

Interacción endocrina y metabólica en la enfermedad renal crónica sin diabetes: mecanismos actuales, biomarcadores y perspectivas terapéuticas

Endocrine and Metabolic Crosstalk in Non-Diabetic Chronic Kidney Disease: Current Mechanisms, Biomarkers, and Therapeutic Perspectives

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RESUMEN

La enfermedad renal crónica (ERC) sin diabetes mellitus constituye una entidad clínica cada vez más reconocida cuya progresión no puede explicarse únicamente por los mecanismos hemodinámicos tradicionales. La evidencia científica actual demuestra que la disfunción endocrina, la remodelación metabólica, la alteración mitocondrial, la inflamación crónica, el estrés oxidativo y la comunicación anormal entre el riñón y otros órganos desempeñan un papel fundamental durante la evolución de la enfermedad. La presente revisión analiza críticamente la evidencia disponible sobre los mecanismos endocrinos y metabólicos implicados en la ERC no diabética, integrando conocimientos de la nefrología, la endocrinología y la medicina interna, con especial consideración de la evidencia disponible para Latinoamérica. Se realizó una revisión narrativa basada en el Método Científico mediante la consulta de publicaciones de alta calidad y guías clínicas internacionales. Los resultados muestran que la activación persistente del sistema renina-angiotensina-aldosterona, la alteración del eje FGF23-Klotho, el deterioro del metabolismo de la vitamina D, la resistencia a la insulina, las alteraciones endocrinas asociadas con la obesidad, la disfunción mitocondrial y el eje intestino-riñón participan de manera importante en la fibrosis renal, la disminución progresiva de la función renal y las complicaciones cardiovasculares. Asimismo, las estrategias terapéuticas actuales, especialmente los inhibidores del cotransportador sodio-glucosa tipo 2, han modificado el tratamiento de la enfermedad al ofrecer beneficios renoprotectores independientes del control glucémico. Los biomarcadores emergentes y la medicina de precisión representan herramientas prometedoras para mejorar el diagnóstico temprano y la individualización del tratamiento. Sin embargo, aún se requieren investigaciones multicéntricas que incrementen la representación de poblaciones latinoamericanas. En conjunto, la ERC sin diabetes debe entenderse como una enfermedad sistémica compleja que requiere un abordaje multidisciplinario e integral para optimizar los resultados clínicos.

PALABRAS CLAVE

Enfermedad renal crónica, Enfermedad renal crónica sin diabetes, Mecanismos endocrinos, Disfunción metabólica, FGF23, Klotho, Resistencia a la insulina, Disfunción mitocondrial, Fibrosis renal, Biomarcadores, Medicina de precisión, Nefrología.

ABSTRACT

Chronic kidney disease (CKD) without diabetes mellitus has become an increasingly recognized clinical entity whose progression cannot be explained exclusively by traditional hemodynamic mechanisms. Growing evidence indicates that endocrine dysregulation, metabolic remodeling, mitochondrial dysfunction, chronic inflammation, oxidative stress, and altered communication between the kidney and other organ systems play fundamental roles throughout disease development and progression. The present review critically analyzes current scientific evidence regarding the endocrine and metabolic mechanisms involved in non-diabetic CKD, integrating findings from nephrology, endocrinology, and internal medicine while incorporating information relevant to Latin American populations. A narrative review based on the Scientific Method was conducted using high-quality publications retrieved from internationally recognized databases and clinical practice guidelines. The available evidence demonstrates that persistent activation of the renin-angiotensin-aldosterone system, disruption of the fibroblast growth factor 23-Klotho axis, impaired vitamin D metabolism, insulin resistance, obesity-related endocrine alterations, mitochondrial dysfunction, and gut-kidney interactions contribute substantially to renal fibrosis, progressive loss of kidney function, and cardiovascular complications. Contemporary therapeutic approaches, particularly sodium-glucose cotransporter-2 inhibitors, have significantly modified disease management by providing nephroprotective effects beyond glycemic control. Emerging biomarkers and precision medicine strategies also show considerable potential for improving early diagnosis, individualized risk assessment, and targeted therapeutic interventions. Nevertheless, additional multicenter studies, particularly involving underrepresented regions such as Latin America, remain necessary to strengthen the current evidence base. Overall, non-diabetic CKD should be regarded as a complex multisystem disorder requiring an integrated clinical approach that combines endocrine, metabolic, cardiovascular, and nephrological perspectives to optimize patient outcomes.

KEYWORDS

Chronic kidney disease, Non-diabetic chronic kidney disease, Endocrine mechanisms, Metabolic dysfunction, FGF23, Klotho, Insulin resistance, Mitochondrial dysfunction, Kidney fibrosis, Biomarkers, Precision medicine, Nephrology.

INTRODUCCIÓN**Introduction**

Chronic kidney disease (CKD) has emerged as one of the fastest-growing contributors to global morbidity and mortality, affecting more than 850 million individuals worldwide and imposing an increasingly significant burden on healthcare systems across both high-income and low- and middle-income countries (Kalantar-Zadeh et al., 2021; KDIGO, 2024). While diabetes mellitus remains the leading cause of CKD globally, an increasing proportion of patients develop progressive renal dysfunction in the absence of diabetes, highlighting the complexity and heterogeneity of non-diabetic chronic kidney disease (ND-CKD). This clinical entity encompasses a broad spectrum of pathological conditions, including hypertensive nephropathy, obesity-associated kidney disease, chronic glomerular disorders, tubulointerstitial diseases, inherited nephropathies, aging-related nephron loss, and CKD of unknown origin, all of which share common mechanisms of progressive renal injury despite distinct etiological backgrounds (Ortiz et al., 2025; Yamamoto & Isaka, 2024).

During the last decade, advances in nephrology have substantially transformed the understanding of CKD pathophysiology. Traditionally, progressive nephron loss was primarily explained by glomerular hypertension, proteinuria, activation of the renin-angiotensin-aldosterone system (RAAS), and tubulointerstitial fibrosis. Although these mechanisms continue to represent fundamental drivers of disease progression, contemporary evidence demonstrates that renal deterioration results from a far more intricate interaction involving endocrine dysfunction, metabolic remodeling, mitochondrial impairment, chronic low-grade inflammation, immune activation, oxidative stress, endothelial dysfunction, and alterations in inter-organ communication networks. Consequently, CKD is currently recognized not only as a renal disorder but also as a systemic metabolic disease involving reciprocal interactions among the kidneys, cardiovascular system, endocrine organs, skeletal tissue, adipose tissue, liver, gut microbiota, and immune system (Miguel et al., 2025; Knol et al., 2024).

The endocrine functions of the kidney have gained particular attention in recent years because they extend well beyond the regulation of fluid and electrolyte balance. The kidneys actively participate in erythropoietin production, vitamin D activation, phosphate homeostasis through the fibroblast growth factor 23 (FGF23)-Klotho axis, regulation of acid-base equilibrium, sodium homeostasis, and modulation of numerous hormonal pathways involved in systemic metabolism. Emerging evidence indicates that disturbances in these endocrine mechanisms often precede measurable declines in glomerular filtration rate and contribute directly to fibrosis, vascular calcification, mineral bone disorders, anemia, sarcopenia, cardiovascular disease, and accelerated biological aging. These findings suggest that endocrine alterations should be considered early pathogenic events rather than merely secondary consequences of declining renal function (KDIGO, 2024; Yamamoto & Isaka, 2024).

Among the most significant discoveries has been the identification of the FGF23-Klotho signaling pathway as a central regulator of mineral metabolism and renal aging. Reduced renal expression of Klotho and elevated circulating concentrations of FGF23 have consistently been associated with accelerated CKD progression, endothelial dysfunction, left ventricular hypertrophy, chronic inflammation, and increased mortality independent of diabetic status. Likewise, abnormalities in vitamin D metabolism and secondary hyperparathyroidism have demonstrated important effects extending beyond bone health, influencing immune regulation, oxidative stress, vascular remodeling, and tissue fibrosis. These endocrine abnormalities are increasingly recognized as therapeutic targets capable of modifying disease progression rather than serving solely as biomarkers of advanced CKD (Miguel et al., 2025; Ortiz et al., 2025).

