7-9,11]

In regions such as French Guiana, where environmental Pb exposure is prevalent, data specifically addressing BLLs in the chronic HD population remain scarce. Moreover, the relative contribution of patient-related factors, residual renal function (RRF), nutritional status, and dialysis-related parameters has not been fully clarified.

Therefore, the objective of this study was to describe the clinical, biological, and dialysis-related characteristics of chronic HD patients according to BLLs and to identify factors associated with elevated BLLs in a single dialysis center in western French Guiana. Given the cross-sectional design, the study aims to identify associations rather than establish causal relationships.

Materials and methods

Study design

This was a monocentric, observational, cross-sectional analytical study conducted to describe BLLs and identify factors associated with elevated BLL in patients undergoing chronic HD. Given the cross-sectional design, the study aimed to assess associations rather than establish causal relationships.

Setting

The study was carried out in the chronic HD unit of the Centre Hospitalier de l'Ouest Guyanais (CHOG), located in western French Guiana, a region characterized by high environmental Pb exposure. Data were collected in December 2022 during the routine annual biological assessment performed on all patients undergoing maintenance HD. Exposure and outcome were assessed simultaneously, with no follow-up period.

Participants

All adult patients (≥ 18 years) receiving chronic maintenance HD at CHOG were eligible if they had been on dialysis for at least 3 months and underwent blood Pb measurement during the annual biological evaluation. Patients with a documented history of occupational Pb exposure were eligible, but none were identified. Written informed consent was obtained from all participants. All eligible patients present during the study period were included; no sampling strategy was applied.

Variables

The primary outcome was elevated BLL (hyperleademia), defined as blood Pb concentration > 85 μg/L, based on the French National Biomonitoring Program (ESTEBAN 2014-2016).[12]

Collected variables included age, sex, body mass index (BMI), diabetes mellitus, hypertension, dialysis vintage (months), weekly dialysis duration (hours/week), dialysis adequacy assessed by single-pool Kt/V, residual urine output (mL/24 h) as a surrogate marker of RRF, hemoglobin, albumin, prealbumin, total proteins, ferritin, transferrin saturation, C-reactive protein (CRP), calcium, phosphate, parathyroid hormone (PTH), beta-2-microglobulin, N-terminal pro-B-type natriuretic peptide, vitamins B9, B12, C, and D, and weekly dose of erythropoiesis-stimulating agents (ESA, μg/kg/week).

RRF

Residual urine output was measured over 24 h and used as a surrogate for RRF. Preservation of RRF is an important determinant of solute clearance and patient outcomes in HD. RRF was considered in all analyses as a potential factor associated with elevated BLL.

Data sources and measurements

BLLs were measured using inductively coupled plasma mass spectrometry, a validated reference method for trace metal analysis. All other biological parameters were analyzed in the hospital's certified laboratory using standardized procedures. Clinical and dialysis-related data were extracted from electronic medical records with identical measurement methods applied to all participants.

Dialysis water quality

The HD unit at CHOG uses a two-step reverse osmosis water treatment system, in accordance with ISO 23500-1 standards for the preparation and quality management of fluids used in HD.[13] This involves pre-treatment with sediment and carbon filtration, followed by two reverse osmosis membranes that work one after the other to get rid of pollutants such as Pb and other heavy metals. During the study period, dialysis water samples were not systematically collected for Pb measurement, so direct exposure to the dialysis water could not be assessed.

The use of a two-step reverse osmosis system is expected to minimize the risk of Pb contamination. Future studies should systematically monitor Pb levels in dialysis water as a potential exposure source.

Bias

Selection bias was minimized by including all eligible patients during the study period. Measurement bias was reduced through standardized laboratory methods. Residual confounding may persist due to unmeasured variables, including socioeconomic status, dietary Pb exposure, and precise assessment of RRF.

Study size

The study size corresponded to the total number of eligible patients undergoing chronic HD at the center during the study period (n = 65). No a priori sample size calculation was performed due to the descriptive and exploratory nature of the study.

Quantitative variables

Continuous variables were summarized using means ± standard deviations (SDs) or medians [interquartile range] as appropriate. BLL was dichotomized according to the predefined threshold of 85 μg/L.

Statistical analysis

Descriptive statistics summarized patient characteristics. Comparisons between patients with and without elevated BLL were performed using appropriate statistical tests based on data distribution. Multivariate logistic regression identified factors associated with elevated BLL. Variables were selected a priori based on clinical relevance and published literature to reduce confounding. Missing data were handled using complete-case analysis. Statistical significance was defined as a two-sided $p < 0.05$. Analyses were conducted using STATA version 16.0.

Results

Study population

A total of 65 adult patients undergoing chronic HD were included. The mean age was 56.3 ± 16.8 years, and 36 patients (55%) were female. Hypertension was present in 61 patients (94%) and diabetes mellitus in 33 patients (50%). The median dialysis vintage (time on dialysis) was 62 months (IQR: 28-104). The mean weekly dialysis duration was 11.8 ± 1.9 h, and the mean dialysis adequacy, assessed by single-pool Kt/V, was 1.17 ± 0.21. Residual urine output, measured over 24 h, varied widely (mean ± SD 273 ± 368 mL/24 h) and was used as a surrogate marker of RRF (Table 1).

Prevalence of elevated BLLs

Elevated BLLs (> 85 μg/L) were observed in 35 patients (54%), whereas 30 patients (46%) had BLLs ≤ 85 μg/L. Median blood Pb concentration was 120 μg/L (IQR: 105-168) in the elevated group and 59.8 μg/L (IQR: 49.1-75.2) in the non-elevated group ($p < 0.001$) (Fig. 1).

Clinical and dialysis characteristics according to BLLs

Patients with elevated BLLs were older than those with lower levels (mean 61.6 ± 14.2 vs. 50.2 ± 16.6 years; $p < 0.01$). The proportion of women was higher in the elevated BLL group (66%) than in the non-elevated group (43%), although this difference was not statistically significant in univariate analysis ($p = 0.07$). Diabetes mellitus was present in 22 (63%) patients with elevated BLL and 21 (70%) with lower BLL. Hypertension was present in 33 (94%) and 28 (93%), respectively. Mean BMI was 26.3 ± 6.7 kg/m^2 in the elevated BLL group and 24.9 ± 5.8 kg/m^2 in the lower BLL group. Residual urine output, reflecting RRF, was markedly lower in patients with elevated BLL (141 ± 279 mL/24 h) compared with those with lower BLL (398 ± 439 mL/24 h; $p < 0.01$) (Table 1).

Biological characteristics according to BLLs

Patients with elevated BLL had higher hemoglobin (11.1 ± 1.95 g/dL vs. 10.1 ± 1.74 g/dL; $p = 0.038$) and higher serum albumin (30.2 ± 3.93 g/L vs. 28.0 ± 3.98 g/L; $p = 0.012$). No significant differences were observed for prealbumin, total protein, ferritin, transferrin saturation, PTH, or weekly ESA dose. Mean CRP levels were lower in the elevated BLL group (10.8 ± 22.1 mg/L) than in the lower BLL group (18.0 ± 18.7 mg/L; $p < 0.01$) (Table 2).

Factors associated with elevated BLLs

Multivariate logistic regression identified several factors independently associated with elevated BLL. Older age was positively associated with elevated BLL ($p = 0.013$), whereas female sex was inversely associated ($p = 0.044$). Among biological parameters, higher serum albumin was positively associated with elevated BLL ($p = 0.009$), whereas lower total protein ($p = 0.038$) and phosphate ($p = 0.025$) were independently associated. Residual urine output, inflammatory markers, ferritin, and weekly ESA dose were not independently associated in the multivariate model (Table 3).

Summary of key findings

More than half of the chronic HD patients had elevated BLLs. An elevated BLL was associated with older age and reduced RRF. Multivariate analysis identified age, sex, albumin, total protein, and phosphate as independent factors associated with elevated BLLs. Preservation of RRF may be clinically relevant in limiting Pb accumulation in this population.

Discussion

In this study, 35 (54%) of chronic HD patients exhibited hyperleademia, with a mean BLL of 120 μg/L, and 23 (66%) were women. The population was predominantly older, with a mean age of 62 years, and none had occupational Pb exposure. Hypertension was

Table 1. Clinical and dialysis characteristics by blood Pb level

Variable	Pb ≤ 85 µg/L (n = 30)	Pb > 85 µg/L (n = 35)	p
Age, years	50.2 ± 16.6	61.6 ± 14.2	< 0.01
Female, n (%)	13 (43)	23 (66)	0.07
Hypertension, n (%)	28 (93)	33 (94)	1
Diabetes, n (%)	21 (70)	22 (63)	0.54
BMI, kg/m^2	24.9 ± 5.82	26.3 ± 6.67	0.38
Dialysis vintage, months	59 [26-110]	64 [30-102]	0.68
Weekly dialysis hours	11.5 ± 1.9	12.0 ± 1.9	0.34
Kt/V	1.13 ± 0.23	1.20 ± 0.20	0.23
Residual urine output, mL/24 h	398 ± 439	141 ± 279	< 0.01

Distribution of clinical and dialysis-related characteristics in chronic hemodialysis patients according to blood lead levels. Data are presented as mean ± standard deviation, median [interquartile range], or number (%). Pb ≤ 85 µg/L: patients with blood lead levels ≤ 85 µg/L; Pb > 85 µg/L: patients with blood lead levels > 85 µg/L p < 0.05 indicate significant differences. Residual urine output is used as a marker of residual renal function.
BMI: body mass index; Pb: lead.

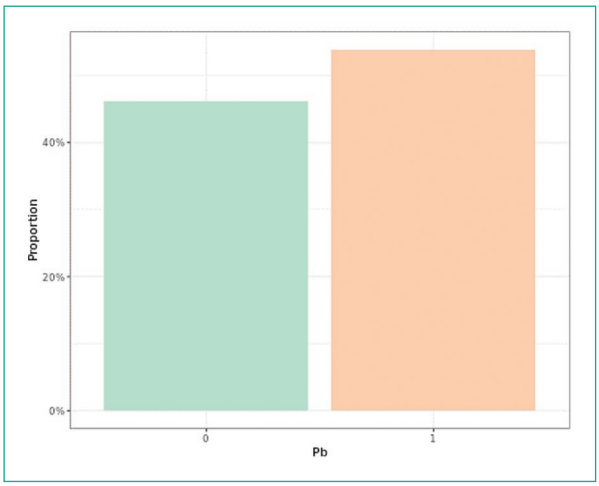


Figure 1. Distribution of patients according to blood lead levels (BLLs). This figure shows the number of chronic hemodialysis patients with low and elevated BLLs. Among the 65 patients, 35 (54%) had BLLs ≥ 85 µg/L (hyperleademia) and 30 (46%) had levels < 85 µg/L. Median values and interquartile ranges are indicated for each group.

