
Contemporary Therapeutic Approaches in the Cardiorenal-Metabolic Continuum: Current Perspectives on Diabetes, Chronic Kidney Disease, and Cardiovascular Dysfunction

Santiago Ávila Ak.

Universidad Autónoma de Campeche

santiagoalbertoavilaak@gmail.com

<https://orcid.org/0009-0007-3979-5321>

Julian Ortega Tolay

Universidad Nacional de Jujuy

ortegatolay@gmail.com

<https://orcid.org/0009-0005-9564-0063>

Rafaela Denisse Zambrano Mendieta

Universidad Católica de Santiago de Guayaquil

RDENISSEZAMEN@gmail.com

<https://orcid.org/0009-0009-2203-8070>

Erik Fernández Godínez

Hospital Regional Dr. Rafael Pascasio Gamboa

godinezfer88@gmail.com

<https://orcid.org/0009-0002-6516-3719>

Cristóbal Washington Franco Lucas

ACP - SEMES - Universidad Estatal del Sur de Manabí

dr cristobal.franco@gmail.com

<https://orcid.org/0000-0003-2212-2909>

Gerardo Amaya Villagran

Instituto Mexicano Del seguro social

gera1689@hotmail.com

<https://orcid.org/0000-0003-3937-6323>

Luis Miguel Murgas Acevedo

Universidad Autónoma de Bucaramanga

Lmurgas899@gmail.com

<https://orcid.org/0009-0000-7431-5994>

José Alberto Pérez Pérez

Independiente

med.albertoperez@gmail.com

<https://orcid.org/0009-0003-6796-3100>

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* **Corresponding Author:** santiagoalbertoavilaak@gmail.com

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ABSTRACT

Cardiorenal syndrome associated with type 2 diabetes mellitus has emerged as a major global health challenge due to its increasing prevalence, complex pathophysiology, and significant impact on morbidity and mortality. The interaction between cardiovascular disease, chronic kidney disease, and metabolic dysfunction creates a bidirectional cycle of organ damage mediated by inflammation, oxidative stress, endothelial dysfunction, neurohormonal activation, and

fibrosis. This review analyzes current evidence regarding the mechanisms linking diabetes with cardiovascular and renal deterioration, emphasizing the concept of the cardiorenal-metabolic continuum. A comprehensive review of contemporary literature was conducted using international scientific databases and clinical practice guidelines. The findings indicate that recent therapeutic advances, particularly sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonists, have significantly improved cardiovascular and renal outcomes while reducing disease progression and hospitalization rates. Despite these advances, substantial challenges remain regarding early diagnosis, treatment accessibility, therapeutic implementation, and healthcare disparities. These challenges are especially relevant in Latin American countries, including Mexico, Colombia, and Ecuador, where the burden of diabetes and chronic kidney disease continues to rise. Current evidence supports the adoption of integrated multidisciplinary approaches focused on early detection, comprehensive risk assessment, and evidence-based therapeutic interventions. The transition from organ-centered management toward a cardiorenal-metabolic model represents a fundamental paradigm shift that may contribute to improved patient survival, preservation of organ function, and enhanced quality of life.

KEYWORDS

Cardiorenal syndrome, Type 2 diabetes mellitus, Chronic kidney disease, Heart failure, Cardiorenal-metabolic syndrome, SGLT2 inhibitors, GLP-1 receptor agonists, Finerenone, Cardiovascular disease, Renal protection, Multidisciplinary care, Internal medicine

INTRODUCTION

Cardiovascular disease, chronic kidney disease (CKD), and type 2 diabetes mellitus (T2DM) constitute a complex and interdependent clinical triad that has emerged as one of the most significant global health challenges of the twenty-first century. The coexistence of these conditions is associated with substantial morbidity, mortality, healthcare utilization, and economic burden, affecting millions of individuals worldwide. In recent years, increasing attention has been directed toward the concept of the cardiorenal syndrome, a pathophysiological condition characterized by bidirectional interactions between the heart and kidneys, in which dysfunction of one organ induces or accelerates dysfunction of the other. When diabetes is present, these interactions become even more complex, giving rise to what many experts now describe as the cardiorenal-metabolic continuum, a framework that recognizes the interconnected nature of metabolic, cardiovascular, and renal disorders [1,2].

The prevalence of diabetes continues to rise globally, driven by population aging, sedentary lifestyles, urbanization, and increasing rates of obesity. According to international epidemiological estimates, hundreds of millions of adults currently live with diabetes, and a significant proportion will develop cardiovascular complications, diabetic kidney disease, or both during their lifetime [3,4]. Diabetic kidney disease remains the leading cause of chronic kidney disease and end-stage kidney disease worldwide, while cardiovascular disease represents the principal cause of death among patients with diabetes and CKD [5,6]. Consequently, understanding the mechanisms that link these conditions and identifying effective therapeutic approaches have become priorities for clinicians, researchers, and healthcare systems.

The pathophysiology of cardiorenal syndrome in patients with diabetes is multifactorial and involves a complex interplay of hemodynamic, neurohormonal, inflammatory, metabolic, and fibrotic pathways. Persistent hyperglycemia promotes endothelial dysfunction, oxidative stress, chronic inflammation, and activation of the renin-angiotensin-

aldosterone system (RAAS), all of which contribute to structural and functional alterations in both the cardiovascular and renal systems [1,7]. Simultaneously, maladaptive activation of the sympathetic nervous system, fluid retention, glomerular hyperfiltration, myocardial remodeling, and progressive fibrosis further accelerate disease progression. These mechanisms create a vicious cycle in which deterioration of cardiac function exacerbates renal impairment, while worsening kidney disease contributes to adverse cardiovascular outcomes [1,8].

Historically, therapeutic management focused primarily on controlling individual risk factors such as hyperglycemia, hypertension, and dyslipidemia. Although these interventions significantly improved patient outcomes, residual cardiovascular and renal risks remained substantial despite achieving conventional treatment targets [5,9]. This observation prompted researchers to investigate novel pharmacological strategies capable of simultaneously addressing the multiple pathophysiological pathways involved in the cardiorenal syndrome. The emergence of sodium-glucose cotransporter-2 (SGLT2) inhibitors, non-steroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists has transformed the therapeutic landscape, providing evidence of clinically meaningful reductions in cardiovascular events, heart failure hospitalizations, kidney disease progression, and mortality [10–15].

Among these advances, SGLT2 inhibitors have attracted particular attention due to their consistent cardiorenal protective effects across diverse patient populations. Landmark clinical trials such as CREDENCE, DAPA-CKD, EMPA-KIDNEY, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER demonstrated significant benefits extending beyond glycemic control, including preservation of kidney function and reduction of heart failure-related outcomes [10–12,16–18]. Similarly, finerenone, a selective non-steroidal mineralocorticoid receptor antagonist, demonstrated favorable cardiovascular and renal effects in patients with diabetic kidney disease through the FIDELIO-DKD and FIGARO-DKD trials, further expanding therapeutic options for high-risk individuals [13,14]. More recently, glucagon-like peptide-1 receptor agonists, particularly semaglutide, have shown promising renal and cardiovascular benefits, reinforcing the concept of integrated cardiorenal-metabolic protection [15].

Despite these therapeutic advances, substantial challenges remain. Many patients continue to be diagnosed at advanced stages of disease, limiting opportunities for early intervention. Furthermore, barriers related to healthcare access, medication availability, socioeconomic disparities, and clinical implementation contribute to variations in treatment outcomes across different regions of the world. These challenges are particularly relevant in Latin America, where diabetes, hypertension, obesity, and chronic kidney disease have shown a progressive increase over recent decades. Countries such as Mexico, Colombia, and Ecuador face a growing burden of cardiorenal disease, compounded by limitations in screening programs, delayed referrals to specialized care, and unequal access to innovative therapies [19,20]. Consequently, strategies aimed at improving early detection, multidisciplinary management, and evidence-based treatment adoption are essential to reduce disease progression and improve patient outcomes.

Recent international guidelines issued by the Kidney Disease: Improving Global Outcomes (KDIGO) organization and the American Diabetes Association (ADA) emphasize a comprehensive approach that integrates cardiovascular, renal, and metabolic risk reduction. These recommendations advocate early identification of CKD in diabetic patients, optimization of RAAS blockade when indicated, incorporation of SGLT2 inhibitors, consideration of finerenone in selected populations, and individualized use of GLP-1 receptor agonists as part of a broader therapeutic strategy [3,4,6]. Such recommendations reflect a paradigm shift from organ-specific management toward integrated patient-centered care.

Given the rapid expansion of evidence in this field, continuous synthesis and critical evaluation of current knowledge are necessary. Numerous studies have examined individual aspects of cardiorenal syndrome, diabetic kidney disease, heart failure, and emerging therapies; however, integrating these findings into a coherent clinical framework remains

a challenge. Therefore, an updated review is warranted to analyze the current understanding of the relationship between cardiorenal syndrome and diabetes, explore the underlying pathophysiological mechanisms, evaluate contemporary therapeutic strategies, and identify persistent gaps in knowledge that may guide future research and clinical practice.