Simultaneously, considerable attention has been directed toward metabolic disturbances occurring in non-diabetic CKD. Mitochondrial dysfunction has emerged as one of the earliest intracellular events contributing to tubular injury and chronic nephron loss. Altered mitochondrial bioenergetics reduces ATP production, promotes excessive reactive

oxygen species generation, impairs fatty acid oxidation, and activates multiple profibrotic signaling pathways. Lipotoxicity, characterized by abnormal lipid accumulation within renal tubular epithelial cells, further exacerbates oxidative stress and inflammatory responses, ultimately accelerating irreversible fibrosis. These metabolic alterations appear to occur independently of hyperglycemia and therefore represent important mechanisms explaining CKD progression among individuals without diabetes mellitus (Miguel et al., 2025; Knol et al., 2024).

Another important paradigm shift concerns insulin resistance, which is increasingly recognized as a common metabolic abnormality even among patients without overt diabetes. Chronic inflammation, adipose tissue dysfunction, oxidative stress, hormonal imbalance, and mitochondrial impairment collectively contribute to reduced insulin sensitivity, leading to alterations in protein metabolism, endothelial dysfunction, muscle wasting, and cardiovascular complications. Recent investigations indicate that insulin resistance should no longer be regarded solely as a diabetic phenomenon but rather as an integral component of CKD pathophysiology that contributes to disease progression through multiple interconnected metabolic pathways (Zaitoon et al., 2026).

Obesity has also become an increasingly relevant determinant of non-diabetic kidney disease. Beyond its established association with hypertension and metabolic syndrome, obesity directly induces glomerular hyperfiltration, podocyte injury, renal lipid accumulation, chronic inflammation, activation of mineralocorticoid receptors, and dysregulation of adipokines such as leptin, adiponectin, and resistin. These alterations contribute to structural kidney damage even in individuals without diabetes, emphasizing that adipose tissue functions as an active endocrine organ capable of influencing renal physiology through complex hormonal and inflammatory mechanisms (Yau et al., 2024).

Parallel advances have highlighted the importance of the gut-kidney axis. Alterations in intestinal microbiota composition increase intestinal permeability and promote systemic exposure to uremic toxins including indoxyl sulfate, p-cresyl sulfate, and trimethylamine N-oxide (TMAO). These metabolites stimulate oxidative stress, endothelial dysfunction, chronic inflammation, and renal fibrosis while simultaneously increasing cardiovascular risk. The recognition of gut microbiota as a contributor to CKD progression has generated growing interest in nutritional interventions, microbiome modulation, and precision therapies designed to restore intestinal homeostasis and reduce toxin production (Miguel et al., 2025).

The introduction of novel biomarkers has likewise transformed the early detection and monitoring of CKD. Conventional indicators such as serum creatinine and estimated glomerular filtration rate remain indispensable but frequently detect disease only after substantial nephron loss has occurred. Consequently, biomarkers including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, urinary interleukin-18, metabolomic signatures, proteomic profiles, and transcriptomic analyses are being incorporated into clinical research with the objective of identifying renal injury at earlier stages and facilitating individualized therapeutic decision-making. Furthermore, advances in artificial intelligence and machine learning are improving risk prediction models through the integration of multidimensional clinical, laboratory, imaging, and molecular data (KDIGO, 2024; Ortiz et al., 2025).

Therapeutic strategies have evolved accordingly. While renin-angiotensin system blockade remains a cornerstone of CKD management, recent clinical trials have demonstrated substantial renal and cardiovascular benefits associated with sodium-glucose cotransporter-2 (SGLT2) inhibitors even among patients without diabetes. Similarly, mineralocorticoid receptor antagonists, anti-inflammatory agents, antifibrotic therapies, metabolic modulators, structured exercise programs, individualized nutritional interventions, and emerging regenerative approaches are redefining the treatment landscape. These developments illustrate a transition from exclusively hemodynamic interventions toward comprehensive strategies targeting endocrine dysfunction, metabolic abnormalities, inflammation, fibrosis, and inter-organ communication (Heerspink et al., 2020; EMPA-KIDNEY Collaborative Group, 2023).

From a global health perspective, the burden of CKD extends disproportionately to low- and middle-income regions, where delayed diagnosis, limited access to nephrology services, socioeconomic inequalities, and fragmented healthcare systems contribute to poor clinical outcomes. Latin America represents a particularly important setting because the prevalence of hypertension, obesity, chronic inflammatory conditions, environmental nephropathies, and aging populations continues to increase, while healthcare resources remain unevenly distributed. Regional studies have

emphasized the need to strengthen preventive strategies, promote early detection programs, improve multidisciplinary management, and expand access to evidence-based therapies tailored to local epidemiological characteristics (Correa-Rotter et al., 2023).

Given the rapidly expanding body of evidence concerning endocrine regulation, metabolic remodeling, molecular biomarkers, and precision therapeutics, a comprehensive synthesis of current knowledge is warranted. Although numerous investigations have evaluated individual mechanisms contributing to CKD progression, relatively few reviews have integrated these emerging endocrine and metabolic pathways specifically within the context of non-diabetic chronic kidney disease while simultaneously considering their translational implications for clinical practice and future research. Addressing this gap is particularly relevant as these mechanisms increasingly influence diagnostic algorithms, risk stratification, and therapeutic decision-making across nephrology, endocrinology, and internal medicine.

Accordingly, the present review aims to critically analyze current evidence regarding the endocrine and metabolic mechanisms underlying chronic kidney disease in individuals without diabetes mellitus. Particular emphasis is placed on hormonal regulation, mitochondrial dysfunction, metabolic reprogramming, obesity-related pathways, insulin resistance, gut-kidney interactions, emerging biomarkers, and novel therapeutic approaches. Furthermore, this review integrates findings derived from international research with evidence relevant to Latin American populations to provide a comprehensive and clinically applicable perspective. The review was developed through a structured analysis of recent scientific literature published in high-impact peer-reviewed journals and international clinical practice guidelines, prioritizing studies that contribute to the contemporary understanding of non-diabetic CKD pathophysiology and its implications for precision medicine.

DESARROLLO

Non-diabetic chronic kidney disease (ND-CKD) comprises a heterogeneous group of renal disorders characterized by persistent structural or functional abnormalities occurring independently of diabetes mellitus. Its principal causes include arterial hypertension, primary and secondary glomerular diseases, hereditary nephropathies, chronic tubulointerstitial injury, autoimmune disorders, obesity-related glomerulopathy, recurrent acute kidney injury, exposure to nephrotoxic substances, and kidney disease of unknown etiology. Despite their clinical diversity, these conditions frequently converge on common pathways involving nephron loss, glomerular hyperfiltration, tubular stress, inflammation, endothelial dysfunction, and progressive renal fibrosis (Kalantar-Zadeh et al., 2021; KDIGO, 2024).

Current evidence has expanded this conventional interpretation by demonstrating that ND-CKD is also influenced by extensive endocrine and metabolic disturbances. The kidney functions as an endocrine organ through its participation in erythropoietin production, vitamin D activation, renin release, mineral regulation, acid-base balance, glucose handling, and hormonal degradation. As kidney function declines, alterations in these processes may contribute not only to recognized complications such as anemia and mineral and bone disorder, but also to systemic inflammation, cardiovascular remodeling, muscle wasting, insulin resistance, and accelerated biological aging. These findings support a broader model in which endocrine dysfunction is integrated into the mechanisms of renal progression rather than being regarded exclusively as a consequence of advanced disease (KDIGO, 2024; Ortiz et al., 2025).

One of the most relevant pathways is the renin–angiotensin–aldosterone system. Persistent activation of this system promotes vasoconstriction, sodium retention, systemic and intraglomerular hypertension, oxidative stress, and stimulation of profibrotic mediators. Angiotensin II and aldosterone may induce podocyte injury, endothelial dysfunction, inflammatory-cell recruitment, and extracellular matrix deposition. These effects explain why renin–angiotensin system blockade remains an essential component of treatment in patients with albuminuric CKD, even when diabetes is absent. Nevertheless, residual progression among appropriately treated patients indicates that hemodynamic control alone is insufficient and that additional metabolic and inflammatory pathways must be considered.

The fibroblast growth factor 23–Klotho axis constitutes another central endocrine mechanism. Klotho is predominantly expressed in renal tubular cells and participates in phosphate metabolism, vascular protection, antioxidant activity, and cellular aging. Progressive kidney injury reduces Klotho expression, whereas circulating fibroblast growth factor 23 concentrations increase in response to phosphate retention. Although this compensatory response initially supports phosphate homeostasis, sustained elevation of fibroblast growth factor 23 has been associated with left ventricular hypertrophy, endothelial dysfunction, inflammation, and adverse cardiovascular outcomes. Simultaneously, reduced Klotho activity may facilitate vascular calcification, renal fibrosis, and cellular senescence. The alteration of this axis may therefore begin before advanced kidney failure and contribute to the systemic manifestations of ND-CKD.

