Review article

Pathophysiological and Diagnostic Aspects of Sarcopenia in Hemodialysis Patients

Zvonimir Sitaš [1*], Dubravka Mihaljević [1]

[1] Department of Nephrology, Clinic for internal diseases, University Hospital Centre Osijek; Department of Internal Medicine and History of Medicine, Faculty of Medicine Osijek, J. J. Strossmayer University, Osijek, Croatia

*Corresponding author: Zvonimir Sitaš, zvonimir.sitas@gmail.com

Abstract

Chronic kidney disease and renal replacement therapy, particularly hemodialysis, contribute to the development of negative protein balance and muscle dysfunction in dialysis patients, from the development of protein-energy malnutrition to sarcopenia. Due to multifactorial etiology and complex pathophysiological patterns, sarcopenia has proven to be a significant predictor of cardiovascular events and is associated with a higher risk of overall mortality. Screening methods of chronic kidney patients and patients on hemodialysis who are at higher risk of developing sarcopenia, as well as diagnostic methods for this group of patients are not clearly defined, hence methods used for the general population of elderly patients, especially based on the revised European consensus on definition and diagnosis of sarcopenia of the European Working Group on Sarcopenia in Older People (EWGSOP2), are utilized in this subpopulation as well. Therefore, there is a need to define new biomarkers of sarcopenia such as the existing 24h urine excretion of creatinine, a product of estimated glomerular filtration of cystatin C and creatinine or myostatin and their use in routine work with dialysis patients to identify this condition among them and reduce morbidity and mortality.

(Sitaš Z, Mihaljević D. Pathophysiological and Diagnostic Aspects of Sarcopenia in Hemodialysis Patients. SEEMEDJ 2023; 7(1); 42-54)

Received: Feb 27, 2023; revised version accepted: Mar 27, 2023; published: Apr 30, 2023

KEYWORDS: sarcopenia, hemodialysis, chronic kidney disease, pathophysiology

Introduction

The word sarcopenia comes from the Greek σάρξ (sarx) which translates to flesh and πενία (penia) meaning loss. It was first introduced in 1989 by Irwin Rosenberg to describe the loss of muscle mass with aging leading to a reduced quality of life as a result of a higher risk of falls, fractures, hospitalizations and ultimately death (1). People suffering from this are at a higher risk of developing adverse outcomes due to bone and mineral disorder as a result of secondary hyperparathyroidism, then the higher rate of depression as a cause of development of anorexia and due to socioeconomic factors, affecting the quality of life that is significantly impaired in dialysis patients. It is estimated that the loss of muscle mass is 1–2% and muscle strength is 1.5–5% per year after the age of 50, primarily the musculature of the lower extremities (2), although muscle volume can be preserved due to myosteatosis and myofibrosis, which will be discussed below. In 1931, Mr. Critchley Macdonald, a British neurologist, was the first to associate aging with a decrease in skeletal muscle mass (3). According to Delmonico et al. in 1,678 subjects after the age of 70, the annual rate of muscle area reduction was 4.9±7.4% in men and 3.2±7.9% in women (4). The prevalence of sarcopenia varies widely in predialysis chronic renal patients of 6–14% (5, 6) and increases in patients on hemodialysis (HD) 4–64% (7, 8), without firm consensus on the prevalence of uremic sarcopenia, although some data suggest the prevalence of uremic myopathy of 50% (9). According to the meta-analysis of Wathanavasin et al., the highest prevalence of sarcopenia is in Europe (29.1%) and the lowest in the US (15.4%) (10). This meta-analysis also showed that sarcopenia is less diagnosed before the hemodialysis procedure (21.5%) compared to after hemodialysis (27.8%), primarily due to volume status, but without statistical significance. Sarcopenia has also been shown to be one of the most important predictors of cardiovascular events (OR 3.80 – 95% CI 1.79-8.09) with a high mortality risk (OR 1.83 – 95% CI 1.40-2.39). Low muscle strength and mass are independent factors of increased mortality in patients on hemodialysis (OR 1.71 – 95% CI 1.20-2.44), all the more so, if they are associated (11).

Pathophysiology and etiology of sarcopenia

Knowledge of the physiology and histology of skeletal musculature is necessary for understanding the pathophysiology and histopathological changes within chronic kidney disease (CKD) and the uremic state. Skeletal muscles belong to the group of transversely striped muscle tissue made of muscle fibers (actin, myosin), i.e. muscle cells that function as syncytium and are formed by fusion of myoblasts – precursor cells (12). Skeletal muscle stem cells play a key role in muscle regeneration. Various stimuli such as exercise, injury, stretching, etc. can activate these cells that are located between the plasma membrane and the basal lamina leading to asymmetric differentiation into myoblasts responsible for tissue regeneration and pluripotent stem cells responsible for self-renewal. Myoblast differentiation requires primary myogenic regulatory factors Myf5 and MyoD, as well as secondary – myogenin and myogenic regulatory factor 4 – MRF4 (13, 14). Muscle fibers can be classified into three groups according to the isoform of the myosin heavy chain – slow oxidative red fibers (type I), fast oxidative red fibers (type IIA) and fast glycolytic white fibers (type IIX) that were represented in different proportions in skeletal muscles depending on muscle function (15). Various factors are associated with histopathological changes in skeletal muscle in patients with advanced, i.e. terminal chronic kidney disease – especially a condition of chronic inflammation, which shows the replacement of muscle fibers with adipose tissue – myosteatosis, or fibrous tissue – myofibrosis and are a reflection of muscle dysfunction (16). In a study conducted on 60 patients on hemodialysis, the cross-section of muscle fibers was higher compared to the control group, which is explained by the development of interstitial edema in the interdialytic period, but the results also showed reduced oxidative capacity due to dysfunction

of the enzyme succinate dehydrogenase and mitochondrial edema with a reduced network of capillaries (17). Uremic toxins such as indoxyl sulfate, p-crescol and inorganic phosphorus, can impair myogenous differentiation in vitro and promote muscular atrophy in mice with CKD by promoting mitochondrial dysfunction (18, 19).

