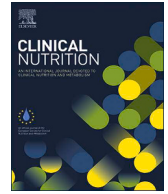




Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/clnu>

Narrative Review

A narrative review of sarcopenia in patients with cardiovascular kidney metabolic syndrome: Another brick in the wall?

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ARTICLE INFO

Article history:

Received 24 March 2026

Accepted 17 April 2026

Keywords:

Cardiovascular kidney metabolic syndrome

Muscle function

Muscle mass

Sarcopenia

Sarcopenic obesity

SUMMARY

Cardiovascular-kidney-metabolic syndrome (CKMS) is a recently launched by American Heart Association to express the importance of interplay among metabolic risk factors, chronic kidney disease, and the cardiovascular system which has profound impacts on morbidity and mortality. The common pathologic processes that impact cardiovascular, kidney and metabolic disorders include but not limited to unhealthy lifestyle (e.g. sedentary life, smoking, lack of exercise, poor nutrition), chronic inflammation, oxidative stress, and endocrine alterations. These risk factors were also implicated as risk factors for sarcopenia development. Indeed, previous studies have shown that the individual components of CKMS were associated with sarcopenia. These studies rarely examined the relationship between CKMS in constellation with sarcopenia until recently but latest studies have consistently showed associated with CKMS as a whole with sarcopenia.

In this narrative review, we summarized the latest and specific studies (n: 44855) regarding the relationship between sarcopenia with CKMS. Additionally, we underlined the common pathogenic mechanisms and potential biomarkers for CKMS, and sarcopenia. We discussed non-pharmacological and pharmacological approaches for management of CKMS and sarcopenia. We also highlighted potential clinical applications and knowledge gaps to be investigated in future studies.

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1. Introduction

Cardiovascular-kidney-metabolic syndrome (CKMS) is defined as a health disorder attributable to connections among obesity, diabetes, chronic kidney disease (CKD), and cardiovascular disease (CVD), including coronary heart disease (CAD), heart failure, atrial fibrillation, stroke, and peripheral artery disease. The clinical significance of poor CKMS health are already recognized, with premature and excess morbidity. CKMS is staged from 0 to 4 as Stage 0 as is defined as absence of excess/dysfunctional adiposity, metabolic risk factors, Stage 1 as having prediabetes or BMI/waist circumference exceeding the threshold, Stage 2 as having metabolic risk factors (Presence of hypertension, diabetes, elevated

fasting serum triglycerides, CKD, or metabolic syndrome. Stage 3 as having subclinical CVD overlapping with CKMS risk factors, very high-risk CKD, or high predicted CVD risk (High 10-year CVD risk predicted by the PREVENT) and Stage 4 as presence of CVD (documented history of angina, CAD, myocardial infarction, heart failure, or stroke) without (4a) or with (4b) kidney failure [1].

Sarcopenia is currently recognized as a condition with progressive loss of both muscle mass strength and physical performance [2,3] that is associated with impaired quality of life and increased disability, frailty, and mortality [4–6]. The relationship between individual components of CKMS with sarcopenia is demonstrated before. Indeed, there is a bidirectional association between sarcopenia and CVD [7]. Sarcopenia can lead to increased adiposity, insulin resistance, and chronic inflammation, and thus, predispose adults to developing cardiovascular events [8]. Reciprocally, chronic inflammatory state, malnutrition, and decreased physical activity observed in patients with cardiac disease which are risk factors for loss of muscle mass and development of

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<https://doi.org/10.1016/j.clnu.2026.106674>

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sarcopenia [9]. Sarcopenia is common in patients with heart failure (HF) [10,11], coronary artery disease [12,13], atrial fibrillation [14] recurrent strokes [15] and peripheral arterial disease [16–18]. Sarcopenia frequently observed with kidney disease, especially among those with end-stage renal disease on hemodialysis. Several studies have documented that a loss of muscle mass and performance is a consistent feature in patients with CKD [19,20]. Sarcopenia is also common in patients with metabolic syndrome [21,22], diabetes [23–25], metabolic dysfunction-associated steatotic liver disease (MASLD) [26,27].

All these studies investigate the relationship with individual components of CKMS but not in a comprehensive manner as an interconnected whole. Indeed, mostly CKMS to sarcopenia risk has been limited to isolated CKMS constructs, and rarely examined CKMS in constellation. However, metabolic, cardiovascular, and renal diseases often coexist, and the pathophysiological interactions are common between these diseases [28]. Compared with traditional approach that focus solely on individual diseases, the CKMS staging system can more comprehensively capture the synergistic impacts of metabolic abnormalities and cardio-renal injuries [1]. Until recently the relationship between CKMS, and sarcopenia is not known however latest studies have performed to investigate the relationship with CKMS, and sarcopenia.

In this narrative review, we have summarized the findings which specifically focused on the relationships between CKMS as a whole with sarcopenia. Additionally, we explore the potential causes of these relationships, identify knowledge gaps and put proposals for future studies.

2. Methods

We performed a review of the literature in English language until February 1, 2026, searching the PubMed, Web of Science, Science direct, Scopus, and Google Scholar online databases using the keywords: “cardiovascular kidney metabolic syndrome and sarcopenia”, “cardiovascular kidney metabolic syndrome and frailty”, “cardiovascular kidney metabolic syndrome and muscle mass”, “cardiovascular kidney metabolic syndrome and muscle function” All randomized trials, prospective or retrospective cohort studies, and cross-sectional studies published are included in this narrative review. Studies that are not regarded as original articles (commentaries, editorials, systematic reviews, meta-analyses and case reports are not included.

3. Results

The clinical studies specifically investigating the relationship between CKMS and sarcopenia is summarized in Table 1. Studies usually showed that sarcopenia -defined by different measures- was associated with CKMS. In addition, as the stage of CKMS increases the having change of sarcopenia increases [29–32]. Not only sarcopenia, but sarcopenic obesity is associated with higher stages of CKMS [33,34]. On the other hand, the relationship between sarcopenia and CKMS is bi-directional and studies showed that sarcopenia and sarcopenic obesity independently associated with cardiovascular disease and major adverse cardiovascular events [33,35]. In patients with CKMS, physically inactive individuals exhibited significantly.

4. Discussion

In this narrative review, we summarized the relationship between CKMS and sarcopenia. The studies showed that CVKD and sarcopenia are related bi-directionally. The reasons for this mutual

relationship is not known completely as CKMS is recently launched.