Table 2. Biological characteristics by blood Pb level

Variable	Pb ≤ 85 µg/L (n = 30)	Pb > 85 µg/L (n = 35)	p
Hemoglobin, g/dL	10.1 ± 1.74	11.1 ± 1.95	0.038
Albumin, g/L	28.0 ± 3.98	30.2 ± 3.93	0.012
Prealbumin, g/L	30.1 ± 8.74	28.1 ± 10.6	0.40
Total protein, g/L	68.4 ± 7.51	67.6 ± 9.30	0.97
Ferritin, ng/mL	752 ± 450	722 ± 490	0.68
CRP, mg/L	18.0 ± 18.7	10.8 ± 22.1	< 0.01
PTH, ng/mL	985 ± 815	1355 ± 1062	0.21
Weekly ESA dose, µg/kg/week	1.11 ± 0.99	1.13 ± 1.64	0.24

p < 0.05 indicates significant differences.
Comparison of key biological parameters between chronic hemodialysis patients with low and elevated blood lead levels. Data are presented as mean ± standard deviation. For Pb ≤ 85 µg/L, the group consists of patients with blood lead levels at or below 85 µg/L; for Pb > 85 µg/L, the group includes patients with blood lead levels above 85 µg/L.
Pb: lead; CRP: C-reactive protein; PTH: parathyroid hormone;
ESA: erythropoiesis-stimulating agent.

present in 61 patients (94%) and diabetes in 33 patients (50%). The median dialysis vintage was 62 months (IQR: 28-104), with a mean weekly dialysis duration of 11.8 ± 1.9 h and a mean single-pool Kt/V of 1.17 ± 0.21, indicating adequate dialysis. Approximately one-fourth of patients were anemic, and all exhibited some degree of EPO resistance. Mean ferritin was 721 µg/L, serum albumin 30 g/L, prealbumin 28 g/L, PTH 1355 ng/mL, and mean CRP 10.8 mg/L. Vitamin C levels were decreased. Residual urine output, natriuresis, kaliuresis, and chloruresis were markedly reduced, reflecting diminished RRF.[14]

Elevated blood lead levels (BLLs) were significantly associated with older age. In contrast, female sex, lower serum albumin, prealbumin, total protein, ferritin levels, and reduced residual urine output were inversely correlated with hyperleademia.[8,9,14] These findings are consistent with previous literature: Colleoni et al. reported that HD patients had higher mean BLLs compared with healthy controls, with associations between blood Pb and PTH concentrations[6]. Huang et al. observed a negative correlation between BLLs and weekly EPO dose, consistent with our data showing a trend toward higher EPO dosing in patients with hyperleademia. However, this association was not statistically significant.[7] Subha Palaneeswari et al. similarly reported elevated blood Pb in maintenance HD patients, highlighting the vulnerability of this population to Pb accumulation due to reduced renal clearance and environmental exposure.[10] Other studies have demonstrated correlations between BLLs, inflammation, and nutritional status, with hyperleademia linked to increased mortality in both diabetic HD and peritoneal dialysis patients.[9,11]

Table 3. Multivariate logistic regression: factors associated with elevated blood lead levels

Variable	Coef.	Std. err.	z	p > |z|	95% CI
Age (years)	0.1051833	0.0423537	2.48	0.013	0.0221715; 0.188195
Sex (2 = female)	–3.475539	1.719931	–2.02	0.044	–6.846398; –0.1043921
Hemoglobin g/dL	0.5072885	0.3986338	1.27	0.203	–0.2740195; 1.288596
Albumin g/dL	0.848085	0.3232747	2.62	0.009	0.2144463; 1.481626
Prealbumin g/dL	–0.1958754	0.1027336	–1.91	0.057	–0.3972099; 0.0054592
Total proteins g/L	–1.737368	0.0837272	–2.08	0.038	–3.378394; –0.0096343
Phosphate µmol/L	–2.05875	0.9150859	–2.25	0.025	–3.852789; –0.2647112
PTH ng/mL	0.0009444	0.0005741	1.73	0.083	–0.0001308; 0.002197
NT-proBNP ng/mL	–8.01e-06	0.0000552	–0.15	0.885	–0.0001162; 0.0001001
Vitamin B12 ng/L	0.0022844	0.001768	1.29	0.198	–0.0011801; 0.0057488
Ferritin ng/mL	–0.0044326	0.003146	–1.41	0.160	–0.0105987; 0.0007735
CRP ng/L	–0.001131	0.0011705	–0.97	0.331	–0.0034253; 0.0011632
Beta-2-microglobulin mg/L	–0.1120197	0.0970493	–1.15	0.248	–0.3022223; 0.0781829
EPO resistance (1 = Yes)	0.6802983	1.504963	0.45	0.651	–2.263975; 3.629972
Residual urine output (mL/24h)	–0.0139753	0.0540623	–0.26	0.794	–0.1199366; 0.0920859
Sodium µmol/L	0.1099135	0.0746391	1.47	0.141	–0.0363765; 0.2562035
_cons	–8.062076	8.236504	–0.98	0.328	–24.20533; 8.081174

Multivariate logistic regression analysis identifying factors independently associated with elevated blood lead levels in chronic hemodialysis patients. Coefficients (Coef.), standard errors (Std. err.), z values (z), p values (p > |z|), and 95% confidence intervals (95% CI) are shown. Pb > 85 µg/L was considered elevated.
Significant associations (p < 0.05) are highlighted.
PTH: parathyroid hormone; CRP: C-reactive protein; EPO: erythropoietin; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Pb exposure can induce oxidative stress and inflammation, potentially contributing to EPO resistance and compounded by hyperparathyroidism, undernutrition, and hypovitaminosis C.[8,9] In our cohort, elevated BLL was associated with a biological inflammatory syndrome (mean CRP 10.8 mg/L), undernutrition (low albumin and prealbumin), and mild iron deficiency (lower ferritin).

A key finding of our study is the negative association between hyperleademia and RRF, as indicated by markedly reduced residual urine output and solute excretion. Preservation of RRF is a critical determinant of survival, toxin clearance, and quality of life in HD patients.[14] Strategies aimed at maintaining RRF could therefore help limit Pb accumulation and its potential adverse effects.

Although not specifically assessed in this study, elevated BLL has been associated with carpal tunnel syndrome and uremic pruritus, likely mediated through similar inflammatory and oxidative mechanisms.[15-17] Regarding nutritional status, although some patients had elevated BMI, low albumin and prealbumin indicate protein-energy malnutrition. This observation aligns with recent evidence showing that obesity does not preclude malnutrition, emphasizing the importance of biochemical and functional markers beyond BMI.[18,19]

Several limitations should be acknowledged. First, the cross-sectional, monocentric design precludes establishing causality; only associations can be inferred. Second, the cutoff for elevated BLLs (> 85 µg/L) was based on the ESTEBAN French national biomonitoring program; while pragmatic, it may not fully reflect clinically relevant thresholds for chronic HD patients. Third, although the dialysis unit uses a two-step reverse osmosis water system, researchers did not directly measure Pb in dialysis water, nor did they assess potential contributions of environmental and socioeconomic factors. Fourth, the small sample size limits the generalizability of our findings. Finally, multivariate analyses included variables selected a

priori based on clinical relevance and published literature; differences observed between univariate and multivariate results reflect adjustment for confounding factors rather than inconsistencies.

Conclusion

Elevated BLLs are frequent in chronic HD patients in western French Guiana, affecting more than half of the studied population. Elevated BLL was associated with older age, female sex, altered nutritional markers, and reduced RRF. Although dialysis adequacy and EPO dosing were not independently associated with elevated blood Pb, maintaining RRF appears crucial for limiting Pb accumulation. These findings demonstrate the need for routine blood Pb screening in at-risk HD populations, careful monitoring of nutritional status using biochemical and functional markers beyond BMI, and strategies aimed at preserving RRF. Future studies, including multicenter longitudinal analyses and systematic assessments of dialysis water quality and socioeconomic factors, are warranted to clarify environmental contributions and potential interventions to reduce Pb exposure in this vulnerable population.

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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 human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

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

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ORIGINAL ARTICLE

Impact of bariatric surgery on glomerular filtration rate and metabolic and lithogenic risk factors

Impacto de la cirugía bariátrica en el filtrado glomerular y los factores de riesgo metabólicos y litogénicos

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Abstract

Objective: *The aim of this study is to determine the impact of bariatric surgery on glomerular filtration rate (GFR) and lithogenic risk factors.* **Material and methods:** *Prospective study conducted at Hospital Maciel (2019–2022). Twenty-five patients undergoing Roux-en-Y gastric bypass or sleeve gastrectomy were included. Clinical, biochemical, and lithogenic parameters were analyzed before and after surgery. Ethical approval was obtained.* **Results:** *a total of 25 patients, 24 were women, mean age was 43.3 (± 10.6) years. RYGB was performed in 16/25 and SG in 9/25. Mean BMI decreased by 16.3 kg/m². Diabetes mellitus remitted in 100% and hypertension in 20%. Measured creatinine clearance decreased by 15 ml/min on average (mean postoperative GFR: 118 ml/min). Urinary calcium, uric acid, oxalate, citrate, ammonium, and creatinine excretion decreased, while natriuria and magnesuria increased. No significant proteinuria was detected.* **Conclusions:** *Bariatric surgery reduced glomerular hyperfiltration and improved the lithogenic profile, with no major differences between surgical techniques. These findings support the renal benefits of bariatric surgery and the importance of long-term follow-up.*

Keywords: *Obesity. Glomerular hyperfiltration. Nephrolithiasis. Bariatric surgery.*

Resumen

Objetivo: *Evaluar prospectivamente el impacto de la cirugía bariátrica (bypass gástrico y gastrectomía vertical) sobre el filtrado glomerular (FG) y los factores de riesgo litogénicos en pacientes con obesidad.* **Material y métodos:** *Estudio descriptivo, observacional y prospectivo realizado en el Hospital Maciel entre marzo de 2019 y enero de 2022. Se incluyeron 25 pacientes sometidos a cirugía bariátrica. Se analizaron las variables antes y después del procedimiento.* **Resultados:** *La cohorte incluyó 24 mujeres y 1 hombre, con edad media de 43 años. El 64% fue sometido a bypass gástrico y el 36% a gastrectomía vertical. El IMC disminuyó en promedio 16,3 kg/m². La diabetes mellitus remitió en el 100% de los casos y la hipertensión arterial en el 20%. No se detectó proteinuria significativa. El FG medido disminuyó, así como disminuyeron calciuria, uricosuria, oxaluria, citraturia, amoniuria y creatininuria; mientras que aumentaron natriuria y magnesu-*

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ria. **Conclusiones:** *La mayoría de los pacientes presentaba hiperfiltración glomerular preoperatoria, que mejora tras la cirugía. Se observó reducción de oxaluria, incluso en pacientes con bypass. Ambas técnicas quirúrgicas mostraron beneficios similares en el perfil litogénico, sin evidencia para preferencia de una sobre otra.*

Palabras clave: *Obesidad. Hiperfiltración glomerular. Litiasis renal. Cirugía bariátrica.*

Introduction

Obesity, defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that poses a risk to health,[1] has reached epidemic proportions worldwide, with a sustained increase over recent decades. Over the past 40 years, its incidence has doubled in both men and women.[2] By 2035, an estimated 54% of the global adult population will have obesity, compared with 42% in 2020.

This condition is a recognized risk factor for the development of chronic kidney disease (CKD), which is present in approximately 20%-25% of patients with obesity.[3] Individuals with obesity have a 3-fold higher risk of developing CKD, even in the absence of other comorbidities.

Furthermore, obesity is associated with a higher prevalence of nephrolithiasis. In industrialized countries, this condition has an annual incidence of approximately 1 per 1000 persons, with a cumulative risk of 5% in women and 13% in men.[4] In a series of 24 patients with obesity, 83% showed abnormalities in the lithogenic profile.[5] This association may be explained by metabolic changes such as decreased urinary pH and increased urinary excretion of oxalate, sodium, phosphorus, and uric acid.[5]

Bariatric surgery is an effective therapeutic option for the treatment of severe obesity and is indicated in patients with a body mass index (BMI) ≥ 35 kg/m². The most widely used techniques are Roux-en-Y gastric bypass and sleeve gastrectomy. Although some studies have described an increased risk of nephrolithiasis and nephropathy after gastric bypass, associated with enteric hyperoxaluria, this effect has not been observed with the same frequency after restrictive procedures such as sleeve gastrectomy.[6]

We present a prospective study evaluating the impact of bariatric surgery-induced weight loss on glomerular filtration rate and lithogenic risk factors in patients with obesity.

