

REVIEW OPEN ACCESS

# Osteosarcopenia in Chronic Kidney Disease: An Overlooked Syndrome?

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## ABSTRACT

**Background:** Healthy ageing relies on maintaining physiological systems, particularly the musculoskeletal system (MKS). After 50, declines in bone density, muscle mass and strength increase the risk of osteoporosis and sarcopenia, leading to frailty, fractures and higher healthcare costs. Osteosarcopenia, combining osteoporosis and sarcopenia, is rising because of the ageing population. Chronic kidney disease (CKD) exacerbates this condition through disruptions in mineral metabolism, hormonal imbalances and inflammation, further compromising musculoskeletal health.

**Aims:** This review examines the pathophysiology of osteosarcopenia associated with CKD, focusing on the role of mineral and hormonal disturbances, chronic inflammation and endocrine dysfunction. It aims to increase clinical awareness and highlight the need for early diagnosis and intervention to mitigate the burden of osteosarcopenia on the quality of life and healthcare systems in ageing CKD populations.

**Methods:** A narrative review of the current literature was conducted, summarising evidence on the mechanisms underlying osteosarcopenia in CKD, including mineral metabolism alterations, inflammatory processes and hormonal imbalances.

**Results:** Osteosarcopenia is a recognised consequence of CKD, contributing to increased morbidity and mortality. The pathophysiology of osteosarcopenia in CKD is multifactorial, involving disruptions in mineral metabolism, inflammation, endocrine dysfunction and physical inactivity. CKD–mineral and bone disorder (CKD-MBD) leads to alterations in calcium, phosphate, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23) and vitamin D metabolism, resulting in impaired bone mineralisation and increased fracture risk. Simultaneously, CKD accelerates muscle wasting through systemic inflammation, anabolic resistance and metabolic derangements, increasing the risk of sarcopenia. Sarcopenic obesity, inflammaging and hormonal dysregulation further exacerbate bone muscle deterioration. Emerging evidence suggests that osteosarcopenia in CKD is a consequence of interconnected pathophysiological pathways rather than isolated conditions. Diagnosis remains challenging because of overlapping clinical features, necessitating integrated assessment tools. Targeted therapeutic strategies, including mineral metabolism correction, resistance exercise and anabolic interventions, are essential to mitigate osteosarcopenia's progression and improve patient outcomes in CKD.

Lara Caldiroli and Paolo Molinari share first authorship.

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**Conclusions:** Osteosarcopenia is a growing concern in ageing CKD populations. Early diagnostic strategies and targeted interventions are essential to mitigate the impact of osteosarcopenia on patient outcomes and reduce associated healthcare costs. Increased clinical awareness and research into effective therapies are crucial for improving the quality of life for individuals affected by CKD and osteosarcopenia.

## 1 | Introduction

### 1.1 | Osteosarcopenia: An Unrecognised Burden

The musculoskeletal (MSK) system plays a central role in enabling human ambulation and acts as a metabolic reservoir for calcium in bones and glucose and amino acids in muscles. However, in the sixth decade of life, a gradual decline in bone mineral density (BMD) (~1%–1.5% per year), muscle mass (~1% per year) and strength (~2.5%–3% per year) occur [1, 2], putting people at risk of osteoporosis and sarcopenia—two conditions classified by the International Classification of Diseases.

Osteopenia and osteoporosis are defined by the World Health Organisation as *T*-scores of –1 and –2.5 standard deviations below the peak bone mass of a young healthy population, respectively [1, 3]. Osteoporosis reduces the micro-architecture of the bone and impairs bone strength [3, 4], whereas sarcopenia is characterised by low muscle strength, low muscle mass and quality, and its severity is defined by the degree/or low functional capacity [1, 4]. Both conditions share common risk factors [1, 3]. They are strongly associated with frailty, falls, fractures, hospitalisation and mortality, leading to increased healthcare expenditure [1, 5].

The term osteosarcopenia, coined by Duque and colleagues, describes a subgroup of older people affected by both osteoporosis and sarcopenia [1, 6]. The combination of low bone density (osteopenia/osteoporosis) and low muscle mass, strength and/or functional capacity (sarcopenia) defines this unique syndrome [3].

With an ageing population expected to increase from ~841 million in 2013 to ~2 billion by 2050 (a proportional increase of 9%), the prevalence of osteosarcopenia is expected to increase, leading to increased incidence of falls, fractures and hospitalisations [1, 7].

Muscle and bone loss often occur together in older people, and many studies have shown a strong relationship between the components (osteoporosis and sarcopenia) of osteosarcopenia [8]. In a cohort of 590 postmenopausal Finnish women, those with sarcopenia had a 12.9 times higher risk [95% confidence interval (CI) 3.1–53.5] of having osteoporosis than those without sarcopenia [9]. In the Sarcophage cohort of 232 older people, those with sarcopenia had a five times higher risk of developing osteoporosis [95% CI 1.16–19.41]. Subsequent cross-sectional and longitudinal studies have provided further support for the bidirectional relationship between osteoporosis and sarcopenia, leading to the development of osteosarcopenia [10, 11].

### 1.2 | The Significance of Osteosarcopenia in CKD

Advanced age is burdened not only by a significant impairment in functional capacity, as described above, but also by the frequent onset of multiple comorbidities. In this context, CKD is a condition that predominantly affects elderly individuals and is frequently associated not only with a significant burden of comorbidities but also with a substantial impairment of the patient's functional status.

CKD is a complex disease characterised by progressive renal dysfunction. The impact of CKD extends beyond renal function to multiple organ systems, including the MSK system.

Among the various systems affected by CKD, the metabolic trophism, osteomuscular health and functional reserve of the patient are among the most important. However, there are currently no clear guidelines and/or expert consensus to guide clinical decision-making.

This review aims to provide clinicians with an overview of the pathophysiology and diagnosis of osteosarcopenia in chronic kidney disease (CKD) in order to raise awareness of this under-recognised MSK syndrome.

## 2 | Pathophysiology of Osteosarcopenia in CKD

Osteosarcopenia is a recognised consequence of CKD and contributes to increased morbidity and mortality. The pathophysiology of osteosarcopenia in CKD involves a complex interplay between hormonal, inflammatory and metabolic factors.

### 2.1 | CKD–Mineral Bone Disorder (CKD-MBD)

CKD is a complex condition involving biochemical changes in the metabolism of calcium, phosphorus, parathormone (PTH), vitamin D and fibroblast growth factor 23 (FGF-23). The main aspects of mineral metabolism are depicted in Figure 1 [12, 13].

