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REVIEW

Unraveling the Cardiorenal Nexus
— Emerging Frameworks and the Role of Exercise Therapy —

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Background: Chronic kidney disease and cardiovascular disease (CKD-CVD) frequently coexist, creating challenges to prognosis, exercise capacity, and quality of life (QOL). CKD is common across cardiovascular conditions, underscoring the need for comprehensive management. Newer concepts of cardiovascular-kidney-metabolic syndrome (CKM) and chronic cardiovascular-kidney disorder (CCKD) emphasize shared risk factors and interconnected pathophysiological mechanisms. Within this paradigm, exercise therapy has emerged as a promising intervention to improve exercise capacity.

Methods and Results: This narrative review synthesizes conceptual advancements in the CKM-CCKD frameworks and summarizes recent literature on exercise therapy within these frameworks. The CKM-CCKD frameworks highlight the importance of addressing common risk factors and mechanisms underlying CKD-CVD. Exercise therapy comprising individualized aerobic programs is being increasingly recognized for its potential. However, its effectiveness can be limited by factors such as anemia, which correlates with impaired peak oxygen uptake and anaerobic thresholds in patients with renal dysfunction. Tailored regimens addressing reduced capacity, multimorbidity, and psychosocial factors, including patient-reported outcomes, further support inclusivity and effectiveness in clinical practice.

Conclusions: Within the CKM-CCKD frameworks, exercise therapy represents an important strategy to target shared risk factors and mechanisms in CKD-CVD. Future work should emphasize evidence-based interventions, early implementation, and individualized approaches to strengthen the translational value of these frameworks and improve QOL in this high-risk population.

Key Words: Anemia management; Cardiorenal syndrome; Cardiovascular disease; Cardiovascular-kidney-metabolic syndrome; Chronic cardiovascular-kidney disorder; Chronic kidney disease; Exercise capacity; Quality of life

Heart failure (HF) patients often exhibit a significant prevalence of chronic kidney disease (CKD), reflecting the complex interactions between the cardiovascular and renal systems. CKD has been identified in 36.8% of patients with HF and reduced ejection fraction (HFrEF) and in 48.3% of those with preserved ejection fraction (HFpEF).[1] Among individuals with chronic coronary syndrome, CKD prevalence has been identified as 22.7%,[2] but was notably increased to 48.9% in hypertensive patients with coronary artery disease (CAD).[3] Optimal management strategies tailored to such populations, as outlined in the HIJ-CREATE substudy, aim to address the clinical overlap between CAD and CKD.[3]

In Asian HF registries, CKD is associated with poorer outcomes. Patients with HFrEF show a 1.43-fold increased risk of death or rehospitalization compared to non-CKD patients, and those with HFpEF face a 2.54-fold higher risk.[4] In cases of acute myocardial infarction treated with percutaneous coronary intervention, higher rates of major adverse cardiovascular events correlated with worsening severity of CKD.[5] Furthermore, renal dysfunction is linked to reductions in peak oxygen consumption ($\dot{V}O_2$) and anaerobic threshold in heart disease populations, showing functional impairments at each stage of renal deterioration.[6] A clinical trial of telerehabilitation further validated these findings, highlighting lower peak $\dot{V}O_2$ values and diminished 6-min walk test distances with declining renal function.[7]

Beyond traditional endpoints such as death and hospitalization, patient-reported outcomes are becoming integral in clinical trials for HF. Lower scores for the Kansas City Cardiomyopathy Questionnaire are prominent among CKD patients, particularly those with diabetic kidney disease.[4] Similarly, overlaps in cardiovascular-kidney-metabolic conditions are associated with declining patient-reported