Materials and methods

We conducted a descriptive, observational, prospective study within the Obesity and Bariatric Surgery Program at *Hospital Maciel* (Montevideo, Uruguay).

Patients with a body mass index (BMI) > 35 kg/m², without known kidney disease, who entered the program between February 2019 and May 2022 were included. Follow-up continued for at least 1 year after surgery.

During the preoperative phase, clinical and biochemical plasma and urinary variables were recorded, with particular emphasis on the lithogenic profile and kidney function. These measurements were repeated 6 months after surgery, with a minimum follow-up of 6 months and a mean follow-up of 24 months.

Variables analyzed

Plasma variables: Creatinine, urea, uric acid, calcium, phosphorus, bicarbonate, intact parathyroid hormone (iPTH), and 25-hydroxyvitamin D.

24-hour urine variables: Citrate, oxalate, uric acid, phosphorus, sodium, calcium, ammonium, magnesium, creatinine, urea, and urinary volume. Twenty-four-hour proteinuria and the protein-to-creatinine ratio were also determined.

Clinical variables: Presence of hypertension, diabetes mellitus, and dyslipidemia.

Statistical analysis

Quantitative variables were expressed as median and IQR, and qualitative variables as absolute frequencies and percentages. Normality was assessed using the Shapiro-Wilk test. Given the sample size and distribution, nonparametric tests (Wilcoxon test) were used to compare paired variables (preoperative vs postoperative).

The study was funded by the *Fondo de Investigación en Nefrología (FOINE)* and approved by the Research Ethics Committee of *Hospital Maciel*.

Results

During the preoperative phase, a total of 66 patients were evaluated. Of these, 25 (24 women and 1 man) underwent bariatric surgery and completed postoperative biochemical follow-up.

Table 1. Comparison of mean values for each variable before and after surgery

Variable	Before surgery	After surgery
Age (years)	43.4 (20-65)	
Sex (F/M)	24/1	
BMI (kg/m²)	46.9 (38.0-70.4)	30.6 (22.0-50.0)
Hypertension, n (%)	15 (60%)	10 (40%)
HbA1c, n (%)	5.9 ± 1.2	5.3 ± 0.44
Creatinine (mg/dL)	0.74 ± 0.18	0.68 ± 0.12
Urea (g/L)	0.30 ± 0.10	0.30 ± 0.07
Uric acid (mg/dL)	5.54 ± 1.67	4.11 ± 0.88
Sodium (mmol/L)	138.7 ± 1.9	140.5 ± 2.2
Calcium (mg/dL)	9.51 ± 0.43	9.56 ± 0.39
Phosphorus (mg/dL)	3.41 ± 0.47	3.8 ± 0.54
Bicarbonate (mmol/L)	25.48 ± 1.76	24.9 ± 1.93
pH	7.35 ± 0.03	7.32 ± 0.03
iPTH (pg/mL)	83.8 ± 38.4	74.6 ± 34.9
Vitamin D (ng/mL)	15.9 ± 8.2	27.6 ± 9.9
Sodium (mEq/24 h)	183.1 ± 105.8	199.7 ± 117.8
Potassium (mEq/24 h)	59.6 ± 16.7	67.5 ± 40.3
Chloride (mEq/24 h)	180.0 ± 101.6	175.0 ± 96.0
Calcium (mg/24 h)	195.7 ± 148.9	155.8 ± 88.7
Phosphorus (mg/24 h)	885.9 ± 277.8	785.6 ± 702.9
Magnesium (mg/24 h)	88.7 ± 46.2	120.8 ± 68.8
Creatinine (mg/24 h)	1351 ± 271	1139 ± 365
Uric acid (mg/24 h)	706.9 ± 290.7	498.9 ± 194.2
Oxalate (mg/24 h)	37.1 ± 17.5	33.9 ± 25.6
Citrate (mg/24 h)	514.8 ± 408.5	465.7 ± 402.2
Ammonium (mg/24 h)	2956 ± 1596	2392 ± 1686
Urinary pH	6.0 ± 0.64	6.0 ± 0.62
Urine output (L)	1.96 ± 0.68	1.68 ± 0.65
24-h proteinuria (g/24 h)	0.14 ± 0.08	0.13 ± 0.11
Protein/creatinine ratio (g/g)	0.12 ± 0.05	0.11 ± 0.09
Calculated CrCl (mL/min)	134.3 ± 40.4	118.1 ± 34.0
Urea clearance (mL/min)	60.8 ± 20.0	54.4 ± 19.8

Mean age was 43.3 ± 10.6 years. Roux-en-Y gastric bypass was performed in 64% of patients, while the remaining 36% underwent sleeve gastrectomy.

Table 2. Differences in mean values before and after surgery

Variable	Difference (mean ± SD)	95% CI	p
Creatinine (mg/dL)	0.057 ± 0.122	0.007; 0.108	0.17
Serum uric acid (mg/dL)	1.436 ± 1.297	0.901; 1.971	< 0.001
Standard bicarbonate (mEq/L)	0.508 ± 2.662	–0.616; 1.632	0.115
pH	0.029 ± 0.044	0.010; 0.047	0.003*
PTH (pg/mL)	5.58 ± 36.4	9.785; 20.952	0.558
Vitamin D (ng/mL)	–11.8 ± 13.1	–17.62; –6.04	0.001*
Urinary pH	0.04	–0.31; 2.10	0.817
Sodium (mEq/24 h)	–16.6 ± 125.1	–68.3; 34.5	0.510
Calcium (mg/24 h)	39.9 ± 120.8	–10.0; 89.7	0.201
Phosphate (mg/24 h)	100.3 ± 527.1	–117.3; 317.9	0.201
Creatinine (mg/24 h)	212.5 ± 320.7	80.1; 344.8	0.003*
Uric acid (mg/24 h)	209.1 ± 323.3	75.6; 342.5	0.005*
Oxalate (mg/24 h)	3.18	–10.4; 5.2	0.174
Citrate (mg/24 h)	49.2	–95.9; 51.2	0.677
Ammonium (mg/24 h)	393	–541; 395	0.231
Magnesium (mg/24 h)	–32.1	–58.3; –30.1	0.021*
Creatinine clearance (mL/min)	16.2	–1.7; 34.2	0.51

Weight and comorbidities

Preoperative BMI was 47 kg/m² (IQR, 38-70.4), decreasing to a mean of 30.6 kg/m² (IQR, 22-50) after surgery, with a mean reduction of 16.3 kg/m².

Before surgery, a total of 60% of patients had hypertension; of these, 33% achieved normalization of blood pressure values at 1 year. Type 2 diabetes mellitus (T2DM) was present in 20%, with complete remission in all cases. The lipid profile improved, with increased HDL cholesterol and decreased triglyceride and LDL cholesterol levels.

Glomerular filtration rate and proteinuria

One patient had reduced glomerular filtration rate preoperatively (Cr, 1.29 mg/dL; CrCl, 59 mL/min), which normalized after surgery (Cr, 1.0 mg/dL). In the overall cohort, creatinine clearance decreased by a mean of 15 mL/min (postoperative mean, 118 mL/min;

Table 3. Pre- and postoperative serum and urinary profile according to type of surgery

Variable	Bypass pre	Bypass post	p Bypass	Sleeve pre	Sleeve post	p Sleeve
Creatinine (mg/dL)	0.698 ± 0.170	0.660 ± 0.114	0.211	0.803 ± 0.197	0.711 ± 0.126	0.018*
Uric acid (mg/dL)	5.88 ± 1.83	4.18 ± 0.96	0.001*	4.95 ± 1.26	4.00 ± 0.74	0.021*
Calcium (mg/dL)	9.55 ± 0.47	9.56 ± 0.45	0.842	9.44 ± 0.35	9.56 ± 0.28	0.395
iPTH (pg/mL)	95.6 ± 40.1	83.5 ± 39.9	0.495	62.8 ± 25.0	59.9 ± 18.0	0.953
Vitamin D (ng/mL)	16.2 ± 9.1	26.3 ± 9.9	0.011*	15.4 ± 6.4	30.5 ± 10.0	0.046*
Urine output (L)	2.06 ± 0.65	1.92 ± 0.67	0.552	1.78 ± 0.73	1.27 ± 0.34	0.123
Urinary pH	5.93 ± 0.48	5.80 ± 0.41	0.187	6.17 ± 0.87	6.11 ± 0.70	0.932
Uric acid (mg/24 h)	722 ± 237	506 ± 191	0.013*	680 ± 383	483 ± 211	0.173
Sodium (mEq/24 h)	212 ± 118	212 ± 112	0.679	131 ± 51	178 ± 131	0.594
Calcium (mg/24 h)	212 ± 171	151 ± 90	0.63	167 ± 102	163 ± 91	0.767
Oxalate (mg/24 h)	40.1 ± 18.8	33.6 ± 18.3	0.196	31.8 ± 14.3	34.5 ± 36.6	0.515
Citrate (mg/24 h)	529 ± 415	379 ± 319	0.148	491 ± 420	620 ± 503	0.214
Phosphate (mg/24 h)	908 ± 254	880 ± 391	0.569	847 ± 329	618 ± 388	0.139

range, 61-184 mL/min). The decrease in urinary creatinine excretion was significant (–212.5 ± 320.7 mg/24 h; p = 0.003). No patient had significant proteinuria.

Lithogenic profile

Preoperatively, 48% of patients had urine output < 2 L, increasing to 64% postoperatively.

Serum variables: Decreases were observed in creatinine, uric acid, bicarbonate, pH, and iPTH, whereas sodium, calcium, phosphorus, and vitamin D increased.

Urinary variables: Urinary calcium, uric acid, oxalate, citrate, ammonium, and creatinine excretion decreased. Urinary sodium and magnesium excretion increased.

The tables 1 through 3 provide detailed preoperative and postoperative comparisons, as well as analyses according to type of surgery.

Discussion

Bariatric surgery is an effective treatment for morbid obesity and its comorbidities. In our cohort, a sustained reduction in BMI was observed, accompanied by improvements in key metabolic parameters such as arterial hypertension, T2DM, and dyslipidemia, findings consistent with national and international series.[7,8]

One of the most relevant mechanisms of kidney damage in obesity is glomerular hyperfiltration. In our sample, 64% of patients showed signs of preoperative hyperfiltration (creatinine clearance, 134 mL/min), which decreased by a mean of 16 mL/min after surgery. Although this reduction did not reach statistical significance (p = 0.051), this borderline value, probably related to the small sample size, reflects a clinically relevant reduction in the context of preoperative glomerular hyperfiltration. Moreover, it emphasizes the importance of direct measurement of glomerular filtration rate in patients with severe obesity. Because estimated glomerular filtration rate equations have limitations in patients with severe obesity, creatinine clearance was measured using 24-hour urine collection, in accordance with current recommendations.[9-11]

Regarding the lithogenic profile:

Oxalate, citrate, and urinary volume: Unlike findings reported in other studies, urinary oxalate excretion did not increase after gastric bypass; instead, a mean reduction of 3.18 mg/day was observed. Hypocitraturia was frequent, and urinary volume decreased by a mean of 280 mL/day. These changes could be related to gastrointestinal losses, reduced fluid intake, or mild postoperative acidosis.[5,12,13]

Uric acid and magnesium: Complete resolution of hyperuricemia and a significant decrease in urinary uric acid excretion were observed. Urinary magnesium excretion

increased significantly, a finding that could be related to supplementation or changes in tubular reabsorption.[14,15]

Urinary ammonium and pH: Ammonium excretion remained elevated, suggesting persistence of a diet with a high acid load. Urinary pH remained stable, consistent with the decrease in urinary citrate excretion.