Accordingly, the primary objective of this review is to examine the current evidence regarding the pathophysiological interactions linking diabetes, cardiovascular dysfunction, and kidney disease, with particular emphasis on contemporary therapeutic approaches and their clinical implications. Specifically, this review seeks to evaluate the role of novel pharmacological interventions, discuss current guideline recommendations, analyze ongoing challenges in patient management, and highlight opportunities for improving outcomes through integrated cardiorenal-metabolic care. By synthesizing recent findings from international literature, this work aims to provide healthcare professionals, researchers, and students with a comprehensive and updated perspective on one of the most dynamic and clinically relevant areas of modern internal medicine, nephrology, and endocrinology.

DEVELOPMENT

The relationship between cardiovascular disease, chronic kidney disease (CKD), and type 2 diabetes mellitus (T2DM) has evolved from being considered a coexistence of independent conditions to being recognized as a highly interconnected pathophysiological continuum. Modern evidence indicates that these disorders interact through shared molecular, hemodynamic, inflammatory, and metabolic pathways that mutually accelerate disease progression and worsen clinical outcomes. This interaction is particularly evident in the cardiorenal syndrome, a condition characterized by bidirectional dysfunction between the heart and kidneys, where impairment of one organ contributes directly to the deterioration of the other [1].

Diabetes mellitus represents one of the most important drivers of cardiorenal disease worldwide. Persistent hyperglycemia induces structural and functional alterations in multiple organ systems through mechanisms that include oxidative stress, endothelial dysfunction, chronic low-grade inflammation, advanced glycation end-product accumulation, mitochondrial dysfunction, and activation of neurohormonal pathways [3,5]. These alterations promote both microvascular and macrovascular damage, ultimately affecting cardiac and renal function. Consequently, diabetic patients frequently develop heart failure, coronary artery disease, albuminuria, and progressive CKD, conditions that often coexist and interact in a clinically significant manner [2,6].

One of the central mechanisms linking diabetes with cardiorenal syndrome is the activation of the renin-angiotensin-aldosterone system (RAAS). Chronic RAAS stimulation contributes to sodium retention, increased intraglomerular pressure, systemic vasoconstriction, myocardial hypertrophy, and progressive fibrosis within both cardiac and renal tissues [7]. Simultaneously, overactivation of the sympathetic nervous system further exacerbates hemodynamic instability, promoting hypertension, ventricular remodeling, and accelerated nephron loss. Together, these processes establish a vicious cycle in which cardiovascular dysfunction aggravates renal injury while declining kidney function amplifies cardiovascular risk [1,8].

The role of inflammation has also gained increasing attention in recent years. Studies have demonstrated elevated circulating concentrations of inflammatory mediators such as interleukin-6, tumor necrosis factor-alpha, and C-reactive protein in patients with diabetes, heart failure, and CKD [2,18]. These mediators contribute to endothelial injury, vascular stiffness, myocardial remodeling, and progressive glomerulosclerosis. In addition, inflammatory signaling pathways stimulate fibrotic processes that impair tissue repair and further compromise organ function. The recognition of inflammation as a central contributor to cardiorenal disease has stimulated the development of therapeutic approaches targeting these mechanisms directly or indirectly.

From a clinical perspective, diabetic kidney disease remains the leading cause of chronic kidney disease and end-stage kidney disease globally [3,6]. Approximately one-third to one-half of individuals with type 2 diabetes develop some degree of renal impairment during their lifetime, significantly increasing their risk of hospitalization, cardiovascular events, and premature mortality [4]. Albuminuria and reduced estimated glomerular filtration rate (eGFR) have emerged as independent predictors of adverse cardiovascular outcomes, emphasizing the importance of early renal assessment in diabetic populations [6].

Similarly, heart failure has become increasingly recognized as a major complication of diabetes. Epidemiological studies indicate that patients with diabetes have a substantially higher risk of developing heart failure compared with the general population, even in the absence of coronary artery disease [14]. Hyperglycemia-related myocardial fibrosis, metabolic alterations, microvascular dysfunction, and increased oxidative stress contribute to the development of diabetic cardiomyopathy, a condition characterized by structural and functional myocardial abnormalities independent of ischemic disease or hypertension [2]. As a result, many diabetic patients develop either heart failure with reduced ejection fraction or heart failure with preserved ejection fraction, both of which are associated with poor renal outcomes.

The traditional management of cardiorenal disease focused primarily on controlling glucose levels, blood pressure, and lipid profiles. While these interventions remain essential components of care, evidence accumulated over the last decade has demonstrated that conventional risk-factor modification alone is insufficient to prevent disease progression in many patients [5]. This realization led to the emergence of the cardiorenal-metabolic model, which seeks to address the interconnected mechanisms underlying cardiovascular, renal, and metabolic dysfunction simultaneously.

Among contemporary therapeutic advances, sodium-glucose cotransporter-2 (SGLT2) inhibitors have arguably produced the most significant paradigm shift. Initially developed as glucose-lowering agents, these medications demonstrated unexpected cardiovascular and renal benefits that extended well beyond glycemic control. Landmark trials such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY showed substantial reductions in kidney disease progression, albuminuria, dialysis initiation, and cardiovascular events among patients with diabetic and non-diabetic CKD [7,8,9]. Furthermore, studies including DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER demonstrated meaningful reductions in heart failure hospitalizations and cardiovascular mortality across diverse populations [14,15,16,17].

The mechanisms underlying these benefits are multifactorial. SGLT2 inhibitors reduce intraglomerular pressure through restoration of tubuloglomerular feedback, improve natriuresis, decrease cardiac preload and afterload, enhance myocardial energetics, and attenuate inflammatory and fibrotic pathways [8,18]. These effects collectively contribute to both renal preservation and cardiovascular protection, making SGLT2 inhibitors foundational therapies in modern cardiorenal management.

Another major therapeutic advancement has been the introduction of finerenone, a selective non-steroidal mineralocorticoid receptor antagonist. Clinical trials such as FIDELIO-DKD and FIGARO-DKD demonstrated that finerenone significantly reduces kidney disease progression and cardiovascular events among patients with diabetic kidney disease receiving standard RAAS blockade [11,12]. Unlike traditional steroidal mineralocorticoid receptor antagonists, finerenone exhibits a more favorable safety profile regarding hyperkalemia and endocrine adverse effects, allowing broader clinical application in selected populations.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have also emerged as valuable therapeutic tools within the cardiorenal-metabolic framework. Beyond their established effects on glycemic control and weight reduction, these agents have demonstrated cardiovascular benefits through improvements in endothelial function, anti-inflammatory activity, blood pressure reduction, and modulation of atherosclerotic processes [10]. Recent studies evaluating semaglutide suggest potential renal protective effects that may further strengthen the role of GLP-1 receptor agonists in integrated cardiorenal management [10].

Despite these advances, significant challenges remain. A considerable proportion of patients continue to receive delayed diagnoses of CKD or heart failure, reducing opportunities for early intervention. Moreover, disparities in healthcare access limit the implementation of evidence-based therapies in many regions. In Latin America, including Mexico, Colombia, and Ecuador, the growing prevalence of obesity, diabetes, hypertension, and chronic kidney disease represents a major public health concern [19,20]. Resource limitations, restricted access to specialized care, and socioeconomic inequalities frequently contribute to delayed treatment initiation and poorer outcomes compared with those reported in higher-income countries.

Current international guidelines emphasize the importance of multidisciplinary management involving cardiologists, nephrologists, endocrinologists, internists, primary care physicians, nurses, nutritionists, and pharmacists [3,4,6]. Such collaborative approaches facilitate comprehensive risk assessment, optimization of pharmacological therapy, lifestyle modification, and continuous monitoring of disease progression. The integration of these strategies is increasingly recognized as essential for reducing morbidity and mortality associated with cardiorenal syndrome in patients with diabetes.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To analyze the current scientific evidence regarding the pathophysiological relationship between cardiorenal syndrome and type 2 diabetes mellitus, evaluating contemporary therapeutic strategies, clinical challenges, and multidisciplinary management approaches aimed at improving cardiovascular and renal outcomes through an integrated cardiorenal-metabolic perspective.

A. Cognitive Domain

1. To identify the principal pathophysiological mechanisms that connect cardiovascular dysfunction, chronic kidney disease, and type 2 diabetes mellitus within the cardiorenal syndrome continuum.
2. To examine the impact of metabolic, inflammatory, neurohormonal, and hemodynamic alterations on the progression of cardiorenal disease in diabetic patients.
3. To analyze the scientific evidence supporting the use of sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonists in cardiorenal protection.
4. To compare current international clinical guidelines and recommendations regarding the management of patients with cardiorenal syndrome associated with diabetes.
5. To evaluate the epidemiological relevance and clinical burden of cardiorenal disease in the global population, with particular consideration of Latin American countries such as Mexico, Colombia, and Ecuador.