#### 2.1.1 | PTH Axis in CKD

The regulation of extracellular calcium levels is essential for cellular functions, with calcitriol controlling calcium absorption in the gut. Calcium directly affects parathyroid cells via the calcium-sensing receptor (CaSR), which detects changes in extracellular calcium levels. A decrease triggers parathyroid hormone (PTH) release, whereas an increase suppresses it. Bone changes in CKD are linked to early disruptions in



**FIGURE 1** | Schematic representations of PTH, vitamin D and FGF-23 metabolism. *Note:* Schematic representations of PTH, vitamin D and FGF-23 metabolism, illustrating their integrated roles in maintaining calcium-phosphate homeostasis. The diagram details the mechanisms of PTH secretion in response to changes in serum calcium, its effects on bone resorption and renal phosphate excretion. It also highlights vitamin D metabolism, including its synthesis from precursors through sunlight and dietary sources, conversion to 25OH-D in the liver and activation to 1,25OH-D in the kidneys, emphasising its role in calcium absorption in the gut and feedback regulation of PTH. Additionally, the figure depicts FGF-23 secretion by osteocytes in response to hyperphosphatemia, its interactions with the Klotho coreceptor and its suppression of calcitriol synthesis and renal phosphate reabsorption. These pathways collectively contribute to the dynamic regulation of mineral metabolism, with dysregulation contributing to the pathophysiology of CKD-MBD. 1,25(OH)<sub>2</sub>D, 1,25(OH) vitamin D; 25(OH)D, 25(OH) vitamin D; 7-DHC, 7 dehydrocholesterol; Ca, calcium; CaSR, calcium sensing receptor; FGF-23, fibroblast growth factor 23; P, phosphate; PTH, parathormone; PTH1r, parathormone 1 receptor; VDR, vitamin D receptor.

phosphorus, calcium, PTH and calcitriol metabolism as renal function deteriorates [14, 15]. In the proximal tubule, PTH inhibits phosphate reabsorption by reducing the abundance of sodium phosphate cotransporters in the apical membrane. PTH likely decreases calcium reabsorption from the proximal tubule, by reducing the reabsorption of sodium, an event necessary for the paracellular movement of calcium across this segment. In the thick ascending limb (TAL), PTH increases calcium permeability and may increase the electrical driving force thereby increasing calcium reabsorption in the TAL. These mechanisms maintain calcium and phosphate balance until GFR declines significantly, after which hyperphosphatemia occurs [14, 16].

### 2.1.2 | Vitamin D in CKD

Vitamin D metabolism relies on sunlight and dietary intake. Sunlight generates cholecalciferol, which is converted to 25OH-D in the liver and then hydroxylated in the kidney to form active vitamin D (1-25OH-D), critical for metabolic functions [17]. CKD patients, even in early stages, show vitamin D deficiency due to interstitial fibrosis and reduced kidney synthesis of 1-25OH-D, inhibited by elevated FGF-23 and phosphate levels [13, 14]. Calcitriol deficiency impairs calcium absorption, decreases systemic VDR levels and reduces CaSR expression in parathyroid cells, further stimulating PTH secretion. Elevated serum phosphorus also exacerbates PTH secretion via CaSR interaction [14, 18]. This creates a feedback loop contributing to secondary hyperparathyroidism. PTH enhances bone turnover through RANK-L and osteoprotegerin signalling, leading to weakened, fragile bones and increased fracture risks, along with vascular calcifications [14, 15].

Vitamin D deficiency also impacts MSK health. Experimental vitamin D deficiency or VDR knockout models reveal muscle atrophy, reduced mass and impaired function [19, 20]. Overexpression of VDR induces muscle hypertrophy, with VDR levels increasing following resistance training [21]. VDR deletion disrupts metabolic pathways and neuromuscular control, exacerbating risks for osteosarcopenia, falls and fractures [22]. These findings highlight the intricate links between vitamin D, bone health and CKD progression.

### 2.1.3 | FGF-23 in CKD

FGF-23's role in bone metabolism remains complex. It suppresses calcitriol synthesis and regulates phosphate excretion,

influencing bone abnormalities in CKD [3, 14, 23]. FGF-23 levels increase before phosphate levels rise [12, 13, 16] and correlate with bone mineralisation changes. Studies suggest that FGF-23 levels rise early in CKD, even before PTH [15, 16, 24]. It stimulates osteoblast-like cell proliferation while inhibiting mineralisation via its coreceptor Klotho [12, 25]. In dialysis patients, high bone turnover associates with elevated serum FGF-23, yet high FGF-23 correlates with normal mineralisation. Regression analysis identifies FGF-23 as an independent predictor of mineralisation lag time [12, 26]. Paediatric CKD patients with high bone turnover and renal osteodystrophy also exhibit improved mineralisation linked to high FGF-23, though bone formation rates remain unaffected [12].

Elevated FGF-23 levels align with high bone turnover, whereas low levels associate with reduced turnover [12]. These findings position FGF-23 as a predictor of bone metabolism and mineralisation changes in CKD patients undergoing dialysis.

PTH and FGF-23 also interact directly within the bone. PTH increases FGF-23 mRNA levels and inhibits sclerostin mRNA in osteoblast-like cells, implicating the Wnt pathway in their actions.

### 2.1.4 | Other Bone Metabolism Biomarkers in CKD

Protein expression studies in CKD patients reveal that as CKD progresses, serum alkaline phosphatase, FGF-23, PTH and osteoprotegerin increase while calcium decreases, leading to heightened bone resorption and reduced mineralisation [12, 27]. Sclerostin, a marker of mature osteocytes, is expressed more in early-stage CKD, whereas FGF-23 expression predominates in early osteocytes. Sclerostin levels rise early in CKD, even before FGF-23 or PTH elevation, as shown in the jck mouse model of progressive kidney disease. Sclerostin negatively correlates with bone formation, osteoblast function and PTH levels in stage 5D CKD patients [12, 15]. Mice and renal osteodystrophy patients exhibit an inverse correlation between sclerostin and PTH levels, with sclerostin predicting low bone turnover and contributing to adynamic bone disease and fractures [28, 29].

Moreover, increased PTH stimulates osteoblasts and osteoclasts via the receptor activator of nuclear factor-kappaB (RANK-L) and osteoprotegerin signalling pathways, leading to increased bone turnover, resulting in a less strong and more fragile bone structure, which contributes to increased fracture risk and changes in vascular metabolism leading to vascular and valvular calcification [14, 15].