Mineral and bone metabolism: Vitamin D levels improved, and the proportion of patients with secondary hyperparathyroidism decreased from 60% to 36%. Three patients developed *de novo* hyperparathyroidism after surgery.

Urinary calcium excretion decreased overall, and no significant differences were found between surgical techniques. Although this study did not assess bone outcomes, a relevant loss of bone mass after bariatric surgery has been demonstrated, particularly beyond the first postoperative year. This loss is especially evident at the femoral neck in patients older than 40 years.[16] These changes reinforce the need for sustained follow-up of mineral and bone metabolism and lithogenic risk during long-term postoperative follow-up.

Taken together, these findings indicate that, although bariatric surgery improves metabolic factors and some lithogenic parameters, mechanisms requiring continued surveillance persist, particularly those related to mineral metabolism and urinary acidity.

Conclusions

This is the first national study to systematically evaluate glomerular filtration rate and the urinary lithogenic profile in patients undergoing bariatric surgery.

We confirmed the favorable impact of the procedure on weight loss and the resolution or improvement of comorbidities. Regarding kidney health, a reduction in the prevalence of glomerular hyperfiltration and beneficial changes in some lithogenic variables were observed.

No significant differences were identified between surgical techniques (gastric bypass vs sleeve gastrectomy) with respect to lithogenic risk; therefore, neither technique can be recommended over the other on the basis of these parameters.

The main limitations of the study were:

- The small number of patients with complete postoperative assessment, partly due to the COVID-19 pandemic;
- nonsimultaneous sample collection;
- the predominance of female patients; and
- potential errors in 24-hour urine collection.

We emphasize the importance of monitoring mineral metabolism in this population.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that OpenAI's ChatGPT was used for manuscript drafting, language editing.

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REVIEW ARTICLE

Why is it important to do research in nephrology in Latin America?

¿Por qué es importante hacer investigación en nefrología en América Latina?

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Abstract

Latin America is one of the regions in the world with the lowest investment in Research and Development. Although the number of articles published in Nephrology and of formally trained research professionals have increased in recent years in our region, a much greater effort is still needed to place research in our specialty at a much higher level than it currently has, and which it deserves given that it is a region with one of the highest rates of incidence and prevalence, and with the highest mortality and burden of chronic kidney disease in the world. It is necessary to prioritize research in Nephrology with greater investment, reduction of bureaucracy and promotion of international collaboration. It is also necessary to reduce inequalities in infrastructure and access to research resources in the region, as well as to provide the necessary conditions to prevent the brain drain to other countries. Generating cutting-edge research in Nephrology would help us to solve, with our own solutions, the serious problem of kidney disease that afflicts our countries.

Keywords: *Nephrology. Research. Latin America. Scientific production.*

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Resumen

América Latina es una de las regiones del mundo con menor inversión en Investigación y Desarrollo. Aunque el número de artículos publicados en Nefrología y de profesionales entrenados formalmente en investigación ha incrementado en los últimos años en nuestra región, aún se requiere un esfuerzo mucho mayor para colocar a la investigación en nuestra especialidad en un nivel mucho mayor del que ahora tiene, y que además le corresponde dado que es una región con unas de las más altas tasas de incidencia y prevalencia, y con la mayor mortalidad y carga de la enfermedad renal crónica en el mundo. Es necesario priorizar la investigación en Nefrología con una mayor inversión, reducción de la burocracia y fomento de colaboración internacional. Asimismo, es necesario reducir las desigualdades en infraestructura y acceso a recursos de investigación en la región, así como proveer de las condiciones necesarias para evitar la fuga de talentos a otros países. Generar investigación de vanguardia en Nefrología nos ayudaría a resolver, con soluciones propias, el grave problema de la enfermedad renal que aqueja a nuestros países.

Palabras clave: *Nefrología. Investigación. América Latina. Producción científica.*

Introduction

Latin America has the highest mortality rate from chronic kidney disease (CKD) in the world, and within our region, CKD is the second leading cause of years of life lost.[1]

The high burden of CKD in the region may be due, at least in part, to the limited capacity of some countries to adequately implement prevention, early diagnosis, and timely treatment of the disease.[2] Lower-income countries in the region also have less developed healthcare systems and therefore reduced capacity to detect CKD, provide treatment to slow progression to advanced stages, and, when necessary, deliver renal replacement therapy.[2]

There are numerous barriers to kidney care in Latin America, including geographic, sociocultural, and economic factors; patient knowledge and attitudes; shortage of human resources and low clinical competence of primary healthcare professionals; limited availability of nephrologists; and restricted access to healthcare services.[3-5] Consequently, potential solutions are multiple; however, one strategy identified by the *Sociedad Latinoamericana de Nefrología e Hipertensión* (SLANH) for several years has been the promotion of local, regional, and multicenter research in different areas of CKD, as its findings could contribute to solving local problems with locally tailored solutions.[4] In our region, nephrology research is needed because:

- The region has unique epidemiological, cultural, socioeconomic, and genetic characteristics—research allows these to be understood and more effective approaches to be developed
- Research is crucial as it generates new knowledge, fosters critical thinking and creativity, and helps solve problems and improve practices
- Research is essential for the advancement of science, technology, and society in general, and should be a strategic priority for countries seeking comprehensive development

Economic investment in research and development

The percentage of gross domestic product allocated by countries to research and development (R&D) varies greatly worldwide.[6] Israel ranks first with 6.3%, followed by Sweden, Taiwan, and South Korea with between 3.5% and 5.0%. Western Europe, Scandinavian countries, Japan, and the United States allocate between 2.7% and 3.4%, while the rest of European countries, China, Australia, and Canada invest between 1.0% and 2.6%. Below 1.0% of GDP allocated to R&D are the remaining countries worldwide; importantly, this group includes all Latin American countries except Brazil, which for several decades has allocated slightly more than this percentage (currently 1.15%). The average GDP invested in R&D in Latin America and the Caribbean is 0.56%, although with significant heterogeneity, with Uruguay (0.63%) and Argentina (0.55%), in addition to Brazil, ranking highest, while Honduras, Trinidad and Tobago, and Guatemala rank among the lowest (0.6% each).[7]

One of the distinctive features of Latin America and the Caribbean is the strong concentration of R&D investment in a few countries: Brazil alone accounts for 62% of the regional effort, while Mexico represents 12% and Argentina 9%. Over the past decade, R&D spending (in millions of US dollars) in the region has been highly variable and, in recent years, often declining, as seen in Brazil (17,000), Mexico (3,800), and Argentina (3,500). However, other countries, albeit on a smaller scale, have made efforts to progressively increase investment, such as Chile (1,137) and Peru (399).[7]

In 2022, the main sources of R&D funding in Latin America and the Caribbean were government (55%) and private and public companies (37%), while higher education institutions (4%), foreign sources (3.6%), and non-profit organizations (0.4%) contributed to a much lesser extent. In contrast, the sectors requesting and executing these funds were predominantly higher education institutions (41%), private and public companies (31%), and government (27%), while non-profit organizations accounted for only 1%.[7,8] In Mexico, the types of research funded include basic research (31%), applied research (30%), and experimental development (39%).

Human resources in research in Latin America

According to the latest report jointly published by the *Organización de Estados Iberoamericanos* (OEI) through its *Observatorio Iberoamericano de la Ciencia, la Tecnología y la Sociedad* (OCTS), and the *United Nations* Educational, Scientific and Cultural Organization (UNESCO),[9] in 2022 there were just over 700,000 researchers (full-time equivalent) in Latin America and the Caribbean, reflecting significant growth from the 483,000 recorded in 2012. However, this figure remains low (2.14 researchers per 1,000 economically active individuals), representing only 4% of the global total, compared with 49% in Asia, 27% in Europe, and 16% in the United States and Canada. When examining the number of researchers by country in Latin America, a pattern similar to R&D spending emerges, with highly heterogeneous distribution: Brazil employed 173,830 researchers in 2017, followed by Argentina with 58,803 and Mexico with 35,045, with significantly lower numbers in Chile, Venezuela, Colombia, Uruguay, and Costa Rica. Regarding gender distribution, in 2021 women represented less than 50% of researchers in most countries, although again with heterogeneity. In Chile, Mexico, and Peru, women accounted for approximately one-third of researchers, whereas in Argentina, Paraguay, Trinidad and Tobago, and Uruguay, they exceeded half of the research workforce.

Brain drain is another issue affecting research human resources in the region. It occurs intermittently, influenced by researchers seeking better professional development and living conditions, and more recently also by crime and violence in their home countries. Although some Latin American countries have attempted to recover their human capital, these efforts remain insufficient; structural governmental issues must be addressed, and research conditions improved—not only to repatriate researchers but also to retain them through fair salaries and working conditions.[10]

According to the most recent data from the *Red Iberoamericana de Indicadores de Educación Superior*,[11] total enrollment in higher education in Latin America increased from 24 million in 2013 to over 31 million in 2021, representing a 30% increase. Of these, master's and doctoral students accounted for 5.6% and 0.8%, respectively. Similarly, the number of higher education graduates in Ibero-America increased significantly, from nearly 3.6 million in 2013 to more than 4.9 million in 2022; among these, master's and doctoral graduates in Latin America accounted for 11.8% and 1.0%, respectively.

Scientific productivity in Latin America

According to the SCImago Journal Rank,[12] in its ranking of countries with scientific articles published between 1996 and 2024, the country with the highest number of published articles, citations, citations per document, and H-index is the United States, followed by China in second place. However, the next three countries (United Kingdom, Germany, and Japan) have higher citations, citations per document, and H-index than China. Among the top 15 countries with the highest number of publications, Brazil is the only Latin American country, ranking 14th; however, its citations, citations per document, and H-index are lower than those of countries immediately above (South Korea) and below (Netherlands), which, notably, have substantially smaller populations than Brazil.

According to data from the US National Science Board,[13] the countries with the highest number of scientific publications between 2003 and 2022 are predominantly high-income countries, but the greatest growth has occurred in upper-middle-income countries (especially China), where a more pronounced increase is observed. In these data, China published 329,000 articles in 2012 and 899,000 in 2022, accounting for 27% of global scientific production, while the United States published 430,000 articles in 2012 and 457,000 in 2022 (14% of global production). Brazil is the only Latin American country on this list, increasing from 48,000 articles in 2012 to 67,000 in 2022, representing 2% of global production, still far behind leading countries. Within Latin America, based on SCOPUS data, the number of publications increased from 120,000 in 2013 to 200,000 in 2022; however, when adjusted for population, this corresponds to 30 articles per 100,000 inhabitants, which remains low.[9]

One strategy to increase scientific productivity in the region is international collaboration, although this has

historically been irregular, with fluctuating rates until the early 2000s. Since 2015, however, there has been a steady increase in collaborative research, currently accounting for more than 40% of publications in Latin America.[12] International collaborations can improve the quality and impact of local scientific production and provide access to resources, advanced technologies, and international funding, thereby expanding scope and relevance.[14]

On the other hand, the main disciplines in which scientific articles are published vary by country. The United States, the European Union, and Japan primarily publish in health sciences, while China leads in engineering and India in computer science and informatics.[13] Latin American countries, in contrast, predominantly publish in physical sciences, followed by life sciences and, third, health sciences.[9]

Scientific articles published in nephrology in Latin America

Among medical publications in Latin America between 1996 and 2022, Brazil ranks first with 474,000 articles, followed at a significantly lower level by Mexico (135,000) and Argentina (90,000), although citations per document and H-index are similar among them. Chile and Colombia have published between 60,000 and 70,000 articles, while the remaining countries have fewer than 30,000 publications.[12]

In nephrology, a similar pattern is observed, with Brazil (3,805 articles), Argentina (1,185), and Mexico (1,106) occupying the top three positions, followed by Colombia (489) and Chile (319), and the remaining countries publishing fewer than 200 articles between 1996 and 2022.[12] On the Clarivate Analytics/Web of Science platform,[15] between 2010 and 2025, nearly half of nephrology publications are concentrated in six countries: Brazil (1,727), Argentina (503), Mexico (470), Colombia (144), Chile (121), and Peru (56).

