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REVIEW

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Effects of hormonal changes on sarcopenia in chronic kidney disease: where are we now and what can we do?

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Abstract

Sarcopenia or muscle wasting is a progressive and generalized skeletal muscle disorder involving the accelerated loss of muscle mass and function, often associated with muscle weakness (dynapenia) and frailty. Whereas primary sarcopenia is related to ageing, secondary sarcopenia happens independent of age in the context of chronic disease states such as chronic kidney disease (CKD). Sarcopenia has become a major focus of research and public policy debate due to its impact on patient's health-related quality of life, health-care expenditure, morbidity, and mortality. The development of sarcopenia in patients with CKD is multifactorial and it may occur independently of weight loss or cachexia including under obese sarcopenia. Hormonal imbalances can facilitate the development of sarcopenia in the general population and is a common finding in CKD. Hormones that may influence the development of sarcopenia are testosterone, growth hormone, insulin, thyroid hormones, and vitamin D. Although the relationship between free testosterone level that is low in uraemic patients and sarcopenia in CKD is not well-defined, functional improvement may be seen. Unlike testosterone, it is known that vitamin D is associated with muscle strength, muscle size, and physical performance in patients with CKD. Outcomes after vitamin D replacement therapy are still controversial. The half-life of growth hormone (GH) is prolonged in patients with CKD. Besides, IGF-1 levels are normal in patients with Stage 4 CKD—a minimal reduction is seen in the end-stage renal disease. Unresponsiveness or resistance of IGF-1 and changes in the GH/IGF-1 axis are the main causes of sarcopenia in CKD. Low serum T3 level is frequent in CKD, but the net effect on sarcopenia is not well-studied. CKD patients develop insulin resistance (IR) from the earliest period even before GFR decline begins. IR reduces glucose utilization as an energy source by hepatic gluconeogenesis, decreasing muscle glucose uptake, impairing intracellular glucose metabolism. This cascade results in muscle protein breakdown. IR and sarcopenia might also be a new pathway for targeting. Ghrelin, oestrogen, cortisol, and dehydroepiandrosterone may be other players in the setting of sarcopenia. In this review, we mainly examine the effects of hormonal changes on the occurrence of sarcopenia in patients with CKD via the available data.

Keywords Sarcopenia; Chronic kidney disease; Hormones; Cachexia; COVID-19

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Introduction

Sarcopenia is the combination of the Greek words *sarcos* (meat) and *penia* (loss). This term was first used in 1989 by Irwin H. Rosenberg. Rosenberg defined sarcopenia as a reduction in muscle mass occurring in association with ageing.[1] Hence, the ageing related sarcopenia can be referred to 'primary sarcopenia' as opposed to the age independent 'secondary sarcopenia' in the context of chronic disease states. The European Working Group on Sarcopenia in Older People (EWGSOP) has reported that sarcopenia is a syndrome characterized by the general and progressive loss of skeletal muscle mass and strength and resulting risks such as physical disability, low quality of life, and death.[2] An increasing number of studies have classified sarcopenia as an independent disease coded as M62.84 in the International Classification of Diseases-10 system (ICD-10) in 2016.[3] In 2018, the definition of sarcopenia was revised by EWGSOP and the main parameters of the disease were determined as muscle strength and muscle mass (*Table* 1, Part a).[4] That consensus positioned the physical performance as a variable that indicates the severity of the disease. Terminology related to sarcopenia is summarized in *Table* 1, Part b.

The incidence of sarcopenia is increased in patients with chronic kidney disease and its aetiology is multifactorial. Hormonal imbalance is one of them. In this review, first, general information about sarcopenia will be given, and then the effects of hormones on the development of sarcopenia in patients with chronic kidney disease will be explained.

Epidemiology

The incidence of sarcopenia increases with age. Muscle mass starts to diminish linearly at the beginning of the fourth decade of life. Such losses of muscle mass account for 8% muscle quantity loss per each decade of life until the age of 70.[5] After 70 years of age, muscle loss per decade increases to 15%, and total loss reaches 50% in the 8th decade.[5] In a study, the incidence of sarcopenia ranged from 5% to 13% between the ages of 60 and 70.[6] That study reported that the sarcopenia incidence ranged from 11% to 50% at the age of 80 and older.[6]

Category

As stated earlier, sarcopenia is considered 'primary sarcopenia' when it is age-related and when no other specific causes are evident. It is called 'secondary sarcopenia' when sarcopenia occurs resulting from one or more causal factors.[7] Sarcopenia categories are presented in *Table* 2.

Risk factors

There are many risk factors that facilitate the development of sarcopenia.[8,9] We can examine them as grouped under the following categories:

1 Structural: Genetic predisposition, gender, and low birth weight
2 Effect of ageing: Reduction in the muscle cell count, hormonal dysregulation, and neuromuscular system changes
3 Lifestyle: Diet, smoking and alcohol use, and physical inactivity
4 Chronic health problems: Diabetes mellitus, chronic kidney disease, liver disease. Other chronic disease states such as liver disease, rheumatoid arthritis, neurologic disorders, and cancer cachexia.

