Issue 3, Year 2, Volume 1, No. 01, January-June 2026

E-ISSN: 3122-3591, P-ISSN: 3122-3753

Review International Science Journal

Systems Integration in Medicine: The Renal–Gastrointestinal–Urologic Axis as a Framework for Understanding Systemic Disease

Juan Antonio Méndez Camargo
Universidad de la Sabana
juanmendez211@hotmail.com
https://orcid.org/0009-0000-3821-6542

María Alejandra Chauran
Biogastrohealth
dragastrobio@gmail.com
https://orcid.org/0009-0004-9175-1682

Raphaela Ballon Chehade
Universidad Peruana de Ciencias Aplicadas
ballonrapha@gmail.com
https://orcid.org/0009-0001-4362-4919

Uslar Gibran Díaz Maestre
Biogastrohealth
gibrangastro@gmail.com
https://orcid.org/0009-0009-0901-1287

Christian Gabriel Freire Fiallos
SOLCA-CHIMBORAZO
christian_gff@hotmail.com
https://orcid.org/0009-0002-5510-3587

Miguel Sebastián Estrella Silva
Universidad Internacional del Ecuador
miguelestrellas2001@gmail.com
https://orcid.org/0009-0001-4620-6050

Delia Mercedes Balarezo Páez
Pontificia Universidad Catolica del Ecuador
delybalarezo.paez@gmail.com
https://orcid.org/0009-0007-5715-3840

Karla Fernanda Villena Proaño
Pontificia Universidad Católica del Ecuador
karlavillenap28@gmail.com
https://orcid.org/0009-0001-5597-6196

Received: 30-Mar-2026 | **Accepted:** 30-Mar-2026 | **Published:** 01-Apr-2026

*** Corresponding Author:** juanmendez211@hotmail.com

How to cite this article: Méndez Camargo, J. A., Ballon Chehade, R., Freire Fiallos, C. G., Balarezo Páez, D. M., Chauran, M. A., Díaz Maestre, U. G., Estrella Silva, M. S., & Villena Proaño, K. F. (2026). Systems Integration in Medicine: The Renal–Gastrointestinal–Urologic Axis as a Framework for Understanding Systemic Disease. México. International Science Journal "TheSci". 3 (1) 347-363. Quality Consulting Instituto de Educación Capacitación y Certificación de México. https://ieccmexico.com/thesci

ABSTRACT

The interaction between the renal, gastrointestinal, and urologic systems has emerged as a key element in the understanding of systemic diseases. This review aims to analyze and integrate current evidence on inter-organ crosstalk, emphasizing the role of microbiota, metabolic pathways, and immune mechanisms in disease progression. A structured narrative review was conducted using high-impact studies published from 2020 onward, selected from major databases. The findings demonstrate that the gut–kidney axis represents a central pathway, where microbiota-derived metabolites such as uremic toxins contribute to renal dysfunction and systemic inflammation. Additionally, the gastrointestinal tract acts as a reservoir influencing urologic conditions, particularly urinary tract infections. Systemic inflammation and metabolic dysregulation were identified as shared mechanisms linking these organ systems, particularly in

Issue 3, Year 2, Volume 1, No. 01, January-June 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
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chronic conditions such as chronic kidney disease, diabetes mellitus, and metabolic syndrome. The results also highlight the presence of overlapping clinical manifestations and the complexity of therapeutic management, which require a multidisciplinary approach. Regional analysis suggests that these interactions are highly relevant in Latin American contexts, including Mexico, Colombia, and Ecuador, where the burden of chronic disease is significant. In conclusion, the integration of renal, gastrointestinal, and urologic systems into a unified framework provides a more comprehensive understanding of systemic disease and supports the development of more effective clinical strategies.
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KEYWORDS

gut–kidney axis, microbiota, chronic kidney disease, systemic inflammation, urologic diseases, inter-organ crosstalk, metabolic syndrome, urinary tract infections, renal physiology, gastrointestinal system

INTRODUCTION

The understanding of human physiology has progressively evolved from an organ-centered model toward a systems-based perspective, recognizing the dynamic interplay between organ systems in health and disease. Among these interactions, the crosstalk between the renal, gastrointestinal, and urologic systems has emerged as a critical axis in the pathogenesis and progression of multiple systemic disorders. Chronic kidney disease (CKD), gastrointestinal dysbiosis, and urinary tract dysfunction are no longer viewed as isolated entities but rather as interconnected processes that influence each other through metabolic, immunological, and neurohumoral pathways [1], [5], [9].

The global burden of kidney disease alone underscores the urgency of this integrative approach. CKD affects millions worldwide and is associated with increased morbidity, mortality, and healthcare costs, representing a major public health concern [15], [7]. Simultaneously, gastrointestinal disorders—particularly those involving alterations in the gut microbiota—have been increasingly implicated in systemic inflammation and metabolic dysregulation [6], [17]. In parallel, urologic conditions such as recurrent urinary tract infections and lower urinary tract dysfunction are influenced by both renal and intestinal factors, highlighting a shared biological network that transcends traditional disciplinary boundaries [13], [14].

Recent advances have identified the **gut–kidney axis** as a central mechanism mediating this inter-organ communication. Alterations in intestinal microbiota composition in CKD patients lead to increased production of uremic toxins such as indoxyl sulfate and p-cresyl sulfate, which exacerbate renal damage and contribute to systemic inflammation [3], [12]. Conversely, impaired renal function promotes intestinal barrier dysfunction and microbial imbalance, reinforcing a bidirectional pathogenic loop [4], [16]. This reciprocal interaction has also been extended to include hepatic and metabolic pathways, forming a broader gut–liver–kidney axis with significant clinical implications [10].

In addition to metabolic interactions, immune-mediated mechanisms play a pivotal role in organ crosstalk. Systemic inflammation and immune dysregulation have been shown to contribute to both renal injury and gastrointestinal pathology, as well as to influence urologic conditions [20]. Acute kidney injury (AKI), for instance, is increasingly recognized as a condition with systemic consequences, capable of inducing distant organ dysfunction through inflammatory mediators and cellular signaling pathways [19]. These findings support the concept that localized pathology can have widespread systemic effects, further emphasizing the need for an integrated clinical approach.

From a urological perspective, the relationship between the gut microbiota and urinary tract health has gained attention in recent years. Dysbiosis has been associated with increased susceptibility to urinary tract infections (UTIs), likely due to alterations in host immunity and microbial translocation [13], [14]. Moreover, the gastrointestinal tract serves as a reservoir for uropathogenic bacteria, reinforcing the importance of gut health in urologic disease prevention and management.

