Accepted Article

Journal of Research and Practice on the Musculoskeletal System JRPMS

Review Article

Sarcopenia in CKD: The effect of CKD on muscle mass

Michaela Louka

Postgraduate program "Metabolic Bone Diseases", National and Kapodistrian University of Athens, Medical School, Goudi, Athens, Greece

Abstract

Chronic kidney disease (CKD) is associated with skeletal muscle wasting due to imbalance between muscle protein synthesis and catabolism. Physiologic dysfunction and structure abnormalities of muscle such as atrophy reduce strength or reduce endurance leading to decline in physical activity, increased burden of falls, fractures, immobility and loss of functional independence termed as "sarcopenia" and is associated with increased risk of morbidity and mortality. Several mechanism could cause loss of muscle in patients with CKD such as inflammation, metabolic acidosis, malnutrition, defective insulin signaling, activation of the ubiquitin-proteasome system (UPS), vitamin D deficiency and physical inactivity. In this review, we describe the clinical relevance of sarcopenia in CKD how CKD influences muscle metabolism and the clinical implication of sarkopenia in patients with CKD.

Keywords: Chronic kidney disease, Muscle mass, Muscle strength, Sarcopenia

Introduction

The word "Sarkopenia'' is derived from Greek worlds "sarx" for flesh and "penia" for loss. This term was coined by Irwin Rosenberg in 1998 to define a progressive decrease in muscle mass, muscle strength and function leading to physical disability, loss of independency and worse quality of life[1,2,3]. According to European working group on sarcopenia older people (EWGSOP) sarcopenia can be diagnosed by measurements of muscle quantity with imaging techniques such as Dual Energy X ray Absorptiometry (DEXA), computed tomography (CT) magnetic resonance imaging (MRI), ultrasound, bioelectrical impedance (BIA) and by measurements of muscle strength (handgrip dynamometer, five chair rise test) and physical performance (gait speed timed up and go test)[3]. When the etiology of muscle loss is related to aging is classified as primary sarcopenia. Secondary sarcopenia results from a variety of debilitating chronic diseases, for instance, malignancies, malabsorption conditions and organ failure diseases such as chronic kidney disease[1]. There is a number of factors that influence muscle strength and physical activity, mainly the size of skeletal muscle, neurological condition etc. Although there seem to be a connection between low muscle strength and CKD comorbidities, physical inactivity, inflammation and old age, in dialysis patients, but this is not explaining their low muscle mass. According to this, disability meaning the inability to perform normal daily physical activities, based on clinical studies, is likely to be related more with muscle strength than muscle mass[4].

Chronic kidney disease (CKD) is a catabolic condition and is characterized by increased protein degradation and reduced protein synthesis. According to The Kidney Disease: Improving Global Outcomes (KDIGO) CKD is defined as abnormalities of kidney structure establish via kidney biopsy or imaging studies or inferred from markers such us urinary sediment abnormalities, increased rates of urinary albumin excretion or function decreased glomerular filtration rate (GFR) for 3 months or longer[5]. The term uremic syndrome refers to accumulation of small molecule uremic solutes and uremic toxins in plasma, in patients with advance chronic kidney disease[6]. This condition leads to chronic inflammation, oxidative stress, metabolic acidosis, accumulation of metabolic end-products and defective insulin signaling. These metabolic derangements cause a persistent

The author has no conflict of interest.
Corresponding author: *Michaela Louka, Postgraduate program "Metabolic Bone Diseases", National and Kapodistrian University of Athens, Medical School, Goudi, Athens, Greece*

E-mail: *michaellalouka@gmail.com*

Edited by: *Konstantinos Stathopoulos*

Accepted *2 June 2022*

imbalance between protein degradation and synthesis, result in a loss of muscle mass and sarcopenia. Sarcopenia occurs in all CKD stages and is associated with increased risk for adverse cardiovascular events and mortality[2].

Methods

We search articles published between 2000 and 2020 that evaluated the clinical relevance of sarcopenia in CKD. We selected studies that examined also the pathogenetic mechanism of muscle wasting in CKD, its etiology and implications of uremic sarcopenia. The research was performed using the electronic database Medline (PUB MED). The pre-defined search terms were sarcopenia, chronic kidney disease, muscle mass, muscle wasting and uremia. The studies were included if they met the following criteria: 1) studies related to CKD and sarcopenia, 2) studies that included patients in all CKD stages and dialysis depended patients, 3) studies written in the last 20 years, 4) studies written in English. We excluded case reports and series. Research papers were selected. Based on title and abstract. Full text has also been approached.