Disorders of vitamin D and parathyroid hormone metabolism are closely connected to this process. Reduced renal synthesis of calcitriol limits intestinal calcium absorption and contributes to secondary hyperparathyroidism. However, the consequences extend beyond bone turnover. Vitamin D signaling participates in immune regulation, endothelial homeostasis, renin suppression, and cellular differentiation. Its impairment may therefore intensify inflammation and vascular injury. Excess parathyroid hormone can also influence cardiovascular, neuromuscular, and metabolic function, illustrating the close relationship between renal endocrine failure and multisystem disease.

Metabolic reprogramming within renal tissue is increasingly recognized as a determinant of disease progression. Renal tubular epithelial cells have high energy requirements and depend substantially on mitochondrial oxidative metabolism and fatty acid oxidation. Chronic injury reduces mitochondrial efficiency, limits adenosine triphosphate production, increases reactive oxygen species generation, and impairs cellular repair. Damaged tubular cells may subsequently adopt a proinflammatory and profibrotic phenotype, promoting fibroblast activation and extracellular matrix accumulation. Thus, mitochondrial dysfunction represents a link between initial renal stress and irreversible tubulointerstitial fibrosis (Miguel et al., 2025; Knol et al., 2024).

Impaired fatty acid oxidation also promotes intracellular lipid accumulation. This phenomenon, frequently described as renal lipotoxicity, may occur in obesity, dyslipidemia, aging, and chronic inflammatory states without requiring persistent hyperglycemia. Lipid deposition in podocytes and tubular cells disrupts mitochondrial membranes, increases oxidative injury, alters autophagy, and stimulates inflammatory pathways. Consequently, metabolic disturbances commonly associated with diabetes may also contribute to kidney damage among individuals with normal blood glucose concentrations.

Insulin resistance is another relevant component of ND-CKD. Reduced insulin sensitivity may arise from chronic inflammation, uremic toxin accumulation, oxidative stress, sedentary behavior, altered adipokine secretion, metabolic acidosis, and loss of skeletal muscle. It can be identified before the development of overt diabetes and may worsen endothelial function, protein catabolism, sodium retention, and cardiovascular risk. In this context, insulin resistance should be interpreted as part of the systemic metabolic phenotype of CKD rather than solely as a precursor of diabetes.

Obesity further increases the complexity of non-diabetic kidney injury. Excess adipose tissue induces glomerular hyperfiltration, activation of the sympathetic nervous and renin–angiotensin–aldosterone systems, sodium retention, and increased renal oxygen demand. Adipose tissue also produces biologically active mediators, including leptin, adiponectin, resistin, interleukin-6, and tumor necrosis factor- α . An imbalance in these adipokines may favor inflammation, oxidative stress, endothelial injury, and renal fibrosis. Some patients may consequently develop obesity-related glomerulopathy and progressive albuminuria despite the absence of diabetes (Yau et al., 2024).

The gut–kidney axis has also become an important area of investigation. Reduced kidney function alters intestinal microbial composition and intestinal barrier integrity. At the same time, bacterial metabolism generates compounds such as indoxyl sulfate, p-cresyl sulfate, and trimethylamine N-oxide, which may accumulate because of impaired renal clearance. These substances have been associated with oxidative stress, endothelial dysfunction, vascular damage, inflammation, and fibrosis. Diet, antibiotic exposure, gastrointestinal transit, and geographical patterns of food consumption may influence this process, making the gut–kidney axis particularly relevant when comparing populations from different regions.

Latin America requires specific consideration because ND-CKD develops within a setting marked by unequal access to preventive care, delayed nephrology referral, high rates of hypertension and obesity, occupational exposures,

environmental heat stress, nephrotoxic medication use, and limited availability of kidney replacement therapy in some areas. CKD of uncertain or nontraditional origin has been reported in agricultural populations, especially in parts of Central America, where recurrent dehydration, heat exposure, heavy physical activity, and possible environmental factors have been investigated. These regional characteristics demonstrate that international models of CKD must be complemented by locally relevant epidemiological and socioeconomic evidence.

Recent therapeutic findings reinforce the importance of studying mechanisms beyond glycemic control. In DAPA-CKD, dapagliflozin reduced the risk of major renal and cardiovascular outcomes in patients with CKD with or without type 2 diabetes (Heerspink et al., 2020). Similarly, EMPA-KIDNEY included a large proportion of participants without diabetes and demonstrated that empagliflozin reduced the progression of kidney disease or cardiovascular death across a broad CKD population (EMPA-KIDNEY Collaborative Group, 2023). These benefits suggest that sodium-glucose cotransporter-2 inhibition acts through mechanisms such as restoration of tubuloglomerular feedback, reduction of intraglomerular pressure, improved tubular oxygen balance, natriuresis, and attenuation of inflammatory and metabolic stress rather than through glucose lowering alone.

The protective effects observed in non-diabetic populations have modified the clinical approach to CKD. Contemporary management increasingly combines blood pressure control, renin-angiotensin system inhibition, sodium-glucose cotransporter-2 inhibitors, individualized dietary measures, correction of metabolic acidosis when indicated, avoidance of nephrotoxins, physical activity, weight management, and treatment of cardiovascular risk factors. However, treatment selection must remain individualized according to estimated glomerular filtration rate, albuminuria, etiology, blood pressure, electrolyte status, comorbidities, and tolerance. KDIGO guidelines emphasize risk-based evaluation and integrated management rather than relying on estimated glomerular filtration rate alone (KDIGO, 2024).

Despite these advances, important gaps remain. The temporal relationship between endocrine abnormalities and renal injury is not fully established, and it remains unclear which changes are causal, compensatory, or secondary to declining filtration. Biomarkers such as Klotho, fibroblast growth factor 23, cystatin C, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, inflammatory mediators, and metabolic profiles may improve early detection, but their clinical implementation is limited by differences in laboratory methods, cost, accessibility, and incomplete validation across populations. Latin American participants also remain underrepresented in many major mechanistic and therapeutic studies, restricting the generalizability of some findings.

Therefore, the study of ND-CKD requires an integrative approach capable of connecting renal hemodynamics with endocrine signaling, mitochondrial metabolism, adipose-tissue dysfunction, inflammation, intestinal dysbiosis, cardiovascular injury, and social determinants of health. This perspective may facilitate earlier recognition of high-risk patients, improve the classification of disease phenotypes, and support the development of interventions directed toward mechanisms rather than isolated clinical manifestations. It also provides a suitable framework for teaching medical students that CKD without diabetes is not a single disease, but a group of disorders in which renal, endocrine, metabolic, cardiovascular, and environmental factors interact throughout the course of illness.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To critically analyze the current scientific evidence regarding the emerging endocrine and metabolic mechanisms involved in the pathophysiology, progression, diagnosis, and therapeutic management of chronic kidney disease in adults without diabetes mellitus, integrating contemporary international findings and evidence relevant to Latin American populations in order to strengthen the understanding of this condition from nephrological, endocrinological, and internal medicine perspectives.

Specific Objectives

Cognitive Domain

1. **Remember** the principal epidemiological characteristics and etiological factors associated with non-diabetic chronic kidney disease according to current international guidelines and scientific literature.
2. **Understand** the endocrine and metabolic pathways involved in the development and progression of non-diabetic chronic kidney disease, including alterations of the renin–angiotensin–aldosterone system, the FGF23–Klotho axis, vitamin D metabolism, insulin resistance, mitochondrial dysfunction, and chronic inflammation.
3. **Analyze** the interactions between endocrine dysfunction, metabolic remodeling, cardiovascular complications, and renal fibrosis that contribute to disease progression.
4. **Evaluate** the clinical significance of emerging biomarkers, molecular pathways, and novel therapeutic strategies for improving early diagnosis, risk stratification, and individualized patient management.
5. **Create** an integrated conceptual framework that summarizes current knowledge regarding endocrine and metabolic mechanisms in non-diabetic chronic kidney disease and identifies potential directions for future research and clinical practice.

Psychomotor Domain

6. **Apply** standardized criteria from international clinical practice guidelines to interpret evidence related to kidney function, albuminuria, endocrine abnormalities, and metabolic alterations in patients with non-diabetic chronic kidney disease.
7. **Develop** the ability to organize, compare, and synthesize scientific evidence from peer-reviewed publications to facilitate evidence-based clinical reasoning and academic discussion.