## 2.2 | CKD Affects Both Bone and Muscle Health

Patients with CKD and low bone turnover are often older individuals with a high prevalence of comorbidities, including malnutrition, inflammation and hypoalbuminemia. These factors contribute to the development and progression of low bone turnover, a condition marked by a lack of proper bone remodelling activity. Several underlying mechanisms and conditions predispose CKD patients to low bone turnover, including insufficient PTH signalling, diminished WNT/ $\beta$ -catenin signalling pathways, malnutrition, systemic inflammation, diabetes mellitus and the presence of uremic toxins (Figure 3) [29, 30]. These disruptions collectively impair bone formation and resorption, leading to skeletal fragility and increased susceptibility to fractures.

Osteoporosis, falls and fractures are particularly common in CKD patients because of abnormalities in calcium, phosphate, PTH and vitamin D metabolism. These disturbances, coupled with cardiovascular calcifications and structural bone abnormalities, contribute to a heightened risk of fractures and other complications [31, 32]. CKD stages 3a-5D are characterised by reduced BMD and mechanical strength, which significantly increases the likelihood of fractures. For individuals with end-stage kidney disease (ESKD), the fracture risk is two to three times higher than in the general population [6, 33, 34]. Moreover, fractures in CKD patients tend to occur at a younger age compared with the general population, reflecting the accelerated bone deterioration associated with the disease [31, 35]. The consequences of these fractures are severe, as CKD patients experience significantly higher morbidity and mortality rates. For example, the mortality risk for dialysis patients is approximately 3.7 times greater than that of the general population [31, 36].

In addition to bone health issues, CKD also significantly impacts skeletal muscle mass. Patients with CKD frequently experience muscle wasting because of increased protein catabolism and reduced protein synthesis, processes exacerbated by uraemia and systemic inflammation [33, 37]. Although muscle mass naturally declines with age, individuals undergoing dialysis face an accelerated rate of muscle loss, surpassing what would typically be expected from ageing alone [38, 39]. This reduction in muscle mass is compounded by frailty and diminished physical activity, further increasing the risk of falls and fractures in this vulnerable population [39–41]. The dual impact of impaired bone and muscle health highlights the importance of addressing both conditions in CKD patients.

Osteosarcopenia, a syndrome defined by the co-occurrence of osteoporosis and sarcopenia, is increasingly recognised as a critical factor in the heightened fracture risk among CKD patients. However, the concept of osteosarcopenia remains relatively new, and most studies investigating its role in falls and fractures have focused on the general population.

## 2.3 | Sarcopenic Obesity

The prevalence of sarcopenic obesity in CKD is reported to be 2%–23% [42].

Baumgartner first proposed the term ‘sarcopenic obesity’ in 2000, defining it as a phenotype in which sarcopenia and excess fat, that is, obesity, coexist [43, 44]. Sarcopenic obesity is an emerging geriatric syndrome that leads to many adverse clinical complications such as frailty, falls, disability, immobility, fractures, cardiometabolic and respiratory diseases, cancer and increased mortality [45–47]. Sarcopenia and obesity are independently associated with the risk of falling, and the risk of fracture is increased in older men with sarcopenic obesity compared with men who are not sarcopenic obese [19, 48]. In addition, obese people have relative BMD deficiency and low bone turnover associated with insulin resistance [19, 49], creating the trinity of osteosarcopenic obesity [19, 50].

Adipogenesis was found to be an expression of biological ageing via the mesenchymal stem cell (MSC) differentiation pathway [33, 51]. Important stages in the development of osteoporosis may be related with the presence of medullary adiposity and/or intramuscular adipose tissue. The presence of adipocytes can have an impact on the microenvironment by altering myogenesis and osteogenesis producing local levels of adipokines, free fatty acids and lipids. This can lead to local lipotoxicity, with a decrease in bone formation and an increase in bone resorption [33, 52].

As a result, the infiltration of fat into muscle fibres has been correlated with cellular dysfunction [33, 53]. In muscle, fat can accumulate between muscle bundles in the form of adipocyte deposits (intramuscular fat) and/or within muscle fibres in the form of fat infiltrates (intramyocellular fat). These infiltrations appear to involve insulin resistance, inflammation and skeletal muscle dysfunction [33, 54, 55].

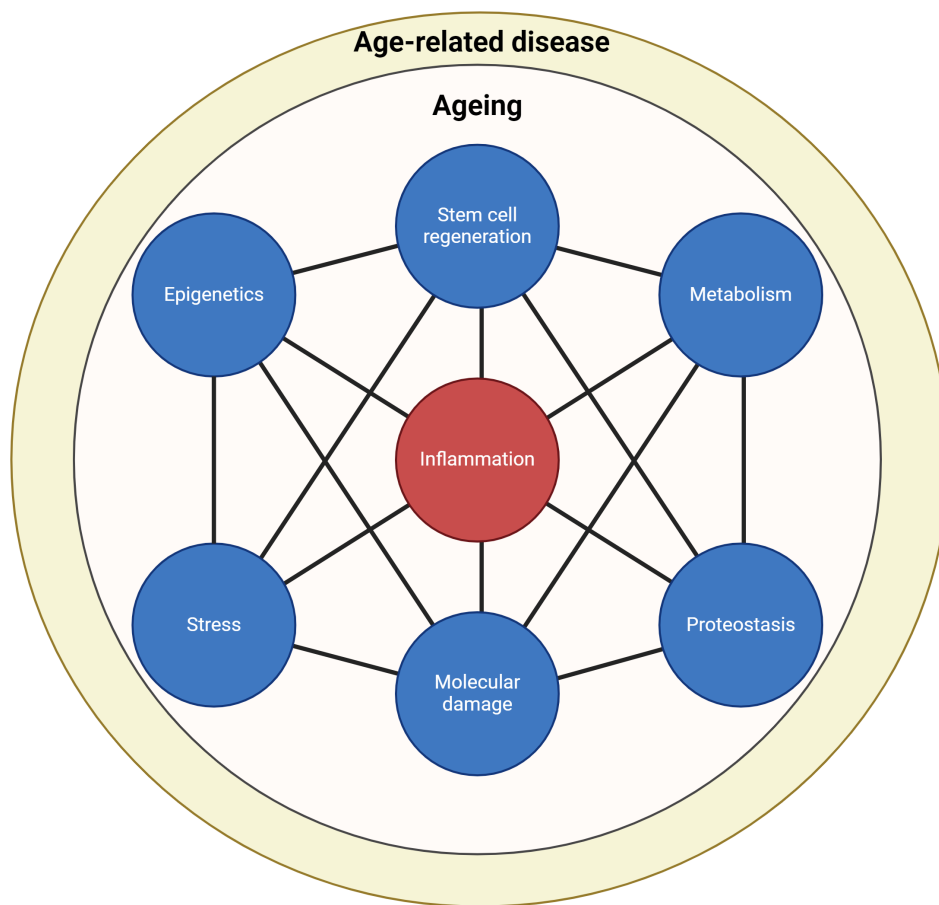
CKD contributes to the development of sarcopenic obesity. This is driven by several interrelated mechanisms affecting muscle and adipose tissue metabolism. CKD-associated insulin resistance impairs glucose uptake by muscle cells, leading to muscle atrophy while promoting fat storage, particularly in visceral adipose tissue [56, 57]. CKD is also characterised by a state of low-grade chronic inflammation, driven by elevated levels of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ . These cytokines promote muscle breakdown (catabolism) while simultaneously stimulating fat accumulation by inducing insulin resistance and promoting adipogenesis [58].