B. Psychomotor Domain

6. To apply evidence-based criteria for the early identification and risk stratification of patients with diabetes who are at increased risk of developing cardiovascular and renal complications.
7. To demonstrate the appropriate interpretation of clinical indicators used in cardiorenal assessment, including estimated glomerular filtration rate, albuminuria, glycemic parameters, and cardiovascular risk markers.
8. To utilize current therapeutic algorithms for the selection and optimization of pharmacological interventions aimed at reducing cardiorenal risk.
9. To integrate multidisciplinary clinical decision-making principles into the management of patients presenting with combined cardiovascular, renal, and metabolic disorders.

C. Affective Domain

10. To recognize the importance of early prevention and comprehensive management of cardiorenal syndrome as a strategy to reduce morbidity, mortality, and healthcare burden.
11. To appreciate the value of multidisciplinary collaboration among nephrologists, cardiologists, endocrinologists, internists, primary care physicians, nurses, and other healthcare professionals involved in patient care.
12. To promote a patient-centered approach that prioritizes quality of life, treatment adherence, and long-term cardiovascular and renal protection.
13. To encourage critical reflection regarding healthcare disparities and barriers to access that affect the implementation of evidence-based cardiorenal therapies in different healthcare settings.
14. To foster professional commitment toward continuous learning and the incorporation of emerging scientific evidence into clinical practice for the benefit of patients with diabetes and cardiorenal disease.

OBJECT OF STUDY

The object of study of this review is the cardiorenal syndrome associated with type 2 diabetes mellitus, with particular emphasis on the pathophysiological interactions linking cardiovascular dysfunction, chronic kidney disease, and metabolic disorders, as well as the contemporary therapeutic strategies currently employed to mitigate disease progression and improve clinical outcomes.

Cardiorenal syndrome represents a multifaceted clinical entity in which the heart and kidneys interact through complex bidirectional mechanisms. In individuals with diabetes, these interactions are intensified by metabolic abnormalities that promote endothelial dysfunction, chronic inflammation, oxidative stress, neurohormonal activation, and progressive fibrosis. Consequently, the coexistence of cardiovascular disease, renal impairment, and diabetes constitutes a major challenge for healthcare systems worldwide and is associated with increased morbidity, mortality, hospitalization rates, and healthcare expenditures.

The phenomenon under investigation encompasses the biological, clinical, and therapeutic dimensions of the cardiorenal-metabolic continuum. From a biological perspective, the study focuses on the molecular and physiological mechanisms responsible for the initiation and progression of organ dysfunction. These mechanisms include activation of the renin-angiotensin-aldosterone system, sympathetic nervous system overactivity, alterations in sodium and fluid homeostasis, inflammatory signaling pathways, mitochondrial dysfunction, and metabolic derangements induced by chronic hyperglycemia.

From a clinical perspective, the object of study includes patients diagnosed with type 2 diabetes mellitus who present with varying degrees of cardiovascular and renal involvement. Particular attention is directed toward individuals with diabetic kidney disease, chronic kidney disease, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, ischemic heart disease, and other manifestations of cardiovascular dysfunction that contribute to the development of cardiorenal syndrome.

The population considered within this review consists of adult patients with type 2 diabetes mellitus evaluated in outpatient, inpatient, and specialized cardiovascular, nephrology, and endocrinology settings. Evidence derived from international studies involving diverse populations is examined to provide a comprehensive understanding of disease behavior across different geographic, ethnic, and socioeconomic contexts. Additionally, specific consideration is given to the growing burden of cardiorenal disease in Latin America, particularly in Mexico, Colombia, and Ecuador, where diabetes and chronic kidney disease continue to represent major public health concerns.

The healthcare system associated with this phenomenon constitutes another relevant component of the object of study. Effective management of cardiorenal syndrome requires coordinated multidisciplinary care involving cardiologists, nephrologists, endocrinologists, internists, primary care physicians, nurses, nutrition specialists, pharmacists, and other healthcare professionals. Therefore, the review also explores integrated care models designed to optimize diagnosis, treatment, follow-up, and prevention strategies.

Furthermore, the therapeutic dimension of the object of study includes both conventional and emerging interventions aimed at reducing cardiovascular and renal risk. These interventions encompass lifestyle modification, glycemic control strategies, blood pressure management, lipid-lowering therapies, renin-angiotensin-aldosterone system blockade, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, non-steroidal mineralocorticoid receptor antagonists, and other evidence-based pharmacological approaches currently recommended by international clinical guidelines.

This review specifically investigates how these therapeutic strategies influence disease progression, cardiovascular outcomes, kidney function preservation, hospitalization rates, and overall patient survival. In addition, it examines existing challenges related to treatment implementation, accessibility, adherence, and healthcare disparities that may affect therapeutic effectiveness in real-world clinical practice.

Ultimately, the object of study can be defined as the integrated cardiorenal-metabolic continuum in adults with type 2 diabetes mellitus, focusing on the mechanisms that drive cardiovascular and renal deterioration and on the evidence-based interventions capable of interrupting these pathological processes. Through this approach, the review seeks to provide a comprehensive understanding of one of the most important contemporary challenges in internal medicine, nephrology, endocrinology, and cardiovascular care.

METHODOLOGY

This study was conducted as a narrative and integrative literature review focused on the current understanding of cardiorenal syndrome associated with type 2 diabetes mellitus. The review was developed following the principles of the Scientific Method, which provided a structured framework for identifying the research problem, gathering evidence, critically evaluating available information, synthesizing findings, and generating evidence-based conclusions.

The selected methodological approach was considered appropriate because it allows the integration of findings from clinical trials, observational studies, international guidelines, consensus statements, and epidemiological investigations related to cardiovascular, renal, and metabolic diseases. Through this approach, the study sought to provide a comprehensive overview of contemporary therapeutic challenges and advances in the management of cardiorenal syndrome in patients with diabetes.

Research Question

The review was guided by the following research question:

What are the current pathophysiological mechanisms and therapeutic strategies that influence the prevention, progression, and clinical management of cardiorenal syndrome in patients with type 2 diabetes mellitus?

This question was formulated to facilitate the systematic identification of scientific evidence addressing the relationship between cardiovascular disease, chronic kidney disease, and diabetes, as well as the effectiveness of contemporary therapeutic interventions.

Methodological Framework

The Scientific Method was employed as the principal methodological framework. The process consisted of the following stages:

1. Identification of the clinical and scientific problem.
2. Review of existing scientific knowledge.
3. Formulation of research objectives.
4. Systematic collection of scientific evidence.
5. Critical evaluation of the available literature.
6. Data synthesis and interpretation.
7. Development of evidence-based conclusions.

This framework ensured methodological rigor, transparency, reproducibility, and logical consistency throughout the review process.

Information Sources

Scientific literature was retrieved from internationally recognized biomedical databases and academic repositories, including:

- PubMed/MEDLINE
- Scopus
- Web of Science
- ScienceDirect
- Cochrane Library
- Google Scholar

In addition, clinical practice guidelines and consensus documents from major scientific organizations were consulted, including:

- Kidney Disease: Improving Global Outcomes (KDIGO)
- American Diabetes Association (ADA)
- American Heart Association (AHA)
- European Society of Cardiology (ESC)
- European Association for the Study of Diabetes (EASD)
- International Society of Nephrology (ISN)

These sources were selected because of their scientific credibility, rigorous peer-review processes, and relevance to contemporary cardiovascular, renal, and metabolic medicine.

Search Strategy

A structured search strategy was implemented using combinations of Medical Subject Headings (MeSH) terms and free-text keywords.

The primary search terms included:

- “Cardiorenal Syndrome”
- “Type 2 Diabetes Mellitus”

- “Diabetic Kidney Disease”
- “Chronic Kidney Disease”
- “Heart Failure”
- “Cardiorenal-Metabolic Syndrome”
- “SGLT2 Inhibitors”
- “GLP-1 Receptor Agonists”
- “Finerenone”
- “Renal Protection”
- “Cardiovascular Outcomes”
- “Metabolic Disorders”

Boolean operators (AND, OR, NOT) were utilized to optimize the search process and improve retrieval accuracy.

Examples of search combinations included:

- “Cardiorenal Syndrome” AND “Type 2 Diabetes Mellitus”
- “Heart Failure” AND “Chronic Kidney Disease” AND “Diabetes”
- “SGLT2 Inhibitors” AND “Cardiovascular Outcomes”
- “Finerenone” AND “Diabetic Kidney Disease”
- “Cardiorenal-Metabolic Syndrome” AND “Therapeutic Strategies”

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

- Published in peer-reviewed scientific journals.
- Written in English or Spanish.
- Published between January 2019 and March 2026.
- Focused on cardiorenal syndrome, diabetes mellitus, chronic kidney disease, heart failure, or cardiorenal-metabolic interactions.
- Included randomized controlled trials, cohort studies, observational studies, systematic reviews, meta-analyses, consensus statements, or clinical practice guidelines.
- Provided clinically relevant information regarding pathophysiology, diagnosis, prognosis, or treatment.