Pathogenesis of sarcopenia is complex. Inactivity, disuse, insulin resistance, inflammation, microvascular changes, hormonal changes, mitochondrial dysfunction, apoptosis, fatty infiltration of skeletal muscles, motor neuron loss, all play a role [36]. The degree of muscle loss is exacerbated by a sedentary lifestyle, prolonged bed rest, smoking and alcohol intake, malnutrition, and anorexia of aging. Obesity has been found to be associated with an increased incidence of sarcopenia [37]. These risk factors are also valid in CKMS (Fig. 1). Indeed, CKMS is characterized by systemic inflammation insulin resistance, mitochondrial dysfunction, endocrine alterations, and all of which promote muscle catabolism and impair muscle protein synthesis [30]. Thus, shared mechanisms may play a role in development of CKMS and sarcopenia which discussed below.

4.1. Shared mechanisms between CKMS and sarcopenia

4.1.1. Physical inactivity

One of the shared mechanisms for CKMS and sarcopenia physical inactivity. Physical activity plays crucial and beneficial role in preventing cardiovascular and metabolic diseases. Exercise prevents hypertension improves endothelial function [38], insulin sensitivity and promotes skeletal muscle glucose uptake, thereby reducing diabetes incidence risk and weight gain [39,40]. Moderate-to-vigorous physical activity are inversely associated with sarcopenia [41,42]. Exercise improves in sarcopenia in individual components of CKMS.

Exercise was beneficial with regard to sarcopenia in HF patients [43,44], in diabetes [45,46], obesity [47–49] and chronic kidney disease [50,51]. Notably, there is a bidirectional pathological association between CKMS syndrome and physical dysfunction. Arteriosclerosis evaluated by pulse wave velocity leads to insufficient tissue perfusion and induces muscle atrophy, promotes the accumulation of inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor (TNF- α), which activates the ubiquitin proteasome system, and accelerates muscle protein breakdown [52,53].

4.1.2. Mitochondrial dysfunction

Exercise also impacts mitochondrial function. Skeletal muscle wasting is observed secondary to mitochondrial dysfunction from reactive oxygen species [54]. In sarcopenia, mitochondrial dysfunction results in the accumulation of mitochondrial damage-associated molecular patterns (mDAMPs), including mitochondrial DNA [55,56]. These mDAMPs activate the Toll-like receptor (TLR) pathway and trigger nuclear factor kappa B (NF- κ B) signaling, thereby increasing the expression of IL-6 and TNF- α [57]. Exercise training activates mitochondrial biogenesis in skeletal muscle, augmenting overall mitochondrial density and oxidative phosphorylation capacity [58]. Interestingly, physical activity-induced mitochondrial biogenesis also occurs in tissues other than skeletal muscle, including brain, liver, adipose tissue and kidney. Over time, the increase in mitochondrial density, coupled with increased heart capacity and blood flow, increases the efficiency of energy utilization and enhancing the overall endurance capacity [59].

4.1.3. Inflammation

Another potential effect of exercise is on inflammation. Exercise reduces in visceral fat mass which secretes inflammatory mediators. Exercise also increases release of anti-inflammatory myokines from contracting skeletal muscle, reduces expression of TLRs on monocytes and macrophages. Exercise increases circulating levels of interleukin 10 (IL-10) and interleukin 1 (IL-1) receptor antagonist and regulatory T cells. Downregulation of TLRs

Table 1

Clinical studies specifically addressing the relationship between cardiovascular kidney metabolic syndrome and sarcopenia.