CKD disrupts several hormonal axes, including reduced levels of anabolic hormones (growth hormone, testosterone and IGF-1) and altered adipokines (leptin and adiponectin), and also contributes to muscle loss and fat accumulation. In addition, protein-energy wasting (PEW), a common complication of CKD, exacerbates muscle wasting while fat mass is maintained or increased [57].

## 2.4 | Inflammageing

CKD is associated with PEW, a condition characterised by the loss of body weight including lean muscle mass. The aetiology of PEW in CKD is complex and multifactorial: reduced food intake because of anorexia, changes in taste, uremic gastritis and the high number of medicines prescribed may all contribute





**FIGURE 2** | Cornerstones of inflammaging. *Note:* Inflammaging, a portmanteau of inflammation and ageing, describes the chronic, low-grade inflammation prevalent in aged individuals. This figure illustrates the complex interplay of various cellular and molecular components contributing to inflammaging. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), alongside activated immune cells like macrophages and T cells, signify the inflammatory milieu characteristic of inflammaging. This sustained inflammatory state is implicated in the pathogenesis of age-related diseases, including cardiovascular disorders, neurodegenerative conditions and metabolic syndromes, ultimately influencing overall health span and longevity.

to reducing energy and protein intake [59, 60]. PEW is also associated with increased production of pro-inflammatory cytokines, in particular IL-6, IL-1 and TNF, and the resulting inflammatory state leads to loss of bone and muscle mass. The term ‘inflammaging’ emerged in 2000 to describe a chronic, low-grade inflammation that increases with age and is a significant risk factor for morbidity and mortality in elderly individuals (Figure 2) [61, 62]. This age-related increase in background inflammation is thought to result from cumulative exposure to environmental and infectious antigens, leading to the production of reactive oxygen species (ROS). ROS stimulate further innate and adaptive immune cytokine release, shifting the immune balance towards chronic inflammation [61, 63]. Studies have linked chronically elevated inflammatory cytokines to the development of sarcopenia, possibly by activating the ubiquitin-protease pathway [62, 64, 65] and by increasing pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 and IL-6, which promote bone resorption [62, 64, 66]. These cytokines promote osteoclastogenesis, the process by which osteoclasts (bone-resorbing cells) are formed. The increased osteoclast activity leads to excessive bone resorption, weakening bone structure and increasing fracture risk [62, 64, 66]. The chronic inflammatory state disrupts the delicate balance between bone formation

and resorption, leading to bone loss characteristic of osteoporosis and osteosarcopenia. Impaired chronic inflammation also interferes with bone regeneration processes. Inflammatory cytokines reduce the activity and survival of osteoblasts, limiting their capacity to repair and regenerate bone tissue. This impaired bone remodelling contributes to reduced bone density and increased susceptibility to fractures, particularly in elderly CKD patients. In addition, epidemiological studies have shown a positive association between both osteoporosis and sarcopenia and C-reactive protein (CRP), which is a marker of active inflammation [67–70]. One known mechanism of communication between the bone and muscles is through factors called myokines, which are released from muscle, and osteokines, which are released from bone, such as osteocalcin. One myokine, myostatin, has been extensively studied. In mice, it has been shown to play an important role in the impaired proliferative capacity of muscle and bone progenitor cells with age [71]. In addition, it has been shown that the Wnt-b-catenin pathway mediates the cross-talk between bone and muscle by controlling both osteogenesis and muscle regeneration [72]. Understand the molecular pathways through which muscle and bone work together offers potentially exciting molecular targets for developing therapies to treat osteosarcopenia.

## 2.5 | Endocrine Dysfunction

Anabolic hormone deficiency may be a contributory factor in the development of MSK disorders.

In particular, hormones associated with the development of sarcopenia and bone loss in CKD are testosterone, myostatin and growth hormone/insulin-like growth factor-1 (IGF-1) [73]. The prevalence of hypogonadism in men with CKD was reported to be 46.4% [74]. When haemodialysis and nondialysis-dependent CKD (NDD-CKD) male patients were compared with healthy controls, testosterone levels and muscle mass were lower in dialysis-dependent patients [74]. The release of myostatin in muscle cells has been linked to inflammation and oxidative stress. Decreased testosterone leads to increased myostatin expression in muscle cells and impaired IGF-1 signalling [75]. This has been suggested to have a negative effect on muscle differentiation and growth by stimulating protein catabolism and reducing protein synthesis [75]. Resistance to the growth hormone/IGF-1 axis leads to low muscle mass and is associated with sarcopenia in end-stage renal disease (ESRD) because of reduced renal clearance of growth hormone, metabolic acidosis, inflammation and uraemia [73]. Conditional deletion of the androgen receptor in satellite cells or fast-twitch muscle fibres further contributes in an osteosarcopenic phenotype [19, 76, 77].

Androgens are also known to determine periosteal bone expansion during puberty via the androgen receptor [19, 78]. Through the androgen receptor in osteoblasts and osteocytes, but not in osteoclasts, androgens also exert antiresorptive effects in bone [76, 79]. Indirectly, the androgen receptor in neuronal cells also prevents the thinning of the cortical bone and the loss of trabecular bone in the vertebral body in mice [80]. It is interesting to note that androgen deficiency increases the skeletal response to mechanical stress [79].