Development of sarcopenia and etiology of muscle dysfunction of patients on hemodialysis is multifactorial and arises from kidney disease itself, hemodialysis procedure and chronic inflammatory response, which contributes to reduced protein synthesis and increased degradation (20) (see Figure 1).

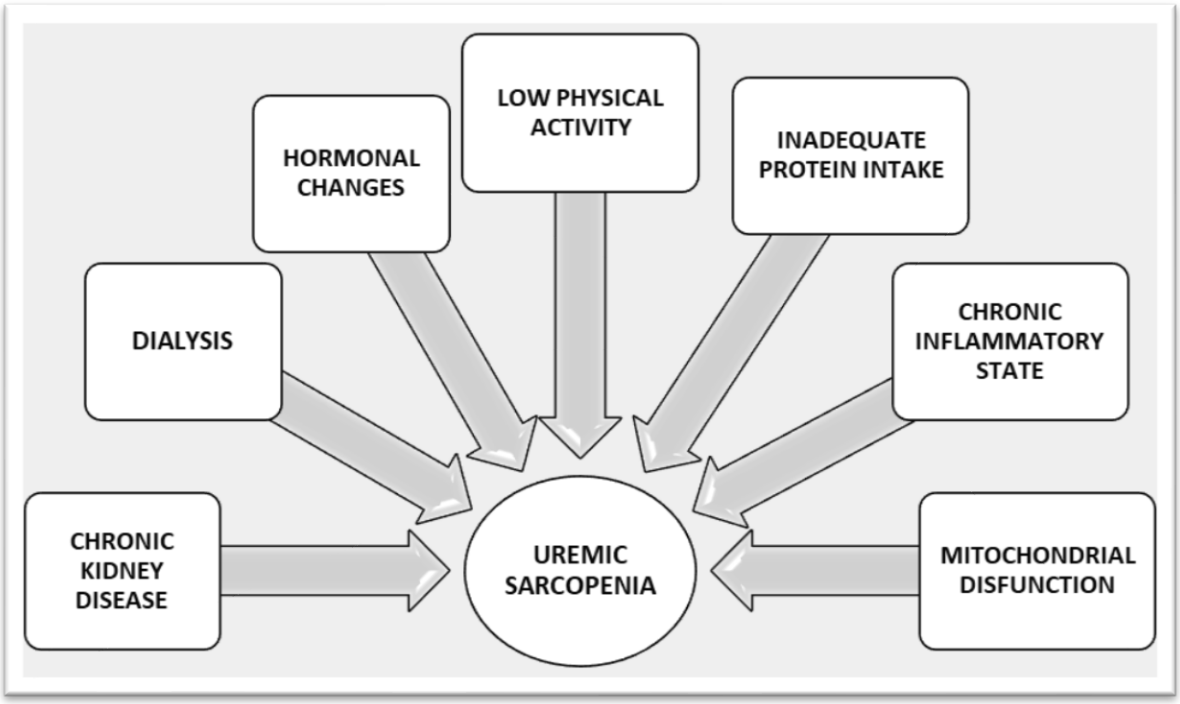

Figure 1. Etiological factors involved in the development of uremic sarcopenia

The development of metabolic acidosis in CKD, vitamin D deficiency and insulin resistance also contribute to the negative protein balance. Metabolic acidosis activates caspase-3 and the ubiquitin-proteasome system – two intracellular pathways responsible for protein degradation and promoting insulin resistance and growth hormone resistance (13, 21). 1,25(OH)2 vitamin D as an active form of vitamin D binds to vitamin D receptors in human muscle tissue, especially to C2C12 myoblasts, and causes reduced cell proliferation and promotes myogenic differentiation by MyoD expression and myostatin suppression (22). Vitamin D deficiency also leads to reduced insulin secretion from pancreatic beta cells promoting insulin resistance (23, 7). Insulin-like growth factor 1 (IGF-1) shares a common intracellular pathway in protein synthesis with insulin, activating mTORC1 via PI3K (phosphatidylinositol-3-kinase)/Act leading to phosphorylation of FOXO proteins and inhibiting their translocation into the nucleus. IGF-1 suppresses both Atrogin-1 and MuRF1 (ubiquitin ligase) which antagonizes skeletal muscle catabolism (24, 25). In patients on hemodialysis, the concentration of testosterone is reduced, which leads to the expression of myostatin and alteration of the IGF-1 signaling pathway (26). Myostatin is a protein that negatively affects the growth of muscle tissue through three signaling pathways. Via activin, IIB receptor activates Smad2/Smad3 and dephosphorylation Act thus disrupting the IGF-1 signaling pathway previously specified. It can also inhibit mTORC1 and induce apoptosis via the p38-caspase pathway (27).

The HD procedure also contributes to the negative balance of protein metabolism. During the HD process, a significant loss of proteins and

amino acids (> 5 g) was observed more pronounced at the beginning and end of the procedure itself (28). Patients with CKD, especially patients on HD, have a decreased appetite due to the action of uremic toxins, chronic inflammation and hormonal disorders – primarily by a decrease in ghrelin and neuropeptide Y, and an increase in leptin (29). Chronic inflammatory condition of patients on HD is associated with the use of biocompatible membranes (30) and the role of the gastrointestinal tract or intestinal dysbiosis is increasingly mentioned. Namely, due to dietary restrictions with reduced fiber intake, protein fermentation and exposure to endotoxins that induce the pro-inflammatory state and disrupt the gastrointestinal barrier increases (31, 32). Pro-inflammatory cytokines such as IL-6 and TNF-alpha reduce the suppression of SOCS-3 protein through the activation of caspase-3 and the ubiquitin-proteasome system. IL-6 also stimulates the expression of Stat3 responsible for the expression of myostatin and leads to muscle degradation (33, 34). The production of pro-inflammatory mediators is induced by the formation of advanced glycation end products (AGE) that accumulate in patients with CKD due to reduced renal clearance and increased production (non-enzymatic changes in protein or lipid amino acids that are reduced by exposure to sugars or their metabolites) and lead to oxidative stress, insulin resistance and endothelial dysfunction (35, 36). Yabuuchi et al. showed that the accumulation of AGE in the muscle tissue of mice leads to mitochondrial dysfunction (by reducing the activity of succinate dehydrogenase and PGC1-alpha and reducing the density of the capillary network) (37). Furthermore, AGE can impair muscle function through associated membrane RAGE receptors whose activity reduces the expression of myogenin (38), impairs the distribution of muscle fibers and increases the rigidity of muscle connective tissue (39). These etiological factors contribute to negative protein balance that can eventually lead to the decline of muscle mass, muscle strength and lower physical activity because patients on HD are at a higher risk of developing sarcopenia compared to the general population and these changes occur at an earlier age.