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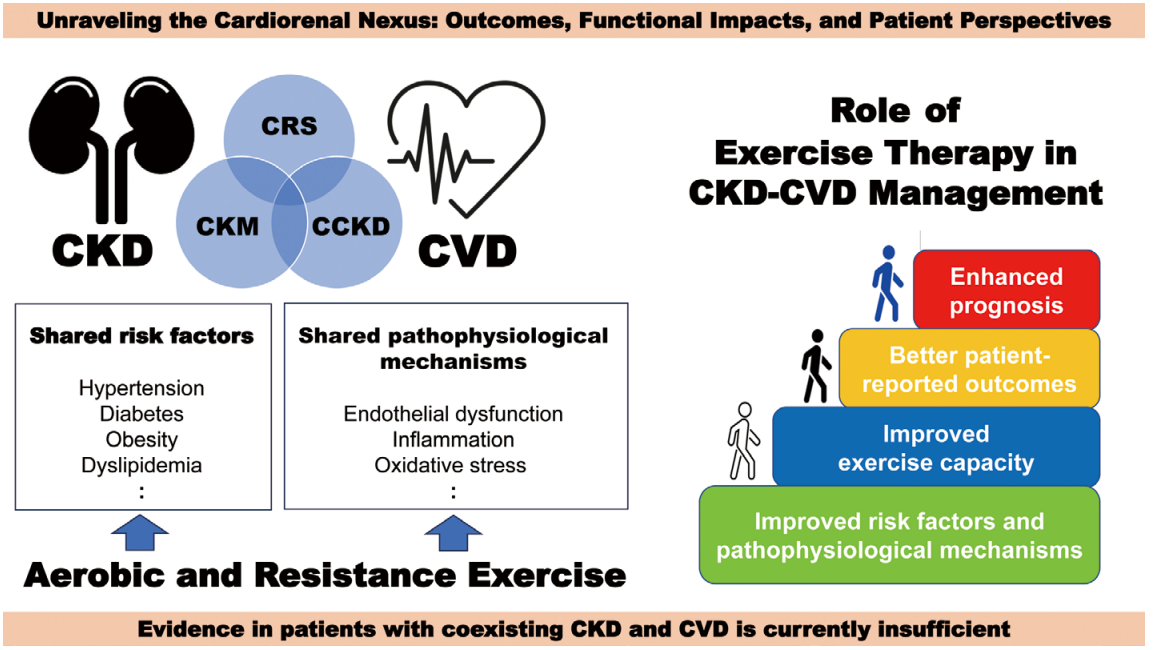

Figure. Conceptual framework of unraveling the cardiorenal nexus: Outcomes, functional impacts, and patient perspectives. CCKD, chronic cardiovascular-kidney disorder; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic syndrome; CRS, cardiorenal syndrome; CVD, cardiovascular disease.

outcomes and quality of life (QOL) in acute HF patients.[8] This evolving focus underscores the importance of addressing both physiological and psychosocial facets in HF care.[9]

Recently, new conceptual frameworks, such as the cardiovascular-kidney-metabolic syndrome (CKM) and chronic cardiovascular-kidney disorder (CCKD), have been proposed to address these challenges. These frameworks provide an integrated and comprehensive perspective for understanding the heart-kidney connection.

This narrative review focuses on these emerging frameworks and aims to provide a comprehensive summary of the interplay between CKD and cardiovascular outcomes, the effects of renal dysfunction on functional capacity in heart disease, and the role of exercise therapy in managing multimorbidity. Additionally, it seeks to outline the current state of knowledge on this topic while identifying existing gaps and proposing future research directions (**Figure**).

Pathophysiological Concepts and Interventional Challenges in Patients With Various Cardiorenal Disorders

The interplay between CKD and cardiovascular disease (CVD) is encapsulated in 3 distinct concepts: cardiorenal syndrome (CRS), CKM, and CCKD. These frameworks aim to elucidate the intricate relationships between the heart, kidneys, and systemic factors, but there are still gaps in understanding their pathophysiology, risk factors, and therapeutic responses. **Table 1** summarizes the conceptual frameworks of CRS, CKM, and CCKD, and **Table 2** summarizes the differences in risk factors and pathophysiological mechanisms present among them.

CRS

CRS is a complex clinical condition characterized by intricate and bidirectional interactions between the heart and kidneys. Dysfunction in one organ, whether acute or chronic, can lead to progressive dysfunction in the other, thus perpetuating a vicious cycle. CRS can be classified into 5 types: acute or chronic cardiac-induced kidney injury, acute or chronic kidney-induced cardiac dysfunction, and secondary CRS involving systemic conditions that affect both organs. Key mechanisms driving CRS include sympathetic nervous system overactivation, persistent renin-angiotensin-aldosterone system (RAAS) activation, oxidative stress, and chronic inflammation. For example, overactivation of the sympathetic nervous system increases renal vasoconstriction, exacerbating ischemia and worsening kidney function, whereas chronic RAAS activation contributes to fluid retention and cardiac strain. Furthermore, inflammation and oxidative stress amplify tissue damage, leading to maladaptive changes in both the cardiac and renal systems. These insights highlight the need for multidisciplinary strategies that simultaneously address the underlying contributors to both heart and kidney dysfunction.[10,11]