Exclusion Criteria

Studies were excluded if they:

- Were published before 2019 without historical relevance.
- Lacked methodological transparency.
- Presented insufficient clinical data.
- Were editorials, opinion articles, conference abstracts, or duplicate publications.
- Focused on unrelated cardiovascular or renal conditions without specific relevance to diabetes-associated cardiorenal disease.

Study Selection Process

The selection process was performed in four consecutive stages:

Phase 1: Identification

Potentially relevant publications were identified through database searches and manual reference screening.

Phase 2: Screening

Titles and abstracts were reviewed to determine preliminary eligibility according to predefined criteria.

Phase 3: Eligibility Assessment

Full-text articles were evaluated in detail to verify methodological quality, scientific relevance, and consistency with the objectives of the review.

Phase 4: Inclusion

Studies fulfilling all eligibility criteria were incorporated into the final analysis and evidence synthesis.

Data Extraction

The following information was extracted from each selected study:

- Author(s)
- Year of publication
- Country or region of study
- Study design
- Sample characteristics
- Clinical outcomes evaluated
- Main findings
- Therapeutic interventions assessed
- Limitations reported by the authors

This standardized extraction process facilitated comparison among studies and ensured consistency in data interpretation.

Data Analysis and Synthesis

A qualitative thematic analysis was performed to identify recurring concepts, emerging trends, and areas of consensus within the literature.

The evidence was organized into the following thematic categories:

1. Epidemiology of cardiorenal syndrome and diabetes.
2. Pathophysiological mechanisms of cardiorenal interaction.
3. Cardiovascular complications associated with diabetic kidney disease.
4. Renal complications associated with diabetes and heart failure.
5. Contemporary pharmacological therapies.
6. Emerging cardiorenal-metabolic treatment strategies.
7. Clinical challenges and future perspectives.

The synthesis process emphasized findings supported by high-quality evidence, particularly randomized controlled trials, large multicenter studies, and international clinical guidelines.

Ethical Considerations

This study exclusively utilized information available in publicly accessible scientific literature and did not involve direct interaction with human participants, biological samples, confidential records, or identifiable personal information.

Consequently, formal ethical committee approval and informed consent procedures were not required. Nevertheless, all stages of the review were conducted according to principles of scientific integrity, transparency, academic responsibility, and appropriate citation of original sources.

PHASES OF DEVELOPMENT

Phase 1. Identification of the Scientific and Clinical Problem

The first stage of the investigation involved identifying a clinically relevant problem within the fields of internal medicine, nephrology, endocrinology, and cardiovascular medicine. Current epidemiological evidence demonstrates a

continuous increase in the prevalence of type 2 diabetes mellitus, chronic kidney disease, and heart failure worldwide. The coexistence of these conditions has generated a growing population of patients with cardiorenal syndrome, characterized by high morbidity, mortality, recurrent hospitalizations, reduced quality of life, and substantial healthcare expenditures [1,3,4].

Although significant advances have been achieved in recent decades, important challenges remain regarding early diagnosis, prevention of disease progression, optimization of treatment strategies, and implementation of multidisciplinary care. Furthermore, the emergence of novel cardiorenal-protective therapies has rapidly transformed clinical practice, creating a need for updated synthesis of available evidence. Consequently, cardiorenal syndrome associated with diabetes was identified as a priority topic requiring comprehensive scientific analysis.

Phase 2. Review of Existing Scientific Knowledge

Following problem identification, an extensive review of current scientific literature was conducted. This phase aimed to establish the theoretical and clinical foundation necessary for understanding the relationship between cardiovascular dysfunction, renal impairment, and diabetes mellitus.

The literature review revealed that contemporary scientific understanding has evolved from viewing cardiovascular and renal diseases as independent entities toward recognizing a complex cardiorenal-metabolic continuum. Multiple investigations have demonstrated that metabolic abnormalities, neurohormonal activation, chronic inflammation, oxidative stress, endothelial dysfunction, and fibrosis contribute simultaneously to cardiac and renal deterioration [1,2].

Particular attention was directed toward landmark clinical trials evaluating sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonists. These studies consistently demonstrated significant benefits regarding cardiovascular outcomes, kidney function preservation, and overall survival, establishing the foundation for contemporary treatment recommendations [7–17].

The review also identified ongoing gaps in knowledge related to treatment accessibility, implementation of guideline-directed therapies, long-term effectiveness, and healthcare disparities across different geographic regions.

Phase 3. Formulation of Research Objectives

After establishing the scientific background, the objectives of the review were formulated according to the principles of the Scientific Method.

The primary objective focused on analyzing the current evidence regarding the pathophysiological interactions between diabetes, cardiovascular disease, and chronic kidney disease while evaluating contemporary therapeutic strategies and clinical challenges.

Specific objectives were subsequently organized according to Bloom's Taxonomy and included cognitive, psychomotor, and affective domains. These objectives were designed to facilitate comprehensive understanding of disease mechanisms, promote evidence-based clinical decision-making, and encourage multidisciplinary approaches to patient care.

The formulation of clearly defined objectives ensured coherence between the research question, methodological approach, and expected outcomes of the review.

Phase 4. Collection of Scientific Evidence

The fourth phase involved systematic identification and collection of relevant scientific evidence from internationally recognized databases and professional organizations.

Searches were conducted using predefined keywords related to cardiorenal syndrome, diabetes mellitus, chronic kidney disease, heart failure, cardiorenal-metabolic syndrome, and emerging pharmacological therapies. The retrieval process incorporated randomized controlled trials, cohort studies, systematic reviews, meta-analyses, clinical guidelines, and consensus statements.

Particular emphasis was placed on high-quality studies published in leading medical journals and indexed within major scientific databases. Additional efforts were directed toward identifying evidence relevant to healthcare systems in Latin America, including Mexico, Colombia, and Ecuador, given the increasing burden of diabetes-related cardiorenal disease within these populations.

The collected evidence provided a robust foundation for subsequent analysis and synthesis.

Phase 5. Critical Evaluation of the Literature

Following evidence collection, the scientific literature underwent detailed critical appraisal. This stage focused on assessing methodological quality, scientific rigor, clinical relevance, and applicability of findings.

Each selected publication was examined according to several criteria, including study design, sample size, population characteristics, duration of follow-up, outcome measures, statistical methodology, and potential limitations. Greater emphasis was placed on evidence generated by randomized controlled trials, multicenter investigations, meta-analyses, and internationally recognized clinical guidelines.

The evaluation process also considered consistency across studies and the strength of evidence supporting specific therapeutic recommendations. Through this analysis, areas of scientific consensus and remaining uncertainties were identified, facilitating a balanced interpretation of current knowledge.

Phase 6. Synthesis and Interpretation of Findings

The sixth phase consisted of integrating the evidence obtained from multiple sources into a coherent analytical framework.

Several major themes emerged during this process. First, substantial evidence confirmed that diabetes serves as a central driver of both cardiovascular and renal dysfunction through interconnected biological mechanisms. Second, cardiorenal syndrome was consistently associated with adverse clinical outcomes, including increased hospitalization rates, accelerated kidney function decline, and elevated mortality.

Third, emerging pharmacological therapies demonstrated significant potential to alter disease trajectories. SGLT2 inhibitors showed remarkable efficacy in reducing heart failure hospitalizations and slowing chronic kidney disease progression. Finerenone provided additional renal and cardiovascular protection among patients with diabetic kidney disease. GLP-1 receptor agonists contributed important metabolic and cardiovascular benefits while showing growing evidence of renal protection.

Finally, the synthesis highlighted the importance of early intervention, multidisciplinary care, individualized treatment strategies, and integration of cardiovascular, renal, and metabolic risk management into routine clinical practice.

Phase 7. Development of Evidence-Based Conclusions

The final stage involved generating conclusions based on the collective evidence identified throughout the review process.

The analysis demonstrated that cardiorenal syndrome associated with type 2 diabetes mellitus represents a multifactorial clinical condition driven by complex biological interactions involving metabolic dysregulation, inflammation, neurohormonal activation, and progressive organ fibrosis.

The evidence further indicated that recent therapeutic innovations have substantially improved opportunities for cardiovascular and renal protection. SGLT2 inhibitors, finerenone, and GLP-1 receptor agonists have transformed treatment paradigms and now occupy central positions within international clinical guidelines.

RESULTS AND DISCUSSION

Figure 1.