Diagnosis of sarcopenia and associated conditions

Skeletal musculature is mostly made of protein and it is the best indicator of protein status. The development of protein-energy malnutrition (PEM) – a term presented in 2007 by the International Society of Renal Nutrition and Metabolism (ISRNM), occurs due to various pathophysiological mechanisms, that include nutritional and metabolic disorders in patients with chronic kidney disease and lead to the development of a state of chronic muscle and adipose tissue catabolism (40, 41). It is associated with chronic inflammation, uremia, anorexia due to decreased appetite, hypoalbuminemia, muscle loss with weight loss or no weight loss and poor clinical outcome. Due to PEM, there is a reduction in protein supplies and energy sources in patients with different CKD stages, leading to a decrease in the functional abilities of the patient. Malnutrition, on the other hand, is an imbalance of energy intake, protein and other nutrients that leads to measurable undesirable effects on tissues and physical functions and can be presented with malnutrition, but also overfeeding (42–45), so we can find it in obese patients too. Such a physiological state can lead to cachexia – a syndrome manifested by severe muscle loss with or without loss of fat tissue (46) and sarcopenia, which, according to the consensus of the EWGSOP2 defines as „a progressive and generalized muscle disorder characterized by low muscle power and reduced quality and quantity of muscle mass“ (47). Quantitative changes are related to the loss of muscle mass and volume, and qualitative to the loss of muscle strength and physical activity (48). In these revised guidelines, the emphasis is on muscle strength because it has a better predictive value for the occurrence of adverse outcomes. If the patient meets the criterion of low muscle strength, it is probably sarcopenia, i.e. presarkopenia, if it meets the second criterion of low muscle quality or quantity, the diagnosis can be confirmed by sarcopenia, and if it meets the third criterion of low physical activity,

sarcopenia is considered severe. According to the International Working Group on Sarcopenia (IWGS), sarcopenia is characterized by low skeletal muscle mass (with an increase in body fat) and decreased muscle function (49). EWGSOP2 consensus provides a broader definition by dividing muscle strength from muscle activity and distinguishes severe sarcopenia.

Sarcopenia can be divided into primary (age-related) when there is no other evident cause and secondary in systemic diseases especially those that can cause inflammatory processes including CKD, conditions of reduced physical activity (sedentary lifestyle, in bedridden patients) and some nutritional factors such as gastrointestinal diseases, malabsorption syndrome, insufficient food intake (9). The main difference between these two groups is that the primary group occurs over a continuous period and is more pronounced after the age of 50, while the secondary is more intense and depends on the conditions that cause it (50). Unlike primary sarcopenia, sarcopenia in chronic kidney patients is characterized by more pronounced protein degradation. EWGSOP2 subcategorizes sarcopenia into acute if it lasts less than 6 months and chronic if it lasts 6 months and more. Such a division places emphasis on periodic assessments of sarcopenia in patients at increased risk (47). In elderly patients, a condition of sarcopenic obesity can be observed, which is presented by reduced muscle mass due to adiposity (51).

For the diagnosis of sarcopenia, a multitude of different tests and methods can be used, the choice of which depends on the patient, the technical availability and the purpose of testing (whether we are examining the progression of the condition or recovery) – see Figure 2.