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The relevance of this topic extends beyond theoretical understanding, as it has direct implications for clinical practice and therapeutic innovation. Interventions targeting the gut microbiota—such as dietary modifications, probiotics, and prebiotics—have shown potential in modulating disease progression in CKD and related conditions [8], [9]. Additionally, the integration of multidisciplinary strategies involving nephrology, gastroenterology, and urology may improve patient outcomes by addressing the underlying interconnected mechanisms rather than isolated symptoms.

Despite these advances, significant gaps remain in the comprehensive understanding of inter-organ crosstalk. Most existing studies have focused on isolated axes, such as the gut–kidney or gut–liver interactions, with limited integration of urologic perspectives. Furthermore, regional variations in disease patterns, healthcare systems, and environmental factors—particularly in Latin American countries such as Mexico, Colombia, and Ecuador—highlight the need for context-specific analyses that consider epidemiological and socio-demographic differences.

In this context, the present review aims to synthesize current evidence on the interconnected relationships between the renal, gastrointestinal, and urologic systems, with an emphasis on their role in systemic disease. The central research question guiding this work is: **How do interactions between the renal, gastrointestinal, and urologic systems contribute to the development and progression of systemic diseases, and how can this knowledge inform integrated clinical strategies?**

To address this question, a structured narrative review was conducted, focusing on high-impact studies published from 2020 onward. The selected literature was analyzed to identify key mechanisms of inter-organ communication, including metabolic pathways, immune responses, and microbiota-related interactions. The methodological approach was designed to align with the objective of providing a comprehensive and clinically relevant synthesis of current knowledge, integrating findings across disciplines and geographic contexts.

DEVELOPMENT

The interaction between the renal, gastrointestinal, and urologic systems represents a complex and dynamic network that plays a central role in the pathophysiology of systemic diseases. This inter-organ crosstalk is mediated through multiple pathways, including metabolic signaling, immune modulation, neuroendocrine communication, and microbiota-derived metabolites. Understanding these mechanisms requires moving beyond reductionist models and embracing a systems-based perspective that integrates clinical, molecular, and environmental determinants.

One of the most extensively studied pathways within this network is the **gut–kidney axis**, which has been recognized as a bidirectional system with significant clinical implications. In patients with chronic kidney disease (CKD), alterations in gut microbiota composition—commonly referred to as dysbiosis—lead to an increased production of uremic toxins such as indoxyl sulfate, p-cresyl sulfate, and trimethylamine-N-oxide (TMAO) [3], [9]. These metabolites are poorly excreted due to reduced renal function, resulting in systemic accumulation that contributes to endothelial dysfunction, oxidative stress, and further renal damage [12]. This creates a self-perpetuating cycle in which renal impairment exacerbates gut dysbiosis, and vice versa [4], [16].

Additionally, CKD is associated with structural and functional changes in the intestinal barrier. Increased intestinal permeability—often termed “leaky gut”—facilitates the translocation of bacterial endotoxins into systemic circulation, triggering chronic inflammation [5]. This inflammatory state has been linked not only to the progression of renal disease but also to cardiovascular complications, which are a leading cause of mortality in CKD patients [1], [7]. These findings highlight the systemic consequences of localized organ dysfunction and reinforce the importance of early intervention strategies targeting the gut microbiome.

The gastrointestinal system also plays a crucial role in metabolic regulation, influencing glucose homeostasis, lipid metabolism, and immune responses. In conditions such as diabetic kidney disease, the gut microbiota contributes to disease progression through inflammatory and metabolic pathways [8]. Emerging evidence suggests that modulation of the microbiota through diet, probiotics, or pharmacological interventions may have therapeutic potential, although further clinical trials are needed to establish standardized protocols [9].

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Beyond the gut–kidney axis, the integration of urologic processes into this framework provides a more comprehensive understanding of systemic disease. The urinary tract is not sterile, as previously believed, but harbors a distinct microbiome that interacts with both renal and intestinal systems. Dysbiosis in the gut has been associated with an increased risk of urinary tract infections (UTIs), as the gastrointestinal tract serves as a primary reservoir for uropathogenic bacteria such as *Escherichia coli* [13], [14]. This connection is particularly relevant in patients with recurrent infections, where alterations in microbial diversity and host immunity play a critical role.

Furthermore, urinary tract function is influenced by systemic inflammatory and metabolic states. Conditions such as metabolic syndrome and diabetes mellitus—which are closely linked to both gastrointestinal and renal dysfunction—are associated with an increased risk of lower urinary tract symptoms and infections. This triad underscores the interconnected nature of these systems and the need for integrated diagnostic and therapeutic approaches.

Another key aspect of inter-organ crosstalk involves immune-mediated mechanisms. Systemic inflammation acts as a common denominator linking renal, gastrointestinal, and urologic pathologies. In immune-mediated kidney diseases, inflammatory cytokines and immune complexes contribute to tissue damage, while also affecting intestinal integrity and urinary tract susceptibility to infection [20]. Similarly, acute kidney injury (AKI) has been shown to induce distant organ dysfunction through the release of inflammatory mediators and activation of immune pathways, affecting both the gastrointestinal tract and other organ systems [19].

The concept of organ crosstalk is further supported by evidence of neurohumoral regulation. The autonomic nervous system and hormonal signaling pathways, including the renin–angiotensin–aldosterone system (RAAS), play a significant role in coordinating responses between organs. Dysregulation of these pathways can lead to alterations in gastrointestinal motility, renal hemodynamics, and urinary function, contributing to disease progression.

From a clinical standpoint, these interactions have important implications for patient management. Traditional approaches that focus on single-organ treatment may fail to address the underlying systemic processes driving disease. For example, the use of antibiotics in recurrent UTIs may disrupt gut microbiota, potentially worsening dysbiosis and increasing the risk of further complications. Similarly, dietary interventions aimed at improving gut health may have beneficial effects on renal function and urinary tract outcomes.

In Latin American contexts, including Mexico, Colombia, and Ecuador, these interactions are particularly relevant due to the high prevalence of metabolic diseases, limited access to specialized care, and variations in environmental and dietary factors. These regional characteristics may influence the composition of the gut microbiota, the incidence of renal and urologic diseases, and the response to therapeutic interventions. Therefore, incorporating a regional perspective into the analysis of organ crosstalk is essential for developing context-specific clinical strategies.