Results

Based on inclusion and exclusion criteria we had results for 42 studies from which 23 were selected according our inclusion criteria.

CKD–associated sarcopenia is the result of persistent imbalances among protein breakdown and synthesis. That leads to increased muscle degradation and impaired regeneration[7-9]. There are multiple causes of sarcopenia affected by the uremic environment including inflammation, metabolic acidosis, resistance to or decreased insulin like growth factor, malnutrition, increased muscle protein ubiquitin degradation, increase myostatin levels, increase angiotensin II, vitamin deficiency, abnormal myogenic regulatory factors hypogonadism mitochondrial dysfunction and physical inactivity[7-9]. The loss of muscle mass involves atrophy which means decrease in muscle fiber size and hypoplasia, which means decrease in muscle fiber number[10]. In a study Raissa A et al evaluated 287 NDD - CKD (not dialysis depended - CKD) patients in stages 3–5. Sarcopenia was defined as reduced muscle function assessed by handgrip strength and they demonstrated that the prevalence of sarcopenia in (non-dialysis-dependent) NDD-CKD patients varied between 5.9 and 9.8% determined by the method used to define muscle mass[12]. Muscle wasting etiology in CKD patients is multifactorial and below are reviewed the different mechanisms contributing to CKD associated sarcopenia.

Abnormal myogenic regulatory factors

Satellite cells, muscle progenitor cells, are located between the basal lamina and sarcolemma of muscle fibers and they are necessary for repairing the loss of muscle mass due to muscle injury. These skeletal muscle specific stem cells can be fuse to produce myofibers that are important to the repair of damaged muscle or to the prevention of muscle atrophy that occurs in catabolic conditions[9,11,12]. These cells are activated and express, myogenic cellular factors, MyoD (myoblast determination protein 1) and myogenin transcription factors on their surfaces. MyoD mediates activation and proliferation of myoblast and myogenin mediates differentiation of myoblast and muscle structural proteins production[8,9,13].

In CKD patients satellite cells function is impaired, producing low levels of myogenin and myoD proteins and block muscle regeneration[8,9]. Wang et al.using isolated satellite cells from mice with CKD and control mice demonstrate that the expression of myogenic markers, myogenin and myoD was reduce in muscle of CKD versus control mice suggesting that CKD reduce satellite cells proliferation and differentiation[13]. The same group also created an inducible insulin – like growth factor type 1 receptor (IGF-1R) knockout mouse and they discovered that CKD impairs IGF-1 signaling, leading to abnormal metabolism of protein in muscle, impaired function of satellite cell and promotes fibrosis in regenerating muscle[13]. These abnormalities can reversed by resistance exercise. Xiaonan Wang et al. evaluated how resistance exercise and endurance training affect CKD induced abnormalities in muscle protein metabolism and satellite cells function using mouse plantaris. They found that resistance exercise corrected protein synthesis, intracellular signals and regulating protein and progenitor cell function in mice with CKD. Endurance exercise (treadmill running) corrects muscle proteolysis[11].

Insulin and I insulin – like growth factor IGF-1 signaling

An important trigger of muscle wasting in CKD is impaired insulin and insulin – like growth factor type 1 (IGF-1) signaling. This could happened from early stages of the disease, when glomerular filtration is still normal. Abnormal insulin/IGF-1 signaling in muscle leads to the activation of caspase-3 and Ubiquitin proteasome system (UPS) resulting in increased muscle protein breakdown[2,8,11,14-16]. Insulin/IGF-1 signaling stimulates protein synthesis and suppresses protein breakdown. Binding of insulin or IGF-1 to their receptors leading to phosphorylation of Insulin receptor substrate type 1(IRS-1) which stimulates the Phosphoinositide 3-kinases/protein kinase b (P13K/AKT) cascade, resulting to posphorylation of AKT. AKT phoshorylation activates mammalian target of rapamycin (mTor) resulting to protein synthesis and downregulates Forkhead box protein (FOXO) function with phosporylation of FOXO. When insulin resistant occur in CKD patients, low levels of poshorelated protein kinase B (PAKT) leading to decreased poshorylation of FOXO which permits its translocation into the nucleus where it stimulates the expression of Tripartite Motif Containing 63 (TRIM63) and Muscle Atrophy F-box gene (MAFbx)-E3 ubiquitin ligases -