Ref	Methods/Patients	Findings
Huang et al. [29]	<ul style="list-style-type: none"> - Cross-sectional study included 5692 participants - Body weight and composition were then assessed by BIA - BFM, body fat percentage BFP, FMI, VFI, FFM, MM, MMI, MFR were recorded - CKMS was defined by AHA criteria [1] and classified into three stages (0–2) - Stages 0 and 1 were combined and defined as the pre-early CKMS stage, whereas stage 2 was defined as the early CKMS stage. 	<ul style="list-style-type: none"> - BFM (kg) 18.5 ± 7.0 vs. 22.7 ± 8.1 - BFP (%), 29.0 ± 7.8 vs. 31.7 ± 8.4 - FMI (kg/m²), 7.0 ± 2.7 vs. 8.6 ± 3.2, - VFI (kg/m²), 7.1 ± 3.8 vs. 11.2 ± 4.1 - FFM (kg) 44.4 ± 8.5 vs. 48.2 ± 10.1 - MM (kg), 41.9 ± 8.1 vs. 45.6 ± 9.7 - MMI (kg/m²), Mean ± SD 67.0 ± 7.6 vs. 64.5 ± 8.1 in pre-early CKMS vs early CKMS stage (<i>P</i> < 0.0001 for all) - MFR, Median (IQR) 2.3 (1.8–3.0) vs 2.0 (1.6–2.8) in pre-early CKMS vs early CKMS stage (<i>P</i> < 0.0001) - Coexistence of adiposity and sarcopenia, mediated 20–57% of the relationship between systemic inflammation and early-stage CKMS manifestations.
Wang et al. [30]	<ul style="list-style-type: none"> - A cross-sectional analysis included 4193 adults - Sarcopenia was defined as an appendicular skeletal muscle mass (ASMM) to BMI ratio <0.789 for men and <0.512 for women. - ASMM was measured via DXA - CKMS was classified into five progressive stages (0–4) according to AHA criteria [1] 	<ul style="list-style-type: none"> - Sarcopenia prevalence increased progressively across CKMS stages, with the highest risk in advanced stages. CKMS stage 2 (OR: 1.58, 95% CI: 1.03–2.43) and stages 3–4 (OR:3.51, 95% CI: 1.54–8.01 - Physically inactive individuals exhibited significantly higher odds of sarcopenia compared to their active counterparts within both CKMS 0–1 (OR:3.53; 95% CI: 1.76–7.09) and CKM stage 2 (OR: 1.86; 95%CI: 1.30–2.67) but not in Stage3 and stage 4 due to a smaller sample size in this subgroup - The highest odds of sarcopenia were observed in individuals with both physical inactivity and advanced CKMS stages (OR:7.62)
Wei et al. [35]	<ul style="list-style-type: none"> - Prospective cohort study included 7428 participants - Sarcopenia was assessed according to 3 components: Muscle mass, muscle strength, and physical performance - HGS (kg), was used to evaluate skeletal muscle strength - Low muscle strength considered below a cutoff point of <28 kg for males and <18 kg for females - Measurement of physical performance included the gait speed, chair stand test, and short physical performance battery (SPPB) test. Participants with a gait speed <1.0 m/s, 5 chair stand tests ≥12 s, or SPPB ≤9 were defined as reduced physical performance - Muscle mass was estimated by ASM. The cut-off value for low muscle mass was 7.00 kg/m² for males and 5.25 kg/m² for females - CKMS was classified into five progressive stages (0–4) according to AHA criteria [1] 	<ul style="list-style-type: none"> - During a median follow-up of 9.0 years, 1392 new cases of heart disease and 605 new cases of stroke observed - Participants with sarcopenia (HR:1.45, 95% CI: 1.23–1.72) exhibited an increased risk of incident CVD compared to those with non-sarcopenia - Higher quintiles of muscle mass presented significantly increased risks of incident CVD than those with the lowest quintile (quintile 2, HR:1.34, 95%, CI:1.15–1.56); (quintile 3, HR:1.41, 95%, CI: 1.19–1.67); (quintile 4, HR:1.71, 95 % CI, 1.40–2.09); (quintile 5, HR:2.20, 95 % CI: 1.75–2.77)
Xin et al. [33]	<ul style="list-style-type: none"> - Prospective cohort study included 6766 participants - Sarcopenia assessed according to three components: Muscle mass, muscle strength, and physical performance - Muscle strength was assessed via HGS - Physical performance was evaluated using the five-time chair stand test and a 2.5-m walking test (converted to a 6-m walk speed). Poor physical performance was defined as a chair stand time ≥12.0 s or a walking speed <1.0 m/s - Muscle mass was estimated using a validated anthropometric equation suitable for Chinese populations, which demonstrated high agreement with DXA ASM: 0.193 × weight (kg)+ 0.107 × height (cm) –4.157 × sex – 0.037 × age – 2.631, where sex was coded as 1 for men and 2 for women. - Skeletal muscle index (SMI) was then calculated by adjusting ASM for height squared (SMI:ASM/height² in m²). - Low muscle mass was defined as an SMI below the lowest sex-specific quintile of the study population with cutoffs of <7.76 kg/m² for men and <6.15 kg/m² for women - Sarcopenia was characterized by either low muscle strength (HGS <18 kg) or reduced physical performance (chair stand test ≥12 s), whereas confirmed sarcopenia required low muscle mass in combination with either criterion. - Participants were stratified into four categories based on the combination of obesity and sarcopenia status: (i) Normal weight without possible sarcopenia or sarcopenia (ii) Normal weight with possible sarcopenia or sarcopenia (iii) obesity without possible sarcopenia or sarcopenia; (iv):Obesity with possible sarcopenia or sarcopenia - CKMS defined according to AHA criteria [1] 	<ul style="list-style-type: none"> - The overall prevalence of CKMS stages 0–4 was 6.4%, 13.1%, 29.5%, 37.4%, and 13.6%, respectively - At baseline, sarcopenic obesity was associated with a significantly higher likelihood of advanced CKMS stages [OR (95% CI): 3.317 (2.533, 4.345)] compared to reference group (participants with optimal body mass index or waist circumference). - Over a median follow-up of 9.0 years, 1322 participants (21.1%) from CKMs stages 0–3 experienced MACEs. - Sarcopenic obesity was associated with an increased risk of MACEs [HR (95% CI): 2.248 (1.789, 2.824)] compared to participant with normal weight without possible sarcopenia or sarcopenia

(continued on next page)

Table 1 (continued)

Ref	Methods/Patients	Findings
Yuan et al. [31]	<ul style="list-style-type: none"> - Cross-sectional study included 4322 participants - CKMS was classified into five progressive stages (0–4) according to AHA criteria [1] - Muscle loss was defined as appendicular lean mass (ALM) adjusted for body mass indexes <0.789 and < 0.512 for men and women 	<ul style="list-style-type: none"> - Of 4322 participants, 397 (9.0%) were diagnosed with relative muscle loss. - Participants in CKMS stages 1–4 exhibited significantly higher risks for relative muscle loss compared with those in stage 0, with odds ratios (95% confidence intervals) of 3.91 (1.96–7.81), 4.16 (2.08–8.32), 4.95 (2.37–10.34), and 7.74 (2.61–22.92), respectively.
Zooravar et al. [32]	<ul style="list-style-type: none"> - Longitudinal cohort study included 5925 adults - CKMS staging followed the AHA classification [1] - ALM was calculated as the sum of lean tissue in both arms and both legs. Individuals were considered to have low lean mass if their ALM/BMI ratio was less than 0.789 for men and less than 0.512 for women 	<ul style="list-style-type: none"> - During a mean follow-up of 125.5 months, 851 deaths occurred. Sarcopenia was significantly associated with increased odds of advanced CKMS stages: (stage 2: OR: 2.236, 95% CI: 1.594–3.135), (stage 3: OR: 3.332, 95% CI: 2.001–5.548) and (stage 4: OR: 3.495, 95% CI: 2.157–5.662) vs. Stage 1. - In patients with CKMS, sarcopenia predicted all-cause mortality (HR: 1.527, 95% CI: 1.274–1.831), CVD mortality (HR: 1.903, 95% CI: 1.299–2.788) and non-CVD mortality (HR: 1.407, 95% CI: 1.124–1.762)
Wei et al. [190]	<ul style="list-style-type: none"> - Two cohorts used: Brisbane systems Genetics study (BSGS, n:614) and Lothian Birth cohorts (LBC, n:1366) - Sarcopenia defined as reduced muscle strength (low handgrip strength), diminished muscle mass, assessed by appendicular lean mass, and impaired physical performance, evaluated through walking speed - CKMS defined by AHA criteria [1] 	<ul style="list-style-type: none"> - Slower walking pace was associated with higher CVD risk (OR: 1.17), and metabolic syndrome risk (OR:2.32) - Lower appendicular lean mass exhibited inverse associations with heart failure with heart failure and atrial fibrillation - Multi-omics identified key shared genes (ANAPC4, UNC50, TPO), with ANAPC4 methylation sites linked to CVD and reduced muscle mass
-Yang et al. [34]	<ul style="list-style-type: none"> - CKMS stages were identified based on the AHA criteria [1] - 8448 participants included baseline - The longitudinal analysis included 4454 participants - The ASM was derived using a well-established anthropometric formula tailored for the Chinese population as: $ASM: 0.193 \times \text{weight (kg)} + 0.107 \times \text{height (cm)} - 4.157 \times \text{sex} - 0.037 \times \text{age} - 2.631$, where sex was coded as 1 for men and 2 for women. - Participants with height-adjusted (ASMM) - (ASMM/Height², kg/m²) below the sex-specific 20th percentile threshold was classified as low muscle mass, within the study cohort: 7.01 kg/m² (men) and 5.25 kg/m² (women). - Low HGS defined as (<28 kg for men and <18 kg for women) - 5-Time chair stand test ≥ 12 s was indicative of low physical performance. <p>Participants divided into (i) normal group: No obesity and sarcopenia</p> <p>(ii) Obesity group: Non-sarcopenic participants with obesity</p> <p>(iii) Sarcopenia group: Possible sarcopenic participants without obesity;</p> <p>(iv) Sarcopenic obesity group: Participants with possible sarcopenia and obesity</p>	<ul style="list-style-type: none"> - At baseline sarcopenic obesity related with higher odds of advanced CKMS (OR 1.51, 95% CI 1.21–1.88), compared to the normal group - In longitudinal analysis over an average of 4-year follow-up, 829 of 4454 individuals with early CKMS stages progressed to advanced CKM stages. - Participants with sarcopenic obesity showed a substantially higher risk of CKMS progression compared to normal group (OR: 1.81; 95% CI: 1.34–2.45) - In subgroup analyses, sarcopenic obesity maintained a positive correlation with advanced CKMS stages, especially among men, older adults, smokers, alcohol consumers, and diabetic patients.