Pathophysiology

Although the mechanism of the development of sarcopenia is unclear, some theories have been suggested besides ageing. There are reductions in the levels of anabolic hormones [testosterone, oestrogen, growth hormone, insulin-like growth factor-1 (IGF-1)].[10,11] The apoptotic activity of myofibrils increase and oxidative stress is invoked by the accumulation of pro-inflammatory cytokines [tumour necrosis factor-alpha (TNF-α)], interleukin (IL- 6), and free radicals.[12] Low levels of circulating angiotensin-II are associated with muscle weakness, decreased IGF-1 levels, and insulin resistance leading to sarcopenia.[13] There are also changes in the mitochondrial functions of muscle cells, and the number of α-motor neurons decrease and sarcopenia is also associated with chronic inflammation.[14]

Table 1 (a) Sarcopenia diagnostic criteria [European Working Group on Sarcopenia in Older People (EWGSOP), 2018] and (b) terminology related to sarcopenia

a: Sarcopenia diagnostic criteria (EWGSOP, 2018)	
Probable sarcopenia is identified when Criterion 1 was detected.	(1) Low muscle strength
Additional documentation of Criterion 2 confirms the diagnosis.	(2) Low muscle mass or quality
Sarcopenia is considered severe when Criteria 1, 2, and 3 are all met.	(3) Low physical performance
b: Terminology related to sarcopenia	
Dynapenia	Muscle weakness without loss of muscle mass.
Sarcopenic obesity	Having abdominal adiposity but also sarcopenia.
Severe sarcopenia	Criteria 1, 2, and 3 in *Table* 1, Part a are all met.

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Table 2 Classification of sarcopenia.

Primary sarcopenia	
Age-related sarcopenia	No factors are evident other than advanced age
Secondary sarcopenia	
Activity-related sarcopenia	Bed ridden status, sedentary lifestyle, and neurologic or other disorders that limit physical activity such as morbid obesity or orthopaedic disorders/deformity
Disease-related sarcopenia	Chronic disease states including advanced organ failure (heart, lungs, liver, kidneys, and brain), inflammatory diseases, malignancies, and endocrine diseases
Nutritional sarcopenia	Inadequate diet for the intake of calories and protein malabsorption, starvation, anorexia nervosa, diseases, or medicine-induced anorexia

Although the biological mechanism of sarcopenia is not fully understood, it is thought that the number of satellite cells involved in muscle regeneration decreases with ageing and this may contribute to the development of sarcopenia.[15] Levels of IGF-1 and androgen—which are effective in the regulation of skeletal muscle development—decrease with ageing.[16]

Diagnosis

Many consensus reports have been developed for the diagnosis of sarcopenia to date. A recent one is the EWGSOP criteria that were updated in 2018 (*Table* 1). Computed tomography, magnetic resonance imaging, ultrasonographic imaging, or dual-energy X-ray absorptiometry can be used to measure muscle mass.[17,18] A hand-grip strength test is usually performed to measure muscle strength. The walking speed test, the get up and go test, and the short physical performance battery can measure physical performance. EWGSOP2 developed an algorithm to identify individuals with sarcopenia to be used in both clinical practice and clinical research (*Figure* 1).[4]

Significance

Sarcopenia has negative consequences including frailty, decreased health-related quality of life, impaired immune system, impaired respiratory functions, and higher likelihood of fall.[19,20] It may sometimes even lead to death.[21]

The relationship between chronic kidney disease and sarcopenia

Chronic kidney disease (CKD) is often called a model of 'accelerated ageing'; therefore, it is likely that the loss of lean mass, reduced skeletal muscle strength, and low physical performance (all components of sarcopenia) are in the same direction as patient-centred outcomes of ageing such as mobility limitations, disability, and mortality as in the general population.[22] Although some criteria have been developed to define sarcopenia,[4] the feasibility of using such criteria in CKD patients has not yet been clarified yet.[23] The type of test used to detect sarcopenia may influence the diagnosis of sarcopenia in CKD patients.[24] For example, the hypervolaemia seen in CKD patients may act on the bioelectrical impedance analysis; but the measurement of the lean mass by dual-energy X-ray absorptiometry is not influenced.[25]

There are various studies in the literature examining the prevalence of sarcopenia and factors involved in sarcopenia in CKD patients and in patients undergoing dialysis. Souza *et al*. conducted a study on 100 patients and found that the frequency of sarcopenia was 11.9% according to the EWGSOP criteria and 28.7% according to the Foundation for the National Institutes of Health criteria. The frequency of sarcopenia increases as the CKD stage advances.[26] Pereira *et al*. found that the frequency of sarcopenia was between 5.9% and 9.8% in 287 non-dialysis CKD patients.[27] The frequency of sarcopenia is a little bit higher in dialysis patients. In a study by Kim *et al*. with 95 haemodialysis patients, an incidence of sarcopenia was found 37% in men and 29.3% in women.[28]

The underlying mechanisms of sarcopenia in the context of CKD revolve around the loss of muscle mass. This is a 'chicken-or-the-egg' conundrum because it is unknown whether reduced physical activity causes muscle loss or whether muscle loss causes reduced activity. Regardless of the initiating factor, the loss of muscle mass in CKD may be attributed to a negative balance of protein homeostasis that leads to increased catabolism and decreased synthesis of muscle.[22,26,28]