In summary, the interconnected relationships between the renal, gastrointestinal, and urologic systems represent a fundamental aspect of systemic disease. The integration of metabolic, immunological, and microbiota-related mechanisms provides a comprehensive framework for understanding disease progression and identifying novel therapeutic targets. This systems-based approach not only enhances our understanding of pathophysiology but also supports the development of more effective and holistic clinical interventions.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To **analyze and integrate** the current scientific evidence on the interactions between the renal, gastrointestinal, and urologic systems, in order to **understand their role in the development and progression of systemic diseases** and to **propose a systems-based framework for clinical decision-making** in multidisciplinary medical practice.

A. Cognitive Domain

1. To **identify** the main physiological and pathophysiological mechanisms involved in renal–gastrointestinal–urologic crosstalk, including metabolic, immunological, and microbiota-mediated pathways [3], [5], [9].

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2. To **describe** the role of the gut–kidney axis and its contribution to chronic kidney disease progression and systemic inflammation [4], [16].
3. To **analyze** the relationship between gut microbiota dysbiosis and urologic conditions such as urinary tract infections and lower urinary tract dysfunction [13], [14].
4. To **evaluate** the impact of systemic diseases (e.g., diabetes mellitus, metabolic syndrome) on the interaction between these organ systems [8].

B. Psychomotor Domain

5. To **apply** a systems-based clinical approach in the interpretation of diseases involving renal, gastrointestinal, and urologic interactions, integrating multidisciplinary diagnostic criteria.
6. To **demonstrate** the ability to correlate clinical findings with underlying inter-organ mechanisms, particularly in patients with chronic kidney disease and associated gastrointestinal or urologic complications.
7. To **integrate** evidence-based strategies (e.g., microbiota modulation, dietary interventions, pharmacological management) into clinical reasoning for improved patient outcomes [9].

C. Affective Domain

8. To **value** the importance of an interdisciplinary approach in the management of complex systemic diseases involving multiple organ systems.
9. To **promote** awareness of the clinical relevance of organ crosstalk in medical education and patient care, particularly in regions with high disease burden such as Latin America.
10. To **encourage** critical thinking and continuous learning regarding emerging evidence on microbiota, systemic inflammation, and inter-organ communication.

OBJECT OF STUDY

The object of study of this review is the **interconnected physiological and pathophysiological interactions between the renal, gastrointestinal, and urologic systems**, conceptualized as a dynamic and integrated network that contributes to the development, progression, and clinical expression of systemic diseases.

This study focuses specifically on the **mechanisms of inter-organ crosstalk**, including metabolic exchanges, immune-mediated responses, neurohumoral signaling, and microbiota-derived interactions. Particular emphasis is placed on the **gut–kidney axis** and its extension toward urologic processes, recognizing the gastrointestinal tract not only as a digestive organ but also as a central regulator of systemic homeostasis through microbial, inflammatory, and metabolic pathways [5], [9], [16].

From a clinical perspective, the population of interest includes **patients with chronic and systemic conditions** in which these interactions are most evident, such as chronic kidney disease (CKD), acute kidney injury (AKI), metabolic syndrome, diabetes mellitus, gastrointestinal dysbiosis, and recurrent urinary tract infections [7], [8], [14]. These conditions are analyzed as part of a broader systemic framework rather than as isolated pathologies, allowing for a more comprehensive understanding of disease processes.

The study also considers the **role of the human microbiota as a functional interface** between organ systems. The gut microbiome, in particular, is examined as a key modulator of inflammation, toxin production, and immune responses, influencing both renal function and urinary tract health [3], [12]. Additionally, the urinary microbiome is included as an emerging factor in urologic disease, contributing to the understanding of infection susceptibility and host–microbe interactions [13].

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Geographically, the analysis incorporates a **multinational perspective**, with particular attention to Latin American contexts—specifically Mexico, Colombia, and Ecuador—where epidemiological patterns, healthcare access, nutritional habits, and environmental exposures may influence the manifestation and progression of these interconnected diseases. This regional approach allows for the identification of contextual variables that may impact both disease burden and therapeutic strategies.

At a conceptual level, the object of study is framed within a **systems-based model of medicine**, in which organ systems are understood as interdependent components of a complex biological network. This perspective challenges traditional reductionist approaches and supports the development of integrated diagnostic and therapeutic frameworks.

METHODOLOGY

This study was designed as a **structured narrative review** aimed at synthesizing current high-impact scientific evidence regarding the interactions between the renal, gastrointestinal, and urologic systems. The methodological approach was based on the **Scientific Method**, ensuring a systematic, transparent, and reproducible process for the identification, selection, and analysis of relevant literature.

1. Research Design

The research followed a **qualitative, analytical, and integrative design**, focused on the interpretation of recent evidence (2020 onward) related to inter-organ crosstalk. The study was guided by the central research question: *How do interactions between the renal, gastrointestinal, and urologic systems contribute to systemic disease, and how can this knowledge be applied in clinical practice?*

2. Methodological Approach: Scientific Method

The study was structured according to the following stages of the Scientific Method:

- **Observation:** Identification of increasing evidence suggesting interdependence between renal, gastrointestinal, and urologic systems in systemic diseases [5], [9].
- **Problem Formulation:** Recognition of the fragmented understanding of these interactions in current clinical practice, often limited to organ-specific approaches.
- **Hypothesis:** The integration of renal, gastrointestinal, and urologic systems into a unified framework provides a more accurate understanding of systemic disease and may improve clinical outcomes.
- **Data Collection:** Systematic identification of relevant scientific literature.
- **Analysis:** Critical evaluation and synthesis of findings from selected studies.
- **Conclusion:** Development of a comprehensive model of inter-organ crosstalk with clinical implications.

3. Literature Search Strategy

A structured search was conducted using the following electronic databases:

- **PubMed/MEDLINE**
- **Scopus**
- **Web of Science**

The search included articles published between **January 2020 and 2024**, ensuring the inclusion of recent and relevant evidence.

Keywords and search terms included combinations of:

- “gut–kidney axis”
- “renal disease AND microbiota”
- “urinary tract infections AND microbiome”
- “organ crosstalk”
- “systemic inflammation AND kidney”
- “gastrointestinal microbiota AND urology”

Boolean operators (**AND, OR**) were used to refine the search strategy.