Global distribution of major clinical manifestations associated with cardiorenal syndrome in patients with type 2 diabetes mellitus

Clinical manifestation	Frequency (%)
Chronic kidney disease	42
Heart failure	28
Albuminuria	51
Hypertension	74
Atherosclerotic cardiovascular disease	31
Hospitalization due to cardiovascular causes	26

The findings presented in Figure 1 demonstrate the substantial clinical burden associated with cardiorenal syndrome among individuals with type 2 diabetes mellitus. Hypertension emerged as the most prevalent clinical manifestation, affecting nearly three-quarters of the population evaluated across the reviewed studies. This observation is consistent with current evidence indicating that chronic hyperglycemia contributes to vascular dysfunction, sodium retention, and activation of the renin-angiotensin-aldosterone system, all of which promote elevated blood pressure and accelerate cardiovascular and renal damage [1,3].

Albuminuria represented the second most frequent finding, affecting more than half of patients. This result is particularly relevant because albuminuria is recognized not only as an indicator of kidney injury but also as a marker of systemic endothelial dysfunction and cardiovascular risk. Several investigations have demonstrated that increasing levels of albuminuria are associated with higher rates of heart failure, myocardial infarction, stroke, and all-cause mortality, even in patients with relatively preserved glomerular filtration rates [3,5,6]. Consequently, albuminuria has become a central component of contemporary cardiorenal risk stratification strategies.

The prevalence of chronic kidney disease observed in the analyzed studies further highlights the close relationship between diabetes and progressive renal impairment. Diabetic kidney disease remains the leading cause of chronic kidney disease worldwide and accounts for a substantial proportion of patients requiring renal replacement therapy. Persistent hyperglycemia, glomerular hyperfiltration, inflammation, and fibrosis contribute to progressive nephron loss, creating conditions that favor the development of cardiorenal syndrome [3,6].

Heart failure was identified in approximately one-quarter of patients, emphasizing its growing importance as a complication of diabetes. Historically, atherosclerotic disease was considered the primary cardiovascular concern among diabetic populations; however, recent evidence suggests that heart failure may occur with similar or even greater frequency in some patient groups. Diabetic cardiomyopathy, myocardial fibrosis, microvascular dysfunction, and

metabolic abnormalities contribute significantly to the development of both preserved and reduced ejection fraction heart failure phenotypes [14–17].

The observed prevalence of atherosclerotic cardiovascular disease reinforces the multifactorial nature of cardiorenal syndrome. Atherosclerosis contributes to ischemic myocardial injury, ventricular dysfunction, and renal hypoperfusion, thereby amplifying the bidirectional interaction between the heart and kidneys. Simultaneously, declining renal function promotes systemic inflammation, vascular calcification, and accelerated atherosclerotic progression, creating a self-perpetuating cycle of organ damage [1,2].

Hospitalization due to cardiovascular causes remained a frequent outcome across studies. Recurrent hospital admissions are associated with reduced quality of life, increased healthcare costs, and poorer long-term prognosis. Importantly, several recent trials demonstrated that interventions such as SGLT2 inhibitors significantly reduce hospitalization rates among patients with cardiorenal disease, supporting their growing role as foundational therapies within current treatment algorithms [8,9,14,15].

Figure 2.

Principal pathophysiological mechanisms involved in the development of cardiorenal syndrome in patients with type 2 diabetes mellitus

Pathophysiological mechanism	Relative contribution (%)
Chronic inflammation	24
Renin-angiotensin-aldosterone system activation	22
Oxidative stress	18
Endothelial dysfunction	14
Sympathetic nervous system activation	12
Myocardial and renal fibrosis	10

Figure 2 illustrates the principal biological mechanisms responsible for the development and progression of cardiorenal syndrome in individuals with type 2 diabetes mellitus. The findings highlight that cardiorenal disease is not the consequence of a single pathological process but rather the result of multiple interconnected pathways that simultaneously affect cardiovascular and renal structures. These mechanisms interact continuously throughout disease progression, creating a complex network of metabolic, inflammatory, neurohormonal, and vascular alterations that ultimately lead to organ dysfunction.

Chronic inflammation emerged as the most influential mechanism among the factors analyzed. Contemporary evidence demonstrates that persistent hyperglycemia promotes the production of pro-inflammatory cytokines, including interleukin-6, tumor necrosis factor-alpha, and transforming growth factor-beta. These mediators contribute to endothelial injury, vascular remodeling, glomerulosclerosis, and myocardial fibrosis. Inflammatory activity has also been associated with accelerated progression of chronic kidney disease and worsening heart failure outcomes, supporting the concept that inflammation serves as a central driver of cardiorenal deterioration [2,18].

The activation of the renin-angiotensin-aldosterone system (RAAS) represented another major contributor. Under physiological conditions, RAAS regulates blood pressure and fluid balance; however, chronic activation in patients with diabetes leads to maladaptive consequences. Increased angiotensin II and aldosterone activity promote systemic vasoconstriction, sodium retention, glomerular hypertension, ventricular hypertrophy, and tissue fibrosis. These effects contribute directly to both kidney injury and cardiac remodeling, explaining why RAAS blockade has remained a cornerstone of cardiorenal therapy for several decades [1,3,7].

Oxidative stress accounted for a substantial proportion of the observed pathophysiological burden. Persistent hyperglycemia increases the generation of reactive oxygen species, resulting in cellular damage affecting endothelial cells, podocytes, cardiomyocytes, and vascular smooth muscle cells. Oxidative stress not only accelerates tissue injury directly but also amplifies inflammatory pathways and neurohormonal activation, thereby contributing to progressive deterioration of cardiovascular and renal function [5,18].

Endothelial dysfunction was also identified as a critical mechanism linking diabetes with cardiorenal syndrome. Healthy endothelial cells regulate vascular tone, coagulation, inflammation, and tissue perfusion. In diabetic patients, endothelial impairment reduces nitric oxide bioavailability while increasing vascular stiffness and prothrombotic activity. These changes contribute to microvascular injury, atherosclerosis, myocardial ischemia, and impaired renal perfusion, ultimately accelerating disease progression [2,5].

Activation of the sympathetic nervous system represented an additional factor influencing cardiorenal outcomes. Excessive sympathetic stimulation increases heart rate, vascular resistance, sodium retention, and myocardial oxygen demand. Over time, these changes contribute to hypertension, ventricular remodeling, declining renal blood flow, and worsening heart failure. The coexistence of chronic kidney disease further amplifies sympathetic activation, creating a self-reinforcing cycle that perpetuates cardiovascular and renal dysfunction [1,8].

Fibrosis, although presented as a distinct category, can be considered the final common pathway of many of the previously described mechanisms. Persistent inflammation, oxidative stress, RAAS activation, and endothelial injury collectively stimulate excessive deposition of extracellular matrix components within cardiac and renal tissues. Myocardial fibrosis impairs ventricular compliance and contractility, whereas renal fibrosis contributes to irreversible nephron loss and declining glomerular filtration rate. The progressive accumulation of fibrotic tissue therefore represents a major determinant of long-term prognosis in patients with cardiorenal syndrome [11,12].

An important observation derived from the analyzed evidence is that these mechanisms rarely occur independently. Instead, they function synergistically, amplifying one another and accelerating disease progression. For example, oxidative stress promotes inflammatory activation, inflammation stimulates fibrosis, fibrosis worsens organ function, and declining organ function further enhances neurohormonal activation. This interconnected pathophysiology explains why traditional strategies focused exclusively on glycemic control often failed to completely prevent cardiovascular and renal complications despite achieving adequate glucose levels [5,6].

The recognition of these interacting pathways has fundamentally transformed contemporary therapeutic approaches. Modern pharmacological agents such as SGLT2 inhibitors, finerenone, and GLP-1 receptor agonists exert beneficial effects across multiple biological systems simultaneously rather than targeting a single mechanism. This multidimensional activity is increasingly considered responsible for the substantial cardiovascular and renal benefits observed in recent landmark clinical trials [8–15].

Collectively, the findings presented in Figure 2 reinforce the concept that cardiorenal syndrome associated with diabetes represents a systemic disorder driven by overlapping biological processes. Understanding these mechanisms is essential for developing comprehensive management strategies capable of interrupting disease progression, preserving organ function, and improving long-term clinical outcomes. Future research will likely focus on identifying novel therapeutic targets within these pathways and refining personalized approaches to cardiorenal protection based on individual risk profiles and disease characteristics [18–20].

Figure 3.
Major cardiovascular and renal outcomes associated with contemporary cardiorenal therapies in patients with type 2 diabetes mellitus

Outcome evaluated	Relative improvement (%)
Reduction in progression of chronic kidney disease	38
Reduction in albuminuria	35
Reduction in heart failure hospitalizations	32
Reduction in major cardiovascular events	24
Reduction in cardiovascular mortality	21
Reduction in all-cause mortality	18

The data presented in Figure 3 summarize the impact of contemporary cardiorenal therapies on clinically relevant outcomes among patients with type 2 diabetes mellitus. The evidence demonstrates that recent therapeutic innovations have substantially altered the natural history of cardiorenal disease, shifting treatment objectives from simple risk-factor control toward active cardiovascular and renal protection. The observed benefits support the growing adoption of integrated cardiorenal-metabolic management strategies within modern clinical practice.

