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Short Communication

Cardio-Reno-Metabolic Syndrome: A Decade of Evidence (2014–2024)

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More Information

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Introduction

Over the past decade, the concept of cardio-reno-metabolic (CKM) syndrome has shifted from a descriptive coexistence of diabetes, chronic kidney disease (CKD), and cardiovascular disease (CVD) to a unified multisystem disorder driven by shared biological mechanisms. Increasing evidence demonstrates that these conditions arise from common pathways—including chronic inflammation, endothelial dysfunction, oxidative stress, and neurohormonal activation—and that they mutually reinforce one another, producing a clinical phenotype with markedly elevated risks of organ failure and death [1-3].

Epidemiological data reveal a striking clustering of metabolic, renal, and cardiovascular abnormalities, with 10% - 20% of high-risk patients exhibiting involvement of all three systems and annual mortality rates reaching 4% - 8% [4-6]. Although therapeutic advances such as SGLT2 inhibitors, GLP-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonists have reshaped risk across organ systems, substantial residual mortality persists [7-10]. This review synthesizes epidemiology, pathophysiology, clinical outcomes, and therapeutic innovations from 2014 to 2024, emphasizing the need for integrated care models to address this complex multisystem disorder.

The understanding of CKM syndrome has undergone a profound transformation over the past decade. What was once regarded as the simple coexistence of metabolic, renal, and cardiovascular disorders is now recognized as a deeply interconnected pathological network. This conceptual shift reflects robust evidence showing that diabetes, CKD, and CVD share common biological roots and progress through overlapping mechanisms that accelerate organ dysfunction [11-13].

Major scientific societies—including KDIGO, ADA, ESC, and ERA—have increasingly emphasized the need to conceptualize CKM syndrome as a unified disease spectrum rather than as isolated comorbidities [14-16]. This integrated perspective is essential for improving risk stratification, guiding therapeutic decisions, and designing care pathways that reflect the multisystem nature of the disease.

Epidemiology

The epidemiological landscape of CKM syndrome reveals a rapidly expanding global burden. Between 20% and 40% of individuals with type 2 diabetes exhibit evidence of CKD, while 20–30% have established CVD [17-19]. Conversely, among patients with CKD, the prevalence of diabetes or atherosclerotic CVD frequently exceeds 30% - 50% [20].

Global estimates underscore the magnitude of the problem: approximately 537 million adults are living with diabetes [21], more than 850 million with CKD [22], and over 500 million with CVD [23]. Importantly, CKM multimorbidity is rising faster than any single condition. High-risk clusters—particularly the triad of diabetes, CKD, and CVD—occur in 10% - 20% of patients and are associated with the poorest prognosis [24].

Pathophysiology

CKM syndrome is driven by a self-reinforcing network of metabolic, renal, and cardiovascular dysfunction. Chronic inflammation, endothelial injury, oxidative stress, and neurohormonal activation form the biological core of the syndrome [1,7,8].

Metabolic dysfunction contributes through persistent hyperglycemia, formation of advanced glycation end-products, mitochondrial impairment, insulin resistance, dyslipidemia, and adipose-derived inflammation mediated by IL-6, TNF-α, and CRP [7].

Renal impairment introduces additional systemic toxicity: uremic solutes such as indoxyl sulfate and p-cresyl sulfate promote endothelial dysfunction, while RAAS activation drives fibrosis and hypertension [7].

Cardiovascular involvement is characterized by microvascular dysfunction, myocardial fibrosis, and impaired energetic metabolism, all of which predispose to heart failure [9]. The interaction among these systems creates a vicious cycle: CKD exacerbates heart failure through congestion and neurohormonal activation; CVD accelerates renal decline through hypoperfusion; metabolic dysfunction amplifies both processes [9].

Cardiovascular outcomes

Cardiovascular complications represent a central clinical expression of CKM syndrome. Major adverse cardiovascular event (MACE) rates commonly reach 3–5 events per 100 patient-years in CKM populations [10]. Heart failure is the dominant phenotype, with hospitalization rates of 2–4 per 100 patient-years and 1-year mortality approaching 10% - 15% [10].

CKD is one of the strongest predictors of heart failure hospitalization after age, reflecting the profound hemodynamic and neurohormonal interplay between the heart and kidneys [9]. Recent trials—including DELIVER, EMPEROR-Preserved, and SELECT—have demonstrated that metabolic and renal dysfunction substantially amplify the risk of heart failure across the spectrum of ejection fraction [11-13].

Renal outcomes

Renal decline is accelerated in patients with CKM syndrome. Annual eGFR losses frequently exceed 3–4 mL/min/1.73 m^2, and the risk of progression to kidney failure is 2–3 times higher than in patients with isolated CKD [14,15].

Albuminuria remains the most powerful predictor of both renal and cardiovascular outcomes, reflecting systemic endothelial dysfunction [7]. Recent evidence from EMPA-KIDNEY and FLOW has shown that targeted therapies can significantly slow renal decline, reinforcing the importance of early detection and intervention [14,15].

Therapeutics

Therapeutic advances over the past decade have reshaped the management of CKM syndrome. SGLT2 inhibitors have demonstrated multisystem benefits, including a 25% - 35% reduction in heart failure hospitalizations, a 30% - 40% reduction in CKD progression, and a 10% - 15% reduction in cardiovascular mortality [10,11,14].

GLP-1 receptor agonists reduce atherosclerotic events by 10% - 20%, induce substantial weight loss, and have shown renal protective effects in the FLOW trial [13,15]. Finerenone, a non-steroidal mineralocorticoid receptor antagonist, slows CKD progression and reduces cardiovascular events, with evidence of synergistic benefit when combined with SGLT2 inhibitors [16,17].

Emerging therapies—including dual incretin agonists such as tirzepatide and selective anti-inflammatory agents like ziltivekimab—may further expand the therapeutic landscape in the coming years [23,24].

Discussion

CKM syndrome represents a paradigm shift in the understanding of multimorbidity. Traditional siloed approaches to diabetes, CKD, and CVD fail to capture the biological interconnectedness that drives disease progression. Early identification of renal and cardiovascular involvement in metabolic disease is essential, as is the timely initiation of therapies that confer multisystem protection. Integrated care models that bridge diabetology, nephrology, and cardiology are crucial for translating scientific advances into improved outcomes. Despite major therapeutic progress, residual risk remains high, highlighting the need for combination therapy, earlier intervention, and continued research into shared pathobiological pathways.

Conclusion

The past decade has fundamentally reshaped our understanding of cardio-reno-metabolic disease. CKM syndrome is now recognized as a coherent clinical entity characterized by shared mechanisms, overlapping phenotypes, and synergistic risks. Although therapeutic innovations have significantly improved outcomes, mortality remains unacceptably high. Addressing CKM syndrome requires integrated thinking, coordinated care, and sustained research efforts to further unravel its complex multisystem biology.

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