Abbreviations: BIA: bioelectrical impedance analysis, AHA: American Heart Association, BFM: Body fat mass, BFP: body fat percentage, FMI: fat mass index, VFI: visceral fat index, FFM: fat-free mass, MM: muscle mass, MMI: muscle mass index MFR: muscle-fat ratio, CKMS: Cardiovascular-kidney-metabolic syndrome, ASMM: appendicular skeletal muscle mass, DXA: dual-energy X-ray absorptiometry, HGS: hand Grip strength, CVD: cardiovascular disorder, SPPB: short physical performance battery, ASM: appendicular skeletal muscle MACE: Major adverse cardiovascular events, ALM: appendicular lean mass.

expression on monocytes inhibits pro-inflammatory cytokine production, antigen presentation, co-stimulatory molecule expression and inhibits monocyte and/or macrophage infiltration into adipose tissue [60].

Chronic inflammation is a molecular hub in the development progression of CKMS. Increased NF- κ B signaling and production of pro-inflammatory cytokines IL-1 β , IL-6, IL-8, IL-12, IL-17A, TNF- α , C-C motif chemokine ligand 2 (CCL-2), monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-beta (TGF- β), Th1/Th17 activation; CD8⁺T cell recruitment are all seen in CKMS with downstream effects including insulin resistance, atherosclerosis, vascular calcification, cardiac fibrosis, diabetic kidney disease, and metabolic liver disease [61]. Furthermore, chronic inflammation is associated with increased risk in components of CKMS including heart failure (HF) and atherosclerotic CVD [62], CKD [63,64], diabetes [65,66], obesity [66,67] and metabolic syndrome [68,69]. Inflammation as suggested above is an important contributor to sarcopenia. Proinflammatory cytokines such as C-reactive protein (CRP), IL-1, IL-6, and TNF- α are key factors in inducing skeletal

muscle mitochondrial dysfunction, leading to increased production of reactive oxygen species that causes activation of the ubiquitin proteasome cascade and increasing muscle proteolysis [70,71]. In addition, IL-6 induces insulin resistance, which hinders the activation of the Akt/mTOR pathway and impedes muscle protein synthesis [72]. Individuals with low appendicular skeletal muscle were found to have significantly higher levels of IL-6 and CRP [73].

4.1.4. Oxidative stress

Oxidative stress is considered a key driver of the CKMS spectrum and strongly contributes to inflammation, hyperglycemia and insulin resistance, activation of the renin-angiotensin system (RAS), and tissue injury [74,75]. Oxidative stress also contributes to sarcoplasmic reticulum/cytosolic calcium dysregulation, contractile protein degradation, motor neuron loss and neuro muscular degeneration [76]. Oxidative stress and inflammation play a synergistic role for development of sarcopenia [77].

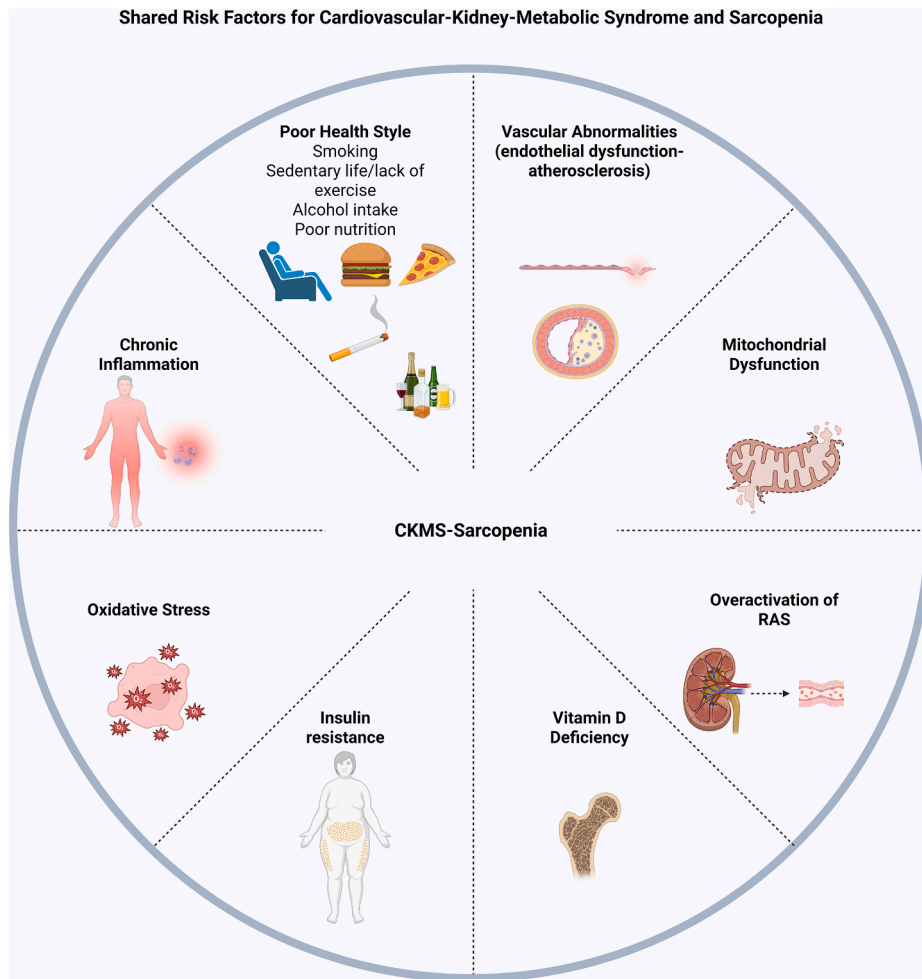


Fig. 1. Shared mechanisms Observed in Cardiovascular-Kidney Metabolic Syndrome and Sarcopenia
Abbreviations: RAS: Renin-Angiotensin System.