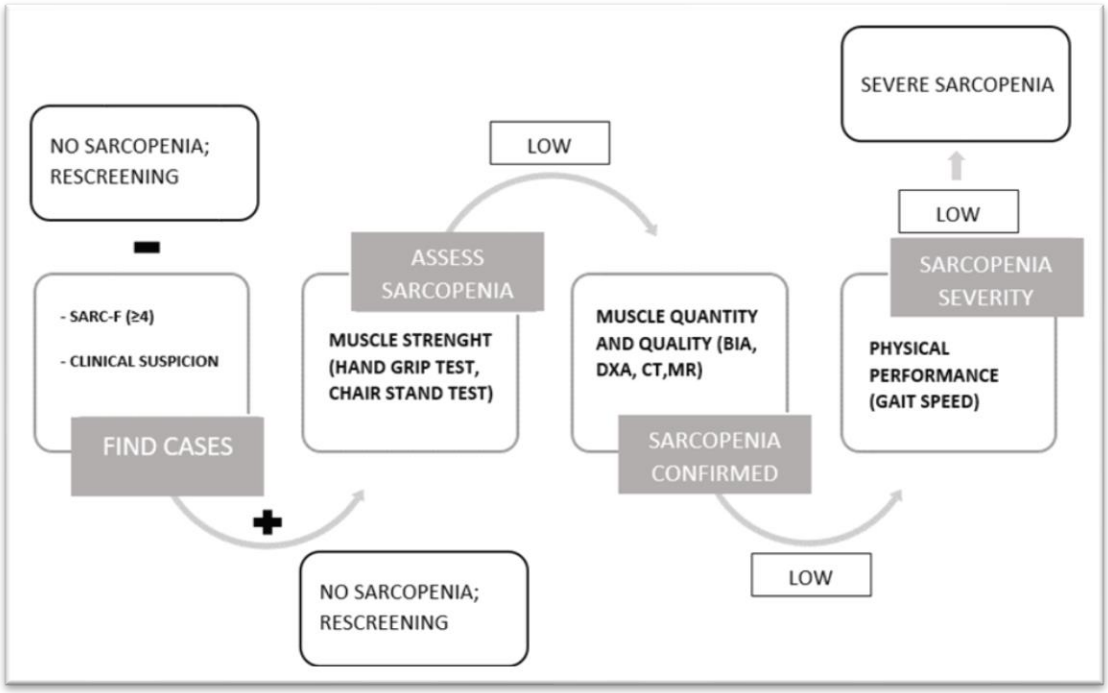

Figure 2. Sarcopenia diagnostic algorithm – adapted according to EWGSOP2

Level of strength, assistance with walking, rising from a chair, climbing stairs and falls are criteria in the 5-item questionnaire (SARC-F) as a screening method for patients with sarcopenia. It includes the patient's subjective attitude about the ability to walk, get up from a chair, climb stairs, strength level, and the existence of falls in the past year. The questionnaire has high specificity in predicting low muscle strength and will detect more severe cases as such (52, 53). If the test is positive (SARC-F ≥4), the first criterion – muscle strength – is examined. To test muscle

strength, the strength of the handshake can be measured with a Jamar dynamometer, which is a simple and inexpensive method and correlates with the strength of other body regions, such as the strength of the upper and lower extremities (54, 55) and should be measured before the hemodialysis procedure (56, 57). The meta-analysis by Hwang et al. showed that people with low muscle strength had a 1.88 times higher risk of overall mortality (58). Vogt et al. suggested cut-off values that would suggest higher mortality in patients on HD, <7 kg in women and <22.5 kg in men (59), while according to EWGSOP2, values <16 kg for women and <27 kg for men. In addition to testing the strength of the handshake, the test of getting up from the chair can be used, which predominantly examines the strength of the muscles of the lower extremities (quadriceps). The test measures the time it takes a patient to get out of the chair 5 times without arm support and the time > 15 s is considered significant. If these tests determine reduced muscle strength, it can be said that sarcopenia is probable and confirmed by testing muscle quality or quantity. Muscle quantity can be shown as appendicular muscle mass (AMM), total skeletal muscle mass (SMM) and cross-section of a specific muscle group. Computed tomography (CT) and magnetic resonance imaging (MRI) are considered the gold standards in non-invasive assessment of muscle mass and myosteatosis (60, 61), but they are not widely used due to expensiveness, radiation exposure and necessary logistics. Alternative methods include densitometry (DXA) and bioelectrical impedance analysis (BIA) which can assess the total and appendicular muscle mass and in the case of BIA and nutritional status of patients on HD with better evaluation of intracellular and extracellular fluid (62, 63) which should be done after the HD procedure. The absolute values of SMM and AMM can be modified according to weight (AMM/weight), height square (AMM/height2) or body mass index (AMM/BMI). The cut-off values for these methods are according to EWGSOP2 AMM/height2 <7 kg/m2 for men and <5.5 kg/m2 for women. The method that can be done at the patient's bedside is an ultrasound measurement of the thickness of the quadriceps femoris muscle (rectus femoris and vastus intermedius) which correlates with nutritional status (9). If any method determines low muscle quality or quantity, we can talk about the existence of sarcopenia whose weight is additionally assessed by the analysis of physical activity. Most often, the walking speed test is used. The cut-off value is ≤ 0.8 m/s. The test is performed by measuring time at a distance of 4 m, walking at the usual walking speed (64, 65).

Diagnostic challenges of sarcopenia in CKD/dialysis patients

Although the diagnostic criteria of sarcopenia are well-defined in the general population, there is no consensus on the diagnosis of uremic sarcopenia in dialysis patients. Most studies apply definitions relating to the elderly population leading to the heterogeneity of the results of the prevalence of sarcopenia in the dialysis population as previously stated. There is a risk of underestimating the prevalence of low muscle mass if in obese patients SMM is modified according to the square of height and in such patients, there is a better modification according to body mass index (66). Furthermore, several studies have shown that low muscle mass in dialysis patients is not associated with increased mortality unlike low muscle strength and low muscle activity defined by a weak hand-grip test and slow gait speed (67, 68), and using this approach overlooks patients only with low muscle strength. This is supported by the KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines according to which hand grip strength is useful in assessing protein energy wasting because the use of BIA and DEXA is determined by volume status, so patients who are in overvolemia or with early changes in muscle structure would be misdiagnosed (69). Fahal et al. (70) examined the contractile properties and muscular strength of dialysis patients with muscle quadriceps biopsy. The main difference between this group of patients and the control was poor muscle relaxation, which can affect muscle strength independently of muscle mass, which is supported by the fact

that 45% of patients had type I and 40% of type II muscle fibers atrophy and fibers type II were significantly lower in malnourished patients, which again shows that muscle mass is not the only determinant of muscle strength. Pereira et al. (71) define sarcopenia in CKD patients treated conservatively by reduced muscle function (hand grip strength – 30% percentile of the reference population), reduced muscle mass (measuring mid-arm muscle circumference) and reduced skeletal musculature index according to bioimpedance analysis (<6.76 kg/m2 in women and < 10.76 kg/m2 in men). Furthermore, if low muscle mass is confirmed, patients may be in pronounced muscle wasting. Therefore, in the assessment of sarcopenia in dialysis patients the focus should be on the components of low muscle strength and physical activity and such patients should be encouraged to change their lifestyle habits, diet and exercise for the preservation of muscle mass and muscle function.

In addition to the aforementioned tests for diagnosis and monitoring of patients with sarcopenia, there was a need to define certain biomarkers for early detection of sarcopenia in patients with CKD. As an endogenous metabolite of skeletal muscle, the determination of creatinine excretion in 24h urine is justified in the assessment of muscle mass (72, 73) with a lack of adequate collection of all-day urine in certain patients. This problem was attempted to be solved by determining a new sarcopenia index – the product of the estimated glomerular filtration of cystatin C and creatinine (74). In the study of Lin et al., this index was independently associated with muscle strength, mass and walking speed in patients with CKD (75). Measurement of serum concentration of myostatin as a muscle consumption biomarker was also considered but with conflicting results of studies due to the influence of age, gender, inflammatory conditions, physical activity and metabolic syndrome. Myostatin values are generally higher in patients with CKD, i.e. patients on HD with greater muscle strength and muscle mass compared to healthy individuals (27, 76).