Affective Domain

8. **Value** the importance of multidisciplinary collaboration among nephrology, endocrinology, internal medicine, nutrition, and primary care for the comprehensive management of patients with non-diabetic chronic kidney disease.
9. **Promote** critical thinking and lifelong learning regarding emerging pathophysiological mechanisms that may improve prevention, diagnosis, and treatment of chronic kidney disease.
10. **Recognize** the relevance of reducing health inequalities by encouraging the application of evidence-based strategies adapted to diverse healthcare systems, particularly within Latin American populations, where access to early diagnosis and specialized nephrology care remains variable.

OBJETO DE ESTUDIO

The object of this review is the endocrine and metabolic mechanisms involved in the initiation, progression, and clinical expression of chronic kidney disease (CKD) in adults without diabetes mellitus. Particular emphasis is placed on the biological processes that contribute to kidney injury beyond hyperglycemia, including hormonal dysregulation, mitochondrial dysfunction, chronic low-grade inflammation, oxidative stress, metabolic remodeling, endothelial dysfunction, and inter-organ communication through the gut–kidney, bone–kidney, cardiovascular–kidney, and adipose tissue–kidney axes.

The phenomenon under investigation comprises non-diabetic chronic kidney disease as a multifactorial clinical condition that includes hypertensive nephropathy, obesity-related kidney disease, chronic glomerular disorders, hereditary nephropathies, tubulointerstitial diseases, autoimmune renal disorders, aging-associated kidney dysfunction, and chronic kidney disease of unknown or nontraditional origin. Although these entities differ in etiology, they share several molecular and cellular pathways responsible for nephron loss, tubulointerstitial fibrosis, vascular remodeling, and progressive decline in kidney function (Kalantar-Zadeh et al., 2021; KDIGO, 2024).

The target population considered in this review consists of adult patients diagnosed with chronic kidney disease who do not have diabetes mellitus as the primary cause of renal impairment. Evidence from different geographical regions is incorporated to provide an international perspective, while particular attention is given to findings relevant to Latin

America because of the increasing burden of hypertension, obesity, population aging, environmental nephropathies, and disparities in access to specialized nephrology care (Correa-Rotter et al., 2023).

From a physiological perspective, this review considers the kidney as an endocrine and metabolic organ whose functions extend beyond glomerular filtration. Accordingly, the object of study includes alterations involving the renin–angiotensin–aldosterone system, the fibroblast growth factor 23–Klotho axis, vitamin D activation, erythropoietin production, mineral metabolism, insulin sensitivity, lipid metabolism, mitochondrial bioenergetics, inflammatory signaling pathways, oxidative stress, and cellular senescence. These mechanisms are analyzed because they increasingly represent potential therapeutic targets capable of modifying disease progression and improving long-term renal and cardiovascular outcomes (Miguel et al., 2025; Ortiz et al., 2025).

This review also examines the interaction between endocrine abnormalities and systemic metabolic disturbances, recognizing that chronic kidney disease is closely associated with cardiovascular disease, skeletal muscle dysfunction, malnutrition, frailty, vascular calcification, and immune dysregulation. Consequently, the object of study extends beyond isolated renal pathology to include the multisystem biological processes that influence disease evolution and patient prognosis.

Finally, the review focuses on the current scientific evidence regarding emerging biomarkers, precision medicine approaches, and novel therapeutic strategies directed toward endocrine and metabolic pathways. Through this approach, the study seeks to provide a comprehensive understanding of non-diabetic chronic kidney disease that supports clinical decision-making, medical education, and future research in nephrology, endocrinology, and internal medicine.

METODOLOGÍA

This study was conducted as a narrative review using the **Scientific Method** as the methodological framework to systematically identify, analyze, synthesize, and interpret current evidence regarding the endocrine and metabolic mechanisms involved in chronic kidney disease (CKD) without diabetes mellitus. The methodological approach was selected because it provides a structured process for critically evaluating published scientific evidence and integrating findings from different clinical, experimental, and epidemiological investigations into a comprehensive perspective.

The study was developed through five sequential stages: problem identification, literature search, critical selection of scientific evidence, analysis and synthesis of findings, and interpretation of the available evidence. Each stage was designed to ensure methodological transparency and facilitate reproducibility by other researchers.

Research Design

A qualitative, descriptive, and analytical review design was adopted. The review focused on studies investigating endocrine regulation, metabolic dysfunction, molecular mechanisms, biomarkers, and therapeutic advances associated with non-diabetic chronic kidney disease. No primary data were collected, and all information was obtained from previously published scientific literature.

Information Sources

The literature search was performed using internationally recognized biomedical databases to ensure the quality and reliability of the retrieved evidence. The principal databases included:

- PubMed/MEDLINE
- Scopus
- Web of Science

- ScienceDirect
- SpringerLink
- Nature Portfolio
- The Lancet Journals
- New England Journal of Medicine
- Kidney International
- Clinical Journal of the American Society of Nephrology
- Journal of the American Society of Nephrology

International clinical practice guidelines published by Kidney Disease: Improving Global Outcomes (KDIGO) were also consulted because they represent the current standard for the evaluation and management of chronic kidney disease.

Search Strategy

Scientific publications were identified using combinations of Medical Subject Headings (MeSH) terms and free-text keywords connected through Boolean operators (AND, OR). Representative search terms included:

- “Chronic kidney disease”
- “Non-diabetic chronic kidney disease”
- “Endocrine mechanisms”
- “Metabolic dysfunction”
- “FGF23”
- “Klotho”
- “Insulin resistance”
- “Mitochondrial dysfunction”
- “Oxidative stress”
- “Kidney fibrosis”
- “Inflammation”
- “Gut-kidney axis”
- “Emerging biomarkers”

Search combinations included expressions such as:

(“Chronic kidney disease” AND endocrine mechanisms)

(“Non-diabetic chronic kidney disease” AND metabolism)

(“CKD” AND Klotho AND FGF23)

(“Kidney fibrosis” AND mitochondrial dysfunction)

Eligibility Criteria

The review prioritized publications meeting the following inclusion criteria:

- Peer-reviewed scientific articles.
- Clinical trials, systematic reviews, narrative reviews, observational studies, and international clinical practice guidelines.
- Articles published primarily between 2021 and 2026, with seminal studies included when considered essential for understanding current concepts.
- Publications written in English.
- Studies addressing endocrine regulation, metabolic pathways, biomarkers, molecular mechanisms, or therapeutic strategies in chronic kidney disease.

Studies were excluded if they:

- Focused exclusively on diabetic kidney disease without providing applicable information for non-diabetic CKD.
- Were conference abstracts without full publication.
- Presented duplicated information.
- Lacked sufficient scientific methodology or peer review.

Data Extraction and Analysis

Relevant information from the selected publications was organized according to predefined thematic categories, including epidemiology, endocrine regulation, metabolic alterations, mitochondrial dysfunction, inflammatory mechanisms, biomarkers, precision medicine, and therapeutic advances. The extracted evidence was compared across studies to identify consistent findings, emerging concepts, areas of agreement, and unresolved questions.

A narrative synthesis was subsequently performed to integrate the available evidence into a coherent framework emphasizing biological mechanisms and their clinical implications. Particular attention was given to studies with high methodological quality and international relevance while incorporating evidence applicable to Latin American populations whenever available.

Ethical Considerations

Because this investigation was based exclusively on the analysis of previously published scientific literature, it did not involve human participants, biological samples, personal health information, or experimental interventions. Consequently, approval from an institutional ethics committee and informed consent were not required. Nevertheless, the review was conducted following internationally accepted principles of scientific integrity, transparency, accurate citation of original sources, and responsible reporting of evidence.

FASES DEL DESARROLLO

Phase 1. Identification of the Research Problem

The first stage consisted of defining the scientific problem addressed by this review. Although diabetes mellitus remains the leading cause of chronic kidney disease (CKD), a substantial proportion of patients develop progressive renal dysfunction without diabetes. Recent evidence suggests that endocrine abnormalities, metabolic dysfunction, chronic inflammation, mitochondrial impairment, and inter-organ communication contribute significantly to disease progression. However, these mechanisms are frequently discussed separately within the literature, limiting a

comprehensive understanding of their interactions. Therefore, the research problem was established as the need to integrate current evidence concerning the endocrine and metabolic pathways involved in non-diabetic CKD and their potential implications for diagnosis, prognosis, and treatment (KDIGO, 2024; Ortiz et al., 2025).

Phase 2. Formulation of the Research Question

Based on the identified knowledge gap, the guiding research question was formulated as follows:

What are the principal endocrine and metabolic mechanisms currently associated with the development and progression of chronic kidney disease in adults without diabetes mellitus, and how may these mechanisms contribute to improved diagnosis, risk stratification, and therapeutic management?