4.1.5. Endothelial dysfunction

Endothelial dysfunction (ED) is a key pathophysiological mechanism that underlie the multidirectional interplay among the metabolic, kidney, and cardiovascular systems. Endothelial dysfunction leads to atherosclerosis, hypertension, and compromised organ perfusion [1,78]. Vascular calcification and stiffness are another phenomenon in CKMS. Hyperglycemia, dyslipidemia, oxidative stress, inflammation advanced glycation end products, and O-GlcNAcylation all enhance osteochondrogenic differentiation of vascular smooth muscle cells leading to vascular calcification and stiffness [79]. Inflammation, insulin resistance and oxidative stress are closely related with vascular calcification, endothelial dysfunction [80–82].

4.1.6. Insulin resistance and ectopic lipid deposition

Skeletal muscle is a primary site for insulin-mediated glucose uptake; consequently, muscle atrophy contributes to systemic IR [83] which in turn promotes endothelial dysfunction [84]. The resulting endothelial dysfunction and the associated microvascular rarefaction significantly impair blood flow and nutrient delivery to skeletal muscle. This creates a state of relative muscle ischemia, which exacerbates metabolic stress, limits exercise capacity, and contributes to further muscle wasting, thereby directly feeding into the sarcopenic process [85–87].

Ectopic lipid deposition is a sign of systemic metabolic dysfunction wherein lipid overflow from dysfunctional adipose

tissue to non-adipose organs. This phenomenon associated with inflammation, oxidative stress, endothelial dysfunction and insulin resistance is one of the fundamental basis for development of CKMS [1]. Ectopic lipid deposition is not a passive process but actively playing a role which disrupt cellular signaling. In skeletal muscle, fatty acids are stored within the muscle as intramyocellular lipids which excess cause insulin resistance. In addition, accumulation of toxic lipid intermediates like diacylglycerols (DAGs) and ceramides and ceramides increases activate inflammatory pathways like NF- κ B [88]. DAGs activate protein kinase C (PKC) and inhibit the insulin receptor substrate 1 (IRS-1), while ceramides activate protein phosphatase 2A (PP2A), which dephosphorylates and deactivates Akt, thereby locally exacerbating insulin resistance and promoting further atrophy [89,90]. Furthermore, lipid droplets can interact with and disrupt mitochondrial membranes, inducing oxidative stress and impairing the energetic capacity necessary for muscle contraction and repair which explains why individuals with similar muscle mass can exhibit vastly different strength and metabolic profiles [91].

4.1.7. Vitamin D deficiency and activation of renin-angiotensin system

Vitamin D deficiency not only impair calcium metabolism, but negatively affect muscle mass. Vitamin D via its receptor Vitamin D receptor (VDR) impacts satellite cell function and maintenance of myogenic differentiation [92,93]. VDR is important for

mitochondrial function and deficiency of VDR increases expression of atrophy-related genes, leading to sarcopenia [94]. Vitamin D deficiency promotes endothelial dysfunction by upregulating the expression of pro-oxidant NADPH oxidase and downregulating endothelial nitric oxide synthase reducing nitric oxide bioavailability [95]. Vitamin D deficiency potentiates RAS leading to increased angiotensin II (AngII), which drives vascular inflammation, smooth muscle cell proliferation, and fibrosis, thereby accelerating atherosclerosis [96]. Emerging evidence also indicates that Vitamin D exerts direct immunomodulatory effects, and its deficiency causes activation of the NF- κ B pathway in both myocytes and vascular cells, amplifying the local inflammatory response [97–99]. Vitamin D receptor (VDR) is crucial for satellite cell function and myogenic differentiation [100]. VDR signaling suppression impairs mitochondrial function and increases expression of atrophy-related genes, leading to sarcopenia [94,101,102].

Increased activity of RAS system has been observed in CKMS. The RAS via AT1 receptors cause vasoconstriction, sodium retention, sympathetic nervous system activation elevated BP, inflammation, oxidative stress that leads to adverse cardiac and renal remodeling [78,103].

Over activation of RAS also associated with insulin resistance and diabetes [104,105] cardiovascular disorders [106] and metabolic syndrome [107]. The classical RAS pathway operating through AngII induces muscle wasting by variety of mechanisms including body weight reduction (via reduction in food intake due to decreased expression of hypothalamic orexin and neuropeptide Y), inhibition of IGF-1 and mammalian target of rapamycin (mTOR) signaling, escalating skeletal muscle proteolysis by fork head box transcription factors (FOXO), and by intensifying caspase activation and muscle RING-finger protein-1 transcription. Additionally, RAS activation increases apoptosis by reducing phospho-Bad (Ser136) expression, and by stimulating cytochrome c release and DNA fragmentation. Last but not the least, RAS through AT1R and AngII stimulates TNF- α , and interleukin-6, induce oxidative stress, disturb mitochondrial energy metabolism, and impair muscle satellite cells which all lead to muscle wasting and decrease muscle regeneration. On the contrary, the non-classical RAS pathway which operates through angiotensin 1-7 and Mas receptor mitigate these mechanisms and protects against muscle wasting [108].