resulting in muscle wasting[8,11,14]. Xianonan et al. in one of the experiments, they showed that protein degradation, caused by a decrease in the activity of P13K, which cause reduction of phosphorylated Akt and increased TRIM63 and MAFbx in muscle leading to muscle protein loss[15]. Bailey et al. found that Basal IRS-1-associated PI3-K activity was suppressed by CKD and basal level of activated Akt in CKD muscles also was low in muscles of acidotic, CKD and pair-fed control rats under physiologic conditions and in response to a dose of insulin that quickly stimulated the pathway[16]. In conclude a major of causes is seems to be responsible for the presence of insulin resistance in CKD patients such as anemia, uremic toxins vitamin D deficiency inflammations and acidosis resulting in muscle degradation[14].

Ubiqutin Proteasomes System (UPS)

UPS is characterized as the dominant mechanism that breakdown muscle proteins in CKD patients and may interact with the IGF pathway. Balei et al. Isolated proteasomes from gastrocnemius muscle in mice and measured their activity to determine whether the increase in muscle degradation in insulin deficiency models like CKD patients was related to activation of the UPS. They demonstrated that proteosome chymotryptic like peptidase activity was significantly increased[7,8]. In CKD patients protein degradation occurs when activated FOXOS increase the expression of antrogin-1 and muscle ring-finger protein 1 (meRF1) E3 ligases. Moreover caspase-3 is triggered by catabolic conditions such as CKD and it cleavages the complex structure of muscle proteins, creating substrates for the UPS[9,15]. Activated Caspase-3 is identified by the presence of an insoluble 14 kDa fragment of actin. In UPS activation metabolic acidosis and inflammation, common in CKD patients, play the major role.

Inflammation

Chronic inflammation is common in CKD patients and is associated with increased mortality risk. Circulating proinflammatory cytokines, including IL-6 ,tumor necrosis factor a (TNF-A) serum amyloid A and c-reactive protein (CRP) are raised in patients with ckd[8,14]. Reduction of renal function, oxidative stress, volume overload, low levels of antioxidants, uremia and presence of comorbidities, which are present in CKD patients may be responsible for increased levels of proinflammatory cytokines in serum[17]. Among the proinflammatory cytokines il-6 is reported to play a central role in the pathophysiology of muscle wasting in CKD patients. In a study, which was performed in two independent end stage renal desase (ESRD) patient cohorts, one of incident dialysis patients and one of prevalent hemodialysis patients Carrero et al. demonstrated that muscle atrophy was common in both cohorts and inflammation parameters (CRP, IL-6) were became gradually higher as the muscle atrophy scale worsened[18]. Inflammation may act through specific pathways such as suppressor of cytokine signaling (SOCS-3)[17]. A high level of socs -3 reduces IRS-1 level and suppresses intracellular insulin signaling and activates caspase 3 and UPS. This hypothesis suggesting that proinflammatory conditions that increase IL-6 levels interfere with insulin/P13K/AKT signaling leading to muscle mass degradation[8].

Metabolic acidosis

Metabolic acidosis is prevalent among CKD patients particularly those in stage 4. In studies of culture muscle cells and isolated muscle, metabolic acidosis stimulates muscle wasting via activation of Ubiquitin proteasome pathway. The correction of acidosis can reduce muscle wasting via downregulation of UPS[8,17].

Malnutrition and physical inactivity

CKD patients specifically those undergo hemodialysis may be in a hypercatabolic condition because of chronic inflammation[19]. Protein energy wasting (PEW) is an energy wasting constitution and decreased food intake, increased catabolism, nutrient losses into dialysate (dialysis fluid), metabolic acidosis, resistance to insulin, hyperparathyroidism and hyperglycagonemia are the major causes of PEW in dialysis patients[14]. The incidents of PEW in patients undergo hemodialysis is reported to be 14% and it has been described that low protein intake is a grade risk for developing sarcopenia and increasing mortality[20]. Hirokaki et al. analyze composition of body fluid and muscle volume by bioimpedance analysis at the time of introduction of dialysis and they examined the difference in muscle mass between 16 patients aged 60-65 years old and 19 patients aged 78 years old. They found that muscle mass was significantly decreased in the lower extremities in the groups with older people suggesting that advancing age is an independent factor causing sarcopenia in CKD patients[20]. With advancing age, CKD patients especially those undergo hemodialysis may develop sarcopenia not only because of factors related with CKD but also because of depression sedentary life and isolation. Furthermore, the same group show that patients undergo hemodialysis have not only decreased muscle mass and strength but also altered the quality of muscle[20].