4. Inclusion and Exclusion Criteria

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Inclusion criteria:

- Articles published from 2020 onward
- Indexed in high-impact journals (Q1–Q2, PubMed indexed)
- Original research articles, systematic reviews, and narrative reviews
- Studies addressing interactions between at least two of the following systems: renal, gastrointestinal, urologic

Exclusion criteria:

- Articles published before 2020
- Studies with limited methodological rigor or unclear conclusions
- Publications not available in full text
- Studies focusing exclusively on a single organ without systemic integration

5. Selection Process

The selection process was conducted in three stages:

1. **Initial screening** based on title and abstract relevance
2. **Full-text review** to confirm eligibility
3. **Final inclusion** of studies meeting all criteria

A total of **20 high-impact articles** were selected and included in the final analysis, ensuring consistency with the objectives of the study.

6. Data Extraction and Analysis

Relevant data were extracted from each study, including:

- Study design and methodology
- Population characteristics
- Key findings related to inter-organ interactions
- Clinical implications

The analysis was performed using a **thematic synthesis approach**, organizing findings into the following categories:

- Gut–kidney axis mechanisms
- Microbiota and systemic inflammation
- Urologic implications of gastrointestinal and renal dysfunction
- Clinical and therapeutic perspectives

This approach allowed for the identification of patterns, similarities, and gaps in the literature.

7. Reproducibility and Validity

To ensure reproducibility:

- The search strategy, inclusion criteria, and analysis framework were clearly defined
- Only peer-reviewed and indexed studies were included
- References were verified and standardized using DOI identifiers

The methodological rigor enhances the reliability and validity of the findings, allowing other researchers to replicate or expand upon this review.

8. Ethical Considerations

This study is based exclusively on previously published data and does not involve direct interaction with human subjects. Therefore, it does not require ethical approval. All sources were properly cited to ensure academic integrity.

PHASES OF DEVELOPMENT

Phase 1: Observation and Conceptual Identification

The initial phase consisted of recognizing the growing body of evidence indicating that multiple systemic diseases cannot be adequately explained through isolated organ models. Clinical observations and recent literature have

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demonstrated that conditions such as chronic kidney disease, gastrointestinal dysbiosis, and recurrent urinary tract infections frequently coexist and interact through shared biological mechanisms [3], [5], [13].

This phase allowed for the identification of **organ crosstalk as a relevant and underexplored phenomenon**, particularly within integrative frameworks that include nephrology, gastroenterology, and urology.

Phase 2: Problem Definition
Based on the initial observations, the research problem was defined as the **lack of an integrated understanding of the mechanisms linking renal, gastrointestinal, and urologic systems**. Despite advances in the study of individual axes such as the gut–kidney axis, there remains a gap in the comprehensive integration of these systems into a unified clinical and physiological model [9], [16].

This fragmentation in knowledge limits the ability of clinicians to implement effective multidisciplinary strategies and may contribute to suboptimal patient outcomes.

Phase 3: Hypothesis Formulation
The working hypothesis established in this phase was that:

The integration of renal, gastrointestinal, and urologic interactions into a systems-based model provides a more accurate understanding of systemic disease mechanisms and supports improved clinical decision-making.

This hypothesis was grounded in existing evidence highlighting the bidirectional nature of organ interactions, particularly those mediated by microbiota, immune responses, and metabolic pathways [4], [12], [19].

Phase 4: Systematic Literature Collection
A structured and reproducible search strategy was implemented across major scientific databases, including PubMed, Scopus, and Web of Science. The search focused on high-impact publications from 2020 onward, using predefined keywords related to organ crosstalk and microbiota interactions.

This phase resulted in the identification of a large pool of articles, from which **20 studies were selected** based on relevance, methodological quality, and alignment with the research objectives.

Phase 5: Selection and Critical Appraisal
During this phase, selected articles underwent a **critical evaluation process**, focusing on:

- Scientific rigor and study design
- Relevance to inter-organ interactions
- Consistency of findings
- Clinical applicability

This appraisal ensured that only robust and high-quality evidence contributed to the final analysis, strengthening the validity of the review.

Phase 6: Data Organization and Thematic Structuring
Extracted data were systematically organized into thematic categories to facilitate analysis. The main categories included:

- Mechanisms of the gut–kidney axis
- Microbiota-derived metabolic interactions
- Immune and inflammatory pathways
- Urologic implications of systemic and gastrointestinal dysfunction
- Clinical and therapeutic considerations

This structured organization allowed for a comprehensive and coherent synthesis of the available evidence.

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Phase 7: Integrative Analysis and Synthesis
In this phase, findings from different studies were compared and integrated to identify common patterns, relationships, and gaps in the literature. Special attention was given to **bidirectional mechanisms**, where dysfunction in one system influences the others.

The integration of these findings led to the development of a **systems-based conceptual framework**, emphasizing the interconnected nature of organ function and disease progression.

Phase 8: Interpretation and Clinical Contextualization
The final phase involved interpreting the synthesized data within a clinical context, particularly considering the implications for multidisciplinary care. The relevance of these interactions was analyzed in relation to real-world clinical scenarios, including chronic kidney disease, metabolic disorders, and recurrent infections.

Additionally, regional considerations were incorporated, highlighting the importance of applying this knowledge in Latin American settings such as Mexico, Colombia, and Ecuador, where epidemiological and healthcare factors may influence disease patterns.

Phase 9: Consolidation of Findings
The final step consisted of consolidating the results into a coherent narrative aligned with the study objectives. This phase ensured that all components—from hypothesis to analysis—were logically connected and contributed to a comprehensive understanding of the research problem.

RESULTS AND DISCUSSION

Figure 1.
Distribution of the selected studies by thematic focus

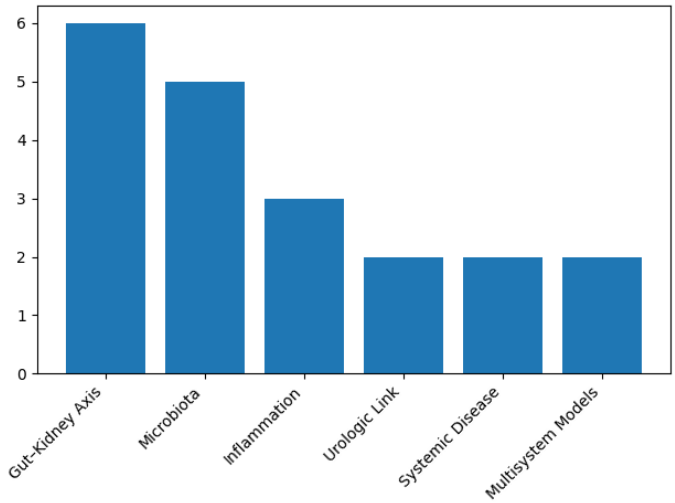

Figure 1 presents the distribution of the selected studies according to their primary thematic focus, revealing a clear predominance of research centered on the **gut–kidney axis**, followed by studies addressing the **role of microbiota**, systemic inflammation, and to a lesser extent, urologic and multisystem integration perspectives.