CKM

CKM encompasses the complex interplay between metabolic risk factors, CKD, and cardiovascular dysfunction. CKM is particularly driven by dysfunctional or excess adipose tissue, which initiates a cascade of pathological processes. These include insulin resistance, hyperglycemia,

Table 1. Conceptual Frameworks of CRS, CKM, and CCKD

Framework	Conceptual focus	Added clinical value beyond CRS
CRS (cardiorenal Syndrome)	Bidirectional interaction between the heart and kidneys, where dysfunction in one organ (acute or chronic) can lead to progressive dysfunction in the other	–
CKM (cardiovascular-kidney-metabolic syndrome)	Systemic effect of metabolic contributors (i.e., dysfunctional adipose tissue, insulin resistance, hyperglycemia, inflammation, oxidative stress) on the progression of CKD and CVD	Through CKM risk staging and patient management algorithms, interventions, including early preventive approaches, contribute to the reduction of CKD and CVD events
CCKD (chronic cardiovascular-kidney disorder)	Shared risk factors (hypertension, diabetes, obesity, dyslipidemia) and shared mechanisms (inflammation, oxidative stress, endothelial dysfunction, mitochondrial dysfunction) that simultaneously contribute to cardiovascular and renal impairments	Treats coexistence of CKD and CVD as a single disorder, supporting clearer diagnosis and unified treatment strategies, and streamlining clinical trial design through combined cardiorenal composite endpoints

CKD, chronic kidney disease; CVD, cardiovascular disease.

Table 2. Differences in Risk Factors and Pathophysiological Mechanisms in CRS, CKM, and CCK

Risk factors and pathophysiological mechanisms	CRS[10]	CKM[12]	CCKD[14,15]
Diabetes	●	●	●
Obesity	●	●	●
Hypertension	●	●	●
Dyslipidemia	●	●	●
Excess/dysfunctional adipose tissue	●	●	
Cytokines	●	●	
Metabolic syndrome		●	●
(Sympathetic) neurohormonal activation	●	●	●
Inflammation	●	●	●
Endothelial dysfunction	●	●	●
Fibrosis	●	●	●
Oxidative stress	●	●	●
Insulin resistance	●	●	
Vascular dysfunction	●	●	●
Atherosclerosis	●	●	●
Myocardial remodeling	●	●	
Anemia	●		
Bone remodeling/mineral bone disorder	●	●	
Albuminuria		●	●
Glomerular sclerosis	●	●	
Tubulointerstitial fibrosis	●	●	
Smoking			●

● Factor or mechanism has been reported in association with each framework. CCKD, chronic cardiovascular-kidney disorder; CKM, cardiovascular-kidney-metabolic syndrome; CRS, cardiorenal syndrome.

systemic inflammation, oxidative stress, and endothelial dysfunction, all of which contribute to the progression of CKD and exacerbate CVD. The systemic nature of CKM demonstrates how metabolic disorders (e.g., obesity and diabetes) can intensify heart-kidney interactions and increase the risk of adverse outcomes such as multiorgan failure. The CKM framework also highlights the importance of integrating preventive strategies, such as improving metabolic health, reducing inflammation, and enhancing risk prediction models. For instance, advancements in staging frameworks and algorithms for CKM risk assessment are critical for tailoring interventions that prevent adverse cardiovascular and renal outcomes. Additionally, the concept promotes a proactive approach to addressing metabolic contributors to organ dysfunction, recognizing that improving metabolic health directly influences kidney and heart health. The key distinction of CKM from CRS is that metabolic abnormalities are not merely risk factors but fundamental mechanisms that worsen and sustain heart-kidney interactions, thereby positioning CKM as a broader construct that encompasses both cardiorenal syndrome and cardiometabolic disease.[12,13]