Chronic kidney disease may facilitate impairments of muscle regeneration process (by decreased production of myogenic regulatory factors and reduced cellular activation). The permanent imbalance between protein breakdown and synthesis in muscles results in muscle loss.[22] Blood levels of myostatin (negative regulator of skeletal muscle mass) increase in patients with CKD.[29] The binding of myostatin to activin-A type-IIB receptors stimulates the expression of atrogens such as atrogin-1 and muscle-ring factor 1—both of these are members of the muscle-specific ubiquitin ligase family.[29,30] Impaired mitochondrial function also contributes to decreased muscular endurance.[31]

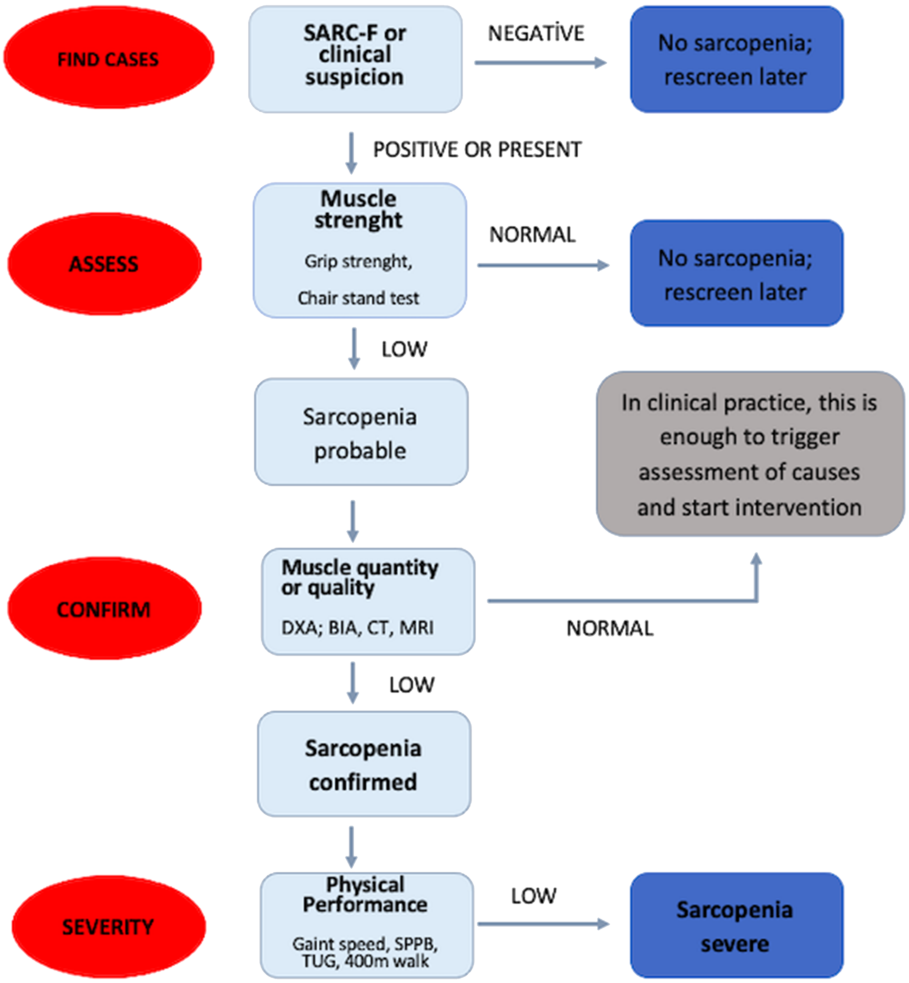

Figure 1 Sarcopenia: EWGSOP2 algorithm for case-finding, diagnosis, and quantifying severity in practice. DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; CT, computed tomography; MRI, magnetic resonance imaging.

Furthermore, increased catabolic processes in CKD are effective in the development of sarcopenia. Chronic inflammation, uraemic toxins, malnutrition, hormonal imbalance (insulin resistance, vitamin D deficiency, and hypogonadism), oxidative stress, and increased ubiquitination are key players in the catabolic process.[22,32] The renin–angiotensin–aldosterone system is up-regulated in CKD; this can impair muscle regeneration and invoke ubiquitin proteasome system proteolytic pathways.[33] We can group the factors involved in the development of sarcopenia in CKD patients as follows **(***Figure* 2**).**

Increased frequency of sarcopenia in CKD patients has been shown to have negative consequences. Pereria *et al*. reported that sarcopenia in CKD was associated with mortality with an hazard ratio of 1.8 (95% CI: 0.78–4.17).[27] In a study on 385 patients with a mean estimated glomerular filtration rate (eGFR) of 41 mL/min/1.73 m^2, each 0.1 m/s decrement in gait speed was associated with a 26% higher risk for death and each 1-s longer 'timed up and go' test result was associated with an 8% higher risk for mortality.[34] In another study on 128 pre-dialysis CKD patients with a median of 2.8 years follow up, decreased handgrip strength was independently associated with a composite outcome of progression to end-stage kidney disease and mortality in men and women and across different stages of pre-dialysis CKD.[35]