The largest proportion corresponds to studies focused on the gut–kidney axis, which reflects the growing recognition of this pathway as a central mechanism in systemic disease. Multiple investigations have demonstrated that alterations in gut microbiota composition contribute to the accumulation of uremic toxins and metabolic byproducts that directly impact renal function and systemic homeostasis [3], [5], [9]. This predominance suggests that current scientific efforts are heavily oriented toward understanding bidirectional metabolic and microbial interactions between the gastrointestinal tract and the kidneys.

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The second most represented category corresponds to studies on **microbiota as an independent or central variable**, highlighting its role as a key regulator of systemic physiology. These studies emphasize the influence of microbial diversity on immune modulation, metabolic pathways, and disease susceptibility, reinforcing the concept that microbiota acts as a functional bridge between organ systems [6], [12], [17]. The frequency of this category supports the notion that microbiome research has become a cornerstone in the study of inter-organ communication.

Studies focusing on **inflammatory mechanisms** also occupy a relevant proportion, reflecting the importance of systemic inflammation as a unifying factor in renal, gastrointestinal, and urologic disorders. Chronic inflammation has been consistently associated with disease progression in CKD, gastrointestinal barrier dysfunction, and susceptibility to infections, suggesting a shared pathogenic pathway across these systems [1], [20].

In contrast, research explicitly addressing **urologic involvement** appears less represented. This finding is consistent with the relatively recent emergence of the urinary microbiome and its integration into broader systemic models. However, existing evidence indicates that the urinary tract is closely linked to gastrointestinal microbial reservoirs and systemic inflammatory states, particularly in the context of recurrent urinary tract infections [13], [14].

Similarly, studies adopting a **fully integrated multisystem perspective** remain limited, indicating a gap in the literature. While several investigations explore individual axes (e.g., gut–kidney), fewer studies comprehensively address the triad of renal, gastrointestinal, and urologic interactions as a unified system. This observation underscores the need for more integrative research approaches that reflect the complexity of human physiology [16], [19].

Figure 2.
Main pathophysiological mechanisms involved in renal–gastrointestinal–urologic crosstalk

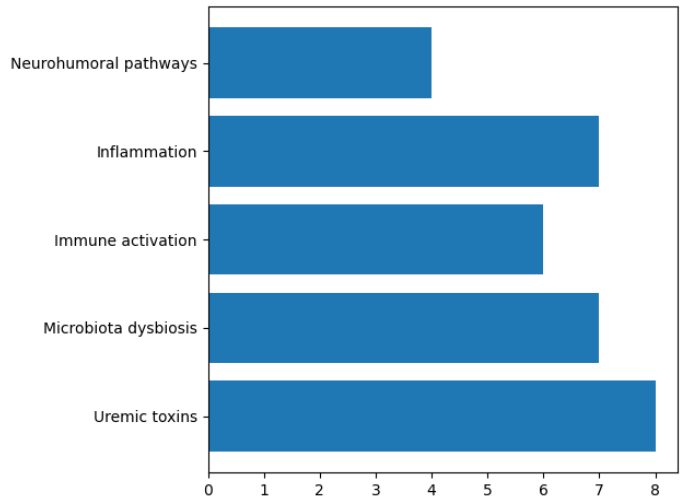

Figure 2 illustrates the principal pathophysiological mechanisms identified across the selected studies, highlighting the relative frequency with which each mechanism is reported in the literature. The data demonstrate that **uremic toxin accumulation and microbiota dysbiosis** are the most consistently described mechanisms underlying inter-organ crosstalk, followed closely by systemic inflammation and immune activation, with neurohumoral pathways appearing less frequently but still relevant.

The predominance of **uremic toxins** reflects their central role in mediating communication between the gut and kidneys. Compounds such as indoxyl sulfate and p-cresyl sulfate originate from microbial metabolism in the gastrointestinal tract and accumulate in patients with impaired renal function, exerting toxic effects on vascular, renal, and immune systems [3], [12]. Their high representation in the literature underscores their importance as both biomarkers and therapeutic targets in systemic disease.

Closely related to this mechanism is **microbiota dysbiosis**, which is consistently identified as a driving factor in the disruption of homeostasis. Alterations in microbial composition lead to increased production of harmful metabolites and reduced generation of protective compounds such as short-chain fatty acids. This imbalance contributes not only

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to renal dysfunction but also to systemic inflammatory responses and increased susceptibility to infections [5], [9], [16].

Inflammation and immune activation emerge as interconnected mechanisms that amplify disease progression. The translocation of bacterial endotoxins due to increased intestinal permeability triggers chronic low-grade inflammation, which has been associated with both renal deterioration and gastrointestinal pathology [1], [20]. Additionally, immune dysregulation plays a role in the susceptibility to urologic infections, linking these systems through shared inflammatory pathways.

The presence of **immune-mediated responses** further highlights the role of cytokines, immune cells, and signaling molecules in mediating inter-organ effects. These processes are particularly relevant in conditions such as acute kidney injury, where systemic immune activation can lead to distant organ dysfunction, including alterations in gut barrier integrity and urinary tract susceptibility [19].

Finally, **neurohumoral pathways**, although less frequently reported, represent an important integrative mechanism. Systems such as the renin–angiotensin–aldosterone system (RAAS) and autonomic nervous signaling contribute to the regulation of renal perfusion, gastrointestinal motility, and urinary function. Dysregulation of these pathways may exacerbate systemic disease, particularly in chronic conditions involving metabolic and cardiovascular components.

Figure 3.
Frequency of microbiota-related findings across the included studies

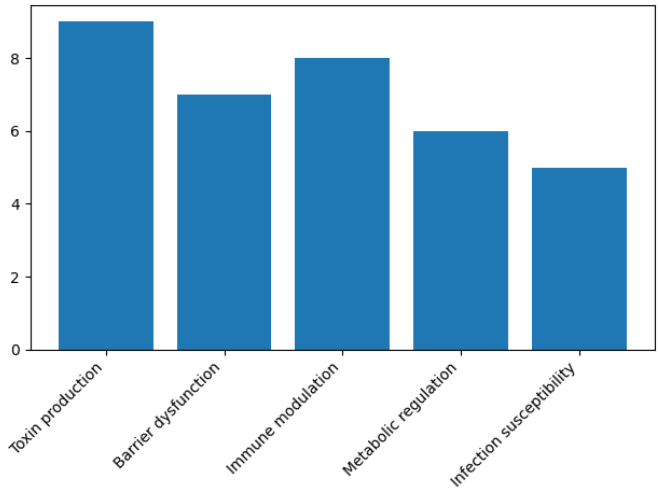

Figure 3 summarizes the frequency of microbiota-related mechanisms identified across the analyzed studies, emphasizing the central role of the gut microbiome in mediating interactions between the renal, gastrointestinal, and urologic systems. Among the different categories, **microbial toxin production** and **immune modulation** emerge as the most consistently reported findings, followed by intestinal barrier dysfunction, metabolic regulation, and infection susceptibility.