CCKD

CCKD introduces a simplified yet comprehensive framework for understanding the mutual progression of heart and kidney diseases. This concept focuses on shared risk factors, including hypertension, diabetes, obesity, and dyslipidemia, that simultaneously contribute to the dysfunction of both organ systems. Unlike CKM, which emphasizes metabolic risk factors, CCKD takes a broader perspective, encompassing structural and functional

changes in the cardiovascular and renal systems. For example, chronic hypertension not only accelerates arterial stiffening but also exacerbates glomerular damage, leading to kidney disease. Similarly, diabetes accelerates both vascular and renal impairments through hyperglycemia-induced oxidative stress and endothelial dysfunction. By addressing these shared drivers of disease progression, CCKD calls for an integrated treatment strategy that combines precision medicine, public health interventions, and interdisciplinary care models. Precision medicine enables the tailoring of treatments to individual patients' risk profiles, whereas public health approaches can address population-level factors, such as obesity and access to care. Compared with traditional CRS subtypes, which are categorized by the sequence of organ dysfunction, CCKD reframes cardiovascular and kidney disease as a single disorder driven by shared risk factors and mechanisms, thereby providing added value for unified diagnosis, treatment planning, and clinical research design.[14,15]

Comparison of CKM and CCKD

CKM and CCKD provide distinct yet complementary frameworks to understand the complex interplay between cardiovascular and renal health. The definition of CKM as a "syndrome" emphasizes the systemic impact of metabolic contributors, such as dysfunctional adipose tissue, insulin resistance, and inflammation, on the progression of kidney and cardiovascular diseases. The CKM framework highlights the clustering of metabolic risk factors prevalent in the general population and their role in exacerbating heart-kidney interactions. CKM also calls for advancements in staging frameworks, risk prediction tools, and preventive strategies to reduce adverse outcomes and improve systemic health.[12,13]

Conversely, CCKD adopts the term "disorder", focusing on the direct structural and functional impairments of the cardiovascular and renal systems caused by shared risk factors, including hypertension, diabetes, obesity, and dyslipidemia. The CCKD framework simplifies the understanding of bidirectional disease progression, advocating for precision medicine and interdisciplinary approaches to address the mutual acceleration of organ dysfunction. This concept prioritizes comprehensive management strategies targeting the shared pathways of the heart and kidneys in the aim to improve patient outcomes.[14,15]

CKM provides a metabolically focused perspective, emphasizing systemic interactions and preventive measures, whereas CCKD takes a disease-specific approach, focusing on common risk factors and clinical interventions, but together, these frameworks offer a holistic understanding of cardiorenal interactions and underscore the need for multidisciplinary strategies to optimize care for affected patients.

Effectiveness of Exercise Therapy in CRS, CKM, and CCKD

Major clinical outcomes in patients with coexisting CKD and CVD include improvements in exercise capacity and prognosis, as well as a slowing of the decline in renal function. The effects of exercise therapy on these outcomes have been increasingly reported.[16–18] However, from the perspectives of CKM and CCKD, there have been no comprehensive reports on the effects of exercise therapy on shared risk factors and pathophysiological mechanisms. Therefore, this narrative review provides a descriptive summary of studies reporting the effects of exercise therapy on shared risk factors and pathophysiological mechanisms, presented separately for patients with CKD (**Table 3**) and those with CVD (**Table 4**). A search of the literature was conducted using PubMed and a combination of MeSH and free text terms to identify relevant studies on the effects of exercise on shared risk factors, such as diabetes, obesity, hypertension, and dyslipidemia, as well as on shared pathophysiological mechanisms including inflammation, endothelial dysfunction, sympathetic activation, and insulin resistance. No restriction was set on the publication period of the literature search. One representative study was selected for each factor, prioritizing randomized controlled trials, reviews, and meta-analyses. The indicators listed in the "Key findings" column of **Table 3** and **Table 4** were cited from the original articles, in which they had been treated as outcome measures.

Reports indicating the effectiveness of exercise therapy were found for almost all items in both diseases.[19–58] Exercise therapy for patients with CKD and CVD may be effective not only in improving exercise capacity but also in addressing the risk factors and pathophysiological mechanisms underlying the complexities of CKD and CVD, thereby potentially contributing to improvements in prognosis and QOL. However, studies specifically targeting patients with coexisting CKD and CVD were notably scarce, highlighting the need to establish evidence in this population. In addition, because there are negative reports on its effects, insufficient investigation of certain items, and inadequate exploration of effective exercise modalities,[59] it will be important to establish the effectiveness of exercise therapy through systematic reviews and meta-analyses and to clarify the items that require further investigation.