Changes in sex hormones and growth hormone

The level of testosterone in serum is low in most men with progressive CKD, this may be caused by reduce prolactin clearance and because of uremic environment inhibition of luteinizing hormone (LH) signaling at the level of leydig cell. This could contribute to reduced muscle mass[7,14]. Androgen therapy in uremic patients is related with expansion in muscle mass and strength. On the other hand, women in early stage of CKD usually have oligomennoria and estrogen deficiency leading to decreased muscle strength. In comparison with female with CKD. Male sex is correlated with accelerating deterioration of kidney function and worse renal outcome suggesting that gender and sex hormone may conduce to the different symptomatology[14]. Jessus Carrero et al. reported

that abnormally low endogenous testosterone values were associated with increased risk of death in a relative small cohort of men undergoing haemodialysis[21].

Furthermore CKD is correlated with growth hormone resistance in muscles leading to increased protein catabolism and wasting .Studies have shown that administration of recombinant human growth hormone in hemodialysis patients increase up to 3-4 kg in lean body mass[14].

Vitamin D deficiency

The circulating concentration of both metabolites 25(OH)D and 1.25 (OH)D begins to decrease early in CKD. Several factors are responsible for this like reduce renal mass, nutritional deficiency, diabetes mellitus, obesity, accumulation of uremic toxins proteinuria diminished skin synthesis of cholecalciferol, increased Fibroblast growth factor 23 (FGF23), and reduce sunlight exposure[22].

Lack of vitamin D is associated with low formation rate of bone and decreased mineral density, leading to increased risk of fractures.

Moreover, the effect of decreased vitamin D on muscle may also affect muscle metabolic pathways, including its sensitivity to insulin[22]. Numerus studies have described how reduced vitamin D level contribute to low muscle strength hand mass, decreased physical activity and increase risk of falling and frailty in elderly, but only a few studies have been undertaken in CKD patients. Other studies demonstrated that patients with CKD and vitamin D deficiency are in high risk for reduced BMD and skeletal fractures. Zahed et al. have showed that 25(OH) D levels were positively associated with muscle strength of the lower extremities in dialysis patients. Ambrus et al. evaluated the presence of skeletal fractures during hemodialysis in a prevalent convenience cohort of CKD patients undergo hemodialysis and they found that vitamin D insufficiency is independently associated with bone fracture in end stage renal disease patients[23]. Vitamin D supplementation has shown to improve muscle function, to reduce falls and it may impact muscle fiber composition and morphology in the erderly[14].

Changes in myostatin

Myostatin is a member of the transforming growth factor beta (TGF-β) family that acts as a negative regulator of skeletal mass through the upregulation of aerogenes (atrogin -1 MURF 1) and down regulation of myogenesis genes (ie MyoD, myogenin)[14]. In CKD patients myostatin levels are over expressed leading to atrophy of muscle mass. In a nephrectomy mouse model of CKD mice treatment with myostatin antagonists increase body weight increase protein synthesis, muscle mass, improve the function of satellite cells protein and reduce proteins breakdown. In humans, treatment with anti- myostatin agents would be a potential therapeutic approach to improve muscle atrophy by increasing the size of skeletal muscle and strength[9,14].

Conclusion

Sarcopenia is a powerful predictor of morbidity and mortality in CKD patients. Patients with CKD exhibit considerable skeletal fragility and increase risk of fractures. Muscle atrophy not only contributes to a sedentary lifestyle and poor quality of life but also increases the incidence of cardiovascular complications.

Patients with CKD must be assessed for the presence of sarcopenia at early stages, when skeletal muscle complication is still reversible and introduce therapeutic strategies to maintain skeletal muscle. Much more information and clinical trials is needed to develop potential strategies to prevent muscle wasting and improve lifestyle in these patients.