Oestrogen plays a crucial role in the maintenance of both bone and muscle health, and its deficiency has been implicated to a significant degree in the pathogenesis of osteosarcopenia, particularly in patients with CKD [81, 82]. Oestrogen is critical for bone homeostasis, primarily through its effects on bone remodelling. It regulates the balance between bone resorption and bone formation by acting on osteoclasts, osteoblasts and osteocytes. Oestrogen suppresses osteoclastogenesis by downregulating receptor activator of nuclear factor  $\kappa$ B ligand (RANKL), a key promoter of osteoclast differentiation, while increasing osteoprotegerin (OPG), a decoy receptor for RANKL. This hormonal action helps to maintain bone mass by limiting excessive bone resorption [81, 83]. In the absence of oestrogen, such as in postmenopausal women or CKD patients with endocrine dysfunction, increased bone resorption occurs, leading to reduced BMD and increased risk of fracture [82]. This problem is compounded by the development of CKD-MBD, which is associated with dysregulation of calcium, phosphate and PTH levels [82]. Oestrogen deficiency exacerbates this condition and accelerates bone loss. In addition, CKD patients are prone to secondary hyperparathyroidism due to impaired renal function, leading to elevated PTH levels, which further increase bone resorption. Studies have shown that oestrogen replacement therapy (ERT) can counteract this

process by reducing PTH levels and markers of bone turnover, ultimately improving BMD and reducing the risk of fracture in postmenopausal women with CKD [82].

In addition, oestrogen also affects muscle mass, which is critical in the context of osteosarcopenia. Oestrogen deficiency contributes to sarcopenia through multiple mechanisms, including impaired muscle protein synthesis, increased inflammation and mitochondrial dysfunction. Oestrogen has been shown to increase muscle protein synthesis by modulating the expression of insulin-like growth factor 1 (IGF-1), a key regulator of muscle anabolism. In CKD patients, where PEW and inflammation are prevalent, the protective effects of oestrogen on muscle mass are further reduced, exacerbating sarcopenia [81, 82]. Oestrogen also has anti-inflammatory effects on pro-inflammatory cytokines such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), both of which are elevated in CKD and contribute to muscle wasting and bone loss. In postmenopausal women with CKD, ERT has been associated with improvements in both bone and muscle parameters [81, 82]. In addition to increasing BMD, oestrogen therapy improves muscle strength and reduces the risk of falls and fractures, which are key factors in preventing osteosarcopenia-related morbidity and mortality. However, the use of ERT in CKD must be carefully considered because of potential risks such as thromboembolic events and cardiovascular complications, especially in people with advanced CKD [81, 82].

## 2.6 | Osteosarcopenia and Physical Activity in CKD Patients

The relationship between physical activity and osteosarcopenia in CKD is complex and multifaceted, involving interactions between muscle and bone metabolism, systemic inflammation and hormonal dysregulation [84]. Physical activity, particularly resistance exercise, has been shown to play a critical role in mitigating the effects of osteosarcopenia by improving both bone and muscle health [84, 85]. One of the central mechanisms by which physical activity influences osteosarcopenia in CKD is by promoting mechanical loading of bone and muscle. Mechanical stimuli are critical for maintaining bone mass and structure by stimulating osteoblast activity and suppressing osteoclast-mediated bone resorption, thereby improving BMD. Physical activity has been associated with increased BMD, which is essential for reducing fracture risk in CKD patients who are already vulnerable to skeletal fragility due to CKD-MBD [86].

In addition to bone health, physical activity is essential for maintaining and increasing muscle mass [87]. CKD patients often experience sarcopenia due to PEW, chronic inflammation and hormonal [87] imbalances, all of which contribute to muscle wasting. Resistance exercise has been shown to counteract muscle wasting by promoting muscle protein synthesis and improving muscle strength, which is particularly important in preventing falls and fractures in patients with CKD and osteosarcopenia [86, 87]. Exercise induces muscle growth by activating the mechanistic target of rapamycin (mTOR) pathway, which regulates muscle protein synthesis,

and by inhibiting myostatin, a negative regulator of muscle growth [87].

Physical activity also has anti-inflammatory effects that are beneficial in the context of osteosarcopenia and CKD. CKD patients have elevated levels of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ , which contribute to both muscle wasting and bone loss [88]. Regular physical activity has been shown to reduce inflammation by modulating cytokine production, which in turn helps maintain muscle mass and bone integrity. The anti-inflammatory effects of exercise are particularly important in patients with CKD, where 'inflammaging' exacerbates the progression of osteosarcopenia [88].

The benefits of physical activity go beyond direct improvements in bone health. Improved physical function and mobility resulting from exercise interventions can improve the overall quality of life of people with CKD, reduce the risk of falls and increase independence [88]. Given the progressive nature of osteosarcopenia in CKD, early and sustained physical activity interventions are essential to delay the onset of severe functional impairment [88].

In conclusion, physical activity has a pivotal role in mitigating the deleterious effects of osteosarcopenia in CKD through the promotion of bone formation, the increase of muscle mass and the reduction of inflammation. Given the high prevalence of sarcopenia and osteoporosis in patients with CKD, the incorporation of structured exercise programmes, particularly resistance training, into the management of CKD may have a significant therapeutic benefit.

### 3 | Diagnosis

#### 3.1 | Diagnosis of Osteoporosis

The gold standard to assess bone mass is dual X-ray absorptiometry (DXA). The diagnosis of osteoporosis is made when any of the following criteria is met [89, 90]:

- History of fractures;
- $T\text{-score} \leq -2.5$  at the lumbar spine, femoral neck, total hip or distal 1/3 radius on DXA exam;
- $T\text{-score}$  between  $-1.0$  and  $-2.5$  with elevated fracture risk as determined by the Fracture Risk Assessment Tool (FRAX) that combine BMD with clinical risk factors [91]

There is general consensus on the fact that DXA should be performed in postmenopausal women aged  $\geq 65$  years regardless the presence or not of risk factors, men aged 70 years or more and younger subjects aged 50–65 years in the presence of risk for fracture, previous fragility fractures, family history of fractures, steroid therapy (daily dose equal or higher than 5 mg), alcohol consumption, smoking habit, presence of diseases that expose to the risk of fractures [89, 92].