Aerobic and Resistance Exercise Recommendations for Patients With CKD and CVD

Aerobic and resistance exercises play a critical role in managing cardiovascular risks and enhancing overall health outcomes in patients with CKD and CVD. Tailored exercise regimens, customized according to individual medical status, are highly effective and supported by various guidelines. According to the European Association of Preventive Cardiology, aerobic exercise should align with existing guidelines for HF, CAD, and peripheral artery disease.[60]

For stable CKD patients, high-intensity interval training (HIIT) has been shown to be feasible and safe, even in advanced stages of CKD, and offers improvements in functional capacity.[60] In patients with diabetes, high-intensity exercise, including HIIT, has been reported to contribute to the prevention of albuminuria progression and glomerulosclerosis, as well as to improvements in estimated glomerular filtration rate (eGFR).[61]

The 2020 European Society of Cardiology guidelines recommend moderate continuous aerobic exercise as the most practical approach for patients in New York Heart Association functional classes I–III.[62] HIIT may provide additional benefits, particularly in improving peak $\dot{V}O_2$, but its efficacy compared to moderate continuous aerobic exercise depends on specific protocols.

The Japanese Circulation Society/Japanese Association of Cardiac Rehabilitation 2021 guidelines similarly support HIIT for stable patients, emphasizing the importance of individualized protocols, such as starting with an exercise intensity of 70% HRmax. They also underscore the need

Table 3. Summary of Studies Reporting the Effects of Exercise Therapy on Shared Risk Factors and Pathophysiological Mechanisms in Patients With CKD

Risk factors and pathophysiological mechanisms	Author (year)	Study design	Sample size*	Exercise	Key findings
Diabetes	Liu et al. (2024)[19]	Systematic review and network meta-analysis	9 RCTs	Resistance exercise therapy + conventional therapy	↓ HbA1c
Obesity	Yamamoto et al. (2021)[20]	Systematic review and meta-analysis	10 RCTs	Aerobic exercise	↓ BMI
Hypertension	Zhang et al. (2019)[21]	Systematic review and meta-analysis	9 RCTs	Mixed	↓ SBP
Dyslipidemia	Toyama et al. (2010)[22]	Prospective trial	N=10 (19)	Exercise training	↓ LDL-C, ↑ HDL-C
Excess/dysfunctional adipose tissue	Baria et al. (2014)[23]	RCT	N=10 (27)	Center-based exercise	↓ Visceral fat
Cytokines	Baião et al. (2023)[24]	Systematic review and meta-analysis	10 studies	Exercise interventions	↓ IL-6
Metabolic syndrome	Wu et al. (2022)[25]	Systematic review and meta-analysis	5 studies	Mixed	↓ Waist circumference
Sympathetic activation	Jeong et al. (2023)[26]	RCT	N=32 (77)	Cycling exercise	→ MSNA (control ↑)
Inflammation	Viana et al. (2014)[27]	Systematic review	24 studies	Mixed	↓ T-lymphocytes, ↓ Monocyte activation
Endothelial dysfunction	Kirkman et al. (2019)[28]	RCT	N=16 (31)	Supervised aerobic exercise (cycling, walking/jogging, or elliptical)	→ Flow-mediated dilation (control ↓)
Fibrosis	Souza et al. (2018)[29]	Animal experiment (rats)	N=15 rats	Resistance training	→ Renal fibrosis (control ↑)
Oxidative stress	Zhao et al. (2023)[30]	Systematic review and meta-analysis	7 RCTs	Aerobic exercise	↓ Oxidative markers
Insulin resistance	Man X et al. (2025)[31]	Qualitative synthesis	1 RCT	Aerobic exercise + resistance training	↓ HOMA-IR
Vascular dysfunction	Wang et al. (2022)[32]	Meta-analysis of randomized trials	18 RCTs	Mixed	↓ Pulse wave velocity
Atherosclerosis	Van Craenenbroeck et al. (2014)[33]	Narrative review	–	Aerobic exercise	↓ Central Aix, ↓ CF-PWV
Myocardial remodeling	Bishop et al. (2023)[34]	Narrative review	–	Exercise training	↓ Left ventricular remodeling
Anemia	Villanego et al. (2020)[35]	Systematic review and meta-analysis	4 RCTs	Mixed	↑ Hemoglobin
Bone remodeling/ mineral bone disorder	Aucella et al. (2024)[36]	Narrative review	–	Physical exercise	↓ Bone resorption, ↑ Bone formation
Albuminuria	Hellberg et al. (2019)[37]	RCT	N=73 (148)	Strength training	↓ U-ACR
Glomerular sclerosis	Yamakoshi et al. (2021)[38]	Animal experiment (rats)	–	Treadmill running	↓ Collagen type I
Tubulointerstitial fibrosis	Zhang et al. (2019)[39]	Animal experiment (mice)	N=6 (18) mice	Aerobic exercise training	↓ Tubulointerstitial fibrosis indices
Smoking	Kim & Cho (2022)[40]	Cross-sectional study	N=909	Regular exercise	↑ Smoking cessation