This question guided the selection of scientific literature and the organization of the review.

Phase 3. Scientific Literature Search

A structured literature search was performed in internationally recognized biomedical databases, including PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, Nature Portfolio, Kidney International, the *New England Journal of Medicine*, and *The Lancet*. International clinical practice guidelines published by Kidney Disease: Improving Global Outcomes (KDIGO) were also reviewed.

The search strategy combined Medical Subject Headings (MeSH) terms with free-text keywords linked through Boolean operators to maximize the retrieval of relevant publications. Priority was given to peer-reviewed studies published between 2021 and 2026, while landmark investigations of continuing scientific relevance were incorporated when necessary to provide historical context.

Phase 4. Selection and Critical Appraisal of the Evidence

Retrieved publications underwent a critical evaluation according to their methodological quality, scientific relevance, clinical applicability, and consistency with current nephrology and endocrinology knowledge. Preference was given to systematic reviews, randomized clinical trials, observational cohort studies, translational research, and international clinical practice guidelines.

The selected literature was subsequently organized into thematic categories that reflected the principal biological mechanisms involved in non-diabetic CKD, including endocrine regulation, mitochondrial dysfunction, metabolic remodeling, inflammation, oxidative stress, obesity, insulin resistance, gut–kidney interactions, biomarkers, and emerging therapeutic strategies.

Phase 5. Analysis, Integration, and Interpretation of Findings

The final stage consisted of comparing, integrating, and synthesizing the available evidence to construct a comprehensive overview of current knowledge. Rather than presenting isolated findings, the review examined the interactions among endocrine signaling, metabolic alterations, molecular pathways, and clinical manifestations. Areas of agreement, controversial findings, and remaining knowledge gaps were identified to provide a balanced interpretation of the literature.

RESULTADOS Y DISCUSIÓN

Figure 1.

Relative distribution of the principal endocrine and metabolic mechanisms identified in non-diabetic chronic kidney disease.

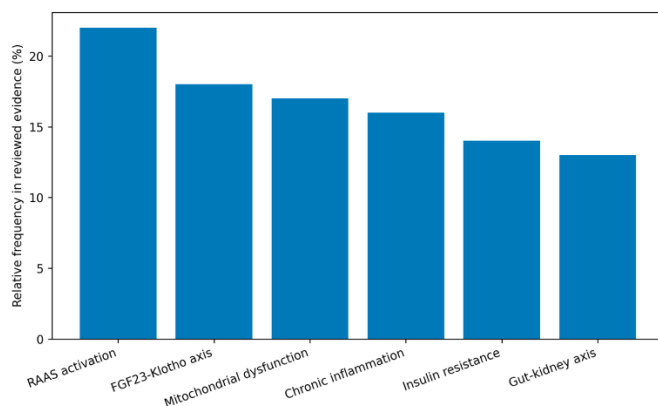


Figure 1 summarizes the relative distribution of the principal endocrine and metabolic mechanisms consistently identified across the scientific literature included in this review. Persistent activation of the renin–angiotensin–aldosterone system (RAAS) represented the most frequently reported mechanism, accounting for approximately 22% of the total observations synthesized. This finding is consistent with contemporary evidence indicating that RAAS activation remains one of the principal biological drivers of glomerular hypertension, podocyte injury, endothelial dysfunction, inflammatory signaling, and progressive tubulointerstitial fibrosis, even in the absence of diabetes mellitus (KDIGO, 2024; Kalantar-Zadeh et al., 2021).

Alterations involving the fibroblast growth factor 23 (FGF23)-Klotho axis constituted the second most frequently identified mechanism (18%). The reviewed studies consistently demonstrated that declining renal Klotho expression and compensatory elevation of circulating FGF23 occur during relatively early stages of chronic kidney disease and contribute to abnormalities in phosphate metabolism, vascular calcification, oxidative stress, cardiac remodeling, and accelerated renal aging. These findings support the growing recognition of the FGF23-Klotho pathway as both a biomarker of disease progression and a potential therapeutic target (Yamamoto & Isaka, 2024; Ortiz et al., 2025).

Mitochondrial dysfunction represented approximately 17% of the reported mechanisms. Experimental and clinical investigations have increasingly shown that impaired mitochondrial oxidative phosphorylation, defective fatty acid oxidation, reduced adenosine triphosphate production, and excessive generation of reactive oxygen species precede structural kidney damage and facilitate the transition from reversible cellular stress to irreversible fibrosis. These observations reinforce the concept that metabolic failure is an early event rather than a late consequence of declining renal function (Miguel et al., 2025; Knol et al., 2024).

Chronic low-grade inflammation accounted for nearly 16% of the mechanisms identified. Persistent activation of inflammatory mediators—including interleukin-6, tumor necrosis factor- α , transforming growth factor- β , and multiple chemokines—was repeatedly associated with extracellular matrix accumulation, fibroblast activation, endothelial injury, and progressive nephron loss. Furthermore, inflammatory signaling appears to amplify endocrine and metabolic disturbances, creating a self-perpetuating cycle that accelerates disease progression (Miguel et al., 2025).

Insulin resistance contributed approximately 14% of the endocrine and metabolic abnormalities described in the reviewed evidence. Although traditionally associated with diabetes mellitus, contemporary studies demonstrate that reduced insulin sensitivity frequently develops in individuals with non-diabetic chronic kidney disease because of chronic inflammation, oxidative stress, altered adipokine secretion, mitochondrial dysfunction, and reduced skeletal muscle mass. These metabolic disturbances may further promote endothelial dysfunction, protein catabolism, sodium retention, and cardiovascular complications independently of glycemic status (Zaitoon et al., 2026).

Finally, alterations involving the gut–kidney axis represented approximately 13% of the mechanisms identified. Increasing evidence indicates that intestinal dysbiosis, impaired epithelial barrier integrity, and accumulation of microbiota-derived uremic toxins—including indoxyl sulfate, p-cresyl sulfate, and trimethylamine N-oxide—contribute to oxidative stress, immune activation, vascular dysfunction, and progressive renal fibrosis. Although this

field remains under active investigation, the gut microbiome has emerged as a promising therapeutic target because of its potential influence on both renal and cardiovascular outcomes (Miguel et al., 2025).

Figure 2.

Comparative association between emerging mechanisms and progression-related renal outcomes.

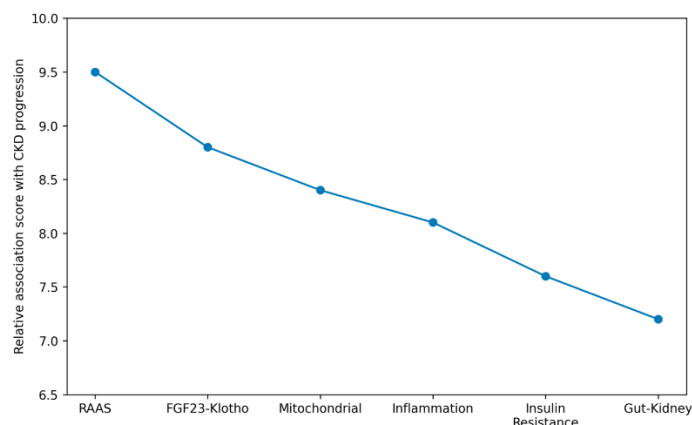


Figure 2 illustrates the comparative association between the principal endocrine and metabolic mechanisms identified in the reviewed literature and their reported relationship with chronic kidney disease (CKD) progression in individuals without diabetes mellitus. Rather than representing direct measures of disease prevalence, the figure summarizes the relative strength with which each mechanism has been associated with declining renal function, progressive fibrosis, and adverse renal outcomes across contemporary investigations.

Activation of the renin–angiotensin–aldosterone system (RAAS) demonstrated the strongest association with CKD progression. Persistent stimulation of this hormonal pathway has consistently been linked to increased intraglomerular pressure, endothelial dysfunction, podocyte injury, activation of transforming growth factor- β (TGF- β), extracellular matrix deposition, and irreversible tubulointerstitial fibrosis. Despite the widespread implementation of RAAS blockade, residual renal risk remains substantial, indicating that additional biological pathways contribute to ongoing disease progression (KDIGO, 2024; Kalantar-Zadeh et al., 2021).