Conclusions

Chronic kidney disease and renal replacement therapy, particularly hemodialysis, contribute to the multifactorial etiology of sarcopenia negative protein-energy balance and increased mortality of chronic kidney patients. Adequate screening systems and diagnostic methods are crucial in the early recognition of patients at elevated risk. Diagnostic tests and methods in the assessment of sarcopenia should be adapted to the conditions in which they are performed, patient groups and systematic monitoring. In conditions of unavailability of tests and methods adapted to dialysis patients, existing methods of assessing muscle strength, muscle quality and quantity, and physical activity can be used according to the EWGSOP2 group of experts with a tendency to find new biomarkers of sarcopenia. Due to the complex pathophysiology of protein catabolism, it is expected to find biomarker panels and their application in the stratification of heterogeneous groups of patients such as patients with CKD with the aim of adequate action and prevention of premature morbidity and mortality. The emphasis should be put on the fact that sarcopenia is a modifiable risk factor for adverse outcomes in CKD patients, using preventive nutritional measures based on data obtained by existing diagnostic methods and tests, so it should be further studied and adequately diagnosed and treated.

Acknowledgement. None.

Disclosure

Funding. No specific funding was received for this study.
Competing interests. None to declare.

References

1. Rosenberg I. H. (1997). Sarcopenia: origins and clinical relevance. The Journal of nutrition, 127(5 Suppl), 990S–991S. https://doi.org/10.1093/jn/127.5.990S

2. von Haehling, S., Morley, J. E., & Anker, S. D. (2010). An overview of sarcopenia: facts and numbers on prevalence and clinical impact. Journal of cachexia, sarcopenia and muscle, 1(2), 129–133. https://doi.org/10.1007/s13539-010-0014-2

3. Doherty T. J. (2003). Invited review: Aging and sarcopenia. Journal of applied physiology (Bethesda, Md. : 1985), 95(4), 1717–1727 https://doi.org/10.1152/japplphysiol.00347.2003

4. Delmonico, M. J., Harris, T. B., Visser, M., Park, S. W., Conroy, M. B., Velasquez-Mieyer, P., Boudreau, R., Manini, T. M., Nevitt, M., Newman, A. B., Goodpaster, B. H., & Health, Aging, and Body (2009). Longitudinal study of muscle strength, quality, and adipose tissue infiltration. The American journal of clinical nutrition, 90(6), 1579–1585. https://doi.org/10.3945/ajcn.2009.28047

5. Zhou, Y., Hellberg, M., Svensson, P., Höglund, P., & Clyne, N. (2018). Sarcopenia and relationships between muscle mass, measured glomerular filtration rate and physical function in patients with chronic kidney disease stages 3-5. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 33(2), 342–348. https://doi.org/10.1093/ndt/gfw466

6. Pereira, R. A., Cordeiro, A. C., Avesani, C. M., Carrero, J. J., Lindholm, B., Amparo, F. C., Amodeo, C., Cuppari, L., & Kamimura, M. A. (2015). Sarcopenia in chronic kidney disease on conservative therapy: prevalence and association with mortality. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 30(10), 1718–1725. https://doi.org/10.1093/ndt/gfv133

7. Lamarca, F., Carrero, J. J., Rodrigues, J. C., Bigogno, F. G., Fetter, R. L., & Avesani, C. M. (2014). Prevalence of sarcopenia in elderly maintenance hemodialysis patients: the impact of different diagnostic criteria. The journal of nutrition, health & aging, 18(7), 710–717. https://doi.org/10.1007/s12603-014-0505-5

8. Kim, J. K., Choi, S. R., Choi, M. J., Kim, S. G., Lee, Y. K., Noh, J. W., Kim, H. J., & Song, Y. R. (2014). Prevalence of and factors associated with sarcopenia in elderly patients with end-stage renal disease. Clinical nutrition (Edinburgh, Scotland), 33(1), 64–68. https://doi.org/10.1016/j.clnu.2013.04.002

9. Clyne N. (1996). Physical working capacity in uremic patients. Scandinavian journal of urology and nephrology, 30(4), 247–252. https://doi.org/10.3109/00365599609182300

10. Sabatino, A., Cuppari, L., Stenvinkel, P., Lindholm, B., & Avesani, C. M. (2021). Sarcopenia in chronic kidney disease: what have we learned so far?. Journal of nephrology, 34(4), 1347–1372. https://doi.org/10.1007/s40620-020-00840-y

11. Studenski, S. A., Peters, K. W., Alley, D. E., Cawthon, P. M., McLean, R. R., Harris, T. B., Ferrucci, L., Guralnik, J. M., Fragala, M. S., Kenny, A. M., Kiel, D. P., Kritchevsky, S. B., Shardell, M. D., Dam, T. T., & Vassileva, M. T. (2014). The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. The journals of gerontology. Series A, Biological sciences and medical sciences, 69(5), 547–558. https://doi.org/10.1093/gerona/glu010

12. Huard, J., Li, Y., & Fu, F. H. (2002). Muscle injuries and repair: current trends in research. The Journal of bone and joint surgery. American volume, 84(5), 822–832.