Although scientific production in Latin America has increased over time (albeit much more slowly than in regions such as Asia-Pacific),[16] another important unresolved issue is improving publication quality. It is estimated that only 10% of Latin American publications appear in high-impact journals, limiting their reach and international recognition.[17]

Patents filed from Latin American countries

Another pending area is patents derived from research products filed and granted in Latin American countries. According to the *Red de Indicadores de Ciencia y Tecnología Iberoamericana e Interamericana*,[7] there has not only been no growth in patent applications in Latin America, but a decline since 2015. Furthermore, most applications come from non-residents (83% on average), such as multinational companies seeking to protect their inventions in the region.

Table 1. Challenges and opportunities for nephrology research in Latin America

Challenges
Low investment in research and development
Brain drain
Inequalities in infrastructure and access to resources among countries
Bureaucracy and difficulties in accessing public funding
Limited presence in high-impact journals
Opportunities
Potential to strengthen regional collaboration
Greater participation of the private sector in science funding
Digital technologies can improve limited access to resources and scientific dissemination

Challenges and opportunities for research in Latin America

In our region, there are both challenges and opportunities for nephrology research (Table 1).

Challenges

- Low investment in R&D, limiting high-impact research, access to advanced technology, and retention of scientific talent. Limited prioritization of science and technology in political agendas, along with economic instability, exacerbates the problem.
- Brain drain, which weakens human capital and limits the capacity to generate knowledge and develop innovative technologies. Low salaries, temporary contracts, and limited access to funding contribute to talent loss.
- Inequalities in infrastructure and access to resources among countries. Approximately 80% of R&D investment is concentrated in Brazil, Mexico, and Argentina. Many researchers have limited access to laboratories, state-of-the-art equipment, and scientific databases, and institutions often rely on outdated infrastructure and they have difficulty accessing high-impact scientific publications.
- Bureaucracy and barriers to accessing public funding. Complex procedures and prolonged timelines discourage researchers from applying for funding.
- Limited presence in high-impact journals. Only 10% of Latin American publications appear in high-impact journals, reducing their reach, recognition, and the ability to attract collaborations and external funding.

Opportunities

- Potential to strengthen regional collaboration. The development of joint research programs can enhance collaboration among countries in the region. The creation of regional networks would facilitate the sharing of resources, infrastructure, and expertise.
- Increased participation of the private sector in science funding. Strategic partnerships between universities, research centers, and public or private companies can generate additional resources, link research to market needs, increase R&D investment, and facilitate technology transfer and innovation commercialization. Scientific societies such as the *Sociedad Latinoamericana de Nefrología e Hipertensión* (SLANH) and national nephrology societies can also play a key role by promoting and funding research, particularly for early-career investigators.
- Digital technologies can improve access to resources and scientific dissemination. Online platforms, open-source tools, and digital repositories can democratize access to knowledge and increase research visibility. Social media and digital platforms, when appropriately regulated, enable new ways to communicate science to broader audiences.

Conclusions

- Scientific production in Latin America has improved in recent years, particularly in health sciences, driven by leading countries; however, significant gaps remain in both quantity and quality of publications.
- It is essential for the region to prioritize R&D investment, reduce bureaucracy, and foster regional and international collaboration to strengthen its position in the global scientific landscape.
- Brain drain and inequalities in infrastructure and access to resources require greater attention.
- Increased private-sector participation in research funding and the use of digital technologies for scientific dissemination can democratize knowledge and enhance visibility.
- Nephrology research is essential for the prevention and treatment of kidney diseases.
- Investing in research will ensure a better future for Latin America, because “a society that does not conduct research does not progress.

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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 human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. 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 or creation of the content of this manuscript.

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CASE REPORT

Primary hyperoxaluria type 3, first case reported in Uruguay

Hiperoxaluria primaria tipo 3, primer caso reportado en Uruguay

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Abstract

Primary hyperoxaluria (PH) comprises a heterogeneous group of autosomal recessive disorders of glyoxylate metabolism. Three genotypic forms (PH1–PH3) are recognized, and diagnosis can be challenging because of marked phenotypic heterogeneity. PH3, the least common form, is caused by pathogenic variants in the HOGA1 gene and generally follows a milder clinical course than PH1 and PH2. We report the case of a young woman with mild hyperoxaluria and preserved renal function with a genetic diagnosis of PH3. Genetic testing identified two pathogenic HOGA1 variants: c.208C>T, p.(Arg70Ter) and c.700+5G>T. This case highlights the broad clinical spectrum of PH3 and underscores the importance of genetic testing in establishing the diagnosis.

Keywords: *Primary hyperoxaluria type 3. Oxaluria. Urolithiasis. HOGA1.*

Resumen

La hiperoxaluria primaria (HOP) comprende un grupo heterogéneo de trastornos autosómicos recesivos del metabolismo del glicoxilato. Se reconocen tres tipos genotípicos de HOP (1 a 3) y, el diagnóstico suele ser desafiante debido a la marcada variabilidad fenotípica. La HOP3 es la forma menos frecuente y es debida a variantes patogénicas en el gen HOGA1. Por lo general, cursa con un cuadro clínico más leve que HOP1 y HOP2. Presentamos el caso de una mujer joven con hiperoxaluria leve y función renal preservada, con diagnóstico genético con alteraciones en el gen HOGA1. El estudio genético identificó dos variantes patogénicas en HOGA1: c.208C>T, p.(Arg70Ter) y c.700+5G>T. Este caso pone de manifiesto el amplio espectro clínico de la HOP3 y la utilidad de las pruebas genéticas en el diagnóstico.

Palabras clave: *Hiperoxaluria primaria tipo 3. Oxaluria. Urolitiasis. HOGA1.*

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Introduction

Hyperoxaluria (HO) is defined as the excessive excretion of oxalates in urine > 40 mg/day (0.46 mmol/day).[1,2] This may be due to: 1) inherited disorders of glyoxylate metabolism resulting in endogenous overproduction of oxalate in the liver, known as primary hyperoxaluria PH, or 2) increased intestinal absorption of oxalates, referred to as secondary hyperoxaluria SH.[3,4] HO *per se* is a risk factor for nephrolithiasis, and in different patient cohorts, mean prevalence rates of 25 to 45% have been observed in kidney stone formers.[4,5]

Case report

A 17-year-old female patient, Caucasian, with a family history of renal lithiasis on the paternal grandfather's side, without a prior metabolic study. History of multiple consultations for urinary symptoms since 2 years of age. She has had variable urinalyses (normal or with occasional presence of calcium oxalate crystals) and recurrent urinary tract infections during childhood and adolescence. At 14 years of age, a cystourethrography was performed, in which a right renal lithiasis was incidentally identified (Fig. 1). Computed axial tomography showed an enlarged right kidney due to dilation of the upper calyceal group, obstructed by staghorn calculi (Fig. 2). During follow-up, she presented recurrent episodes of ureteral colic. At age 15, she required endourological intervention and extracorporeal lithotripsy. A follow-up imaging study showed the presence of multiple microlithiasis and hydronephrosis (Fig. 3). At 16 years of age, she attended her first nephrology consultation. In the initial evaluation, preserved glomerular filtration rate (GFR) was noted (serum creatinine 0.6 mg/dL, creatinine clearance 108 mL/min). Serum parameters (electrolytes, calcium, phosphorus, magnesium, uric acid, bicarbonate, and parathyroid hormone) were within normal limits. From the urinary metabolic study, only a mildly increased oxaluria of 43.7 mg/day/1.73 m^2 was observed. Given both the family and personal history of the patient, a young individual with recurrent lithiasic activity and signs of hyperoxaluria to rule out SH, further questioning was conducted to identify elements suggestive of excess dietary oxalate, pyridoxine use, or vitamin supplementation, all of which were denied. Plasma oxalate determination was requested, showing a value lower than 1.5 μmol/L (reference value: lower than 2 μmol/L). The lithogenic study was repeated, showing an oxaluria of 50.4 mg/day/1.73 m^2. Based on the previously described findings, a probable PH was proposed, which, in the absence of secondary causes, renal function impairment, and oxalosis, would correspond to type 3. Genetic testing was performed in coordination with *Centro de Referencia Nacional de Defectos Congénitos y Enfermedades Raras (CRENADECER*), Uruguay. Genetic sequencing was carried out at MedGenome laboratory (India). Interpretation and classification of variants were performed according to the criteria of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) were conducted by ATGen laboratory (Uruguay). Genetic testing identified two heterozygous pathogenic variants in HOGA1: c.208C>T and c.700+5G>T. These findings are consistent with PH3, assuming variants are in trans. The patient remains on conservative treatment (fluid intake > 3 L/day) and pharmacological therapy with potassium citrate.

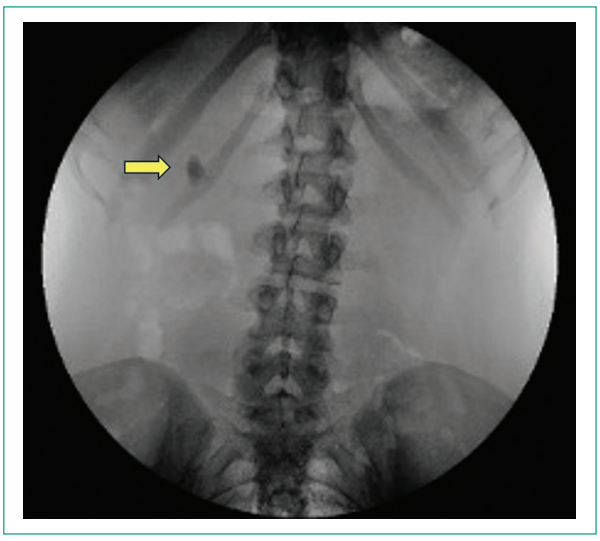


Figure 1. Cystourethrography. At the level of the right renal silhouette, a radiopaque image measuring 12 × 7 mm is observed, possibly related to renal lithiasis.