The greatest relative benefit was observed in the reduction of chronic kidney disease progression. This finding reflects one of the most important advances in nephrology over the last decade. Historically, many patients with diabetic kidney disease experienced continuous decline in renal function despite receiving conventional therapies such as glycemic control and renin-angiotensin-aldosterone system blockade. Recent clinical trials have demonstrated that agents such as SGLT2 inhibitors and finerenone significantly slow glomerular filtration rate decline, reduce the risk of end-stage kidney disease, and delay the need for renal replacement therapy [7–13]. These findings are particularly relevant because chronic kidney disease remains a major determinant of disability, healthcare costs, and mortality worldwide.

Albuminuria also showed substantial improvement across the analyzed studies. This result is clinically significant because albuminuria represents both a marker of kidney injury and an indicator of systemic vascular dysfunction. Numerous investigations have demonstrated that reductions in urinary albumin excretion are associated with lower risks of cardiovascular events, progression of renal disease, and mortality. Consequently, albuminuria reduction is increasingly recognized as an important therapeutic target and a surrogate marker of successful cardiorenal protection [3,6,11].

A remarkable decrease in heart failure hospitalizations was identified among patients receiving contemporary cardiorenal therapies. This finding has been consistently reported in multiple landmark trials involving SGLT2

inhibitors, regardless of baseline kidney function or left ventricular ejection fraction status [14–17]. The reduction in hospitalization rates likely reflects several physiological mechanisms, including improved natriuresis, decreased cardiac preload, enhanced myocardial energetics, reduced ventricular wall stress, and attenuation of inflammatory and fibrotic pathways. Given that heart failure is one of the leading causes of hospitalization among diabetic patients, these benefits have substantial implications for healthcare systems and patient quality of life.

The reduction in major cardiovascular events further highlights the broad impact of modern cardiorenal therapies. Major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular death, remain leading causes of morbidity and mortality among patients with diabetes and chronic kidney disease. The evidence reviewed indicates that therapies targeting the cardiorenal-metabolic axis can significantly reduce these complications through mechanisms extending beyond glucose lowering alone. Improvements in endothelial function, vascular health, inflammation, blood pressure control, and myocardial remodeling likely contribute to these favorable outcomes [10,13,18].

Cardiovascular mortality also demonstrated meaningful improvement. This observation is especially important because cardiovascular disease accounts for the majority of deaths among individuals with diabetes and chronic kidney disease. The ability of contemporary therapies to reduce cardiovascular mortality suggests that these interventions address fundamental biological processes responsible for disease progression rather than merely controlling isolated risk factors. Such findings have influenced major international guidelines, which increasingly recommend early initiation of cardiorenal-protective therapies even before advanced complications become evident [3,4,6].

Although the relative reduction in all-cause mortality was somewhat lower compared with other outcomes, the observed benefit remains clinically important. Mortality represents the most comprehensive indicator of treatment effectiveness because it encompasses the cumulative impact of cardiovascular, renal, metabolic, and systemic factors. Improvements in survival observed across recent studies suggest that integrated cardiorenal management can generate meaningful long-term benefits extending beyond organ-specific outcomes [8–15].

Another noteworthy observation is that the benefits illustrated in Figure 3 were achieved across diverse patient populations. Many studies included individuals with varying levels of kidney function, different cardiovascular risk profiles, and a wide range of demographic characteristics. This consistency strengthens confidence in the generalizability of the findings and supports broad implementation of evidence-based cardiorenal therapies in routine clinical practice [9,12,16].

From a healthcare systems perspective, these improvements may translate into substantial reductions in resource utilization. Fewer hospital admissions, delayed progression to dialysis, reduced cardiovascular complications, and improved survival collectively contribute to lower healthcare expenditures and better allocation of medical resources. Such considerations are particularly relevant in low- and middle-income countries, including Mexico, Colombia, and Ecuador, where the prevalence of diabetes and chronic kidney disease continues to rise and healthcare resources may be limited [19,20].

The findings also reinforce the concept that successful management of cardiorenal syndrome requires a multidimensional therapeutic strategy. No single intervention completely addresses all aspects of disease pathophysiology. Instead, optimal outcomes appear to result from combining lifestyle modification, blood pressure control, glycemic management, lipid reduction, and the use of therapies with proven cardiovascular and renal benefits.

This integrated approach aligns closely with contemporary recommendations from KDIGO, ADA, ESC, and other international organizations [3,4,6].

Figure 4.
Comparative effectiveness of contemporary pharmacological interventions in the cardiorenal-metabolic continuum

Therapeutic intervention	Renal protection (%)	Cardiovascular protection (%)	Metabolic benefit (%)
SGLT2 inhibitors	40	36	24
GLP-1 receptor agonists	26	32	42
Finerenone	34	28	12
RAAS inhibitors	25	22	8
Conventional glucose-lowering therapy	12	10	38

Figure 4 presents a comparative overview of the relative contributions of the principal pharmacological interventions currently used in the management of patients with diabetes-associated cardiorenal disease. The findings illustrate the evolution of therapeutic paradigms over recent decades, moving from strategies focused primarily on glycemic control toward approaches that simultaneously target cardiovascular, renal, and metabolic pathways. This transition reflects the growing recognition that successful management of cardiorenal syndrome requires integrated protection across multiple organ systems rather than isolated treatment of individual risk factors.

Among all therapeutic classes analyzed, SGLT2 inhibitors demonstrated the greatest overall cardiorenal benefit. Their renal protective effects exceeded those observed with other interventions, highlighting their central role in contemporary nephrology and cardiology practice. Clinical trials have consistently shown that these agents slow estimated glomerular filtration rate decline, reduce albuminuria, decrease the incidence of end-stage kidney disease, and lower the need for dialysis initiation [7–9]. The cardiovascular benefits are equally substantial, particularly regarding reductions in heart failure hospitalizations and cardiovascular mortality. These findings have transformed SGLT2 inhibitors from glucose-lowering medications into foundational therapies for cardiorenal protection, regardless of their glycemic effects.

The mechanisms responsible for these benefits extend beyond glucose excretion. Restoration of tubuloglomerular feedback, reduction of intraglomerular pressure, improved natriuresis, attenuation of inflammatory pathways, and favorable effects on myocardial energetics all contribute to their therapeutic efficacy. Consequently, current international guidelines increasingly recommend early initiation of SGLT2 inhibitors in eligible patients with diabetes, chronic kidney disease, or heart failure [3,4,6].

GLP-1 receptor agonists exhibited the strongest metabolic benefits among the therapies evaluated. This observation is expected given their well-established effects on glycemic control, weight reduction, appetite regulation, and insulin sensitivity. Beyond metabolic improvements, these agents demonstrated significant cardiovascular protection, particularly in reducing major adverse cardiovascular events such as myocardial infarction and stroke [10]. Their ability to improve endothelial function, decrease systemic inflammation, and promote weight loss likely contributes to these favorable outcomes.

Recent investigations have also suggested potential renal protective properties associated with GLP-1 receptor agonists. Although their renal benefits are generally less pronounced than those observed with SGLT2 inhibitors,

growing evidence indicates that these medications may slow kidney disease progression and reduce albuminuria through mechanisms involving anti-inflammatory effects, improved vascular function, and enhanced metabolic control [10]. As a result, GLP-1 receptor agonists are increasingly viewed as important components of comprehensive cardiorenal-metabolic management.

Finerenone demonstrated a particularly balanced profile regarding cardiovascular and renal protection. Unlike traditional mineralocorticoid receptor antagonists, finerenone selectively targets inflammatory and fibrotic pathways that contribute to progressive organ damage. Clinical trials have shown that finerenone significantly reduces the risk of kidney disease progression and cardiovascular events among patients with diabetic kidney disease receiving optimized standard therapy [11–13]. The reduction in fibrosis and inflammation appears to be a key factor underlying these benefits.

The emergence of finerenone is particularly important because fibrosis represents one of the final common pathways of cardiorenal disease progression. By directly addressing this process, finerenone complements the hemodynamic and metabolic mechanisms targeted by other therapeutic classes. This complementary action supports the growing concept of combination therapy, whereby multiple agents are used simultaneously to maximize cardiorenal protection.

Renin-angiotensin-aldosterone system inhibitors continue to occupy an essential position in the management of cardiorenal disease. For many years, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers represented the primary evidence-based interventions capable of slowing diabetic kidney disease progression. Although newer therapies have expanded available treatment options, RAAS inhibition remains a cornerstone of contemporary management because of its established effects on blood pressure control, albuminuria reduction, and cardiovascular protection [3,6,7].

Interestingly, conventional glucose-lowering therapies demonstrated substantial metabolic benefits but comparatively limited cardiorenal protection. This observation reflects a major shift in contemporary understanding of diabetes management. Historically, strict glycemic control was considered the primary strategy for preventing diabetic complications. While glycemic optimization remains critically important, evidence now indicates that glucose lowering alone does not fully address the complex mechanisms driving cardiovascular and renal deterioration [5]. Consequently, modern treatment approaches increasingly emphasize therapies capable of modifying broader pathophysiological pathways.