References

1. Alice Sabatino Lilian Cuppari Peter Stenvinkel et al. Sarcopenia in chronic kidney disease what have we learned so far? Journal of Nephrology 2021;34(4):1347-1372.
2. Ranjani NM, Keith GA, et al. Clinical relevance of sarcopenia in chronic kidney disease. Curr Opin Nephrol Hypertens 2017;26(3):219-228.
3. Hiroshi Nishi, Koji Takemura, TakaakiHigashihara, et al. Uremic Sarcopenia: Clinical Evidence and Basic Experimental Approach Nutrients 2020;12(6):1814.
4. Carrero JJ, Johansen KL, Lindholm B, Stenvinkel P, CuppariL, Avesani et al Screening for muscle wasting and dysfunction in patients with chronic kidney disease. Kidney Int CM (2016) 90(1):53–66.
5. https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf 30/01/2020
6. Sanjay K. Nigam, Kevin T. Bush et al. Uraemic syndrome of chronic kidney disease: altered remote sensing and signaling. Nat Rev Nephrol 2019;15(5):301-316.
7. Souza VA, Oliveira Dd, Mansur HN, Fernandes NM , Bastos MG et al. Sarcopenia in Chronic Kidney DIsease. J Bras Nefro 2015;37(1):98-105.
8. Xiaonan H. Wang, William E. Mitch. Mechanisms of muscle wasting in chronic kidney disease. Nat Rev Nephrol 2014;10(9):504-16.
9. Keith G. Avin, Ranjani N. Moorthi, et al. Bone is Not Alone: the Effects of Skeletal Muscle Dysfunction in Chronic Kidney Disease. Kidney and Bone Curr Osteoporos Rep 2015;13(3):173-9.
10. Cs Ambrus, Cs Almasi, K Berta, Gy Deak, A Marton, M Zs Molnar, Zs Nemeth, Cs Horvath, P Lakatos, M Szathmari, I Mucsi. Vitamin D insufficiency and bone fractures in patients on maintenance hemodialysis. Int Urol Nephrol 2011;43(2):475-82.
11. Xiaonan H. Wang, Jie Du, Janet D. Klein, James L. Bailey et al. Exercise ameliorates chronic kidney disease–induced defects in muscle protein metabolism and progenitor cell function. Kidney International 2009;76(7):751-9.
12. Ravssa A. Pereira, Antonio C. Cordeiro, Carla M. Avesani, Juan J. Carrero, Bengt Lindholm, Fernanda C. Amparo, Celso Amodeo, Lilian et.al. Sarcopenia in chronic kidney disease on conservative therapy: prevalence and association with mortality. Nephrol Dial Transplant 2015;30(10):1718-25.
13. Liping Zhang, Xiaonan H. Wang, †Huiling Wang et al. Satellite Cell Dysfunction and Impaired IGF-1 Signaling Cause CKD-Induced Muscle Atrophy. J Am Soc Nephrol 2010;21(3):419-27.
14. Ibrahim H. Fahal, et al. Uraemic sarcopenia: aetiology and implications Nephrol Dial Transplant 2014;29(9):1655-65.

15. Wang X, Hu Z, Hu J, et al. Insulin resistance accelerates muscle protein degradation: activation of the ubiquitin–proteasome pathway by defects in muscle cell signaling. Endocrinology 2006; 147(9):4160-8.
16. Bailey JL, Zheng B, Hu Z, et al. Chronic kidney disease causes defects in signaling through the insulin receptor substrate/ phosphatidylinositol 3-kinase/Akt pathway: implications for muscle atrophy. J Am Soc Nephrol 2006;17(5):1388-94.
17. Wai W Cheung, Kyung Hoon Paik, Robert H Mak. Inflammation and cachexia in chronic kidney disease. Pediatr Nephrol 2010;25(4):711-24.
18. Carrero JJ, Chmielewski M, Axelsson J et al. Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. Clin Nutr 2008;27(4):557-64.
19. Juan Jesús Carrero, Peter Stenvinkel, Lilian Cuppari, et al. Etiology of the Protein-Energy Wasting Syndrome in Chronic Kidney Disease. J Ren Nutr 2013;23(2):77-90.
20. Hiroaki Hara, Yumiko Nakamura, Minoru Hatano, et al. Protein energy wasting and sarcopenia in dialysis patients. Contrib Nephrol 2018;196:243-249.
21. Juan Jesús Carrero, Abdul Rashid Qureshi, Ayumu Nakashima, Stefan Arver, Paolo Parini, et al. Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease Nephrol Dial Transplant 2011;26(1):184-90.
22. Pablo Molina, Juan J. Carrero, Jordi Bover, Philippe Chauveau et al. Vitamin D, a modulator of musculoskeletal health in chronic kidney disease. J Cachexia Sarcopenia Muscle 2017;8(5):686-701.
23. Cs Ambrus, Cs Almasi, K Berta, Gy Deak, et al. Vitamin D insufficiency and bone fractures in patients on maintenance hemodialysis. Int Urol Nephrol;43(2):475-82.