Discussion

PH was first described in 1925 by Lepoutre.[6] Currently, it is considered a rare disease and represents a heterogeneous group of autosomal recessive genetic abnormalities of glyoxylate metabolism that result in excessive hepatic production of oxalate, which subsequently accumulates in various organs, including the kidney.[7]

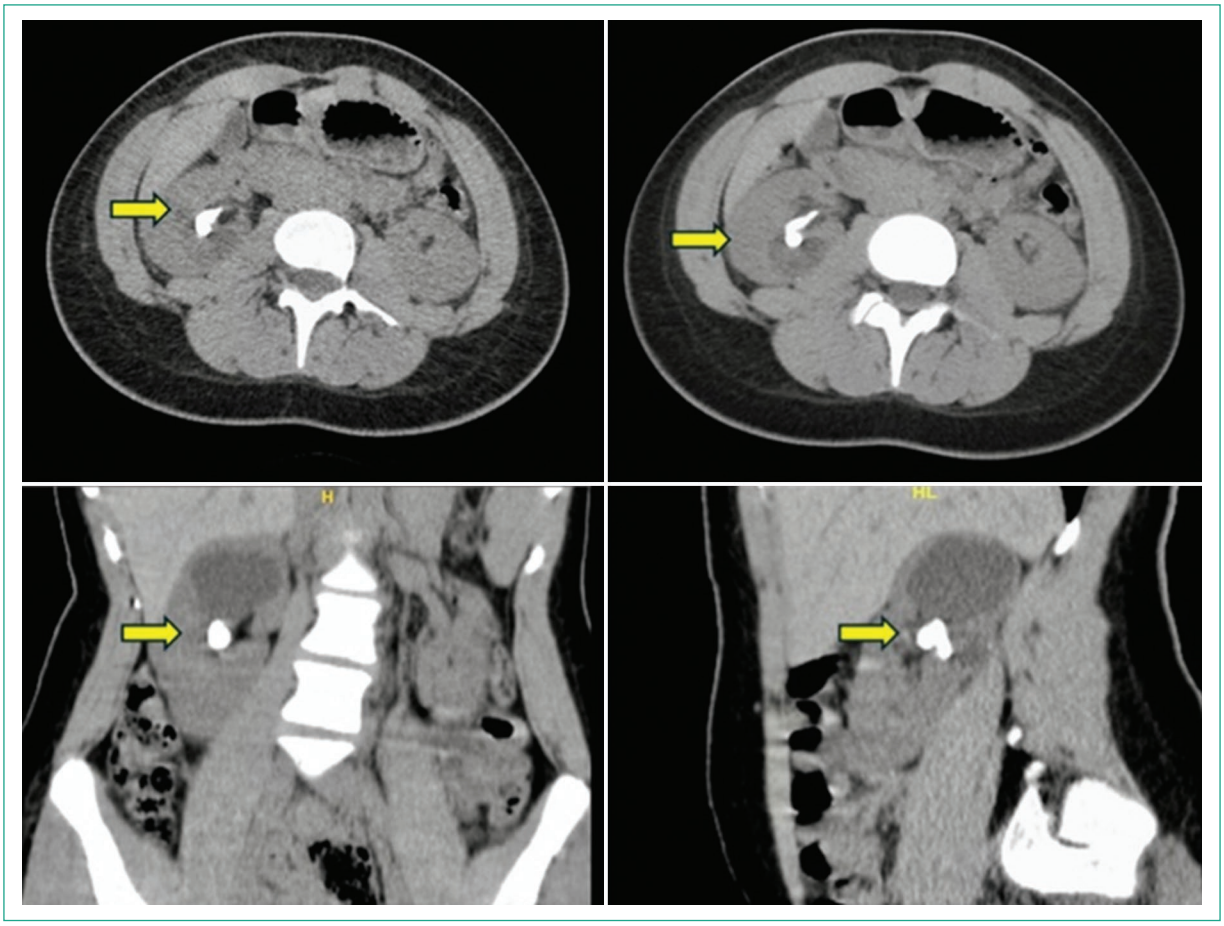


Figure 2. Computed tomography 2021. Enlarged right kidney due to dilation of the upper calyceal group, obstructed by a staghorn calculus of approximately 21 mm in its largest axis, with no evidence of nephrocalcinosis. Upper pole parenchymal thinning. No images suggestive of duplicated collecting system were observed in the non-contrast study.

Renal damage occurs due to direct tubular toxicity of oxalate, intratubular and interstitial deposition of calcium oxalate (nephrocalcinosis), and obstruction by stones. When GFR decreases (< 40 mL/min/1.73 m^2), the kidney loses the ability to maintain oxalemia at normal levels. This favors oxalate supersaturation and the formation of tissue deposits.[7,8]

Types of HP

To date, 3 types of PH have been described (types 1-3).[9] PH type 1 (PH1) is the most common, representing between 70 and 80% of cases. Its prevalence is 1 to 3 cases per million population (pmp) in the United States and Europe. It is caused by a mutation in the alanine–glyoxylate aminotransferase (AGXT) gene, which encodes the enzyme alanine-glyoxylate aminotransferase (AGT), located on chromosome 2q36-37. This mutation leads to increased levels of glycolate, glyoxylate, and oxalate. PH type 2 (PH2) is caused by a mutation in the glyoxylate reductase/hydroxypyruvate reductase (GRHPR) gene, located on chromosome 9p11. It represents approximately 10% of cases. It causes increased levels of glyoxylate, L-glycerate, and oxalate. PH type 3 (PH3) is a recently characterized and rare disease described by R. Belostosky in 2010. It represents between 8–10% of PH cases. It is caused by a mutation in the hydroxy-oxoglutarate aldolase 1 (HOGA1) gene, located on chromosome 10q24.2, which is responsible for encoding the liver-specific enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA), whose mechanisms of action are not yet fully understood. HOGA may act by inhibiting GRHPR or may be transported to the cytosol where it is converted into glyoxylate by an unknown form of cytosolic aldolase, resulting in increased oxalate production.[8-10]

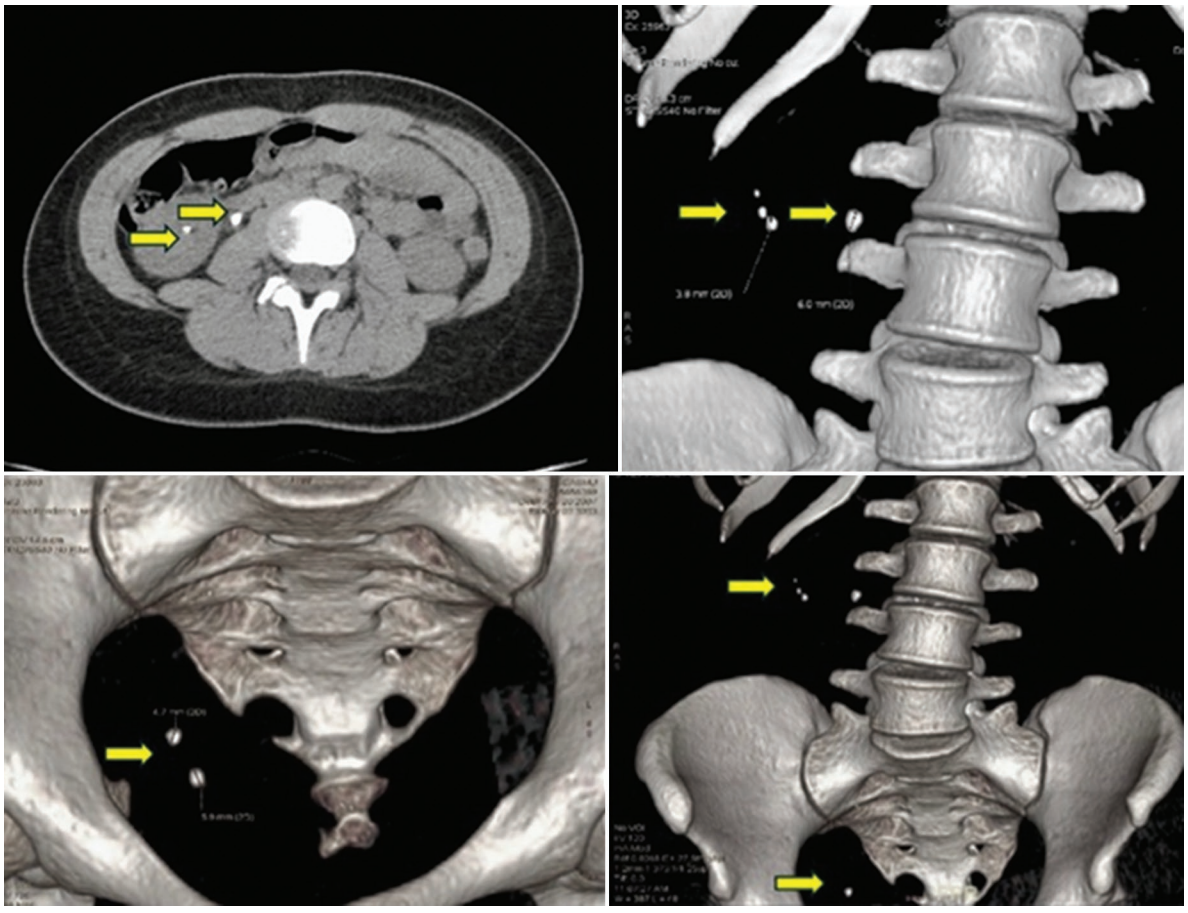


Figure 3. Computed tomography (2023). Right kidney of normal shape and size, with rounded hypodense images of cystic appearance. In the inferior calyceal group, three microlithiasis are present (size < 5 mm). At the ureteropelvic junction, a stone of approximately 6 mm in largest diameter is observed. Mild hydronephrosis. The distal ureter beyond the stone is not clearly identified. In the ipsilateral minor hemipelvis, two calcific density images of approximately 5 mm and 6 mm are identified, whose exact topography cannot be determined (ureteral stones? phleboliths?). Left kidney of normal shape, size, and density, without images of lithiasis or dilation of excretory cavities.

Epidemiology

PH is a rare disease, with an estimated prevalence of 1 to 3 cases per million population (pmp). PH3 would represent between 7 and 12% of identified PH cases.[1,4,9,11] According to population genomic estimates, the prevalence of PH3 would be > 1:136,000.[12,13] In Latin America, there are no data on the prevalence or incidence of PH, although there are case reports, mainly type 1. In Uruguay, cases of PH1 have been reported.[14,15] We have not found any case report of PH3 in Latin America or in Uruguay.

Clinical presentation

The clinical presentation of PH is heterogeneous, which is due to the rarity of the disease and the limited information obtained from case series. PH1 is the most severe form and more frequently progresses to end-stage chronic kidney disease (CKD). The age of presentation is variable (5 and 5.5 years). Clinical manifestations may vary according to age and type of renal damage: oxalosis in infants, recurrent lithiasis in children, occasional stone formation in adults, recurrent disease after kidney transplantation, and cases detected through family screening. Systemic oxalosis is common. PH2 has a more moderate clinical presentation. The age of symptom onset is variable (3-7 years). It is characterized by lithiasic activity (presence of stones, less frequently associated with obstructive uropathy, macroscopic hematuria, renal colic, and urinary infections). Renal disease and its progression are variable and generally occur in adulthood.