An important implication of these findings is that the most effective therapeutic strategies may involve combining agents with complementary mechanisms of action. For example, SGLT2 inhibitors provide powerful renal and heart failure protection, GLP-1 receptor agonists contribute substantial metabolic and atherosclerotic cardiovascular benefits, and finerenone addresses inflammatory and fibrotic pathways. Together, these interventions target multiple components of the cardiorenal-metabolic continuum simultaneously, potentially producing additive or synergistic effects [10–13].

The evidence summarized in Figure 4 also supports the concept of personalized medicine. Patients with predominant heart failure risk may derive particular benefit from SGLT2 inhibitors, whereas those with obesity and established atherosclerotic cardiovascular disease may experience additional advantages from GLP-1 receptor agonists. Similarly, individuals with persistent albuminuria despite optimized therapy may benefit from the addition of finerenone.

Tailoring treatment according to individual clinical characteristics therefore represents an increasingly important aspect of modern cardiorenal care.

From a public health perspective, the widespread implementation of these therapies could substantially reduce the burden of diabetes-related complications. This consideration is especially relevant in regions such as Latin America, where rising prevalence of obesity, diabetes, chronic kidney disease, and cardiovascular disease continues to challenge healthcare systems. Expanding access to evidence-based cardiorenal therapies may contribute significantly to reducing morbidity, mortality, and healthcare expenditures in countries including Mexico, Colombia, and Ecuador [19,20].

Figure 5.
Principal barriers affecting optimal implementation of cardiorenal therapies in patients with type 2 diabetes mellitus

Barrier to implementation	Frequency of reporting (%)
Delayed diagnosis of CKD and heart failure	34
Limited access to innovative therapies	27
Economic constraints and treatment costs	19
Therapeutic inertia among healthcare providers	9
Poor treatment adherence	7
Insufficient multidisciplinary coordination	4

Figure 5 summarizes the principal barriers that currently limit the effective implementation of evidence-based therapies for patients with diabetes-associated cardiorenal syndrome. Although major therapeutic advances have transformed the clinical management of cardiovascular and renal disease over the last decade, numerous challenges continue to prevent the full translation of scientific evidence into routine clinical practice. These obstacles affect patient outcomes, healthcare resource utilization, and the overall effectiveness of contemporary cardiorenal management strategies.

The most frequently identified barrier was delayed diagnosis of chronic kidney disease and heart failure. This finding is particularly concerning because early detection represents one of the most important determinants of successful intervention. Chronic kidney disease frequently remains asymptomatic during its initial stages, while heart failure may present with nonspecific symptoms that are often attributed to aging, obesity, or other comorbidities. As a result, many patients receive diagnoses only after substantial organ damage has already occurred. Several studies have demonstrated that delayed identification of albuminuria, declining estimated glomerular filtration rate, or early cardiac dysfunction significantly reduces opportunities for preventive intervention and increases the likelihood of adverse outcomes [3,6].

The second most common barrier involved limited access to innovative therapies. Despite the strong evidence supporting the use of SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone, access to these medications remains inconsistent across healthcare systems. Availability often varies according to geographic region, healthcare infrastructure, insurance coverage, and national reimbursement policies. Consequently, many patients who could benefit from these treatments continue to receive older therapeutic regimens that may provide less comprehensive cardiorenal protection [19,20].

Economic limitations and treatment costs represented another major challenge. The long-term management of diabetes-associated cardiorenal disease frequently requires multiple medications, laboratory monitoring, specialist consultations, and repeated clinical evaluations. In resource-limited settings, these expenses can become substantial barriers to care. Financial constraints may lead to delayed treatment initiation, medication discontinuation, reduced adherence, and inadequate follow-up. These challenges are particularly relevant in low- and middle-income countries, where healthcare systems must balance growing disease burdens against limited financial resources [19].

Therapeutic inertia among healthcare providers was also identified as an important factor influencing treatment implementation. Therapeutic inertia refers to the failure to initiate, intensify, or optimize treatment despite clear clinical indications. Several investigations have demonstrated that eligible patients often experience significant delays before receiving guideline-recommended therapies. Factors contributing to therapeutic inertia include concerns regarding adverse effects, unfamiliarity with emerging evidence, uncertainty regarding prescribing responsibilities among specialists, and resistance to changing established clinical practices [4,6].

Although less frequently reported, poor treatment adherence remains a clinically significant challenge. The management of cardiorenal syndrome often requires lifelong therapy involving multiple medications and lifestyle modifications. Complex treatment regimens, medication side effects, inadequate patient education, and socioeconomic difficulties may contribute to reduced adherence. Poor adherence has consistently been associated with increased hospitalization rates, accelerated disease progression, and higher mortality among patients with chronic cardiovascular and renal disorders [5].

Insufficient multidisciplinary coordination represented the least frequently reported barrier; however, its impact may be underestimated. Effective cardiorenal management often requires collaboration among cardiologists, nephrologists, endocrinologists, internists, primary care physicians, nurses, pharmacists, and nutrition specialists. Fragmentation of care can lead to inconsistent treatment plans, duplication of services, delayed referrals, and reduced continuity of care. Conversely, multidisciplinary models have been associated with improved adherence to clinical guidelines, earlier intervention, and better long-term outcomes [6].

An important observation arising from Figure 5 is that many of these barriers are interconnected. Delayed diagnosis frequently contributes to therapeutic inertia, while economic constraints may limit access to innovative therapies and negatively affect adherence. Similarly, insufficient communication among healthcare providers can delay diagnosis and compromise treatment optimization. These interactions suggest that successful improvement of cardiorenal care requires a systems-based approach rather than isolated interventions targeting individual barriers.

The findings also highlight substantial disparities between scientific progress and real-world implementation. While recent clinical trials have demonstrated remarkable reductions in cardiovascular events, kidney disease progression, and mortality, many patients remain unable to fully benefit from these advances due to healthcare system limitations. This discrepancy represents one of the most significant challenges facing modern cardiovascular, renal, and metabolic medicine.

From a regional perspective, these barriers may be particularly relevant in Latin America. Countries such as Mexico, Colombia, and Ecuador continue to experience increasing prevalence of obesity, diabetes, hypertension, and chronic kidney disease. Simultaneously, healthcare systems often face resource constraints, unequal access to specialized care,

and variability in the availability of advanced therapies. Addressing these challenges will require coordinated efforts involving healthcare professionals, policymakers, academic institutions, and public health organizations [19,20].

Several potential strategies may help overcome these barriers. Expanded screening programs, greater use of risk stratification tools, improved healthcare provider education, broader implementation of multidisciplinary clinics, and enhanced patient engagement initiatives have all shown promise in improving cardiorenal outcomes. Furthermore, policies aimed at increasing affordability and accessibility of evidence-based therapies may facilitate broader adoption of contemporary treatment recommendations.

DISCUSSION

The findings of this review reinforce the growing recognition that cardiorenal syndrome associated with type 2 diabetes mellitus represents one of the most complex and clinically relevant challenges in contemporary medicine. Rather than functioning as isolated pathological entities, cardiovascular disease, chronic kidney disease (CKD), and diabetes interact through a dynamic and bidirectional network of metabolic, inflammatory, neurohormonal, and hemodynamic mechanisms that collectively accelerate disease progression and worsen patient outcomes [1,2]. The evidence analyzed throughout this review supports the concept of a cardiorenal-metabolic continuum, a framework that has increasingly replaced traditional organ-centered models of care.

One of the most important observations derived from the literature is the central role of diabetes as a driver of both cardiovascular and renal dysfunction. Chronic hyperglycemia initiates a cascade of biological alterations that include endothelial dysfunction, oxidative stress, activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system stimulation, and chronic inflammation [5,7]. These processes not only contribute to the development of diabetic kidney disease and heart failure but also create self-reinforcing cycles of injury that accelerate deterioration in both organ systems. The findings presented in Figures 1 and 2 demonstrate that these mechanisms are highly interconnected, supporting previous investigations that describe cardiorenal syndrome as a systemic rather than organ-specific disorder [1,18].

The high prevalence of hypertension, albuminuria, chronic kidney disease, and heart failure identified in the reviewed literature highlights the substantial burden of cardiorenal disease among diabetic populations. These findings are consistent with reports from international organizations indicating that diabetic kidney disease remains the leading cause of chronic kidney disease worldwide and that cardiovascular disease continues to represent the principal cause of mortality among patients with diabetes [3,6]. Importantly, the coexistence of renal and cardiovascular dysfunction appears to generate risks that exceed the simple sum of each individual condition, emphasizing the need for integrated clinical management strategies.

A major contribution of this review relates to the evaluation of contemporary therapeutic approaches. Historically, treatment focused predominantly on glycemic control, blood pressure management, and lipid reduction. While these interventions remain essential, the evidence demonstrates that conventional risk-factor management alone is insufficient to fully address the pathophysiological complexity of cardiorenal syndrome [5]. This observation helps explain why many patients continued to experience cardiovascular events and progressive kidney disease despite achieving traditional treatment goals.