In addition, it is essential to screen all patients at risk for secondary osteoporosis. Among these, patients with CKD are at particularly high risk because of osteomalacia

resulting from secondary hyperparathyroidism on one hand and vitamin D deficiency induced by renal insufficiency on the other [93].

However, in patients with CKD, the interpretation of DXA results is more complex because of kidney disease-specific factors:

1. Altered bone mineralisation: CKD is associated with impaired bone mineralisation due to impaired phosphate balance, elevated FGF-23 and secondary hyperparathyroidism. These factors can reduce bone quality, and altered BMD measurements may not accurately reflect bone strength or fracture risk. In particular, patients with CKD may have low turnover bone disease (adynamic bone disease), where BMD may appear normal or even elevated despite reduced bone strength [94, 95].
2. Vascular calcification: Vascular calcification is common in CKD patients and can interfere with DXA scans. Calcification of arteries and soft tissues can lead to falsely high BMD measurements and mask the true extent of osteoporotic bone loss [96].
3. Variability in bone turnover: CKD-BD encompasses a range of conditions from high bone turnover (osteitis fibrosa) to low turnover (adynamic bone disease). These conditions may present normal or increased BMD but involve significant structural abnormalities of the bone. Advanced imaging techniques and biochemical markers of bone turnover, including PTH, alkaline phosphatase and markers of bone resorption (e.g., C-telopeptide), are essential for accurate diagnosis and treatment decisions [97].

#### 3.2 | Diagnosis of Sarcopenia

According to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), sarcopenia can be defined according to three criteria: reduction of muscle strength, reduction of muscle mass and muscle quality and reduction of functional capacity [98].

The first criterion, low muscle strength, identifies probable sarcopenia. The second criterion, low muscle mass or quality, confirm the diagnosis. The simultaneous presence of the three criteria determines the severity of the sarcopenia condition.

Figure 4 shows the cut values for each criterion suggested by the EWGSOP2.

Muscle strength can be assessed using a handheld dynamometer, an inexpensive and non-invasive tool suitable for daily clinical practice. Alternatively, the chair test (sit-to-stand test with five repetitions) can be used to evaluate lower limb strength. For muscle mass evaluation, dual-energy X-ray absorptiometry (DXA), computed tomography (CT) and magnetic resonance imaging (MRI) are the gold standards. However, their use is often limited to research settings. Bioimpedance offers a practical, non-invasive and cost-effective bedside alternative, quantifying muscle mass as appendicular skeletal mass (ASM) in absolute terms or normalised for height ( $\text{ASM}/\text{m}^2$ ).



Emerging in the nephrological-nutritional field, muscle ultrasound (US) is a portable and non-invasive technique that can be applied in routine clinical practice by trained healthcare professionals. Muscle US correlates well with gold-standard methods like MRI and CT in detecting changes in muscle volume and structure [99, 100]. The anterior thigh, particularly the rectus femoris (RF) muscle, is a preferred site for US measurements, as it represents the largest muscle group crucial for patient mobility. Quadriceps thickness correlates with muscle strength and remains measurable even in severe muscle depletion [101].

US also provides insights into muscle quality, now included in the revised European consensus on sarcopenia diagnosis [98]. Echo intensity (EI), a key US parameter, reflects muscle texture and fat infiltration [102]. S. Wilkinson et al. demonstrated correlations between US-derived muscle texture parameters and MRI findings in CKD patients, highlighting the potential of US in identifying muscle mass reduction and increased fat infiltration [103]. For further details, see Figure 3.

The diagnosis of sarcopenia in CKD is particularly challenging because of the complex interplay between muscle wasting and renal dysfunction. CKD-specific factors like chronic inflammation, metabolic dysfunction and PEW contribute to muscle catabolism, complicating sarcopenia diagnosis [104]. Elevated inflammatory markers, such as CRP and IL-6, exacerbate muscle loss and can make it difficult to distinguish sarcopenia from other conditions. In addition, PEW, which is the result of inadequate protein intake and metabolic imbalances, has overlapping diagnostic criteria with sarcopenia, which further complicates the clinical assessment [105].

Diagnostic tools that have traditionally been used for sarcopenia, such as BIA and DXA, may be unreliable in patients with CKD due to fluid imbalances, such as oedema, which can confound measurements of muscle mass. More advanced imaging techniques, including MRI and CT scans, may provide more accurate assessments in this population [106]. In addition, patients with CKD often experience a decline in physical function and frailty, which is associated with sarcopenia but may also be influenced by other factors such as anaemia and cardiovascular comorbidities, further complicating the diagnosis [107].

### 3.3 | Diagnosis of Osteosarcopenia

In the literature, there is very limited data regarding a precise definition of osteosarcopenia, particularly in the context of CKD. Our goal in this section is to provide the clearest possible guidance that can be utilised by both clinicians and researchers to assess and define this condition in their patients. However, it should be noted that the recommendations provided here are based on our clinical experience in managing this patient population and on data from the literature addressing sarcopenia and osteoporosis in the context of CKD. These guidelines have not yet been codified in any official recommendations.

In fact, very often, the literature suggests methods that, although recognised as gold standards (e.g., DEXA and MRI for

the evaluation of body composition), are however not used by most of common nutritional-nephrological laboratories because they are not available, expensive, invasive and not repeatable within short periods.

Osteosarcopenia is a condition that results from the simultaneous presence of osteopenia and sarcopenia so the identification of this new syndrome lies in verifying the copresence of both conditions. It could be defined as

1. Osteopenia ( $T$ -score  $\leq -1$  and  $\geq -2.5$  at the lumbar spine, femoral neck, total hip or distal 1/3 radius on DXA exam) combined with established sarcopenia (reduction in skeletal muscle mass and/or impairment in physical performance) [1, 6, 31]
2. Osteoporosis ( $T$ -score  $\leq -2.5$  at the lumbar spine, femoral neck, total hip or distal 1/3 radius on DXA exam) and risk of sarcopenia (impairment in muscle strength, without established reduction in muscle mass and/or physical performance)
3. Copresence of established osteoporosis ( $T$ -score  $\leq -2.5$  at the lumbar spine, femoral neck, total hip or distal 1/3 radius on DXA exam) and sarcopenia (reduction in skeletal muscle mass and/or impairment in physical performance)

These definitions, particularly the definition of osteoporosis, are also applicable to CKD patients. In fact, although CKD-MBD presents a complex pathophysiology, the key factor for diagnosis ultimately remains bone density. When bone density is impaired, it indicates the presence of osteoporosis, regardless of whether this impairment is due to osteomalacia and/or vitamin D deficiency, both of which are characteristic features of CKD-MBD [93].