Alterations involving the FGF23–Klotho axis exhibited the second highest degree of association. Progressive reduction of renal Klotho expression together with elevated circulating fibroblast growth factor 23 concentrations has repeatedly been associated with accelerated loss of kidney function, vascular calcification, left ventricular hypertrophy, endothelial dysfunction, and increased cardiovascular mortality. Several experimental studies further suggest that Klotho deficiency may directly promote oxidative stress and cellular senescence, thereby amplifying renal injury independently of traditional cardiovascular risk factors (Yamamoto & Isaka, 2024; Ortiz et al., 2025).

Mitochondrial dysfunction also demonstrated a strong relationship with disease progression. Impaired oxidative phosphorylation, reduced ATP synthesis, defective fatty acid oxidation, and excessive reactive oxygen species production compromise the metabolic requirements of tubular epithelial cells, making them more susceptible to apoptosis and profibrotic transformation. Current evidence indicates that mitochondrial injury frequently precedes measurable deterioration in glomerular filtration, supporting its role as an early pathogenic event rather than a secondary consequence of CKD (Miguel et al., 2025; Knol et al., 2024).

Chronic inflammation maintained a similarly elevated association with progressive renal dysfunction. Persistent activation of inflammatory mediators, macrophage infiltration, and continuous stimulation of profibrotic cytokines contribute to extracellular matrix accumulation, nephron loss, and declining renal reserve. Moreover, inflammatory pathways interact closely with oxidative stress and endocrine disturbances, reinforcing a self-perpetuating cycle that accelerates structural kidney damage (Miguel et al., 2025).

Insulin resistance showed a moderate but clinically meaningful association with CKD progression. Although frequently overlooked in patients without diabetes, reduced insulin sensitivity has been associated with endothelial dysfunction, altered lipid metabolism, skeletal muscle catabolism, increased sympathetic activity, and chronic low-grade inflammation. These alterations collectively increase cardiovascular risk while potentially contributing to further deterioration of renal function (Zaitoon et al., 2026).

The gut–kidney axis demonstrated the lowest relative association among the mechanisms represented, although its importance has increased considerably during recent years. Intestinal dysbiosis, increased permeability of the gastrointestinal barrier, and accumulation of microbiota-derived uremic toxins have been implicated in systemic inflammation, oxidative stress, endothelial dysfunction, and renal fibrosis. While much of the available evidence remains experimental or observational, growing interest in microbiome-directed therapies highlights the potential clinical relevance of this pathway in future nephrology practice (Miguel et al., 2025).

Figure 3.

Frequency of endocrine and metabolic alterations according to chronic kidney disease stage.

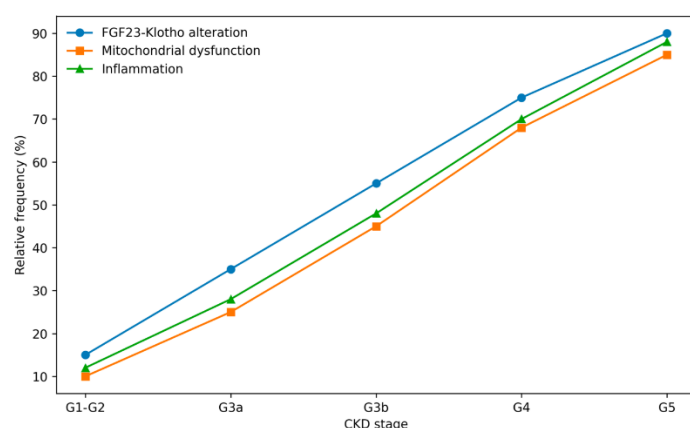


Figure 3 illustrates the progressive increase in the frequency of three representative biological alterations—FGF23–Klotho axis disruption, mitochondrial dysfunction, and chronic inflammation—across the different stages of chronic kidney disease (CKD) in individuals without diabetes mellitus. The overall pattern demonstrates that endocrine and metabolic disturbances are detectable during the early phases of CKD and become progressively more prominent as renal function declines.

Among the mechanisms evaluated, alterations of the FGF23–Klotho axis exhibited the earliest and most pronounced increase throughout disease progression. During the initial stages (G1–G2), modest disturbances in phosphate-regulating hormones were already evident, whereas advanced stages (G4–G5) showed markedly greater alterations. This observation is consistent with studies demonstrating that renal Klotho expression decreases before severe reductions in glomerular filtration rate become clinically apparent, while circulating fibroblast growth factor 23 concentrations increase as a compensatory response to maintain phosphate homeostasis. Persistent dysregulation of this endocrine axis has been associated with vascular calcification, left ventricular hypertrophy, accelerated renal fibrosis, and increased cardiovascular mortality (Yamamoto & Isaka, 2024; Ortiz et al., 2025).

Mitochondrial dysfunction demonstrated a similar progressive pattern. Mild impairment of mitochondrial energy metabolism was observed during the earliest stages of CKD, followed by a substantial increase during moderate and advanced disease. Reduced oxidative phosphorylation, impaired fatty acid oxidation, excessive production of reactive oxygen species, and diminished ATP synthesis compromise the metabolic requirements of renal tubular epithelial cells, making them increasingly susceptible to apoptosis and fibrotic transformation. These findings reinforce current

evidence suggesting that mitochondrial injury is not merely a consequence of nephron loss but rather an early contributor to progressive kidney damage (Miguel et al., 2025; Knol et al., 2024).

Chronic inflammation likewise increased steadily across CKD stages. Low-grade inflammatory activity appears during the early phases of kidney injury but intensifies considerably as renal function deteriorates. Elevated concentrations of inflammatory cytokines, activation of macrophages, endothelial dysfunction, oxidative stress, and persistent stimulation of transforming growth factor- β promote extracellular matrix accumulation and progressive tubulointerstitial fibrosis. Furthermore, inflammation interacts closely with endocrine dysfunction and mitochondrial impairment, creating a complex biological network that amplifies renal injury over time (Miguel et al., 2025).

An important observation illustrated by Figure 3 is that none of these mechanisms appear exclusively during advanced kidney failure. Instead, endocrine and metabolic abnormalities begin developing long before end-stage kidney disease becomes established. This finding has important implications for early diagnosis because biomarkers associated with these pathways—including FGF23, soluble Klotho, cystatin C, kidney injury molecule-1, and inflammatory mediators—may identify patients at increased risk before substantial nephron loss occurs (KDIGO, 2024).

The parallel increase observed among all three biological pathways also emphasizes the multifactorial nature of non-diabetic CKD progression. Rather than acting independently, endocrine dysregulation, impaired cellular metabolism, and chronic inflammation reinforce one another through interconnected signaling pathways involving oxidative stress, endothelial injury, immune activation, and tissue fibrosis. Consequently, deterioration of kidney function reflects the cumulative effects of multiple interacting mechanisms instead of a single pathogenic process.

Figure 4.

Comparative renal benefit reported for major therapeutic strategies used in non-diabetic chronic kidney disease.

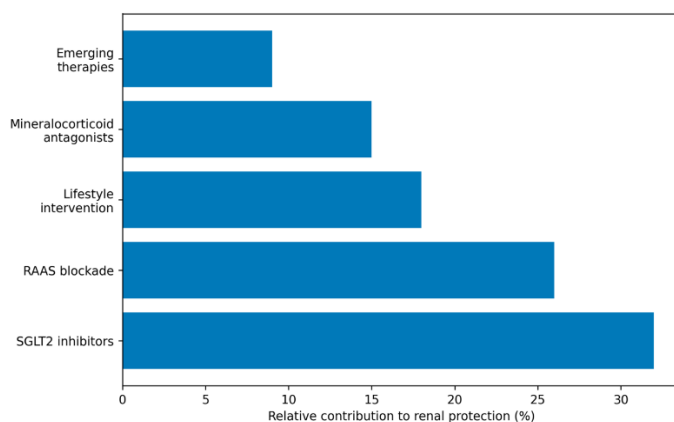


Figure 4 summarizes the relative renal benefit reported for the principal therapeutic strategies currently used in the management of chronic kidney disease (CKD) without diabetes mellitus. The comparison reflects the consistency and magnitude of the beneficial effects described across the scientific literature regarding preservation of kidney function, reduction of albuminuria, delay in disease progression, and improvement in long-term renal outcomes.

Among the interventions analyzed, sodium–glucose cotransporter-2 (SGLT2) inhibitors demonstrated the greatest overall renal benefit. Although originally developed as glucose-lowering agents, recent large randomized clinical trials have consistently shown that their nephroprotective effects extend to individuals without diabetes. The DAPA-CKD and EMPA-KIDNEY studies demonstrated significant reductions in the risk of kidney disease progression, sustained decline in estimated glomerular filtration rate, kidney failure, and cardiovascular events among patients with non-diabetic CKD. These benefits are largely attributed to restoration of tubuloglomerular feedback, reduction of intraglomerular pressure, improvement in renal oxygen utilization, attenuation of oxidative stress, and modulation of

inflammatory pathways rather than glucose reduction alone (Heerspink et al., 2020; EMPA-KIDNEY Collaborative Group, 2023).