Sarcopenic obesity and chronic kidney disease

There is a reverse epidemiology between obesity and CKD. Lu *et al*. found that U-shaped association is seen between body mass index and clinical outcomes in patients with CKD, and also worse outcomes were seen in patients with body mass index under 25 kg/m^2.[36] 'Obesity paradox' or a better definition named 'sarcopenic obesity' have been discussing recently. This phenomenon defines the patients who has especially abdominal adiposity but also sarcopenia. In a study, sarcopenic obesity was found to be associated with an increased risk of death in individuals without CKD, whereas such a relationship was not demonstrated in those with

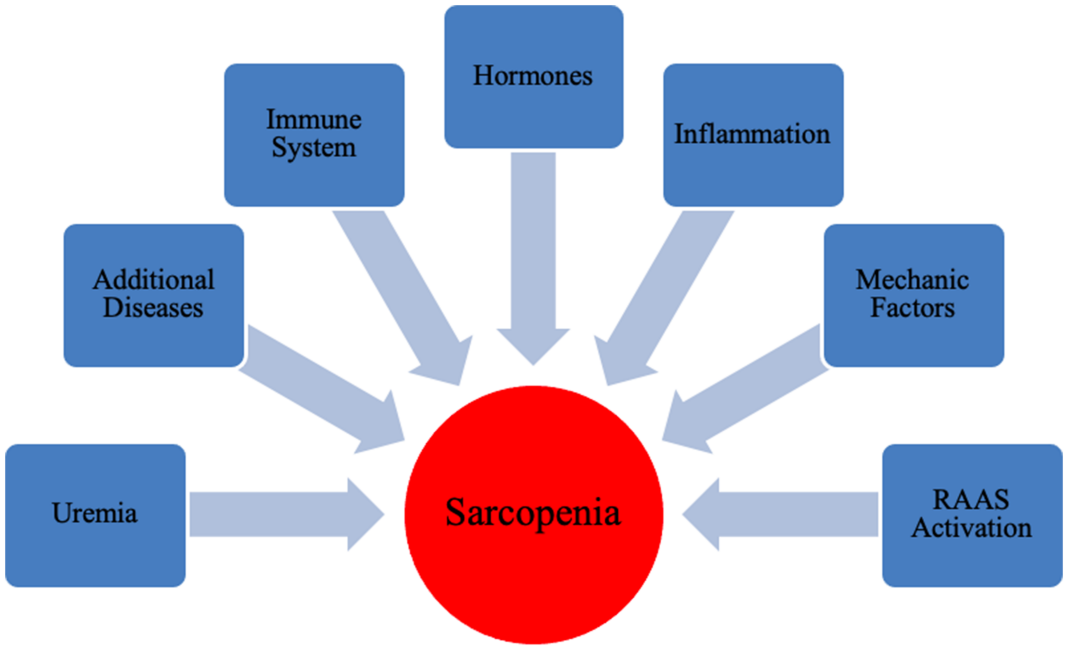

Figure 2 Factors affecting the development of sarcopenia in patients with chronic kidney disease.

CKD.[37] It is well defined in patients with end-stage renal disease, Honda *et al*. demonstrated that sarcopenic obesity is associated with more inflammatory situation and increased mortality.[38] There is a clear need for more clinical investigations about sarcopenic obesity and CKD.

Effects of hormones on the development of sarcopenia

Hormones play an important role in the development of muscle mass and regulation of muscle strength including in patients with CKD.[10,11] Hormones that influence the development of sarcopenia are testosterone, growth hormone (GH), insulin, thyroid hormones, and vitamin D. In the next part of the review, hormones essentially responsible for the development of sarcopenia in CKD patients will be detailed with the light of the studies showing the effects of such hormones on the development of sarcopenia in patients with and without CKD.

Testosterone

Testosterone and chronic kidney disease

Regarding the patients with CKD or undergoing dialysis, hypogonadotropic hypogonadism with low testosterone levels, suppression of the pituitary–testicular axis, high LH levels and testicular calcification in secondary hyperparathyroidism due to CKD may be seen in the majority of the cases. It appears that uraemic metabolites occurring in advanced stages of CKD affect the testicle more than the hypothalamic or pituitary function. Previous trials have shown a negative correlation between endogenous testosterone levels and CKD Stages 1–5. Recently, we showed that this deficiency is very common (65% in male Turkish HD patients).[39–41]

Testosterone and sarcopenia

Testosterone is an important anabolic hormone required for muscle protein synthesis, muscle mass, and strength.[42] Testosterone increases protein synthesis, reduces its breakdown, and increases the size of Types I and II muscle fibres. It also helps to transport mesenchymal stem cells to satellite cells

and inhibits the pathway to adipocyte progenitor cells.[40] A decrease in testosterone levels and anabolic effects with age or in chronic diseases (along with inflammatory conditions) mayF lead to bone loss as well as a reduction in muscle mass and strength.[40,43]

Myostatin is a hormone released from the muscle that inhibits muscle growth. A decrease in testosterone causes an increase in myostatin expression and impairment in IGF-1 signal transduction.[44] Accordingly, testosterone deficiency is an important factor in the development of sarcopenia. With the use of testosterone, the pro-inflammatory processes that cause muscle atrophy can be reduced by increasing protein synthesis and increasing muscle mass and strength.[45] In rat studies, the effects of sarcopenia on cell metabolism were reversed with testosterone supplementation.[46]