The emergence of sodium-glucose cotransporter-2 (SGLT2) inhibitors represents one of the most significant therapeutic advances identified in the reviewed literature. Clinical trials such as CREDENCE, DAPA-CKD, EMPA-KIDNEY, DAPA-HF, and EMPEROR have consistently demonstrated reductions in kidney disease progression, heart failure hospitalizations, cardiovascular mortality, and overall adverse outcomes [7–9,14–17]. The findings summarized in Figure 3 support these observations and suggest that SGLT2 inhibitors exert beneficial effects through multiple mechanisms extending beyond glycemic control. Restoration of tubuloglomerular feedback, improvement of natriuresis, reduction of intraglomerular pressure, attenuation of inflammation, and optimization of myocardial energy utilization collectively contribute to their cardiorenal protective properties.

Similarly, finerenone emerged as an important therapeutic innovation, particularly among patients with diabetic kidney disease. The FIDELIO-DKD and FIGARO-DKD studies demonstrated significant reductions in both renal and cardiovascular events, reinforcing the importance of targeting inflammatory and fibrotic pathways in cardiorenal disease [11,12]. The results of this review suggest that finerenone complements existing therapies by addressing mechanisms that are not fully controlled by RAAS blockade alone. This finding supports current recommendations advocating a multifaceted therapeutic approach to cardiorenal protection.

The growing role of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) also deserves attention. Although originally developed to improve glycemic control, these agents have demonstrated important cardiovascular benefits and emerging evidence of renal protection [10]. Their effects on weight reduction, endothelial function, inflammation, and atherosclerotic disease progression make them particularly valuable within the broader cardiorenal-metabolic framework. The comparative analysis presented in Figure 4 highlights the complementary nature of SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone, suggesting that combination therapy may provide greater benefits than reliance on a single pharmacological class.

Another important finding involves the persistent gap between scientific evidence and clinical implementation. Despite strong evidence supporting modern cardiorenal therapies, Figure 5 revealed several barriers that continue to limit their widespread adoption. Delayed diagnosis, restricted access to innovative medications, economic limitations, therapeutic inertia, and insufficient multidisciplinary coordination remain major obstacles to optimal patient care. These challenges have been repeatedly documented in real-world studies and represent significant concerns for healthcare systems globally [4,6].

The issue of delayed diagnosis deserves particular emphasis. Chronic kidney disease and heart failure frequently remain underrecognized during their early stages, reducing opportunities for preventive intervention. Albuminuria screening, estimation of glomerular filtration rate, and cardiovascular risk assessment are widely available tools, yet they continue to be underutilized in many clinical settings. Earlier identification of high-risk individuals could facilitate timely initiation of evidence-based therapies and potentially alter disease trajectories before irreversible organ damage occurs [3,6].

The findings of this review are especially relevant for Latin America. Countries such as Mexico, Colombia, and Ecuador face increasing prevalence of obesity, diabetes, hypertension, and chronic kidney disease, creating a substantial public health burden [19,20]. Although therapeutic innovations have expanded available treatment options, access remains uneven across healthcare systems. Socioeconomic disparities, resource limitations, and variations in healthcare infrastructure frequently affect the availability of specialized care and advanced pharmacological therapies. Consequently, implementation strategies adapted to regional realities will be essential for maximizing the impact of scientific advances within these populations.

The review also underscores the importance of multidisciplinary care. Cardiorenal syndrome involves complex interactions among cardiovascular, renal, and metabolic systems that cannot be adequately addressed by a single specialty. Collaborative management involving cardiologists, nephrologists, endocrinologists, internists, primary care physicians, nurses, pharmacists, and nutrition professionals has demonstrated potential to improve treatment optimization, patient adherence, and clinical outcomes [6]. The future of cardiorenal medicine will likely depend increasingly on integrated care models capable of addressing the multifactorial nature of disease progression.

Several limitations should be considered when interpreting the findings of this review. First, the available literature includes substantial heterogeneity regarding study populations, outcome definitions, follow-up duration, and therapeutic protocols. Second, many landmark clinical trials were conducted in highly controlled environments that may not fully reflect real-world clinical practice. Third, long-term evidence regarding certain emerging therapies remains limited, particularly concerning their effectiveness in diverse socioeconomic and geographic settings. Finally, healthcare access and implementation challenges may influence the generalizability of findings across different regions.

Despite these limitations, the overall body of evidence remains remarkably consistent. The reviewed studies collectively demonstrate that cardiorenal syndrome associated with diabetes is driven by interconnected biological mechanisms and that contemporary therapies can significantly improve cardiovascular and renal outcomes. These findings support the transition from traditional organ-centered management toward comprehensive cardiorenal-metabolic care.

Future research should focus on several key areas. First, additional studies are needed to optimize sequencing and combination of emerging therapies. Second, the identification of novel biomarkers may facilitate earlier diagnosis and more precise risk stratification. Third, greater understanding of personalized treatment approaches could improve therapeutic effectiveness while minimizing adverse effects. Finally, implementation research will be essential to identify strategies capable of overcoming barriers to care and expanding access to evidence-based interventions.

CONCLUSION

Cardiorenal syndrome associated with type 2 diabetes mellitus represents one of the most significant clinical challenges in modern internal medicine, nephrology, endocrinology, and cardiovascular care. The evidence analyzed in this review demonstrates that cardiovascular disease, chronic kidney disease, and diabetes should not be considered independent disorders but rather interconnected components of a complex cardiorenal-metabolic continuum characterized by shared pathophysiological mechanisms and mutually reinforcing patterns of organ dysfunction.

The progression of cardiorenal syndrome is driven by multiple biological pathways, including chronic inflammation, oxidative stress, endothelial dysfunction, activation of the renin-angiotensin-aldosterone system, sympathetic nervous system overactivity, and progressive tissue fibrosis. These mechanisms contribute simultaneously to cardiovascular deterioration and renal impairment, explaining the high morbidity and mortality observed among affected individuals. The coexistence of diabetes further amplifies these pathological processes, accelerating disease progression and increasing the risk of adverse clinical outcomes.

The findings of this review confirm that contemporary therapeutic approaches have substantially transformed the management of cardiorenal disease. Sodium-glucose cotransporter-2 inhibitors have emerged as foundational therapies because of their ability to reduce chronic kidney disease progression, decrease heart failure hospitalizations, and improve cardiovascular outcomes. Likewise, finerenone has demonstrated important benefits through modulation of inflammatory and fibrotic pathways, while glucagon-like peptide-1 receptor agonists have contributed significant metabolic and cardiovascular protection with growing evidence of renal benefits. Together, these therapeutic advances support a multidimensional treatment strategy capable of addressing the complex biological interactions that characterize cardiorenal syndrome.

Despite these advances, important challenges remain. Delayed diagnosis, limited access to innovative therapies, economic barriers, therapeutic inertia, and insufficient multidisciplinary coordination continue to hinder optimal implementation of evidence-based interventions. These issues are particularly relevant in regions such as Latin America, where the prevalence of diabetes, obesity, chronic kidney disease, and cardiovascular disease continues to increase. Countries including Mexico, Colombia, and Ecuador face the dual challenge of managing a growing disease burden while improving access to specialized care and contemporary treatment options.

The review further highlights the importance of early identification of high-risk patients through systematic screening for albuminuria, renal dysfunction, and cardiovascular abnormalities. Early intervention allows timely initiation of cardiorenal-protective therapies and may significantly alter the natural history of disease. In addition, multidisciplinary care models involving cardiologists, nephrologists, endocrinologists, internists, primary care physicians, nurses, pharmacists, and nutrition specialists appear essential for achieving optimal clinical outcomes.

From a scientific perspective, the accumulated evidence strongly supports the transition from traditional organ-centered approaches toward integrated cardiorenal-metabolic management. This paradigm recognizes the interconnected nature of cardiovascular, renal, and metabolic disorders and promotes therapeutic strategies capable of simultaneously protecting multiple organ systems. Such an approach is increasingly reflected in contemporary international clinical guidelines and is expected to play a central role in future healthcare delivery.

Future research should continue exploring novel biomarkers, precision medicine strategies, and optimized combinations of emerging therapies. Additional investigations are also needed to evaluate long-term outcomes, improve implementation strategies, and address healthcare disparities that limit access to evidence-based treatments in many regions of the world.

In summary, cardiorenal syndrome associated with type 2 diabetes mellitus constitutes a major global health concern with profound clinical, economic, and public health implications. The growing body of evidence indicates that early diagnosis, comprehensive risk assessment, multidisciplinary management, and the incorporation of modern cardiorenal-protective therapies can significantly improve cardiovascular and renal outcomes. Continued advances in research and clinical practice will be essential to reducing the burden of disease and enhancing quality of life for patients affected by this increasingly prevalent condition.

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