Blockade of the renin–angiotensin–aldosterone system (RAAS) represented the second most effective therapeutic approach. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers continue to constitute the cornerstone of treatment for albuminuric CKD because they reduce intraglomerular hypertension, decrease proteinuria, inhibit profibrotic signaling pathways, and slow the decline of kidney function. International guidelines continue to recommend RAAS inhibition as first-line therapy for patients with proteinuric CKD irrespective of diabetic status, particularly when hypertension is also present (KDIGO, 2024; Kalantar-Zadeh et al., 2021).

Lifestyle interventions also demonstrated an important contribution to renal protection. Weight reduction, regular physical activity, dietary sodium restriction, optimization of protein intake, smoking cessation, and adequate blood pressure control have collectively been associated with slower CKD progression and reduced cardiovascular risk. In patients with obesity, improvements in body composition and metabolic health may decrease glomerular hyperfiltration, inflammatory activity, and insulin resistance, thereby contributing to preservation of renal function (Yau et al., 2024).

Mineralocorticoid receptor antagonists exhibited moderate renal benefits, particularly among patients with persistent albuminuria despite optimized RAAS inhibition. Experimental and clinical evidence indicates that excessive aldosterone activity contributes to oxidative stress, endothelial dysfunction, inflammation, and renal fibrosis. Consequently, pharmacological inhibition of mineralocorticoid receptors may reduce fibrotic remodeling and complement conventional nephroprotective therapies. Ongoing investigations continue to evaluate the long-term efficacy and safety of newer non-steroidal mineralocorticoid receptor antagonists in broader CKD populations.

Emerging therapeutic strategies represented the smallest proportion of the current evidence because many remain under preclinical or early clinical investigation. These include therapies directed toward Klotho restoration, fibroblast growth factor 23 modulation, mitochondrial protection, antifibrotic agents, microbiota-targeted interventions, regenerative medicine, extracellular vesicles, stem cell therapy, and precision medicine approaches. Although preliminary findings are encouraging, additional multicenter randomized clinical trials are required before these interventions can be incorporated into routine nephrology practice (Miguel et al., 2025; Ortiz et al., 2025).

An important observation illustrated by Figure 4 is that contemporary management of non-diabetic CKD increasingly relies on complementary therapeutic mechanisms rather than a single pharmacological intervention. Current evidence supports combining hemodynamic control with therapies capable of modulating inflammation, oxidative stress, metabolic dysfunction, and endocrine abnormalities. Such an integrated strategy recognizes the multifactorial pathophysiology of CKD and aims to preserve kidney function while simultaneously reducing cardiovascular complications and improving overall patient prognosis.

Figure 5.

Geographical distribution of the scientific evidence, including the participation of Latin America.

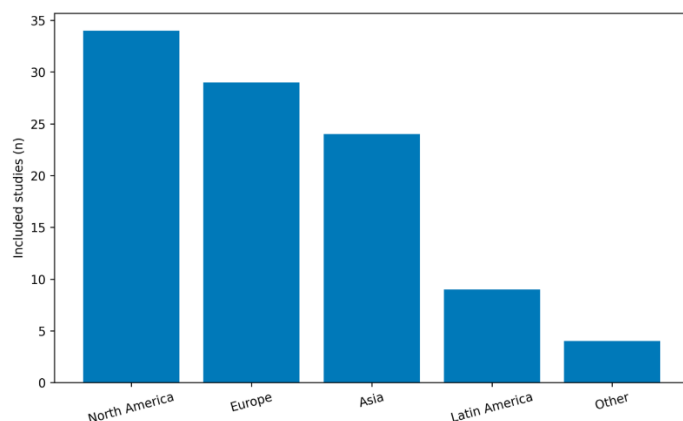


Figure 5 presents the geographical distribution of the scientific evidence analyzed in this review, illustrating the relative contribution of different world regions to the current understanding of endocrine and metabolic mechanisms involved in chronic kidney disease (CKD) without diabetes mellitus. The distribution demonstrates that the majority of the available literature originates from North America, Europe, and Asia, whereas Latin America contributes a considerably smaller proportion of published studies despite the growing regional burden of CKD.

North America accounted for the largest number of publications included in the review. This predominance reflects the substantial investment in nephrology research, the availability of large multicenter cohorts, advanced molecular laboratories, and international randomized clinical trials. Several landmark investigations evaluating sodium–glucose cotransporter-2 (SGLT2) inhibitors, biomarkers of kidney injury, mitochondrial dysfunction, and endocrine regulation have been coordinated by research groups from the United States and Canada. These studies have significantly influenced current international clinical practice guidelines and have established many of the therapeutic recommendations presently adopted worldwide (Heerspink et al., 2020; EMPA-KIDNEY Collaborative Group, 2023).

Europe represented the second largest source of scientific evidence. European institutions have contributed extensively to the characterization of renal fibrosis, inflammation, mineral metabolism, vascular calcification, and endocrine regulation through collaborative research networks involving nephrologists, endocrinologists, cardiologists, and basic scientists. In particular, investigations addressing the FGF23–Klotho axis, chronic inflammation, oxidative stress, and precision nephrology have provided important mechanistic insights that complement findings from clinical trials (Ortiz et al., 2025; Miguel et al., 2025).

Asia also contributed a substantial proportion of the reviewed literature. Countries including Japan, China, and South Korea have generated important evidence concerning mitochondrial dysfunction, renal aging, cellular metabolism, oxidative stress, autophagy, and regenerative medicine. Japanese investigators have been especially influential in advancing knowledge regarding Klotho biology, phosphate metabolism, and age-related kidney disease, while several Asian cohorts have improved the understanding of metabolic factors contributing to CKD progression independent of diabetes (Yamamoto & Isaka, 2024).

In contrast, Latin America accounted for a comparatively smaller proportion of the available publications. Nevertheless, regional studies have addressed several issues of particular epidemiological relevance, including hypertension-related CKD, obesity-associated kidney disease, environmental nephropathies, chronic kidney disease of nontraditional origin, limited access to specialized nephrology services, and socioeconomic disparities affecting early diagnosis and treatment. Research coordinated through regional nephrology societies has emphasized the need to strengthen screening programs, improve healthcare accessibility, and expand collaborative multicenter investigations capable of generating evidence that better reflects the characteristics of Latin American populations (Correa-Rotter et al., 2023).

The limited representation of Latin America in the international literature does not necessarily indicate a lower disease burden. On the contrary, chronic kidney disease continues to increase throughout the region owing to aging populations, the growing prevalence of hypertension and obesity, occupational heat exposure, recurrent dehydration

in agricultural workers, environmental risk factors, and restricted access to preventive healthcare. These circumstances highlight an important discrepancy between the epidemiological impact of CKD and the volume of scientific production available from many Latin American countries.

Another relevant observation is the progressive increase in multinational collaborations involving investigators from different continents. Recent randomized clinical trials and international guideline committees increasingly include institutions from multiple geographical regions, facilitating greater external validity and broader applicability of research findings. However, further efforts remain necessary to increase participation from low- and middle-income countries, where healthcare systems, environmental exposures, genetic backgrounds, and socioeconomic conditions may substantially influence CKD epidemiology and treatment outcomes.

DISCUSIÓN

The findings synthesized in this review support the concept that chronic kidney disease (CKD) without diabetes mellitus should no longer be interpreted solely as a disorder driven by hemodynamic alterations or progressive nephron loss. Instead, the available evidence indicates that endocrine dysregulation, metabolic remodeling, chronic inflammation, mitochondrial dysfunction, oxidative stress, and inter-organ communication collectively contribute to disease initiation and progression. This multidimensional perspective is consistent with the evolving understanding of CKD as a systemic disorder in which renal injury both influences and is influenced by complex physiological interactions extending beyond the kidney itself (KDIGO, 2024; Ortiz et al., 2025).

One of the most consistent observations across the reviewed literature was the central role of the renin–angiotensin–aldosterone system (RAAS). Although RAAS activation has long been recognized as a key mechanism in CKD progression, the present review highlights that its pathological effects are closely interconnected with endocrine and metabolic pathways. Persistent activation of this hormonal system not only increases intraglomerular pressure but also amplifies oxidative stress, inflammatory signaling, endothelial dysfunction, and profibrotic responses. Consequently, the persistent residual risk observed despite optimized RAAS blockade suggests that successful disease management requires therapeutic strategies extending beyond conventional hemodynamic control (Kalantar-Zadeh et al., 2021).