Testosterone and sarcopenia in chronic kidney disease

Uraemic patients have significantly lower free testosterone.[47,48] The CKD population is at high risk for muscle atrophy and sarcopenia due to both the existing testosterone deficiency and the resulting complications of CKD, inflammation, and malnutrition (*Figure* 3). Although there are no randomized controlled trial (RCT) evaluating the relationship between testosterone levels and sarcopenia in CKD patients in the literature the effect of testosterone replacement on sarcopenia has been investigated based on the very high probability of this relationship. Functional improvement and significant increase in lean body mass have been noted with nandrolone in both male and female dialysis patients, but unfortunate side effects include erectile dysfunction, gynecomastia, and increased CV risk.[45,48]

A 24-week RCT studied the effects of oxymetholone, an anabolic steroid with a lower androgenic effect, on HD patients. A significant improvement was found in patients' grip strength and physical function. Selective androgen receptor modulators [GTx-024 (enobosarm)] are anabolic for muscle and have lower side effects and are promising in this regard. Although these drugs have not yet been tried in CKD or dialysis patients, several studies showed that they improve lean body mass and physical function in chronic diseases. In another RCT reported by Johansen *et al*. in which 69 patients completed the study, nandrolone, an anabolic steroid, was shown to increase quadriceps muscle cross-sectional area and lean body mass.[49] The available data suggest that they have positive effects on muscle and bone.[50] But further studies are needed to evaluate the long-term effects of both androgens and anabolic steroids and their effectiveness, benefits, and risks in patients with CKD.

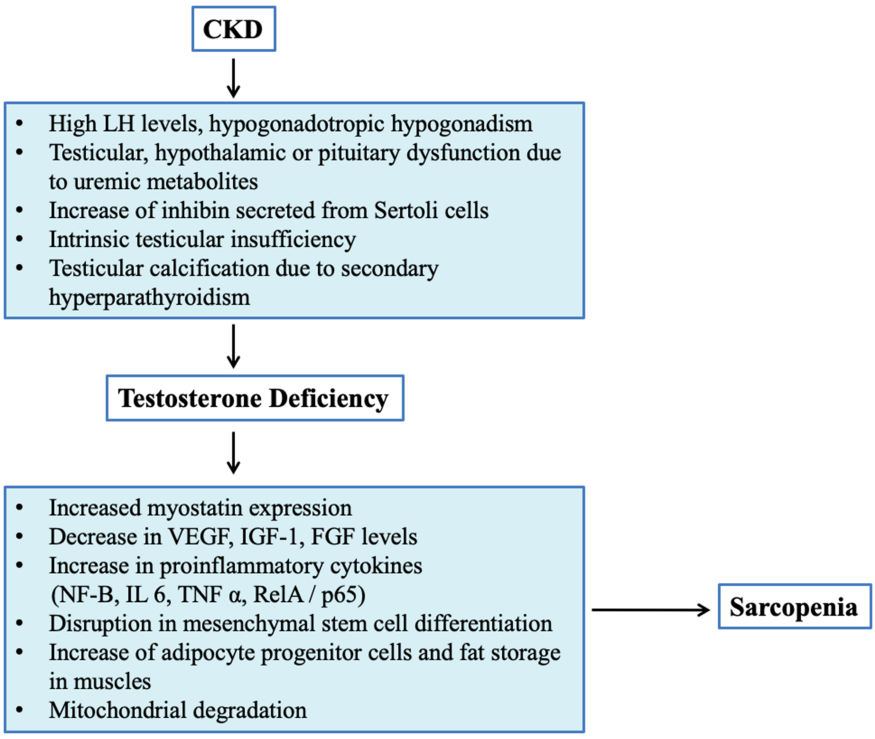

Figure 3 Chronic kidney disease (CKD), testosterone deficiency, and sarcopenia.

Vitamin D

Vitamin D and chronic kidney disease

Vitamin D deficiency is observed from the early stages of CKD.[51] A reduction in kidney mass, dietary restrictions, nutritional deficiencies, impaired skin synthesis of cholecalciferol, diabetes mellitus, obesity, accumulation of uraemic toxins, proteinuria, reduction of reabsorption due to megalin in the proximal tubule, and increased FGF23 levels play a role in this process.[52]

Vitamin D and sarcopenia

Vitamin D is one of the main molecules of muscle and bone physiology.[53] Vitamin D regulates myokines and osteokines (vascular endothelial growth factor, insulin-like growth factor-1, follistatin, fibroblast growth factor, osteoglycine, sclerostin, and osteocalcin) in muscle and bone tissue. Vitamin D also has favourable effects on increasing the diameter and number of type II muscle fibres and muscle cells, which are effective in neuromuscular performance.[54] Sarcopenia, muscle weakness, falls, and increased fracture frequency have been shown to correlate to vitamin D deficiency.[55] In vitro studies have reported that vitamin D reduces myostatin in cultured muscle cells and increases muscle and bone mass. Vitamin D replacement not only increases muscle regeneration and muscle strength but also reduces falls and prevents fractures.[54] Studies on vitamin D in sarcopenia remain contradictory.[56,57]