Nephrocalcinosis is frequent, around 80%. PH3 has a highly heterogeneous clinical phenotype. The age of presentation is variable (mean age: 2 years), with evidence of recurrent lithiasic activity and related symptoms (urinary symptoms and recurrent urinary infections). Oxaluria in PH3 may be 63 mg/day/1.73 m^2 or even lower. The presence or progression to chronic kidney disease is unusual.[9,11,16]

Martin-Higueras et al. recently published the largest cohort study of patients with PH3 to date. They compared the database of the European Hyperoxaluria Consortium (OxalEUROPE) with the German Hyperoxaluria Center (GHC). In this cohort, the age of disease onset is highly variable, with a mean age of 1.2-1.8 years (0.7-48 years). The age at diagnosis ranged from 4.6 to 6 years (0.25-79.2 years). Regarding clinical presentation, urolithiasis was the most frequent finding both at onset and throughout the disease, followed by nephrocalcinosis and urinary tract infections. Nephrocalcinosis occurred in only 10% of patients. Urinary oxalate excretion was similar across the three PH types. With respect to CKD during follow-up, 46% presented stage 1 CKD, and < 2% stages 4 and 5. In literature, there are few PH3 cases that have progressed to end-stage CKD; therefore, its real prevalence remains undetermined.[17-19]

In the case of our patient, we estimate that urinary symptoms present from a very early age could be associated with the disease. Clinical suspicion (young patient, incidental finding of kidney stones, onset of lithiasic activity in childhood or youth, preserved renal function, and particularly in the presence of HO with mildly increased values and absence of evident secondary causes) was suggestive of the diagnosis, based on the recommendations of the expert consortium of the European Rare Kidney Disease Reference Network (ERKnet) and OxalEurope published in 2023.[8]

Diagnosis

Oxaluria values > 90 mg/day (1 mmol/day) should raise suspicion of PH. Generally, in PH types 1 and 2, oxaluria levels are > 135 mg/day. PH3 has a milder clinical expression, with a variable age of symptom onset and, in few cases, progression to end-stage CKD.[11] There are metabolic tests that may suggest PH. Elevated urinary glycolate excretion in PH1, the presence of L-glyceric acid in PH2, and finally the presence of hydroxy-oxoglutarate in urine, which can be used for the diagnosis of PH3. Unfortunately, these tests are not available in all settings and may be costly.[11,13]

The diagnosis of PH is suspected when suggestive clinical findings are identified, such as recurrent renal lithiasic activity, presence of calcium oxalate stones, lithiasic disease from childhood or adolescence, impaired glomerular filtration, or nephrocalcinosis, together with increased urinary oxalate excretion. Confirmation is made through genetic studies.[13]

Genetic diagnosis

The diagnosis of PH through genetic testing has important implications for clinical management and, in some cases, for family planning, especially in patients with PH1, where early diagnosis can prevent renal failure.[13] In 2010, Belostotsky et al. published a cohort study of 16 patients from 9 unrelated families with a type of PH not characterized as type 1 or 2. They identified mutations in a gene located on chromosome 10 (10q24.2), which encodes the enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA1). This enzyme is the last in the hydroxyproline-glyoxylate pathway within the mitochondria and catalyzes the formation of glyoxylate, a precursor of oxalate. Its deficiency causes the third type of PH, currently known as PH3.

Loss of function of this enzyme leads to increased levels of 4-hydroxyglutamate, 2,4-dihydroxyglutarate, 4-hydroxy-2-oxoglutarate, and oxalate in urine.[10,20] Currently, the mechanism by which urinary oxalate increases due to this enzymatic deficiency is not fully understood. Following Belostotsky's study, different mutations in the HOGA1 gene have been reported in various populations. Currently, around 57 variants have been described in the literature, including missense, nonsense, frameshift, splice-site variants, and variants of unknown significance. According to ACMG pathogenicity criteria, heterozygous HOGA1 variants have been classified into 43 pathogenic or likely pathogenic variants, 9 variants of uncertain significance, and 5 likely benign variants. Of note, there is broad genotypic heterogeneity, as several pathogenic variants recur with high frequency. Other variants are family-specific or have low frequency. Approximately 70% of PH3 alleles correspond to eight variants (most frequent) associated with the disease across populations. These variants are: c.554C>T (p.Thr185Met), c.569C>T (p.Pro190Leu), c.700+5G>T, c.834_834+1delGGinsTT, c.834+1G>T, c.834G>A (p.Ala278), c.860G>T (p.Gly287Val), and c.944_946delAGG (p.Glu315del).[21,22]

In our patient, the presence of alteration in HOGA1 was demonstrated, with two heterozygous variants classified as associated pathogenic: c.208C>T, p.(Arg70Ter), and c.700+5G>T.

The c.700+5G>T mutation is a splice variant with an allelic frequency of 42-44% (63% in Caucasian populations and 35% in European populations).[21] Phenotypically, the clinical expression of this variant is more frequent in women (Caucasian and Asian), with a highly variable age of symptom onset between 1 and 9 years. It generally presents as urinary infections or bilateral renal lithiasis, with recurrent lithiasic activity and some degree of renal disease.[9,19] As was the case in our patient.

The c.208C>T, p.(Arg70Ter) variant is of the nonsense type and the most widely reported in Caucasian patients. Data on its phenotypic expression are scarce. Detection of this variant has been reported in a patient who was compound heterozygous for this mutation and c.700+5G>T, which confirms the autosomal recessive nature of the disease if both are in trans.[22,23]

Treatment

PH still has no specific treatment. The main pillars of PH management are based on early diagnosis (early intervention in family groups and family planning, early referral to a nephrologist for the etiological study of lithiasis).[8,13] Another aspect of treatment is the management of disease manifestations, which can be divided into: a) conservative and pharmacological treatment to reduce urinary calcium oxalate supersaturation through: 1) increased fluid intake > 3 liters per day in adults (1.5 ml/1.73 m^2 in children), to achieve a diuresis of at least 2.5 L/day, 2) oral administration of a calcium oxalate crystallization inhibitor, such as potassium or sodium citrate, and the use of thiazides, which will be discussed later, 3) pyridoxine (vitamin B6), an effective strategy in patients with PH1, although its therapeutic response must be evaluated, defining an adequate response as a reduction in oxaluria > 30% after three months of treatment, 4) reduction of intake of foods rich in oxalate (spinach, chocolate, nuts); b) monitoring of lithiasic activity (through imaging methods with regular follow-up), with the aim of detecting stones that may cause obstruction or renal damage, and treating stones endourologically or by lithotripsy when indicated; c) prevention and/or treatment of urinary tract infections; d) avoidance of elevated oxalemia levels in patients with GFR < 40 mL/min to prevent oxalosis. If plasma oxalate > 35-50 μmol/L, dialysis or transplantation is required to reduce the risk of multiorgan complications due to calcium oxalate deposition.[13,16,24] Our patient follows a low-oxalate diet, high fluid intake, and potassium citrate therapy.

There are new treatments under investigation based on the hypothesis that inhibition of the hepatic isoform of lactate dehydrogenase (LDHa) could reduce oxalate production in all three types of PH. In this context, it is worth highlighting the introduction of two new therapies (Lumasiran and Nedosiran) based on RNA interference (RNAi) in patients with PH1, which could substantially reduce endogenous oxalate production. Another drug under investigation is Stiripentol, an LDHa inhibitor.[24,25] These are currently not available in Latin America.

Conclusions

PH is a rare disease. Its wide genotypic and phenotypic spectrum makes diagnosis a challenge for nephrologists and is often delayed. Among the three types of PH, type 3 has the least severe phenotype. Due to its rarity, it may go unnoticed for several years after symptom onset. PH3 generally begins at an early age (between 2 and 3 years), and recurrent lithiasis and urinary tract infections are the most frequent clinical presentations. In some individuals, PH3 may manifest in adulthood. Oxaluria in PH3 may range from mildly elevated values above normal to very high levels, similar to those seen in types 1 and 2. This is probably the first documented case of PH3 in Latin America in a young patient without renal damage and the first case reported in Uruguay. Genetic testing in patients with suspected PH is essential. The diagnosis of PH3 is established through suggestive phenotypic findings and confirmation of concomitant biallelic pathogenic (or likely pathogenic) variants in HOGA1 identified by molecular genetic testing. The most common variant is c.700+5G>T in Caucasian and European subjects. Further studies are needed, probably multicenter, including cohorts of patients with PH3 to better understand its clinical course and to expand research on its treatment.

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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 human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. 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 or creation of the content of this manuscript.

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CLINICAL CASE

Arginine vasopressin deficiency in a patient with systemic lupus erythematosus. Case report

Deficiencia de hormona arginina-vasopresina en paciente con lupus eritematoso sistémico. Caso clínico

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Abstract

Lymphocytic hypophysitis is a rare condition that requires a high index of suspicion in patients with arginine vasopressin deficiency (AVP-D), especially in the presence of a systemic autoimmune disease. Currently, there are no non-invasive studies available for its diagnosis nor a clear treatment guideline to follow. We present a patient with a recent onset of systemic lupus erythematosus who was diagnosed with AVP-D, manifested by polyuria that began at the end of her last pregnancy and the most plausible diagnosis was lymphocytic hypophysitis. She demonstrated significant improvement with exogenous desmopressin and immunosuppressive treatment.

Key words: *Systemic lupus erythematosus. Arginine vasopressin deficiency. Central diabetes insipidus. Polyuria. Autoinmune hypophysitis. Lymphocytic hypophysitis.*

Resumen

La hipofisitis linfocitaria es una entidad poco frecuente. Se debe tener un alto índice de sospecha en pacientes con deficiencia de hormona arginina-vasopresina (AVP-D), sobre todo en presencia de una enfermedad autoinmune sistémica. No existen hasta el momento estudios no invasivos que la diagnostiquen ni una pauta clara de tratamiento a instaurar. Presentamos una paciente con debut reciente de un lupus eritematoso sistémico que se realiza diagnóstico de AVP-D manifestada por poliuria de inicio al final de su último embarazo, cuyo diagnóstico más probable es una hipofisitis linfocitaria y que presentó una excelente evolución con desmopresina exógena y tratamiento inmunosupresor.

Palabras clave: *Lupus eritematoso sistémico. Deficiencia de hormona arginina-vasopresina. Diabetes insípida central. Poliuria. Hipofisitis autoinmune. Hipofisitis linfocitaria.*

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Introduction

Arginine vasopressin (AVP) is synthesized in magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus. It exhibits pulsatile secretion and a circadian rhythm with peak nocturnal release. It is synthesized as part of a larger precursor molecule (copeptin). Precursor proteins are packaged into secretory granules that travel along long axons through the infundibular stalk to the neurohypophysis, where they are stored. AVP secretion is primarily regulated by changes in plasma osmolality. AVP is the principal regulator of water homeostasis and acts at the renal level through binding to the arginine vasopressin receptor 2 (AVPR2) on the basolateral membrane of the collecting duct, resulting in water reabsorption and a consequent increase in urine osmolality.[1]

AVP deficiency or resistance, previously grouped under diabetes insipidus syndrome, corresponds to a condition characterized by excessive excretion of hypotonic urine (polyuria, defined as diuresis > 50 mL/kg/day), with urine osmolality < 300 mOsm/kg. If thirst mechanisms remain intact, this is accompanied by compensatory increases in water intake (polydipsia) to preserve body homeostasis. The net result is aqueous polyuria with preserved plasma osmolality and normal natremia. Conversely, if fluid intake decreases, hypernatremia and plasma hyperosmolality develop.[2,3]

Changes to AVP have an estimated prevalence of 1 in 25,000 individuals. They can be subdivided into AVP deficiency (AVP-D) and AVP resistance (AVP-R). AVP-D, previously termed central diabetes insipidus due to its hypothalamic–pituitary origin, is characterized by partial or complete deficiency of hormone secretion. AVP-R, previously termed nephrogenic diabetes insipidus due to its renal origin, is characterized by a lack of renal response to adequate hormone levels. The main differential diagnosis is primary polydipsia, in which polyuria is an appropriate response to increased fluid intake. Determining the etiology of aqueous polyuria is crucial given its therapeutic implications. These three entities can be differentiated by a water deprivation test.[2,3] In recent years, additional diagnostic approaches have been described, including copeptin measurement, hypertonic saline infusion test (HSI), and arginine stimulation.[1,4]

AVP-D is usually caused by hereditary or acquired factors, including traumatic, tumoral, infectious, vascular, pharmacological causes, or infiltrative diseases such as autoimmune disorders (autoimmune hypophysitis).[5,6]

Within autoimmune hypophysitis, lymphocytic hypophysitis has been described, characterized by diffuse lymphocytic infiltration of the pituitary gland, which may affect the anterior lobe, posterior lobe, or both.[7] Although definitive diagnosis is histopathological, in recent years several authors have proposed clinical, biochemical, and radiological criteria that allow diagnosis without the need for invasive procedures.[8]

This is the case of a patient who, in the context of the onset of systemic lupus erythematosus (SLE), was diagnosed with AVP-D, with lymphocytic hypophysitis as the most likely etiology. Informed consent was obtained from the patient for publication of the clinical case, maintaining anonymity.