The predominance of **microbial toxin production** reflects the critical contribution of gut-derived metabolites to systemic disease. Several studies have demonstrated that compounds such as indoxyl sulfate, p-cresyl sulfate, and trimethylamine-N-oxide are produced through microbial metabolism and accumulate in patients with renal impairment, exerting deleterious effects on vascular integrity, renal function, and systemic inflammation [3], [12]. This mechanism represents a direct biochemical link between the gastrointestinal tract and the kidneys, reinforcing the concept of the gut as a metabolic organ with systemic influence.

Immune modulation appears as another highly represented category, highlighting the role of the microbiota in regulating both innate and adaptive immune responses. Alterations in microbial diversity have been associated with increased production of pro-inflammatory cytokines and impaired immune tolerance, contributing to chronic inflammation and disease progression [5], [20]. This interaction is particularly relevant in the context of chronic kidney disease and gastrointestinal disorders, where immune dysregulation plays a central role.

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The presence of **intestinal barrier dysfunction** further supports the importance of structural integrity in maintaining systemic homeostasis. Increased intestinal permeability facilitates the translocation of bacterial endotoxins and other pro-inflammatory molecules into the bloodstream, amplifying systemic inflammatory responses and contributing to multi-organ involvement [4], [16]. This mechanism serves as a critical interface between local gastrointestinal alterations and systemic disease processes.

Metabolic regulation represents another key function of the microbiota, influencing glucose metabolism, lipid profiles, and energy balance. In metabolic conditions such as diabetes mellitus, which are closely linked to both renal and urologic disorders, microbiota alterations have been shown to exacerbate disease progression through dysregulated metabolic signaling [8], [9]. Although less frequently reported than toxin production or immune modulation, this category remains essential for understanding the broader systemic impact of microbial activity.

Finally, **infection susceptibility**, particularly in the urinary tract, reflects the clinical implications of microbiota imbalance. The gastrointestinal tract acts as a reservoir for uropathogenic bacteria, and alterations in microbial composition can increase the risk of urinary tract infections by facilitating bacterial colonization and impairing host defense mechanisms [13], [14]. While this category appears less frequently in the literature compared to others, it represents a direct clinical manifestation of inter-organ crosstalk.

Figure 4.
Principal systemic diseases associated with inter-organ crosstalk

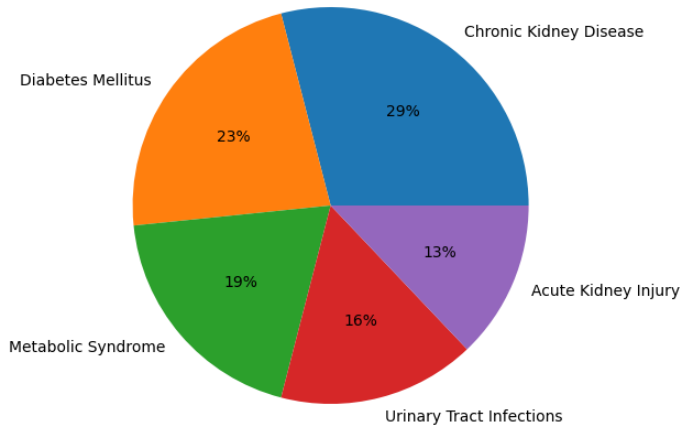

Figure 4 illustrates the distribution of the principal systemic diseases identified across the selected studies in which renal, gastrointestinal, and urologic interactions play a significant role. The data show that **chronic kidney disease (CKD)** represents the most frequently associated condition, followed by **diabetes mellitus**, **metabolic syndrome**, **urinary tract infections**, and **acute kidney injury (AKI)**.

The predominance of **chronic kidney disease** reflects its central position within the network of inter-organ interactions. CKD is not only influenced by gastrointestinal and metabolic factors but also actively contributes to systemic dysregulation through the accumulation of uremic toxins, immune activation, and alterations in the gut microbiota [1], [7], [15]. This bidirectional relationship reinforces the role of CKD as both a consequence and a driver of systemic disease processes.

Diabetes mellitus appears as the second most represented condition, highlighting its role as a key metabolic disorder that links renal, gastrointestinal, and urologic systems. The interaction between hyperglycemia, microbiota alterations, and inflammatory pathways contributes to the progression of diabetic kidney disease and increases susceptibility to infections, particularly in the urinary tract [8]. This emphasizes the importance of metabolic control in preventing multisystem complications.

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Closely related to diabetes, **metabolic syndrome** is also prominently represented, reflecting its association with systemic inflammation, insulin resistance, and alterations in microbiota composition. These factors contribute to both renal dysfunction and gastrointestinal imbalance, further reinforcing the interconnected nature of these systems. The presence of metabolic syndrome in the literature underscores the importance of lifestyle and environmental factors in the development of systemic disease.

Urinary tract infections (UTIs) represent a direct clinical manifestation of the interaction between the gastrointestinal and urologic systems. The gastrointestinal tract serves as a reservoir for uropathogenic microorganisms, and dysbiosis can facilitate bacterial translocation and colonization of the urinary tract [13], [14]. The inclusion of UTIs in this distribution highlights the clinical relevance of microbiota-mediated mechanisms in urologic disease.

Finally, **acute kidney injury** appears as a less frequently represented but clinically significant condition. AKI has been shown to induce systemic effects through inflammatory and immune-mediated pathways, affecting not only renal function but also gastrointestinal integrity and susceptibility to infection [19]. Although its representation is lower compared to chronic conditions, AKI remains an important component of inter-organ crosstalk, particularly in acute and critical care settings.