4.2. Screening and diagnosis of sarcopenia and CKMS

Diagnosis of CKMS is based on the criteria suggested by AHA recently [1]. Screening for early signs and stages of sarcopenia is important because therapeutic interventions are likely to be most effective before sarcopenia has reached to advanced stages and is critical for mitigating the risk of subsequent severe complications [109]. There are various diagnostic criteria for sarcopenia such as the European Working Group on Sarcopenia in Older People (EWGSOP) 1, EWGSOP 2 guidelines, the Asian Working Group for Sarcopenia (AWGS) 2014, AWGS 2019 [110]. However, as suggested above, assessment of sarcopenia necessitates the evaluation of muscle mass, muscle strength, and physical performance. For muscle mass evaluation, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), computed tomography (CT) and MRI, are used [111]. Handgrip strength mostly used for muscle strength assessment. Handgrip strength test is notably straightforward, portable, quick and cost-effective [112]. Physical performance is evaluated using metrics such as usual gait speed and the 6-min walk test [111]. Recently, algorithm for screening and diagnostic approach is recommended for sarcopenia [36]. Briefly, a HGS is a good start for assessing sarcopenia as it is simple

and cost effective as suggested. If HGS is weak, muscle mass measurement is recommended. If muscle mass is reduced; measurement of physical function is advised which discriminate sarcopenia and severe sarcopenia [36]. When CKMS and sarcopenia is found simultaneously it is even more important to take non-medical and medical treatment options immediately as these conditions are interrelated and augmenting each other (Fig. 2). These interventions re described below.

4.3. Non-Medical Management of CKMS and sarcopenia

4.3.1. Improving physical activity

Modifiable factors for sarcopenia include physical inactivity, poor diet, and smoking [113]. As suggested above, physical inactivity is an important risk factor both for CKMS and sarcopenia. Combination of aerobic exercise (e.g., brisk walking, cycling) and resistance training (e.g., weight lifting) provides synergistic effects. Exercise is beneficial for cardiovascular, renal and metabolic health [114]. Aerobic exercise potently activates AMPK, enhancing mitochondrial biogenesis, fatty acid oxidation, and glucose uptake via GLUT4 translocation, thereby ameliorating systemic IR and reducing ectopic lipid deposition [91,115]. Concurrently, resistance training directly stimulates the PI3K/Akt/mTOR pathway, promoting muscle protein synthesis and hypertrophy, while also upregulating IRS-1 expression and enhancing insulin sensitivity in muscle [116]. Both exercise modalities improve endothelial function which upregulate eNOS expression and NO bioavailability [117]. Regular exercise also reduces systemic inflammation by lowering circulating levels of pro-inflammatory cytokines (e.g., TNF- α , IL-6) and by stimulating the release of anti-inflammatory myokines such as irisin and interleukin-15 from muscle, which promote lipid oxidation [118]. In patients with both HF and sarcopenia, aerobic activity is associated with reduced hospitalizations and mortality, which is thought to be a result of reductions in skeletal muscle inflammatory markers, isoform of nitric oxide synthase, myostatin, and an increase in the skeletal muscle cross-sectional area [119]. Short-term (2 days) moderate-intensity resistance exercise effectively reduced blood glucose levels and blood glucose fluctuations in elderly patients with T2M and sarcopenia [120]. In patients with CKD, studies showed that regular exercise improved physical function, cardiovascular outcomes and quality of life [121]. On the other hand, strongest evidence for the treatment and prevention of sarcopenia is derived from studies on exercise intervention programs including resistance, aerobic and combination that have been shown to increase muscle mass, strength, and physical performance [36]. In adults with 80–99 years of age with sarcopenia; combined resistance and balance exercise twice weekly for 12 weeks improved performance of activities of daily living, with a 10% absolute risk reduction in the number of falls compared with resistance exercise alone [122].

4.3.2. Smoking cessation

Smoking cessation is another important step. There is no doubt that smoking is a risk factor for cardiovascular, kidney and metabolic diseases. In patients with CKMS, smoking was associated with increased CVD [123]. Smoking is also risk factor for sarcopenia [124,125]. Thus smoking cessation not only beneficial for CVD but also for sarcopenia.

4.3.3. Nutritional management

Nutritional management is another intervention for both CKMS and sarcopenia. The dietary management of CKMS is recently reviewed from Stage 0 to stage 4. Briefly, calorie restriction in creating an energy deficit and inducing weight loss is recommended. Adopting a healthy dietary intake patterns such as plant

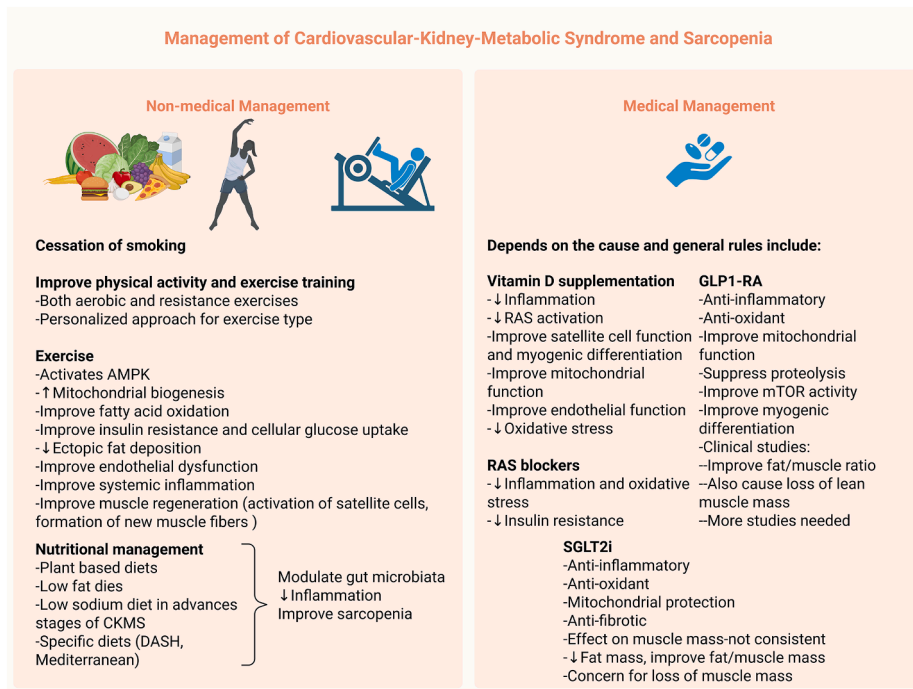


Fig. 2. Medical and Non-Medical Management of Cardiovascular-Kidney-Metabolic Syndrome and Sarcopenia

Abbreviations: AMPK: 5' AMP-activated protein kinase, DASH: Dietary Approaches to Stop Hypertension, RAS: Renin-Angiotensin System, GLP-1 RAs: Glucagon-like peptide-1 receptor agonists, mTOR: mammalian target of rapamycin, SGLT2i: Sodium-Glucose Cotransporter-2 Inhibitors.