Figure 4 suggests a possible path to follow for osteosarcopenia diagnosis. The first step for diagnosis is a careful history to identify a potential risk condition. In the case of elderly patients or those with cognitive problems, it is important to also involve family members and caregivers for a more complete collection of information. The history collects medical, social and lifestyle information and presence of previous falls and fractures. Since osteosarcopenia is a recently diagnosed syndrome, there are no data relating to the association of fractures and falls in CKD patients. According to the Network Europe Consensus for the prevention of falls [108], a fall is an event where a person comes to rest inadvertently on the ground or other lower level. To investigate falls occurrence, during history collection, patients should be asked 'In the past 3 months, have you had any falls including a slip or trip in which you lost your balance and landed on the floor or ground or lowest level?' [109].

During the medical history collection, it could be advisable to administer the SARC-F questionnaire [110]. This tool encourages self-reporting of signs suggestive and characteristic of sarcopenia, and it allows the detection of a potential risk of sarcopenia [98]. The SARC-F is a 5-item questionnaire that investigates as many components, strength, assistance in walking, rise from a chair, climb stairs and falls, that could be affected in the presence of sarcopenia. Each component has a score from 0 to 2 points, and the total score varies from

0 to 10 where 0 means 'good' and 10 means 'worst'. SARC-F was shown to be a valid tool to identify people at risk of sarcopenia [110]. Du et al. examined the validity of the SARC-F questionnaire for screening sarcopenia among 105 CKD patients in conservative therapy and 125 patients on haemodialysis and found that it had low-to-moderate sensitivity but high specificity for screening sarcopenia among patients with CKD [111]. In any case, SARC-F can be recommended as a simple method to apply in the first step of osteosarcopenia risk screening to identify patients who need subsequent specific investigations.

#### 4 | Translational Perspectives

The complex pathophysiology of osteosarcopenia in CKD is driven by hormonal dysregulation, chronic inflammation and metabolic dysfunction. Effective therapeutic strategies must target these multifactorial processes to prevent or minimise both bone and muscle loss.

A cornerstone of management is the treatment of CKD-MBD [112]. This includes the use of phosphate binders and dietary phosphate restriction to control hyperphosphatemia, and vitamin D supplementation to improve calcium absorption and reduce PTH levels [112]. Calcimimetics further reduce bone turnover and the risk of osteoporosis by modulating calcium and phosphate homeostasis [112].

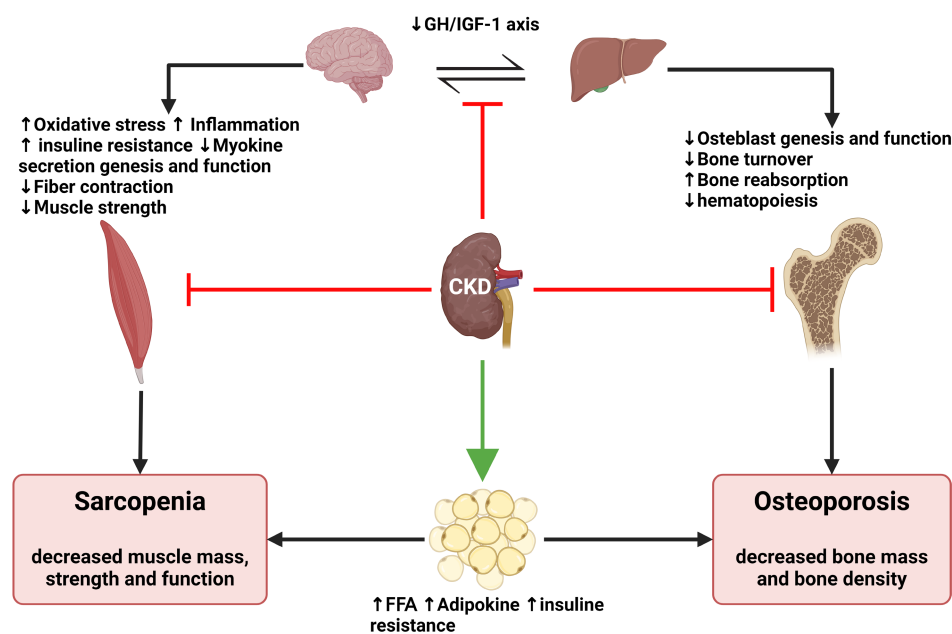
Given the important role of inflammation in osteosarcopenia, anti-inflammatory interventions are crucial. Targeting

pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  with biological therapies or anti-inflammatory agents, coupled with an anti-inflammatory diet rich in omega-3 fatty acids, can attenuate systemic inflammation, preserve lean muscle mass and support bone integrity [113].