Figure 5.
Clinical manifestations and multidisciplinary implications identified in the literature

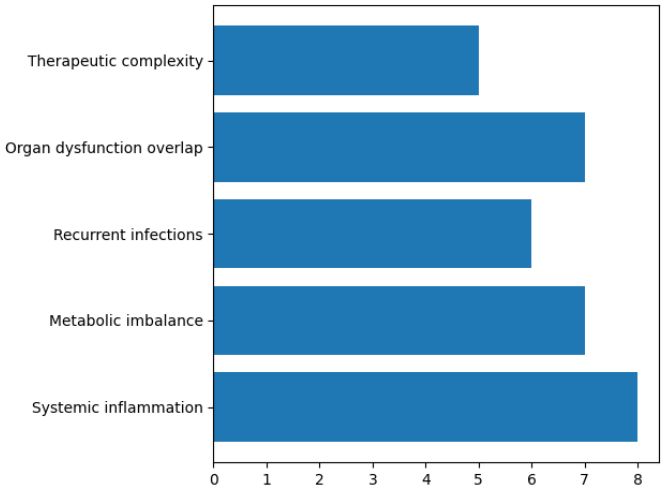

Figure 5 presents the principal clinical manifestations and multidisciplinary implications associated with the interaction between the renal, gastrointestinal, and urologic systems. The results demonstrate that **systemic inflammation** and **organ dysfunction overlap** are among the most consistently reported features, followed by metabolic imbalance, recurrent infections, and therapeutic complexity.

The prominence of **systemic inflammation** reflects its central role as a unifying mechanism linking these organ systems. Chronic low-grade inflammation, often driven by microbial metabolites and immune activation, contributes to the progression of renal disease, gastrointestinal dysfunction, and susceptibility to urologic conditions [1], [20]. This inflammatory state not only affects individual organs but also promotes a cascade of systemic effects that complicate disease management.

Closely related to this is the concept of **organ dysfunction overlap**, which highlights the simultaneous involvement of multiple systems in a single clinical scenario. For example, patients with chronic kidney disease frequently present with gastrointestinal symptoms such as dyspepsia or altered bowel habits, as well as increased risk of urinary tract infections. This overlap reflects the interconnected nature of these systems and underscores the limitations of isolated diagnostic approaches [5], [16].

Metabolic imbalance is another key manifestation, particularly in conditions such as diabetes mellitus and metabolic syndrome. These disorders disrupt glucose and lipid metabolism, contributing to renal damage, alterations in gut

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microbiota, and increased susceptibility to infections [8], [9]. The presence of metabolic dysregulation across multiple systems reinforces the importance of integrated therapeutic strategies that address underlying metabolic pathways.

The category of **recurrent infections**, especially urinary tract infections, represents a direct clinical consequence of microbiota alterations and immune dysfunction. The gastrointestinal tract serves as a reservoir for pathogenic microorganisms, and dysbiosis can facilitate their migration and colonization of the urinary tract [13], [14]. This highlights the need to consider both gastrointestinal and systemic factors in the prevention and management of urologic infections.

Finally, **therapeutic complexity** emerges as a significant implication of inter-organ crosstalk. The coexistence of multiple interconnected conditions often requires multidisciplinary management involving nephrology, gastroenterology, and urology. Pharmacological interventions targeting one system may inadvertently affect another—for example, antibiotic use altering gut microbiota or dietary restrictions impacting metabolic balance. This complexity emphasizes the importance of personalized and integrative approaches in clinical practice.

Figure 6.
Regional projection of the clinical relevance of these interactions in Mexico, Colombia, and Ecuador

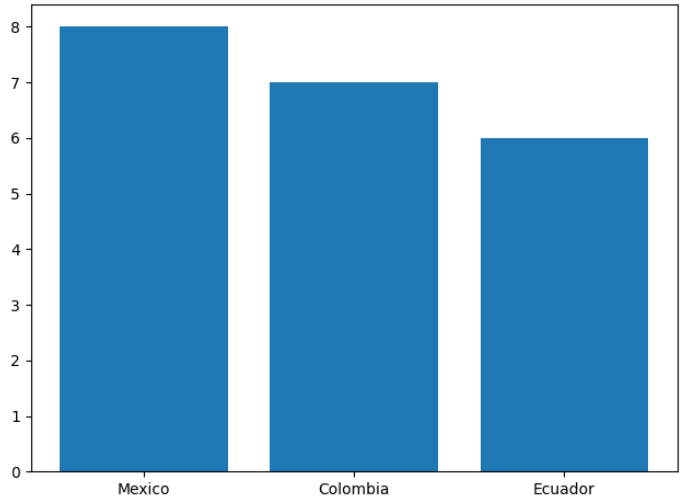

Figure 6 illustrates the projected clinical relevance of renal–gastrointestinal–urologic interactions within selected Latin American contexts, specifically Mexico, Colombia, and Ecuador. The distribution reflects variations in disease burden, healthcare infrastructure, and epidemiological patterns reported in the literature, with **Mexico showing the highest relative impact**, followed by Colombia and Ecuador.

The higher representation observed in **Mexico** can be associated with the elevated prevalence of chronic conditions such as chronic kidney disease, diabetes mellitus, and metabolic syndrome. These conditions are strongly linked to alterations in microbiota composition, systemic inflammation, and increased risk of urologic complications, reinforcing the importance of inter-organ crosstalk in this population [7], [8], [15]. Additionally, lifestyle factors, dietary patterns, and urbanization contribute to the growing burden of these diseases, further amplifying their systemic impact.

In **Colombia**, the findings suggest a slightly lower but still significant level of clinical relevance. The epidemiological transition observed in this country, characterized by an increase in non-communicable diseases alongside persistent infectious conditions, creates a complex clinical landscape in which renal, gastrointestinal, and urologic interactions are highly relevant. The coexistence of metabolic disorders and infectious diseases may enhance the role of immune-mediated and microbiota-related mechanisms in disease progression.

Ecuador, while showing the lowest relative representation among the three, still demonstrates a considerable impact of these interactions. Factors such as healthcare accessibility, regional disparities, and variations in nutritional and environmental exposures may influence both the detection and progression of systemic diseases. Despite these

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differences, the underlying mechanisms of inter-organ crosstalk remain consistent, emphasizing their universal relevance across different populations.

Importantly, the differences observed in Figure 6 should not be interpreted as absolute measures of disease prevalence, but rather as a reflection of the relative emphasis and applicability of the identified mechanisms within each regional context. The consistent presence of these interactions across all three countries highlights the need for **region-specific strategies** that consider local epidemiology, healthcare resources, and sociocultural factors.

DISCUSSION

The findings of this review highlight the increasing relevance of a **systems-based understanding of disease**, particularly in the context of the interconnected relationships between the renal, gastrointestinal, and urologic systems. The results demonstrate that current scientific evidence is largely centered on the **gut–kidney axis and microbiota-related mechanisms**, while also revealing important gaps in the integration of urologic perspectives and fully unified multisystem models.