Vitamin D and sarcopenia in chronic kidney disease

Chronic kidney disease population is at high risk for sarcopenia, both due to malnutrition, inflammation, and various complications as well as vitamin D deficiency seen in CKD (*Figure* 4). The relationship between low 25(OH) D levels and lower muscle strength and mass, body imbalance and falls, worse physical performance, and frailty in older individuals or individuals with chronic diseases has been studied many times. However, trials on the role of vitamin D on sarcopenia in the CKD population are rare.[58,59] Gordon *et al*. showed that there is a positive relationship between 1.25 (OH) 2D levels and muscle size and physical performance in CKD patients, and Zahed *et al*. found an association between 25 (OH) D levels and lower extremity muscle strength in haemodialysis patients.[60,61] Taskapan *et al*. reported that vitamin D supplementation significantly improved physical performance (as assessed by the ascent and climb time test, the walking speed test, and the stair climbing test) in patients with severe vitamin D deficiency [average 25 (OH) D $<$ 7 ng/mL (17.5 nmol/L)] with CKD Stages 3–4 and peritoneal dialysis.[62] Vitamin D supplementation seems

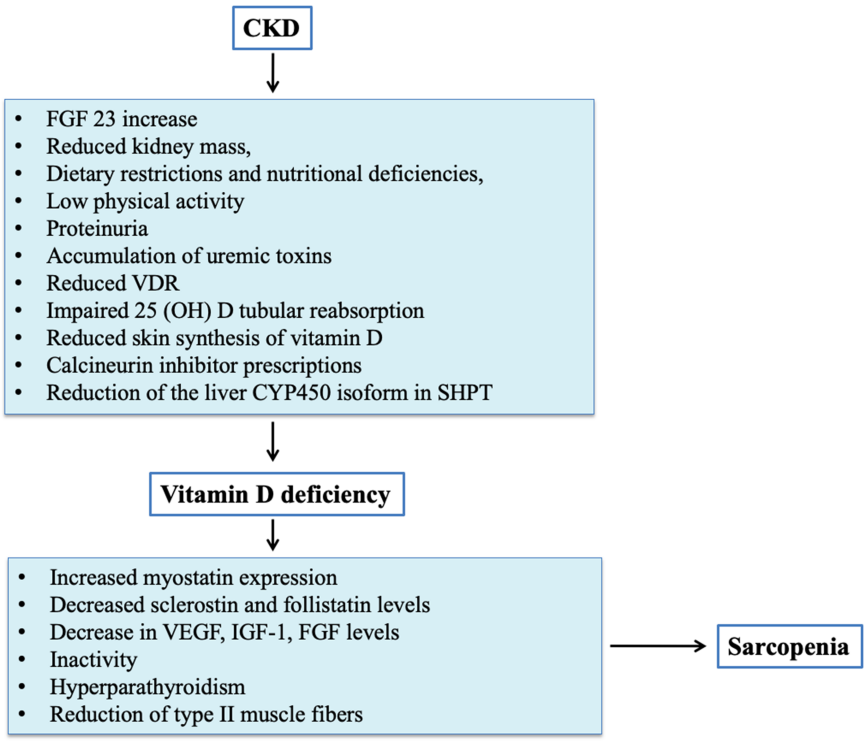

Figure 4 Chronic kidney disease (CKD), vitamin D deficiency, and sarcopenia.

beneficial for the treatment of sarcopenia in CKD and dialysis populations, but it requires larger RCTs both in CKD and dialysis patients. Studies investigating the relationship between vitamin D levels and sarcopenia in patients with CKD in *Table* 3.

Growth hormone

Growth hormone and chronic kidney disease

The kidneys play an important role in the elimination of GH. The half-life of GH is prolonged in patients with CKD. IGF-1 levels are normal in patients with Stage 4 CKD—a minimal reduction is seen in the end-stage renal disease.[64] Factors causing growth hormone resistance in patients with CKD are shown in *Figure* 5.[64] Some researchers argue that metabolic acidosis (common in most patients with CKD) deepens with increasing CKD stage and causes IGF-1 signal impairment.[65]

Growth hormone and sarcopenia

Sarcopenia is associated with decreased GH and IGF-1 levels. Studies also suggest that the GH/IGF-1 axis increases muscle mass but has no effect on muscle strength.[66]

Growth hormone and sarcopenia in chronic kidney disease

Growth hormone receptors are found in many tissues as well as muscle. Metabolic acidosis, inflammation, reduced food intake, and uraemia are known to reduce the effectiveness of GH. At the same time, unresponsiveness or resistance to IGF-1 may occur in haemodialysis patients. Metabolic acidosis, hyperparathyroidism, inflammation, and signal transduction are delayed after GH receptor activation. They can increase in IGF binding protein and its metabolites may explain this phenomenon.[67]