based diets with low-fat dairy is a feasible option. In more severe stages of CKMS low sodium diet can be implemented to ameliorate excess extracellular volume and hypervolemia. Specific diet types such as DASH diet or Mediterranean diet (MedDiet), is also promising [126]. MedDiet rich in monounsaturated fats, fiber, and polyphenols, have anti-inflammatory effects by modulating gut microbiota and reducing proinflammatory cytokines (e.g., TNF- α , IL-6, CRP) [127]. Gut microbiome is modulated by high fiber which promotes the production of anti-inflammatory short-chain fatty acids (SCFAs), and polyphenols and monounsaturated fats directly attenuates inflammatory pathways [128]. The robust anti-inflammatory and cardio protective benefits of the MedDiet, which found that supplementation with extra-virgin olive oil or nuts significantly reduced the incidence of cardiovascular events and lowered key inflammatory biomarkers [129]. Indeed, the beneficial impact of MedDiet has already demonstrated in sarcopenia [130]. Similarly, the Dietary Approaches to Stop Hypertension (DASH) Diet, although originally designed to lower blood pressure, shares relevant anti-inflammatory properties [131]. DASH diet rich in fiber, potassium, magnesium, and coupled with a reduction in saturated fat, confers significant benefits for vascular health. This nutrient profile, by mitigating chronic inflammation, is also highly relevant for preserving muscle health, thereby offering a complementary dietary approach to address the sarcopenia-atherosclerosis comorbidity [132]. In a recent study including 6210 participants DASH diet demonstrates a robust inverse association with sarcopenia [133]. Supplements including long-chain omega-3 polyunsaturated fatty acids (EPA and DHA) has been demonstrated to attenuate muscle loss [134,135]. Adequate high-quality protein intake, particularly leucine-rich sources like whey stimulates muscle protein synthesis via mTOR activation, countering anabolic resistance [136,137]. Indeed, incorporating protein concentrates (e.g., whey) or branched-chain amino acids, such as leucine, into the diet can increase the rate of

mixed skeletal muscle protein synthesis [138]. However, recommendation for protein supplementation in CKMS should not be straightforward. For example, high protein diet may cause intraglomerular hypertension, which may result in kidney hyperfiltration, glomerular injury, and proteinuria. It is possible that long-term high protein intake may lead to *de novo* CKD. Furthermore, high protein intake increase dietary acid load, phosphate content, gut microbiome dysbiosis, inflammation and increased uremic toxin generation [139]. Also in patients with HF, there are a limited number of trials assessing the impact of protein and amino acid supplementation on physical capacity and quality of life [140]. Thus in patient with CKMS and sarcopenia, the individual components of CKMS should be taken into consideration and personalized and shared decisions should be applied. Lastly, polyphenols and minerals (magnesium, zinc) which further support anti-inflammatory and antioxidant defenses is useful for protecting muscle mass [141–146].

4.4. Medical Management of CKMS and sarcopenia

4.4.1. Testosterone supplementation

One of the reasons for sarcopenia development especially in elderly patients is testosterone deficiency. A decrease in testosterone levels and anabolic effects with age or in chronic diseases (along with inflammatory conditions) may lead to bone loss as well as a reduction in muscle mass and strength [147]. Testosterone deficiency has detrimental effects and induces myostatin expression, decrease in IGF-1 levels, increase pro-inflammatory cytokines, decrease satellite cell function, increase fat deposition in muscles and induce mitochondrial degeneration [148]. Some studies showed that testosterone supplementation was associated with increased lean body mass, stair-climbing power, and decreased fat mass [149,150] while others showed no effects [151,152]. In addition, testosterone supplementation may be

related with serious side effects including atrial fibrillation, of acute kidney injury, and of pulmonary embolism [153,154]. Based on these, testosterone therapy cannot be recommended as a routine therapy for sarcopenia in CKMS but individualized approach is needed.

4.4.2. Vitamin D supplementation

As suggested above vitamin D deficiency is a risk factor for CKMS and sarcopenia and cardiovascular disease [155]. In patients with CKMS, reduced serum 25(OH)D levels demonstrated significant associations with elevated all-cause and CVD mortality risk [156]. Vitamin D supplementation also increased muscle strength in patients with sarcopenia [157]. Thus in patients both with CKMS and sarcopenia vitamin D supplementation seems a feasible option although no RCT performed in this patient group.

4.4.3. RAS blockers

As suggested above, activation of classical RAS plays a role in development of both CVD and sarcopenia. Importantly trials showed consistent benefit of RAS blockage for cardiovascular disorders and diabetic kidney disease [158–162]. In HF patients, RAS inhibition is associated with a lower prevalence of muscle wasting and higher muscle strength [163,164]. In patients with ESRD, RAS inhibitors decreased sarcopenia [165]. In patients with HF and diabetes, renin-angiotensin system activation is associated with responsible for the development of muscle wasting [166] and in patients with HF and diabetes, use of Renin-angiotensin system inhibitors associated with significantly lower muscle wasting [167].

4.4.4. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP1-RAs) and sodium-glucose cotransporter 2 inhibitors

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP1-RAs) is another class of medications that hold promise. Benefits of GLP1-RAs on kidney disease and cardiovascular disease has already shown [168,169]. They also improve metabolic syndrome and decrease liver steatosis and fibrosis [170–172]. Recently, GLP-RA have been suggested as a tool for sarcopenia prevention and treatment via direct effects on muscle as anti-inflammatory, antioxidant, and mitochondrial-supportive mechanisms. They also modulate of key signaling pathways such as PI3K/Akt/mammalian target of rapamycin (mTOR) and AMP-activated protein kinase-PGC-1 α , suppression of proteolytic activity, and promotion of myogenic differentiation [173]. In contrast, findings from large-scale trials have raised concerns that a significant proportion of the weight loss achieved with GLP-1RA treatment may derive from lean body mass-particularly skeletal muscle-which could be detrimental in populations already at risk for sarcopenia [168,174]. These medications are associated with substantial lean body mass loss, comprising 15–45% of total weight reduction [175]. However, studies also showed that in patients with preserved HF, semaglutide improved 6-min walk distance compared to placebo [176]. Additionally, weight loss is accompanied by some loss of lean mass, but fat loss predominates. In STEP-1 (semaglutide), lean mass decreased by -9.7% while fat mass fell by -19.3%, with the proportion of lean mass increasing by ~3 percentage points [174]. Based on this, GLP-1RAs provide substantial weight loss and cardio metabolic benefits but may compromise skeletal muscle integrity, whereas exercise supports muscle maintenance and functional health. When patient is started GLP-1RAs for cardiovascular disease, the regular surveillance for muscle mass and function would be of potential importance.