*Sample size is expressed as N=intervention group (total number of participants). BMI, body mass index; CCKD, chronic cardiovascular-kidney disorder; CF-PWV, carotid-femoral pulse wave velocity; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic syndrome; CRP, C-reactive protein; CRS, cardiorenal syndrome; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; MSNA, muscle sympathetic nervous activity; RCT, randomized controlled trial; SBP, systolic blood pressure; U-ACR, urine-albumin-creatinine ratio.

for further research to establish the long-term effects of HIIT.[63]

Meanwhile, the American College of Sports Medicine advocates for moderate-intensity aerobic exercise at 40–59% of oxygen consumption reserve or 12–13 on the Borg scale. Vigorous-intensity aerobic exercise may offer greater benefits for selected patients but should be prescribed cautiously based on individual therapeutic goals. These recommendations are detailed in their latest guidelines.[64]

Resistance training complements aerobic exercise by reversing muscle mass loss and improving conditioning without excessive cardiac strain. A routine of 1–3 sets of 8–12 repetitions at 60–80% of 1-repetition maximum, performed twice weekly, is advised. Incorporating a variety of exercises targeting all major muscle groups enhances effectiveness.[65]

Overall, exercise prescriptions should follow the FITT model (frequency, intensity, time, and type) and be tailored to the patient's condition and goals. Aerobic activities such as walking, cycling, or swimming are recommended 3–7 days per week at moderate intensity. Integrating resistance training further reduces cardiovascular risks and improves health outcomes. Although the effectiveness of HIIT has been increasingly recognized in recent years, its effects in

Table 4. Summary of Studies Reporting the Effects of Exercise Therapy on Shared Risk Factors and Pathophysiological Mechanisms in Patients With CVD

Risk factors and pathophysiological mechanisms	Author (year)	Study design	Sample size	Exercise	Key findings
Diabetes	Fontes-Oliveira et al. (2020)[41]	Retrospective cohort study	N=1,607	Aerobic training+resistance training+flexibility exercises	↓ HbA1c
Obesity	Pedersen et al. (2019)[42]	RCT	N=26 (55)	Aerobic interval training	↓ BMI
Hypertension	Iellamo et al. (2014)[43]	RCT	N=18 (moderate continuous training), N=18 (high-intensity interval training)	Moderate continuous training, high-intensity interval training	↓ SBP, DBP
Dyslipidemia	Lee et al. (2025)[44]	Systematic review and meta-analysis	11 studies	Mixed	↑ HDL-C
Excess/dysfunctional adipose tissue	Moholdt et al. (2012)[45]	RCT	N=35 (107)	Aerobic interval training	↑ Serum adiponectin
Cytokines	Luo et al. (2025)[46]	Narrative review	–	Mixed	↓ CRP, ↓ IL-6, ↓ TNF-α
Metabolic syndrome	Nalini et al. (2013)[47]	Cohort study	N=167	Aerobic exercise+resistance training	↓ Waist circumference
(Sympathetic) neurohormonal activation	Braith & Edwards (2003)[48]	Narrative review	–	Exercise training	↓ Plasma norepinephrine
Inflammation	Jaconiano & Moreira-Gonçalves (2022)[49]	Narrative review	–	Exercise training	↓ TNF-α, IL-6
Endothelial dysfunction	Pearson & Smart (2017)[50]	Systematic review and meta-analysis	16 studies	Mixed	↑ Flow-mediated dilation
Fibrosis	Xu et al. (2020)[51]	Editorial	–	Exercise training	Protect against myocardial fibrosis
Oxidative stress	Yuan et al. (2025)[52]	Narrative review	–	Exercise training	↑ Ca^{2+} uptake and release
Insulin resistance	Iellamo et al. (2014)[43]	RCT	N=18 (moderate continuous training), N=18 (high-intensity interval training)	Moderate continuous training, high-intensity interval training	↓ HOMA-IR
Vascular dysfunction	Hambrecht et al. (2000)[53]	Systematic review and meta-analysis	14 RCTs	Mixed	↓ Carotid-femoral pulse wave velocity
Atherosclerosis	Vesterbekkmo et al. (2023)[54]	RCT	N=30 (60)	High-intensity interval training	↓ PAV, TAV_{norm}
Myocardial remodeling	Liu et al. (2022)[55]	Narrative review	–	Exercise training	↓ Left ventricular remodeling
Anemia	Wang et al. (2013)[56]	Prospective controlled trial	N=30 (90)	Aerobic interval training	↑ Hemorheological
Bone remodeling/ mineral bone disorder	Kanazawa et al. (2020)[57]	Animal experiment (mice)	42 mice	Treadmill exercise training	↓ Bone resorption, ↑ Bone formation
Smoking	Taylor et al. (1988)[58]	RCT	N=97 (142)	Aerobic exercise	↓ Cigarette consumption