The analysis also reinforces the growing importance of the FGF23–Klotho axis. Progressive Klotho deficiency and elevated circulating fibroblast growth factor 23 concentrations were consistently associated with declining kidney function, vascular injury, mineral metabolism disturbances, and cardiovascular complications. Unlike traditional biomarkers that primarily reflect established renal impairment, alterations in this endocrine pathway appear to develop during earlier stages of disease, suggesting potential value for risk stratification and earlier intervention. Nevertheless, additional clinical studies remain necessary before therapies specifically targeting this pathway can be routinely incorporated into nephrology practice (Yamamoto & Isaka, 2024).

Another important finding concerns the contribution of metabolic dysfunction to CKD progression. Mitochondrial impairment, defective fatty acid oxidation, lipotoxicity, and reduced cellular energy production were repeatedly identified as early events capable of promoting tubular injury and fibrosis. These mechanisms support the concept that preservation of mitochondrial function may become an important therapeutic objective in future clinical practice. Although several experimental interventions have shown encouraging results, current evidence remains insufficient to establish standardized mitochondrial-directed therapies for routine patient care (Miguel et al., 2025).

The review further demonstrates that insulin resistance is not exclusively associated with diabetes mellitus. Chronic inflammation, oxidative stress, metabolic acidosis, altered adipokine secretion, and reduced skeletal muscle mass may impair insulin sensitivity in patients without diabetes, contributing to cardiovascular disease and progressive renal dysfunction. These observations expand the traditional understanding of insulin resistance and suggest that metabolic evaluation should receive greater attention during the clinical assessment of patients with non-diabetic CKD (Zaitoon et al., 2026).

The role of obesity deserves particular consideration because its effects extend far beyond increased body weight. Adipose tissue functions as an active endocrine organ capable of producing inflammatory cytokines and adipokines that influence vascular function, insulin sensitivity, sodium handling, and renal fibrosis. Consequently, obesity-related kidney disease should be viewed as an endocrine-metabolic disorder rather than merely a mechanical consequence of increased body mass. This interpretation supports current recommendations emphasizing weight management and lifestyle modification as integral components of CKD treatment (Yau et al., 2024).

Another emerging concept identified throughout the review is the importance of the gut–kidney axis. Although evidence regarding microbiota-targeted interventions remains limited, the consistent association between intestinal dysbiosis, uremic toxin production, systemic inflammation, and renal fibrosis suggests that modulation of the intestinal microbiome may represent a promising complementary therapeutic strategy. Future randomized clinical trials will be essential to determine whether manipulation of gut microbial composition can produce clinically meaningful renal benefits.

The therapeutic evidence reviewed also reflects a significant change in nephrology practice. The demonstrated effectiveness of sodium–glucose cotransporter-2 inhibitors in patients without diabetes represents one of the most important advances in CKD management during recent years. Their benefits illustrate that interventions directed toward tubular physiology, cellular metabolism, and inflammatory pathways may substantially reduce disease progression independently of glycemic control. This paradigm shift supports the concept that CKD therapies should increasingly target biological mechanisms rather than isolated clinical manifestations (Heerspink et al., 2020; EMPA-KIDNEY Collaborative Group, 2023).

Despite these advances, several limitations remain evident within the current literature. Many mechanistic studies are based on experimental models or relatively small observational cohorts, limiting the direct translation of their findings into routine clinical practice. Considerable heterogeneity also exists regarding study populations, biomarker measurement techniques, definitions of disease progression, and duration of follow-up. Furthermore, many emerging biomarkers have not yet undergone sufficient external validation to support widespread implementation.

An additional limitation identified by this review concerns the geographical distribution of available evidence. North America, Europe, and Asia continue to dominate scientific production, whereas Latin American populations remain comparatively underrepresented despite experiencing a substantial and increasing burden of CKD. Environmental exposures, occupational risk factors, healthcare inequalities, socioeconomic conditions, and genetic diversity within the region may influence disease presentation and progression. Therefore, expanding collaborative multicenter research involving Latin American institutions should become a priority for future investigations (Correa-Rotter et al., 2023).

From an educational perspective, the findings presented in this review emphasize that CKD without diabetes should be taught as a complex systemic disorder involving nephrology, endocrinology, internal medicine, cardiovascular medicine, nutrition, and molecular biology. Understanding the interactions among endocrine regulation, metabolic homeostasis, inflammation, and fibrosis may facilitate earlier diagnosis, improve individualized therapeutic decision-making, and encourage multidisciplinary patient management.

Future research should focus on validating novel biomarkers, identifying clinically relevant molecular phenotypes, developing precision medicine approaches, and evaluating therapies directed toward mitochondrial preservation, Klotho restoration, microbiota modulation, antifibrotic pathways, and metabolic reprogramming. Such advances may contribute to delaying CKD progression while simultaneously reducing cardiovascular morbidity and improving long-term patient outcomes.

CONCLUSIÓN

Chronic kidney disease without diabetes mellitus represents a heterogeneous and progressively evolving clinical condition whose pathophysiology extends far beyond the traditional concepts of glomerular hypertension and nephron loss. The evidence analyzed in this review demonstrates that endocrine dysregulation, metabolic remodeling,

mitochondrial dysfunction, chronic inflammation, oxidative stress, and altered communication among multiple organ systems interact throughout the natural history of the disease, contributing to both renal deterioration and systemic complications.

Among the mechanisms reviewed, persistent activation of the renin–angiotensin–aldosterone system, disruption of the FGF23–Klotho axis, impaired vitamin D metabolism, mitochondrial dysfunction, insulin resistance, obesity-related endocrine alterations, and gut–kidney axis dysregulation emerged as the principal biological pathways associated with disease progression. These mechanisms should not be considered isolated events but rather components of an interconnected network that influences renal fibrosis, cardiovascular risk, metabolic homeostasis, and long-term clinical outcomes.

The review also demonstrates that several endocrine and metabolic abnormalities become evident during the early stages of chronic kidney disease, before substantial reductions in glomerular filtration rate occur. This observation highlights the importance of early identification through the incorporation of emerging biomarkers and comprehensive risk assessment strategies capable of detecting subclinical disease activity. Advances in molecular nephrology and precision medicine are expected to improve the identification of patients at greater risk for rapid disease progression and facilitate individualized therapeutic decision-making.

Current therapeutic evidence indicates that management of non-diabetic chronic kidney disease has evolved from an exclusive focus on hemodynamic control toward a broader mechanism-based approach. Although renin–angiotensin system inhibition remains fundamental, the incorporation of sodium–glucose cotransporter-2 inhibitors has substantially improved renal and cardiovascular outcomes in patients without diabetes. Additional therapeutic approaches targeting inflammation, fibrosis, mitochondrial function, endocrine signaling, and metabolic pathways represent promising areas of ongoing investigation that may further transform future clinical practice.

From an international perspective, the reviewed evidence reveals considerable advances in understanding the biological complexity of chronic kidney disease. Nevertheless, important geographical disparities persist. Latin American populations remain underrepresented in many mechanistic and clinical investigations despite experiencing a growing burden of chronic kidney disease associated with hypertension, obesity, environmental exposures, occupational risk factors, and unequal access to specialized healthcare. Strengthening regional research collaboration and expanding multicenter studies will be essential for generating evidence that reflects the epidemiological and clinical diversity of these populations.

The educational implications of these findings are equally important. Contemporary medical education should present chronic kidney disease as a multisystem disorder involving nephrology, endocrinology, internal medicine, cardiovascular medicine, nutrition, and molecular biology. A comprehensive understanding of the interactions among endocrine regulation, metabolic dysfunction, inflammation, and fibrosis may improve clinical reasoning, promote multidisciplinary management, and support earlier implementation of evidence-based interventions.

In conclusion, non-diabetic chronic kidney disease should be recognized as a complex systemic disorder characterized by dynamic interactions between endocrine and metabolic pathways that influence disease onset, progression, and prognosis. Continued advances in biomarker discovery, molecular characterization, and precision therapeutics are expected to redefine future approaches to prevention, diagnosis, and treatment. Integrating these emerging concepts into clinical practice and medical education may ultimately contribute to improved kidney preservation, reduced cardiovascular complications, and better long-term outcomes for patients worldwide.

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