13. Seale, P., & Rudnicki, M. A. (2000). A new look at the origin, function, and "stem-cell" status of muscle satellite cells. Developmental biology, 218(2), 115–124. https://doi.org/10.1006/dbio.1999.9565

14. Demonbreun, A. R., Biersmith, B. H., & McNally, E. M. (2015). Membrane fusion in muscle development and repair. Seminars in cell & developmental biology, 45, 48–56. https://doi.org/10.1016/j.semcdb.2015.10.026

15. Spangenburg, E. E., & Booth, F. W. (2003). Molecular regulation of individual skeletal muscle fiber types. Acta physiologica Scandinavica, 178(4), 413–424. https://doi.org/10.1046/j.1365-201X.2003.01158.x

16. Wilkinson, T. J., Gould, D. W., Nixon, D. G. D., Watson, E. L., & Smith, A. C. (2019). Quality over quantity? Association of skeletal muscle myosteatosis and myofibrosis on physical function in chronic kidney disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 34(8), 1344–1353. https://doi.org/10.1093/ndt/gfy139

17. Lewis, M. I., Fournier, M., Wang, H., Storer, T. W., Casaburi, R., Cohen, A. H., & Kopple, J. D. (2012). Metabolic and morphometric profile of muscle fibers in chronic hemodialysis patients. Journal of applied physiology (Bethesda, Md. : 1985), 112(1), 72–78. https://doi.org/10.1152/japplphysiol.00556.2011

18. Alcalde-Estévez, E., Sosa, P., Asenjo-Bueno, A., Plaza, P., Olmos, G., Naves-Díaz, M., Rodríguez-Puyol, D., López-Ongil, S., & Ruiz-Torres, M. P. (2021). Uraemic toxins impair skeletal muscle regeneration by inhibiting myoblast proliferation, reducing myogenic differentiation, and promoting muscular fibrosis. Scientific reports, 11(1), 512. https://doi.org/10.1038/s41598-020-79186-1

19. Chung, L. H., Liu, S. T., Huang, S. M., Salter, D. M., Lee, H. S., & Hsu, Y. J. (2020). High phosphate induces skeletal muscle atrophy and suppresses myogenic differentiation by increasing oxidative stress and activating Nrf2 signaling. Aging, 12(21), 21446–21468. https://doi.org/10.18632/aging.103896

20. Raj, D. S., Sun, Y., & Tzamaloukas, A. H. (2008). Hypercatabolism in dialysis patients. Current opinion in nephrology and hypertension, 17(6), 589–594. https://doi.org/10.1097/MNH.0b013e32830d5bfa

21. Hu, Z., Wang, H., Lee, I. H., Du, J., & Mitch, W. E. (2009). Endogenous glucocorticoids and impaired insulin signaling are both required to stimulate muscle wasting under pathophysiological conditions in mice. The Journal of clinical investigation, 119(10), 3059–3069. https://doi.org/10.1172/JCI38770

22. Harada, K., Suzuki, S., Ishii, H., Aoki, T., Hirayama, K., Shibata, Y., Negishi, Y., Sumi, T., Kawashima, K., Kunimura, A., Shimbo, Y., Tatami, Y., Kawamiya, T., Yamamoto, D., Morimoto, R., Yasuda, Y., & Murohara, T. (2017). Impact of Skeletal Muscle Mass on Long-Term Adverse Cardiovascular Outcomes in Patients With Chronic Kidney Disease. The American journal of cardiology, 119(8), 1275–1280. https://doi.org/10.1016/j.amjcard.2017.01.003

23. Sharma, D., Hawkins, M., & Abramowitz, M. K. (2014). Association of sarcopenia with eGFR and misclassification of obesity in adults with CKD in the United States. Clinical journal of the American Society of Nephrology : CJASN, 9(12), 2079–2088. https://doi.org/10.2215/CJN.02140214

24. Stitt, T. N., Drujan, D., Clarke, B. A., Panaro, F., Timofeyva, Y., Kline, W. O., Gonzalez, M., Yancopoulos, G. D., & Glass, D. J. (2004). The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. Molecular cell, 14(3), 395–403. https://doi.org/10.1016/s1097-2765(04)00211-4

25. Mori K. (2021). Maintenance of Skeletal Muscle to Counteract Sarcopenia in Patients with Advanced Chronic Kidney Disease and Especially Those Undergoing Hemodialysis. Nutrients, 13(5), 1538. https://doi.org/10.3390/nu13051538

26. Sun, D. F., Chen, Y., & Rabkin, R. (2006). Work-induced changes in skeletal muscle IGF-1 and myostatin gene expression in uremia. Kidney international, 70(3), 453–459. https://doi.org/10.1038/sj.ki.5001532

27. Bataille, S., Chauveau, P., Fouque, D., Aparicio, M., & Koppe, L. (2021). Myostatin and muscle atrophy during chronic kidney disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 36(11), 1986–1993. https://doi.org/10.1093/ndt/gfaa129

28. Martins, A. M., Dias Rodrigues, J. C., de Oliveira Santin, F. G., Barbosa Brito, F.dosS., Bello Moreira, A. S., Lourenço, R. A., & Avesani, C. M. (2015). Food intake assessment of elderly patients on hemodialysis. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation, 25(3), 321–326. https://doi.org/10.1053/j.jrn.2014.10.007

29. Carrero J. J. (2011). Mechanisms of altered regulation of food intake in chronic kidney disease. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation, 21(1), 7–11. https://doi.org/10.1053/j.jrn.2010.10.004

30. Stenvinkel, P., Carrero, J. J., von Walden, F., Ikizler, T. A., & Nader, G. A. (2016). Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 31(7), 1070–1077. https://doi.org/10.1093/ndt/gfv122

31. Mafra, D., & Fouque, D. (2015). Gut microbiota and inflammation in chronic kidney disease patients. Clinical kidney journal, 8(3), 332–334. https://doi.org/10.1093/ckj/sfv026

32. Sabatino, A., Regolisti, G., Brusasco, I., Cabassi, A., Morabito, S., & Fiaccadori, E. (2015). Alterations of intestinal barrier and microbiota in chronic kidney disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant

Association - European Renal Association, 30(6), 924–933. https://doi.org/10.1093/ndt/gfu287

33. Zhang, L., Du, J., Hu, Z., Han, G., Delafontaine, P., Garcia, G., & Mitch, W. E. (2009). IL-6 and serum amyloid A synergy mediates angiotensin II-induced muscle wasting. Journal of the American Society of Nephrology : JASN, 20(3), 604–612. https://doi.org/10.1681/ASN.2008060628

34. Zhang, L., Pan, J., Dong, Y., Tweardy, D. J., Dong, Y., Garibotto, G., & Mitch, W. E. (2013). Stat3 activation links a C/EBP δ to myostatin pathway to stimulate loss of muscle mass. Cell metabolism, 18(3), 368–379. https://doi.org/10.1016/j.cmet.2013.07.012