*Sample size is expressed as N=intervention group (total number of participants). Ca^{2+}, calcium ion; CVD, cardiovascular disease; DBP, diastolic blood pressure; PAV, percent atheroma volume; TAV_{norm}, normalized for segment length; TNF-*α*, tumor necrosis factor-*α*. Other abbreviations as in Table 3.

patients with coexisting CKD and CVD, who often present with complex pathophysiology, require further investigation. In addition to their complex pathophysiology, the high prevalence of frailty, sarcopenia, and nutritional problems such as protein-energy wasting makes HIIT challenging to implement or potentially less effective in this population. Therefore, it is necessary to explore effective exercise therapies for patients who are not suitable candidates for HIIT.[66]

Anemia in the Cardiorenal Patient and Exercise Therapy

Anemia is a significant concern in patients with CKD and CVD, often exacerbating the challenges associated with these conditions.[67] The interplay between CKD and CVD in the context of CRS establishes a vicious cycle in which anemia worsens both heart and kidney function. Although numerous risk factors and pathophysiological mechanisms are involved in cardiorenal dysfunction, anemia is particularly important because it can act as a limiting factor for exercise therapy. Recently, however, a new perspective has emerged suggesting that exercise itself may support anemia management in patients with CVD. Therefore, this section focuses on anemia in this patient population and explores the role of exercise therapy in addressing anemia-related complications.

Patients with CKD and CVD frequently exhibit anemia

as a result of impaired erythropoietin (EPO) production, inflammation, and iron deficiency. Marques Vidas et al. highlight that anemia management in CRS should address HF, CKD, and anemia concurrently by incorporating iron supplementation, EPO-stimulating agents, and other emerging therapies.[68] Exercise therapy, although not a replacement for pharmacological interventions, has shown promising adjunctive effects in enhancing physical capacity and ameliorating some of the physiological consequences of anemia.

Research by Takeuchi et al. showed that patients with both CKD and anemia undergoing percutaneous coronary intervention had significantly higher rates of major adverse cardiovascular and cerebrovascular events and all-cause death, underscoring the critical need to address anemia in such populations.[69] Furthermore, a study by Saitoh et al. observed that the combined presence of CKD and anemia correlates with substantial reductions in physical function, thus emphasizing the importance of interventions that can mitigate these effects.[70]

Exercise therapy may serve as a viable strategy to counteract these limitations. Ogura et al. found that anemia substantially reduces exercise capacity in CKD patients, with the most pronounced impact occurring in those with an eGFR $<45\,mL/min/1.73\,m^2$.[6,71] This reduction in exercise capacity underscores the need for tailored aerobic and resistance training regimens. For instance, aerobic interval training has been shown to improve peak $\dot{V}O_2$ and erythrocyte rheological functions, although its benefits may be attenuated in anemic patients with HF.[56]

Physical exercise, especially when individualized, has been associated with positive effects on hemoglobin levels. A systematic review and meta-analysis by Villanego et al. revealed evidence supporting the role of exercise in improving hemoglobin levels, which resulted in a standardized mean difference of 0.3 (95% confidence interval: 0.1 to 0.5).[35] Aucella et al. further supported this finding, reporting that short-term physical exercise can promote EPO production, muscle synthesis, and angiogenesis, all of which contribute to enhancing hemoglobin levels.[36]

Bianchi and von Haehling emphasize the global benefits of exercise therapy in anemic patients with HF, including increased red blood cell production and improved EPO efficiency.[72] However, Patel et al. found that low hemoglobin levels were a significant mediator of reduced peak $\dot{V}O_2$, accounting for approximately 35% of this reduction in patients with renal dysfunction.[73]