Case report

NN, woman, 33 years old, with no relevant past medical history, presented with precordial pain that began 2 weeks prior to consultation. The pain was persistent, mild in intensity, stabbing in nature, localized, and relieved by the knee-chest position. Concurrently, she reported arthralgia in the hands, knees, and ankles, with swelling, warmth, and erythema, as well as photosensitivity with malar rash, xerophthalmia, and xerostomia. Laboratory findings at admission included anemia (hemoglobin 8.3 g/dL; hematocrit 25.5%), microcytic hypochromic, with platelets and leukocytes within normal range; creatinine 0.8 mg/dL; blood urea nitrogen 0.3 g/L; natremia 138 mEq/L; potassium 4.6 mEq/L; chloride 100 mEq/L. Urinalysis showed density 1003, without proteinuria or microhematuria, and unremarkable urinary sediment. Electrocardiogram showed PR depression, narrow QRS complexes with low voltage, and diffuse concave ST-segment elevation. Chest radiography revealed an increased cardiothoracic index, without pulmonary parenchymal abnormalities and with clear costophrenic angles. Transthoracic echocardiography demonstrated circumferential pericardial effusion with a maximum thickness of 19 mm over the right ventricular wall, with hemodynamic compromise evidenced by right atrial diastolic collapse and significant variability in mitral and tricuspid inflow. Emergency pericardial drainage was performed, obtaining 400 cc of hemorrhagic fluid. Fluid analysis revealed an exudate with low cellularity composed predominantly of neutrophils, negative microbiological studies, and pathological anatomy showing a chronic fibroproductive inflammatory process without specific inflammatory features. Etiological evaluation revealed antinuclear antibodies (ANA) 1/2564, anti-histone antibodies positive, anti-DNA 95 UI/mL

Table 1. Water deprivation test

Parameter	Baseline	3 hours after initiation of water deprivation	1 hour after desmopressin administration	2 hours after desmopressin administration
Sodium (mEq/L)	138	145	144	142
Plasma osmolality (mOsm/kg)	287	296	295	296
Urine osmolality (mOsm/kg)	117	99	204	479

(within normal range), complement levels within normal range (C3 197 mg/dL, C4 25 mg/dL), negative rheumatoid factor, negative antiphospholipid antibodies, and negative antineutrophil cytoplasmic antibodies (ANCA). A diagnosis of SLE was established with serosal involvement (pericarditis with severe pericardial effusion requiring urgent drainage due to right chamber compromise), articular involvement (arthralgia with inflammatory signs), and cutaneous involvement (malar rash, photosensitivity). Due to the severity of pericardial involvement, treatment with intravenous methylprednisolone 1 g for 3 consecutive days was initiated, followed by oral prednisone 20 mg/day, hydroxychloroquine 200 mg/day, and methotrexate 7.5 mg/week, with good clinical response.

A nephrologist was consulted due to polyuria up to 10 L/day. The patient reported a history of polyuria beginning at the end of her last pregnancy 10 years earlier, which was uncomplicated. Term newborn delivered vaginally, with uneventful puerperium, without intra- or postpartum hemorrhage, and without agalactorrhea or amenorrhea. Fluid intake was consistent with polyuria.

Urine osmolality was 104 mOsm/kg. A water deprivation test confirmed AVP-D (Table 1). Brain magnetic resonance imaging with sellar focus and gadolinium showed an empty sella and tentorial findings suggestive of inflammation (Fig. 1). The patient reported nonspecific symptoms suggestive of thyroid hypofunction (hair loss, brittle nails, constipation), with thyroid-stimulating hormone (TSH) 2.6 μUI/mL (reference range, 0.4-4.5 μUI/mL) and thyroxine (T4) 1.49 ng/dL (reference range 0.8-2 ng/dL). There was no asthenia, adynamia, orthostatic hypotension, or hypoglycemia. Adrenocorticotropic hormone (ACTH) was not measured due to prior corticosteroid therapy for SLE. There was no decrease in muscle strength or increase in body fat; growth hormone (GH) was not measured. Menstrual cycles were irregular, with decreased libido, without dyspareunia or climacteric syndrome.

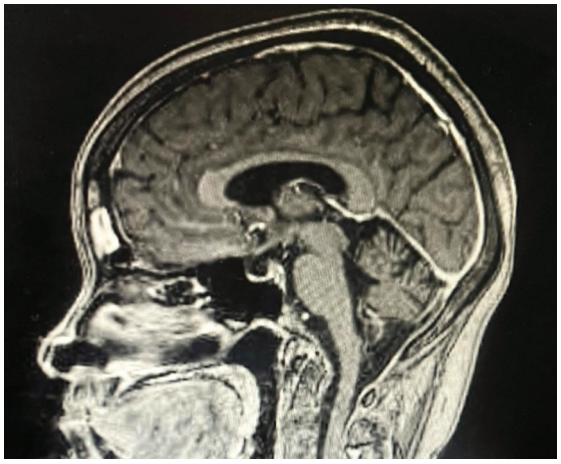


Figure 1. Brain magnetic resonance imaging with sellar focus, T1-weighted sequence.

Follicle-stimulating hormone (FSH) in the follicular phase was 4,1 mUI/mL (reference range 3,5-12,5 mUI/mL), luteinizing hormone (LH) 5,1 mUI/mL (reference range 1,7-15 mUI/mL), estradiol 111 pg/mL (reference range 20-150 pg/mL), and prolactin (PRL) 62,6 ng/mL (reference range 2-25 ng/mL). Oxytocin (OT) was not measured. Supportive treatment for AVP-D was initiated with desmopressin 1 puff (100 mcg) every 12 hours. Lymphocytic hypophysitis was considered the most likely etiology. The patient was already receiving corticosteroid and immunosuppressive therapy for SLE. At follow-up, diuresis remained approximately 2 L/day with appropriate fluid intake, normal natremia, and no additional complications.

Discussion

We present the case of a young patient with new-onset SLE in whom a retrospective diagnosis of AVP-D was established, manifested by polyuria beginning at the end of her last pregnancy, with reduced urine osmolality

and preserved plasma osmolality and natremia in the setting of free access to water. During the water deprivation test, urine osmolality remained < 700 mOsm/kg, thereby excluding primary polydipsia. To elucidate the etiology of the AVP disorder, desmopressin was administered, resulting in an increase in urine osmolality that confirmed the diagnosis of complete AVP-D.[2,3]

Recently, alternative diagnostic approaches have been described, particularly plasma copeptin measurement. Given the difficulty in measuring plasma AVP, copeptin provides a reliable indirect surrogate. Plasma levels can be assessed following hypertonic saline infusion or arginine stimulation; the former has higher diagnostic accuracy, whereas the latter is simpler to perform and better tolerated by patients.[1,4]

AVP-D is most commonly due to acquired causes, whereas hereditary etiologies are rare. Among acquired causes, traumatic (particularly postsurgical), neoplastic, infectious, vascular (due to impaired pituitary blood supply, as in Sheehan syndrome), and infiltrative diseases such as autoimmune disorders (autoimmune hypophysitis) have been described.[5,6]

Autoimmune hypophysitis may present clinically with symptoms due to mass effect (headache, visual disturbances) or with manifestations of pituitary hormone deficiencies (ADH, OT, TSH, ACTH, GH, LH, FSH, PRL). On brain MRI with sellar focus, findings may include pituitary enlargement, relatively homogeneous contrast enhancement, thickening of the infundibular stalk, and loss of the posterior pituitary bright spot on T1-weighted images. In later stages, as in the present case, an empty sella may be observed.[9,10]

Autoimmune hypophysitis can be classified according to etiology as primary or secondary. Primary forms can be further subdivided histopathologically into lymphocytic, granulomatous, xanthomatous, necrotizing, or IgG4-related hypophysitis. Secondary forms may be associated with systemic autoimmune diseases such as SLE and vasculitis, neoplasms and paraneoplastic syndromes, infections, and medications such as immune checkpoint inhibitors.[7,8]

Lymphocytic hypophysitis is the most common cause of autoimmune hypophysitis (68% of primary hypophysitis cases). Its prevalence ranges from 0.24 to 0.88 per 100,000 inhabitants. It typically affects young women, often with onset in late pregnancy or the postpartum period, as in the present case. It is associated with other autoimmune diseases in approximately 30% of cases. According to the anatomical region involved, it is classified into lymphocytic adenohypophysitis (anterior pituitary), lymphocytic infundibuloneurohypophysitis (posterior pituitary), and lymphocytic panhypophysitis (both).[7,9,10]

Given the patient's sex, age, autoimmune background, onset of symptoms at the end of pregnancy, and MRI findings of an empty sella, AVP-D of acquired etiology due to autoimmune hypophysitis – specifically lymphocytic hypophysitis – was considered the most likely diagnosis. It should be noted that hypophysitis may also represent a rare manifestation of SLE; however, in this patient, whose polyuria began at the end of pregnancy and whose SLE onset occurred 10 years later, this possibility was considered less likely. Although the onset of polyuria coincided with the end of pregnancy, which could suggest Sheehan syndrome, the absence of obstetric hemorrhage, hypotension, or shock made this diagnosis unlikely.[7,10,11]

Currently, no specific antibodies are available for the diagnosis of lymphocytic hypophysitis; however, recent studies have proposed rabphilin-3 as a potential biomarker.[5,7] The gold standard for diagnosis remains transsphenoidal pituitary biopsy, although risks and benefits must be carefully weighed. Histopathologically, lymphocytic infiltration of the pituitary gland is observed, predominantly in the interstitium but also involving pituitary acini, with possible formation of lymphoid follicles with germinal centers. Initially, glandular hyperplasia and hypertrophy may be present, followed by fibrosis and atrophy over time.[9]

Management of lymphocytic hypophysitis remains controversial. Treatment is generally supportive, addressing hormonal deficiencies and symptoms related to mass effect. AVP-D is treated with exogenous desmopressin. Immunosuppressive therapy is debated, with glucocorticoids considered first-line; however, there is no consensus regarding optimal dosing or duration. Donegan et al. conducted a systematic review evaluating glucocorticoid use in lymphocytic hypophysitis. Subgroup analysis comparing high-dose glucocorticoids with observation showed higher odds of recovery of anterior pituitary function (OR, 3,41) and radiographic regression (OR, 3,13) in patients receiving high-dose glucocorticoids, but also a higher likelihood of requiring additional therapies (OR, 4,37). No statistically significant difference was observed in AVP-D recovery (OR, 0,9; 95% CI, 0,26-3,10). Surgery is reserved for cases with rapid neurological deterioration due to space-occupying lesions accessible via a transsphenoidal approach. Cortisol and gonadotropin axes often improve with immunosuppressive therapy, whereas AVP-D is generally refractory.[7,9,12]

In this patient, biopsy was not pursued due to procedural risks and the favorable clinical course with desmopressin

and ongoing immunosuppressive therapy for SLE. Additionally, the presence of an empty sella on MRI may indicate a late stage of the disease with fibrosis and glandular atrophy, suggesting irreversibility of the condition.[9,10]

Intestinal necrosis associated with ion-exchange resin therapy is rare but potentially life-threatening. Early suspicion, identification of risk factors, and timely multidisciplinary management are essential for patient survival.

Conclusions

Lymphocytic hypophysitis is an uncommon entity that should be considered in patients with AVP-D, particularly in the presence of systemic autoimmune disease. Multidisciplinary management is essential for favorable outcomes in patients who develop this condition.

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Conflicts of interest

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Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

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