35. Linden, E., Cai, W., He, J. C., Xue, C., Li, Z., Winston, J., Vlassara, H., & Uribarri, J. (2008). Endothelial dysfunction in patients with chronic kidney disease results from advanced glycation end products (AGE)-mediated inhibition of endothelial nitric oxide synthase through RAGE activation. Clinical journal of the American Society of Nephrology : CJASN, 3(3), 691–698. https://doi.org/10.2215/CJN.04291007

36. Kellow, N. J., & Savige, G. S. (2013). Dietary advanced glycation end-product restriction for the attenuation of insulin resistance, oxidative stress and endothelial dysfunction: a systematic review. European journal of clinical nutrition, 67(3), 239–248. https://doi.org/10.1038/ejcn.2012.220

37. Yabuuchi, J., Ueda, S., Yamagishi, S. I., Nohara, N., Nagasawa, H., Wakabayashi, K., Matsui, T., Yuichiro, H., Kadoguchi, T., Otsuka, T., Gohda, T., & Suzuki, Y. (2020). Association of advanced glycation end products with sarcopenia and frailty in chronic kidney disease. Scientific reports, 10(1), 17647. https://doi.org/10.1038/s41598-020-74673-x

38. Chiu, C. Y., Yang, R. S., Sheu, M. L., Chan, D. C., Yang, T. H., Tsai, K. S., Chiang, C. K., & Liu, S. H. (2016). Advanced glycation end-products induce skeletal muscle atrophy and dysfunction in diabetic mice via a RAGE-mediated, AMPK-down-regulated, Akt pathway. The Journal of pathology, 238(3), 470–482. https://doi.org/10.1002/path.4674

39. Haus, J. M., Carrithers, J. A., Trappe, S. W., & Trappe, T. A. (2007). Collagen, cross-linking, and advanced glycation end products in aging human skeletal muscle. Journal of applied physiology (Bethesda, Md. : 1985), 103(6), 2068–2076. https://doi.org/10.1152/japplphysiol.00670.2007

40. Fouque, D., Kalantar-Zadeh, K., Kopple, J., Cano, N., Chauveau, P., Cuppari, L., Franch, H., Guarnieri, G., Ikizler, T. A., Kaysen, G., Lindholm, B., Massy, Z., Mitch, W., Pineda, E., Stenvinkel, P., Treviño-Becerra, A., & Wanner, C. (2008). A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney international, 73(4), 391–398. https://doi.org/10.1038/sj.ki.5002585

41. Obi, Y., Qader, H., Kovesdy, C. P., & Kalantar-Zadeh, K. (2015). Latest consensus and update on protein-energy wasting in chronic kidney disease. Current opinion in clinical nutrition and metabolic care, 18(3), 254–262. https://doi.org/10.1097/MCO.0000000000000171

42. Rocco, M. V., Paranandi, L., Burrowes, J. D., Cockram, D. B., Dwyer, J. T., Kusek, J. W., Leung, J., Makoff, R., Maroni, B., & Poole, D. (2002). Nutritional status in the HEMO Study cohort at baseline. Hemodialysis. American journal of kidney diseases : the official journal of the National Kidney Foundation, 39(2), 245–256. https://doi.org/10.1053/ajkd.2002.30543

43. Kloppenburg, W. D., de Jong, P. E., & Huisman, R. M. (1999). Low calorie intake in dialysis patients: an alternative explanation. American journal of kidney diseases : the official journal of the National Kidney Foundation, 33(6), 1202–1204. https://doi.org/10.1016/s0272-6386(99)70168-x

44. Thunberg, B. J., Swamy, A. P., & Cestero, R. V. (1981). Cross-sectional and longitudinal nutritional measurements in maintenance hemodialysis patients. The American journal of clinical nutrition, 34(10), 2005–2012. https://doi.org/10.1093/ajcn/34.10.2005

45. Fouque, D., Kalantar-Zadeh, K., Kopple, J., Cano, N., Chauveau, P., Cuppari, L., Franch, H., Guarnieri, G., Ikizler, T. A., Kaysen, G., Lindholm, B., Massy, Z., Mitch, W., Pineda, E., Stenvinkel, P., Treviño-Becerra, A., & Wanner, C. (2008). A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney international, 73(4), 391–398. https://doi.org/10.1038/sj.ki.5002585

46. Cruz-Jentoft, A. J., Baeyens, J. P., Bauer, J. M., Boirie, Y., Cederholm, T., Landi, F., Martin, F. C., Michel, J. P., Rolland, Y., Schneider, S. M., Topinková, E., Vandewoude, M., Zamboni, M., & European Working Group on Sarcopenia in Older People (2010). Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing, 39(4), 412–423. https://doi.org/10.1093/ageing/afq034

47. Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A. A., Schneider, S. M., Sieber, C. C.,

Topinkova, E., Vandewoude, M., Visser, M., Zamboni, M., & Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2 (2019). Sarcopenia: revised European consensus on definition and diagnosis. Age and ageing, 48(1), 16–31. https://doi.org/10.1093/ageing/afq034

48. Noce, A., Marrone, G., Ottaviani, E., Guerriero, C., Di Daniele, F., Pietroboni Zaitseva, A., & Di Daniele, N. (2021). Uremic Sarcopenia and Its Possible Nutritional Approach. Nutrients, 13(1), 147. https://doi.org/10.3390/nu13010147

49. Fielding, R. A., Vellas, B., Evans, W. J., Bhasin, S., Morley, J. E., Newman, A. B., Abellan van Kan, G., Andrieu, S., Bauer, J., Breuille, D., Cederholm, T., Chandler, J., De Meynard, C., Donini, L., Harris, T., Kannt, A., Keime Guibert, F., Onder, G., Papanicolaou, D., Rolland, Y., … Zamboni, M. (2011). Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. Journal of the American Medical Directors Association, 12(4), 249–256. https://doi.org/10.1016/j.jamda.2011.01.003