In summary, anemia remains a limiting factor in the efficacy of exercise therapy for patients with CKD and CVD, but the potential benefits of exercise are undeniable. Exercise interventions tailored to individual patient needs can mitigate some of the physiological challenges posed by anemia, thus improving physical capacity and QOL. Importantly, anemia management and exercise therapy should be considered complementary strategies rather than separate approaches. Correction of anemia may enhance the efficacy and safety of exercise interventions, while exercise itself can support anemia management through improved hemoglobin levels and EPO efficiency. Thus, integrating both interventions, either sequentially or concurrently, may provide synergistic benefits in patients with CKD and CVD. However, further research is warranted to optimize these strategies and better integrate them into comprehensive anemia management protocols.

Study Limitations

First, as a narrative review, the selection of studies was based on the authors' subjective judgment, which may limit its comprehensiveness and systematic approach. Second, the review focused predominantly on studies reporting positive effects of exercise therapy and did not sufficiently include research in which outcomes were neutral or negative, potentially leading to an imbalance in the representation of evidence. This limitation highlights the need for future systematic reviews and meta-analyses to ensure a fair and inclusive synthesis of findings.

Furthermore, research specifically targeting patients with concurrent CKD and CVD is notably sparse. The challenge in identifying such studies led to their exclusion in this review. Dedicated studies with refined designs are urgently needed to address the unique needs of this comorbid population. By adopting methodologies that prioritize inclusivity and comprehensiveness, future research can fill these gaps and strengthen the evidence base.

Conclusion and Future Directions

Conclusion

The interplay between CKD and CVD represents a complex challenge that requires a nuanced approach. Emerging concepts such as CRS, CKM, and CCKD provide valuable frameworks for understanding the bidirectional relationships between the cardiovascular and renal systems. Exercise therapy has shown promise in improving prognosis and enhancing QOL in CKD-CVD patients, but evidence specific to tailored interventions for this population remains limited. Future research should focus on systematically synthesizing the effectiveness of exercise therapy through rigorous systematic reviews and meta-analyses.

Future Directions

Development of Evidence-Based Exercise Therapy Designing exercise interventions guided by the principles of CRS, CKM, and CCKD is critical. Research must prioritize evaluating the effect of tailored exercise programs on the unique pathophysiological dynamics of CKD-CVD patients.

Validation of Early Exercise Therapy Given the importance of addressing risk factors in CKM and CCKD, evidence supporting the effectiveness of early-stage exercise interventions should be generated. Studies should explore the role of exercise therapy in preventing cardiorenal dysfunction and its contribution to long-term health improvements.

Personalization of Exercise Programs Developing adaptable exercise regimens for patients with frailty, reduced physical capacity, or multiple comorbidities is necessary. Personalized approaches will help overcome barriers to traditional therapies and ensure the inclusivity of CKD-CVD patients in clinical programs.

Introduction of the Conceptual Framework of Sensory Frailty for Future Research Finally, we believe perspectives on vision-related issues warrant further attention in patients with cardiorenal dysfunction.[74] We propose a conceptual framework of sensory frailty to describe the vulnerability associated with sensory impairments, particularly visual impairment (VI), and their potential effect on physical function and recovery.[75] Although not yet a formally defined clinical syndrome, this concept reflects emerging evidence linking sensory decline to frailty-related outcomes. A recent

multicenter prospective cohort study in Japan found that patients with VI undergoing Phase I cardiac rehabilitation exhibited significantly slower walking speeds (0.89 vs. 1.01 m/s, $P<0.001$), which corresponds to sarcopenia.[75] VI was also independently associated with both walking speed and length of hospital stay, suggesting its relevance to physical vulnerability and rehabilitation outcomes.[75] These findings underscore the importance of incorporating sensory assessments into clinical care. To optimize outcomes for CKD-CVD patients, it is essential to adopt a multidimensional approach that integrates the physiological, psychosocial, and sensory domains. Advancing research in these underexplored areas will be key to establishing robust evidence and improving clinical practice.

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Conflicts of Interest

The authors declare that there are no conflicts of interest to disclose.

Ethics Statement

Not applicable.

Authors' Contributions

K.P.I.: Conceptualization, Methodology, Writing - Original Draft; A.O.: Conceptualization, Methodology, Writing - Review & Editing.

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