The GH/IGF-1 axis has an important place in the aetiopathogenesis of sarcopenia in patients with CKD via inflammation. In a study of 139 hypoalbuminaemic chronic haemodialysis patients, human GH administration was relatively safe, increased lean body mass, and, most importantly, improved mortality-related factors.[68] In another RCT involving 20 haemodialysis patients, a 6 month GH treatment decrease adipose tissue especially in the abdominal region with an increase in lean body mass.[69] The most important contribution of the study is that serum IGF-1 level was decreased in the placebo group after 6 months of treatment while a significant increase was observed in the treatment group. This study also proves that there is a gradual decrease in IGF-1 level in CKD patients despite renal replacement therapy. This treatment has encouraging results, a low side effect profile, and has also been used in other diseases such as growth hormone deficiency but not yet been studied in ESRD. A randomized controlled trial named OPPORTUNITY™, published by Kopple *et al*., which was terminated early due to slow patient recruitment, evaluated the effects of recombinant human growth hormone (hGH) in stable haemodialysis patients. Decreases in body weight, total bod fat, and C-reactive protein levels in the hGH group were demonstrated, while no difference was found in mortality, lean body mass, and serum albumin level.[70] In this context, studies including long-term data on the use of GH-based therapies for sarcopenia in the CKD patient group are needed. We also believe that its use with anti-inflammatory approaches should be studied.

Thyroid hormones

Thyroid hormones and chronic kidney disease

There is a very tight relationship between the thyroid and the kidneys; their interactions with each other are uninterrupted and very important. Subclinical hypothyroidism and low T3 syndromes are more common in individuals with CKD than in healthy individuals, via reduced Iodine clearance and chronic inflammation.[71] In a study of 510 CKD patients, hypothyroidism and subclinical hypothyroidism were observed in 10% and 14.9% of the cohort, respectively.[72]

Table 3 Relationship between vitamin D levels and sarcopenia in patients with CKD

Author	Year	*N* included in analyses	Patient characteristics	CKD stage	Study design	Conclusions
Hoffmann MR et al.[63]	2016	60	18–80 y	Stage 1–4	RCT	Serum 25(OH)D concentrations were inversely associated with total mass, weight, appendicular skeletal mass, and sarcopenia occurred more frequently in patients with 25(OH)D concentrations ≥100 nmol/L
Zahed et al.[61]	2014	135	50–70 y	HD	RCT	There was a significant relation between 25-OHD level and muscle force
Gordon et al.[60]	2012	26	50–75 y	Stage 3–4	RCT	Gait speed, distance walked in 6 min and sit-to-stand time were associated with serum 1,25OH2D values

CKD, chronic kidney disease; m, months; *N*, number; RCT, randomized controlled trial; T, testosterone; wk, week; y, years.

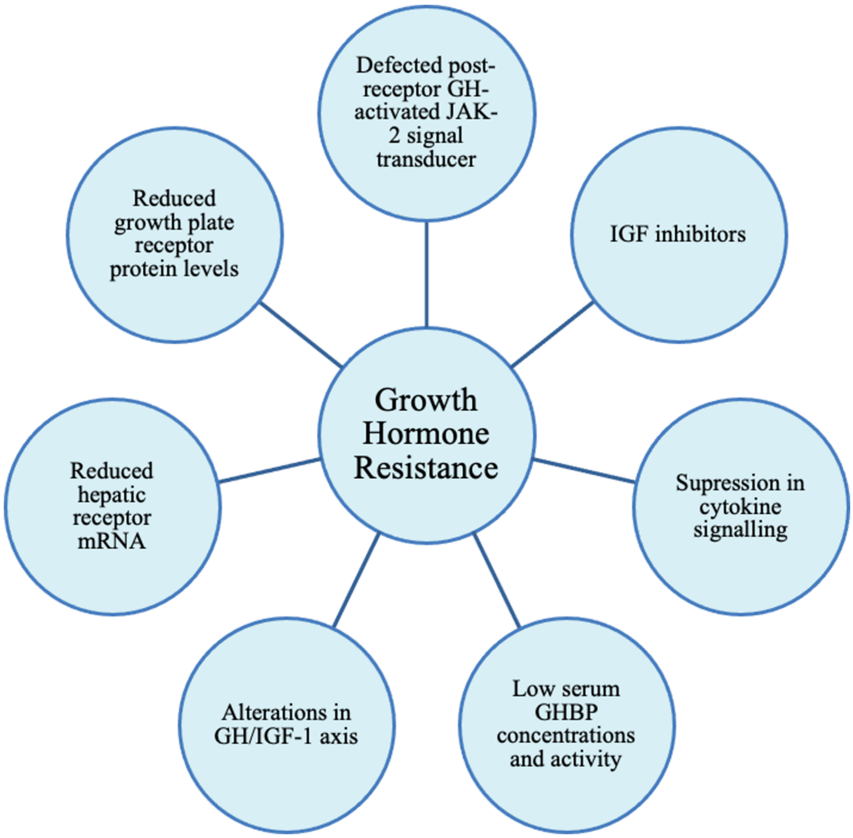

Figure 5 Factors associated with growth hormone resistance in patients with chronic kidney disease.