Likewise, sodium-glucose cotransporter 2 inhibitors (SGLT2i) are another class of medications that showed consistent cardiovascular kidney benefit of SGLT2i [177,178]. SGLT2i also effective in

metabolic associated Fatty liver disease which they decreased liver fat content [179,180]. Some studies have shown that these medications improve sarcopenia [181]. and Skeletal Muscle Mass/Fat Mass Ratio, some showed neutral effect [182–184] others showed increased risk for sarcopenia [185,186]. A recent meta-analysis including 18 studies with 1430 participants showed that SGLT2i significantly reduced body weight, body mass index, waist circumference, visceral fat area, fat mass, percentage body fat, lean mass, and skeletal muscle mass. However, skeletal muscle mass was evaluated in seven studies in 206 SGLT-2 inhibitors users and 201 non-users in this meta-analysis. Authors acknowledge that only a few randomized trials met the conditions, and most of them had small sample sizes with a short follow-up period [187]. Thus data on SGLT2i-associated effects on skeletal muscle are limited and controversial. The reasons for these discordant findings were not explained but there is an urgent need for research, and there is unmet need to clarify these issues to avoid the unfavorable decrease in muscle mass. In addition, protective measures should be planned to avoid muscle loss if SGLT2i is proven to induce sarcopenia [188].

5. Clinical perspectives

As health care providers, we have a major role in management of CKMS-and sarcopenia in a comprehensive manner and clinical perspectives to achieve this goal is outlined in Fig. 3. During daily practice clinical priorities, lack of training, time shortage, difficulty in accessing tools and devices may prevent clinicians conducting sarcopenia assessment especially in patients with multiple comorbidities such as CKMS. However, CKMS and sarcopenia have bidirectional relationships and impairs health status synergistically and comprehensive evaluation is important. Early identification and targeted interventions may help reduce CKMS progression and sarcopenia. Indeed, there is an urgent need for interventions that not only address the CKMS but also incorporate sarcopenia assessment. Given that sarcopenia often occurs in the setting of prolonged immobility, end-organ damage/failure, chronic inflammation, malnutrition, biomarkers that integrate multi “omics” could be helpful for detection and longitudinal assessments of sarcopenia. A working group from the TAME trial (Targeting Aging With Metformin) has accordingly recommended the following: hemoglobin A1c, CRP, N-terminal pro-B-type natriuretic peptide, (NT-proBNP), insulin, IGF-1, cystatin C, IL-6, TNF- α receptor I or II, GDF15, but also noted a paucity of evidence [189].

Interventions to promote healthy lifestyles (e.g. increasing physical activity, smoking cessation, healthy diet) should be implemented for all patients. Routine screening for sarcopenia with easy to perform, valid and reliable methods especially in the later stages of CKMS may not only improve psychological well-being but also enhance treatment adherence, self-management behaviors, and ultimately cardio-metabolic outcomes. To accomplish these tasks, collaboration with dietitians to implement solutions based on local resources to ensure that sarcopenia assessment to be done in timely manner. In resource constrained conditions simple measures such as weight, body mass index, mid-arm muscle circumference can be applied. Handgrip strength test can also be used since its simple, inexpensive and minimal training is needed. For elderly people it is important to involve caregivers in the nutrition assessment process. Adequate intake of energy and protein is also important. Furthermore, muscle mass screening should be incorporated into the routine clinical assessment for young patients diagnosed with CKM syndrome, especially those in the early stages of the condition, which enables early interventions. When sarcopenia is diagnosed, detailed work-

Clinical Implications
<p>Evaluation of early risk factors and early diagnosis (sedentary life/exercise/unhealthy food)</p> <p>Initiate screening programs and simple measures for CKMS-Sarcopenia</p> <ul style="list-style-type: none"> -Measure weight/height, comprehensive physical examination -For frail patients→check CKMS end organ damage (i.e. EKG, microalbuminuria, fundoscopic examination) -For patients with CKMS: <ul style="list-style-type: none"> –Start with simple tests (i.e. check hand-grip strength, gait speed, chair-stand test, mid-arm muscle circumference) –Advanced tests when indicated (i.e. muscle mass measurement) –Non-medical management for every individual –Medical management for selected patients as a team based approach based on shared decision making

Fig. 3. Clinical implications of management of cardiovascular-kidney metabolic syndrome and sarcopenia.

up is necessary to identify underlying causes. The management of sarcopenia should involve systematic approach including healthy behavioral pattern and when underlying medical condition is elucidated, medical treatment should be started according without delay with regular follow-up scheduled.

6. Conclusions

Sarcopenia is a multifactorial condition characterized by an imbalance between muscle protein synthesis and degradation, influenced by aging, inflammation, hormonal changes, neuromuscular alterations, and reduced physical activity. Sarcopenia and CKMS share common mechanisms and recent studies showed that they occur concurrently. Screening and testing for sarcopenia may be particularly important among those with CKMS and management of sarcopenia and CKMS should be considered simultaneously. For all patients, education about healthy behaviors is very important. If needed, pharmacologic treatment in addition to non-pharmacologic measures should be started after shared decision making. Although, studies included in this narrative review already showed that sarcopenia and CKMS were associated; these studies are observational and new mechanistic and randomized studies are needed to understand underlying mechanisms in both conditions. Furthermore, new technologies are needed to screen specific biomarkers associated with both CKMS, and sarcopenia. It is also important to verify the strength of the association between each CKMS stage and the incidence, and long-term adverse outcomes of sarcopenia in different CKMS stages.

Author contributions

BA conceived and designed the narrative review, led the literature identification and synthesis, developed the conceptual framework, and drafted the manuscript. MK contributed to methodological interpretation, and critically revised the manuscript. REA contributed to conceptual framework, and methodology and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Authorship

No one eligible for authorship has been excluded from the list of authors.

Data sharing

No new data were created or analyzed in this study. Data from the literature are cited within the manuscript.

Ethics approval

Not applicable.

Declaration of generative AI use

Non declared.

Funding

None declared.

Conflict of interest

The authors declare that they have no competing interests.

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