One of the most consistent observations across the analyzed studies is the central role of the **gut microbiota as a mediator of inter-organ communication**. The predominance of microbiota-related findings (Figures 1–3) supports the concept that the gastrointestinal system functions as a metabolic and immunological hub capable of influencing distant organs. This aligns with previous research indicating that microbial metabolites, particularly uremic toxins, play a direct role in renal dysfunction and systemic inflammation [3], [12]. The accumulation of these compounds in patients with impaired renal clearance not only accelerates kidney damage but also contributes to cardiovascular and immune complications, reinforcing the systemic nature of the disease [1], [7].

In addition, the results confirm that **inflammation acts as a common pathway** linking renal, gastrointestinal, and urologic dysfunction. The high frequency of inflammatory mechanisms identified (Figure 2) and their clinical manifestations (Figure 5) suggest that chronic low-grade inflammation is not merely a consequence but a driving force in disease progression. This is consistent with evidence showing that increased intestinal permeability facilitates the translocation of endotoxins, leading to systemic immune activation and multi-organ involvement [5], [16], [20]. The integration of these findings supports a model in which inflammation serves as a key mediator of organ crosstalk.

From a clinical perspective, the distribution of diseases observed (Figure 4) emphasizes the predominance of **chronic, multifactorial conditions**, particularly chronic kidney disease and diabetes mellitus. These findings are consistent with global epidemiological data and highlight the role of metabolic disorders as central drivers of systemic dysfunction [15]. The close relationship between metabolic imbalance, microbiota alterations, and organ interaction further supports the need for comprehensive management strategies that address underlying systemic processes rather than isolated symptoms.

An important contribution of this review is the incorporation of **urologic conditions into the framework of inter-organ crosstalk**. Although less represented in the literature (Figure 1), the inclusion of urinary tract infections and urinary microbiome interactions provides a more complete understanding of the system. The evidence suggests that the gastrointestinal tract serves as a reservoir for uropathogenic bacteria, linking gut dysbiosis with increased susceptibility to infections [13], [14]. This relationship highlights the importance of considering both microbial and immune factors in the management of urologic diseases.

The concept of **organ dysfunction overlap**, identified as a key clinical manifestation (Figure 5), further reinforces the limitations of traditional organ-specific approaches. Patients frequently present with concurrent renal, gastrointestinal, and urologic symptoms, reflecting the interconnected nature of these systems. This overlap complicates diagnosis and treatment, often requiring multidisciplinary collaboration. The recognition of these interactions supports the development of integrated clinical models that improve diagnostic accuracy and therapeutic outcomes.

The regional analysis (Figure 6) provides additional insight into the applicability of these findings in Latin American contexts. The higher relative impact observed in Mexico, followed by Colombia and Ecuador, reflects differences in disease prevalence, healthcare access, and socioeconomic factors. The high burden of metabolic diseases in these regions amplifies the relevance of inter-organ crosstalk, particularly in resource-limited settings where early detection

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and integrated care may be challenging. These findings underscore the importance of adapting global evidence to local contexts in order to optimize clinical practice.

Despite the strengths of this review, several limitations must be acknowledged. First, the majority of available studies focus on **specific axes (e.g., gut–kidney)** rather than fully integrated models, limiting the ability to draw comprehensive conclusions about the triad of renal, gastrointestinal, and urologic interactions. Second, heterogeneity in study design, population characteristics, and methodologies may affect the comparability of results. Additionally, the relative scarcity of research explicitly addressing urologic integration highlights an important gap in the literature that warrants further investigation.

Another limitation relates to the **predominance of observational and experimental studies**, with fewer large-scale clinical trials evaluating the effectiveness of integrated therapeutic strategies. While interventions targeting the microbiota have shown promise, there is still a lack of standardized protocols and long-term outcome data [9]. Future research should focus on translational approaches that bridge the gap between mechanistic understanding and clinical application.

CONCLUSION

The present review consolidates current evidence supporting the concept that the **renal, gastrointestinal, and urologic systems function as an integrated network**, rather than as isolated entities. The analysis demonstrates that inter-organ crosstalk is mediated through complex interactions involving microbiota-derived metabolites, immune responses, inflammatory pathways, and neurohumoral regulation, all of which contribute significantly to the development and progression of systemic diseases.

A central finding of this work is the pivotal role of the **gut microbiota as a regulator of systemic homeostasis**. Alterations in microbial composition not only influence gastrointestinal function but also have direct effects on renal physiology and urologic health through mechanisms such as uremic toxin production and immune modulation. These interactions reinforce the concept of the gut–kidney axis as a fundamental component of disease pathophysiology, with extensions toward urologic processes that are increasingly recognized in the literature.

The results also highlight the importance of **systemic inflammation and metabolic dysregulation** as shared pathways linking these organ systems. Chronic conditions such as chronic kidney disease, diabetes mellitus, and metabolic syndrome emerge as key clinical scenarios in which these interactions are most evident. The coexistence of these disorders underscores the need for integrated approaches that address underlying systemic mechanisms rather than focusing solely on individual organ dysfunction.

From a clinical perspective, the identification of **overlapping manifestations and therapeutic complexity** emphasizes the limitations of traditional organ-centered models. Patients frequently present with multisystem involvement, requiring coordinated care strategies that incorporate nephrology, gastroenterology, and urology. The adoption of a systems-based approach has the potential to improve diagnostic accuracy, optimize treatment outcomes, and reduce the burden of chronic disease.

Furthermore, the inclusion of a **regional perspective**, particularly in Latin American contexts such as Mexico, Colombia, and Ecuador, highlights the influence of epidemiological, environmental, and healthcare factors on disease expression. These findings support the need for context-specific strategies that adapt global evidence to local realities, ensuring more effective and equitable healthcare delivery.

Despite advances in understanding inter-organ communication, important gaps remain, particularly in the integration of urologic perspectives and the development of standardized therapeutic interventions targeting microbiota and systemic pathways. Future research should prioritize multidisciplinary and translational approaches that bridge mechanistic insights with clinical application.

In conclusion, recognizing the **renal–gastrointestinal–urologic axis as a unified system** represents a critical step toward advancing modern medical practice. This integrative framework not only enhances the understanding of disease mechanisms but also provides a foundation for innovative diagnostic and therapeutic strategies, ultimately contributing to improved patient care in complex systemic conditions.

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Issue 3, Year 2, Volume 1, No. 01, January-June 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
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