Thyroid hormones and sarcopenia

Skeletal muscle is one of the main targets of thyroid hormones. T3 is crucial for muscle growth, contraction–relaxation cycles, energy provision, glucose homeostasis, and muscle damage repair.[73] T3 accelerates Myh1-2-4 gene expression while decreasing Myh7 gene expression.[74] Intracellular T3 levels are very important for muscle building.[75] Smooth muscle mitochondrial functions can also be regulated by T3. There are many studies in the literature evaluating the effects of thyroid hormones on skeletal muscle. Muscle surface area is smaller in elderly patients with subclinical hypothyroidism compared to euthyroid age-matched controls.[76] When this group of patients is rendered euthyroid with treatment, there is an improvement in both muscle strength and muscle surface area.[77]

Thyroid hormones and sarcopenia in chronic kidney disease

Unfortunately, there is no clinical study about the net effects of thyroid hormones on sarcopenia in patients with CKD. Low T3 syndrome is very common in this patient population, and the association of T3 with the development of sarcopenia is amorous. It is beneficial for patients to determine levels of thyroid hormones and whether replacement of these hormones makes any changes on muscle loss or not with clinical studies over a large number of sarcopenic CKD patients. Removing the pressure on the mechanism enables conversion from peripheral T4 to T3 and may also be beneficial for sarcopenia in this patient group. Therefore, the putative effects of anti-inflammatory drugs through thyroid hormone modulation on causing sarcopenia are another important research topic.

Insulin resistance

Insulin resistance and chronic kidney disease

Chronic kidney disease patients develop insulin resistance (IR) from the earliest period even before GFR decline begins. Although the cause of IR in this patient group is not known, lack of physical activity, chronic inflammation, oxidative stress, vitamin D deficiency, metabolic acidosis, anaemia, and unknown uraemic toxins have been suggested.[78] IR also contributes to the progression of CKD.[79]

Insulin resistance and sarcopenia

The relationship between IR and sarcopenia may be more descriptive in the name of sarcopenic obesity. Sarcopenic

obesity describes a process characterized by fat accumulation in skeletal muscle as discussed earlier. Skeletal muscle is an important organ in the regulation of serum glucose. Therefore, there is a complex interaction between insulin resistance and sarcopenia.[80]

Insulin resistance and sarcopenia in chronic kidney disease

Simply, IR reduces glucose utilization as an energy source. It also increases hepatic gluconeogenesis, decreases muscle glucose uptake, and leads to impaired intracellular glucose metabolism via phosphatidylinositol 3 kinase and protein kinase B pathways.[81] Deger *et al*. evaluated the anabolic effects of insulin in 33 HD patients and 17 healthy subjects including the evaluation of muscle biopsy. They showed that HD patients responded less to hyperinsulinaemia and amino acid infusion; they also demonstrated that HD patients had impaired insulin sensitivity markers and tissue mitochondrial biogenesis.[82] The same group showed that the IR indicator HOMA is associated with muscle protein degradation in non-diabetic haemodialysis patients.

Uchiyama *et al*. found that IR and sarcopenia were more prominent in mice with CKD in an experimental animal model. Disruption of the insulin-related signalling, mitochondrial dysfunction in the skeletal muscles, and a reduction in intestinal tight junction proteins and adipocyte cell size were all observed.[83] The authors suggested that uraemic dysbiosis may induce IR; therefore, IR and sarcopenia might also be a new pathway for targeting. Despite all this validity of old and new information, a new treatment agent for IR has not yet been found in the patient group with CKD.

Other hormones

Ghrelin

Ghrelin is a hormone produced in the stomach fundus. Ghrelin and its analogues increase nutrient intake and release GH via cyclic CMP/nitric oxide pathways. Due to its effects on appetite and nutritional deficiency and GH secretion, deficiency of this hormone increases the risk of developing sarcopenia. Ghrelin levels decrease in CKD and this has been associated with malnutrition–inflammation–anaemia syndrome and metabolic acidosis. In CKD-associated cachexia, new therapeutic approaches such as ghrelin agonists and melanocortin receptor antagonists are promising and are currently at an experimental level awaiting confirmation by RCTs in these patients.[84]

Oestrogen

In older women, muscle mass and strength decrease associated with the loss of oestrogen after menopause. Oestradiol directly increases Myo D—one of the key factors involved in human skeletal muscle cells.[85] Oestrogen deficiencies are associated with the development of sarcopenia, and women who received oestrogen replacement in the postmenopausal period have been shown to have more muscle strength than those who do not. However, comprehensive studies on this topic are needed to reach a clear conclusion about the relationship between oestrogen and sarcopenia in CKD population.[86]

Cortisol

A slight increase in cortisol levels can be seen with ageing and in CKD leading to an increase in protein degradation. This situation has been linked to muscle atrophy. However, there are no comprehensive clinical studies on the subject.[87]

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) levels are associated with muscle mass and strength and decrease with age and in CKD. Higher DHEA levels in this group improve muscle mass and reduce falls in the elderly population, but no study has yet investigated the relationship between DHEA levels and sarcopenia in patients with CKD.[88]

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The authors certify that they comply with the ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[89]

Conflict of interest

S. D. A. reports receiving fees from Abbott, Bayer, Boehringer Ingelheim, Cardiac Dimension, Cordio, Impulse Dynamics, Novartis, Occlutech, Servier, and Vifor Pharma, and grant support from Abbott and Vifor Pharma. K. K. Z. has received honoraria and/or support from Abbott, AbbVie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, Ardelyx, Astra-Zeneca, Aveo, BBraun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Kissei, Novartis, Pfizer, Regulus, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZS Pharma. Other authors have no competing interests to declare.

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