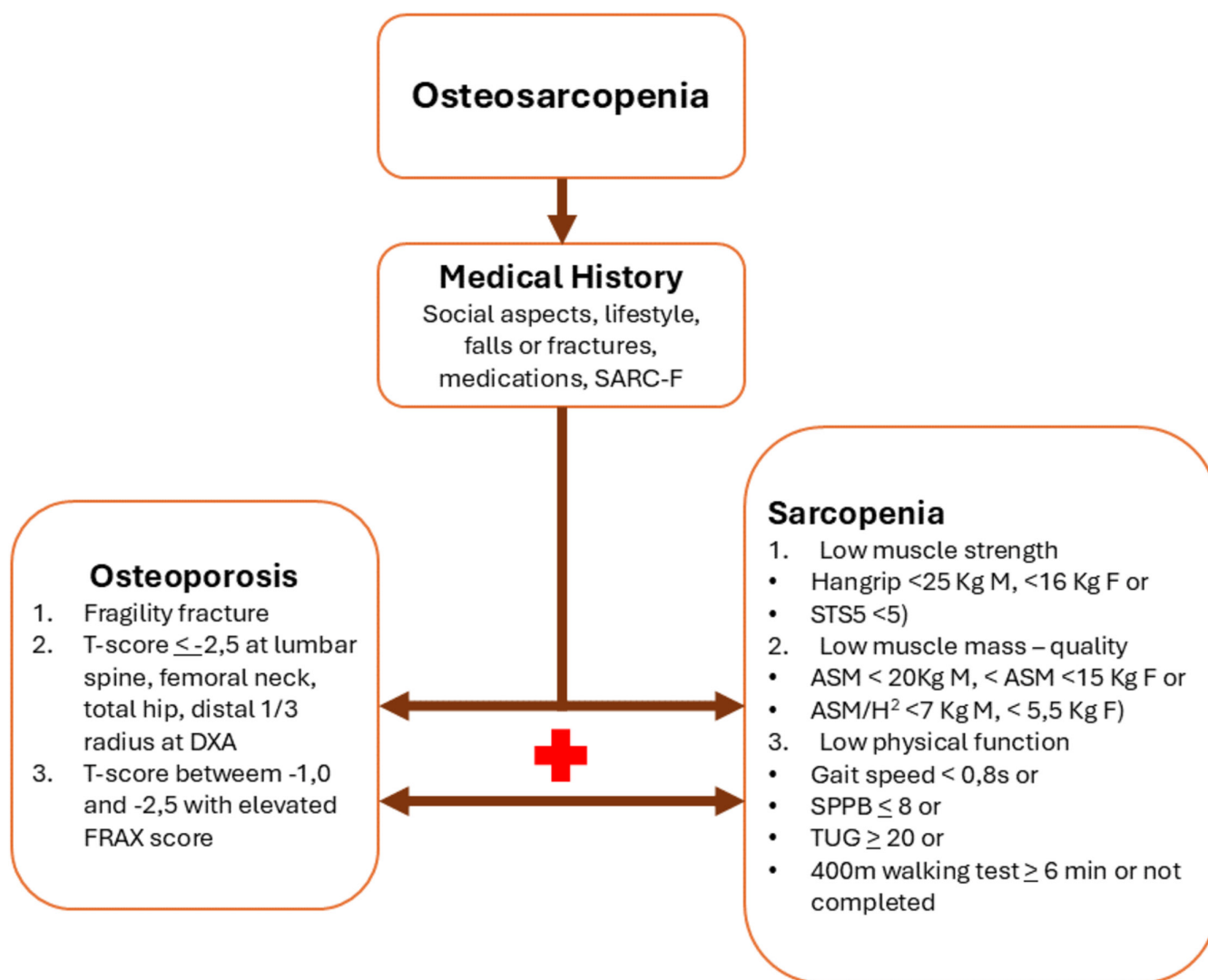
Skeletal muscle maintenance is another important therapeutic focus. Resistance exercise is highly effective in increasing muscle mass, improving strength and stimulating bone formation [84]. Myostatin inhibitors, which promote muscle regeneration, offer an additional avenue for muscle preservation [114]. In addition, therapies targeting the growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis may further stimulate muscle protein synthesis and bone formation, thus helping to counteract sarcopenia in CKD patients [115].

Sclerostin inhibition is a promising new approach to bone health. Sclerostin antibodies, such as romosozumab, improve bone formation by increasing osteoblast activity and addressing the low bone turnover often seen in CKD [116]. Hormone replacement therapies, including testosterone supplementation for hypogonadal men and oestrogen therapy for postmenopausal women, can also improve BMD and reduce fracture risk [116].

For patients with sarcopenic obesity, weight management and physical activity are essential components of treatment. Nutritional support, including tailored protein intake and supplementation with amino acids or creatine, plays an important role in promoting muscle anabolism and maintaining bone health, especially in malnourished CKD patients [117].



**FIGURE 3** | Main factors associated with osteosarcopenia development. *Note:* This figure depicts the multifactorial pathways leading to osteosarcopenia development in chronic kidney disease (CKD). Reduced renal function in CKD disrupts mineral and hormonal homeostasis, resulting in secondary hyperparathyroidism, elevated fibroblast growth factor 23 (FGF-23) and decreased vitamin D synthesis. These disturbances contribute to bone loss, osteoporosis and increased fracture risk. Concurrently, CKD-induced inflammation, metabolic acidosis and uremic toxins impair skeletal muscle integrity, promoting sarcopenia. The reciprocal relationship between bone and muscle further exacerbates the progression of osteosarcopenia, leading to frailty, disability and heightened mortality risk in CKD patients. GH, Growth hormone; IGF, Insuline growth factor; CKD, Chronic Kidney Disease; FFA, Free fatty acids.



**FIGURE 4** | Flowchart to diagnose osteosarcopenia. ASM, appendicular skeletal muscle mass; DXA, dual X-ray absorptiometry; F, female; FRAX, Fracture Risk Assessment Tool; M, male; SARC-F, strength, assistance with walking, rising from a chair, climbing stairs and falls; SPPB, short physical performance battery; STS5, 5 times sit-to-stand; TUG, timed up-and-go.

Finally, emerging therapies such as Klotho enhancement—via gene therapy or pharmacological agents—represent a promising frontier for protecting both muscle and bone health [118]. Overall, a comprehensive and individualised therapeutic approach integrating pharmacological, nutritional and physical interventions is essential to combat the adverse effects of osteosarcopenia and improve clinical outcomes in CKD patients.

## 5 | Conclusion

In conclusion, osteosarcopenia has recently been recognised as a major complication in CKD, reflecting the convergence of osteoporosis (bone loss) and sarcopenia (muscle loss) in this population. This condition is gaining attention because of its multifactorial pathophysiology and significant impact on morbidity and mortality in CKD patients. The recognition of osteosarcopenia as a distinct clinical entity in CKD stems from increasing evidence highlighting the interrelationship

between bone and muscle homeostasis, both of which are profoundly disrupted in CKD. Osteosarcopenia thus represents a new clinical symptom of CKD, driven by a combination of CKD-related mineral disturbances, chronic inflammation, hormonal imbalances and malnutrition. Recognising and treating osteosarcopenia in CKD is essential to improve patient outcomes and reduce the risk of fractures, falls and disability.

This review highlights a need for comprehensive diagnostic strategies that address both bone and muscle health, especially using accessible and non-invasive techniques such as MRI. The integration of these diagnostic tools in the nephrological-nutritional setting is critical to the effective management and treatment of osteosarcopenia. Given the increasing prevalence of CKD and its associated complications, early detection and targeted intervention of osteosarcopenia could reduce the high morbidity and mortality associated with this condition. Ongoing research into the molecular mechanisms of osteosarcopenia and its treatment is essential to improve the quality of life of patients with CKD.

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## Conflicts of Interest

Simone Vettoretti served as a consultant at advisory boards for Merk Sharp & Dohme, Astra Zeneca, Boehringer and Ingelheim and held a sponsored lecture by Dr. Shär. Lara Caldiroli worked as a consultant for Dr. Shär.

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