50. Molfino, A., Chiappini, M. G., Laviano, A., Ammann, T., Bollea, M. R., Alegiani, F., Rossi Fanelli, F., & Muscaritoli, M. (2012). Effect of intensive nutritional counseling and support on clinical outcomes of hemodialysis patients. Nutrition (Burbank, Los Angeles County, Calif.), 28(10), 1012–1015. https://doi.org/10.1016/j.nut.2012.01.008

51. Johnson Stoklossa, C. A., Sharma, A. M., Forhan, M., Siervo, M., Padwal, R. S., & Prado, C. M. (2017). Prevalence of Sarcopenic Obesity in Adults with Class II/III Obesity Using Different Diagnostic Criteria. Journal of nutrition and metabolism, 2017, 7307618. https://doi.org/10.1155/2017/7307618

52. Morley, J. E., Abbatecola, A. M., Argiles, J. M., Baracos, V., Bauer, J., Bhasin, S., Cederholm, T., Coats, A. J., Cummings, S. R., Evans, W. J., Fearon, K., Ferrucci, L., Fielding, R. A., Guralnik, J. M., Harris, T. B., Inui, A., Kalantar-Zadeh, K., Kirwan, B. A., Mantovani, G., Muscaritoli, M., … Society on Sarcopenia, Cachexia and Wasting Disorders Trialist Workshop (2011). Sarcopenia with limited mobility: an international consensus. Journal of the American Medical Directors Association, 12(6), 403–409. https://doi.org/10.1016/j.jamda.2011.04.014

53. Bahat, G., Yilmaz, O., Kılıç, C., Oren, M. M., & Karan, M. A. (2018). Performance of SARC-F in Regard to Sarcopenia Definitions, Muscle Mass and Functional Measures. The journal of nutrition, health & aging, 22(8), 898–903. https://doi.org/10.1007/s12603-018-1067-8

54. Ibrahim, K., May, C., Patel, H. P., Baxter, M., Sayer, A. A., & Roberts, H. (2016). A feasibility study of implementing grip strength measurement into routine hospital practice (GRImP): study protocol. Pilot and feasibility studies, 2, 27. https://doi.org/10.1186/s40814-016-0067-x

55. Leong, D. P., Teo, K. K., Rangarajan, S., Lopez-Jaramillo, P., Avezum, A., Jr, Orlandini, A., Seron, P., Ahmed, S. H., Rosengren, A., Kelishadi, R., Rahman, O., Swaminathan, S., Iqbal, R., Gupta, R., Lear, S. A., Oguz, A., Yusoff, K., Zatonska, K., Chifamba, J., Igumbor, E., … Prospective Urban Rural Epidemiology (PURE) Study investigators (2015). Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet (London, England), 386(9990), 266–273. https://doi.org/10.1016/S0140-6736(14)62000-6

56. Pinto, A. P., Ramos, C. I., Meireles, M. S., Kamimura, M. A., & Cuppari, L. (2015). Impact of hemodialysis session on handgrip strength. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia, 37(4), 451–457. https://doi.org/10.5935/0101-2800.20150072

57. Delanaye, P., Quinonez, K., Buckinx, F., Krzesinski, J. M., & Bruyère, O. (2018). Hand grip strength measurement in haemodialysis patients: before or after the session?. Clinical kidney journal, 11(4), 555–558. https://doi.org/10.1093/ckj/sfx139

58. Hwang, S. H., Lee, D. H., Min, J., & Jeon, J. Y. (2019). Handgrip Strength as a Predictor of All-Cause Mortality in Patients With Chronic Kidney Disease Undergoing Dialysis: A Meta-Analysis of Prospective Cohort Studies. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation, 29(6), 471–479. https://doi.org/10.1053/j.jrn.2019.01.002

59. Vogt, B. P., Borges, M. C. C., Goés, C. R., & Caramori, J. C. T. (2016). Handgrip strength is an independent predictor of all-cause mortality in maintenance dialysis patients. Clinical nutrition (Edinburgh, Scotland), 35(6), 1429–1433. https://doi.org/10.1016/j.clnu.2016.03.020

60. Inhuber, S., Sollmann, N., Schlaeger, S., Dieckmeyer, M., Burian, E., Kohlmeyer, C., Karampinos, D. C., Kirschke, J. S., Baum, T., Kreuzpointner, F., & Schwirtz, A. (2019). Associations of thigh muscle fat infiltration with isometric strength measurements based on chemical shift encoding-

based water-fat magnetic resonance imaging. European radiology experimental, 3(1), 45. https://doi.org/10.1186/s41747-019-0123-4

61. Therkelsen, K. E., Pedley, A., Hoffmann, U., Fox, C. S., & Murabito, J. M. (2016). Intramuscular fat and physical performance at the Framingham Heart Study. Age (Dordrecht, Netherlands), 38(2), 31. https://doi.org/10.1007/s11357-016-9893-2

62. Raimann, J. G., Abbas, S. R., Liu, L., Zhu, F., Larive, B., Kotanko, P., Levin, N. W., Kaysen, G. A., & FHN Trial (2014). Agreement of single- and multi-frequency bioimpedance measurements in hemodialysis patients: an ancillary study of the Frequent Hemodialysis Network Daily Trial. Nephron. Clinical practice, 128(1-2), 115–126. https://doi.org/10.1159/000366447

63. Dou, Y., Liu, L., Cheng, X., Cao, L., & Zuo, L. (2011). Comparison of bioimpedance methods for estimating total body water and intracellular water changes during hemodialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 26(10), 3319–3324. https://doi.org/10.1093/ndt/gfq854

64. Maggio, M., Ceda, G. P., Ticinesi, A., De Vita, F., Gelmini, G., Costantino, C., Meschi, T., Kressig, R. W., Cesari, M., Fabi, M., & Lauretani, F. (2016). Instrumental and Non-Instrumental Evaluation of 4-Meter Walking Speed in Older Individuals. PloS one, 11(4), e0153583. https://doi.org/10.1371/journal.pone.0153583

65. Rydwik, E., Bergland, A., Forsén, L., & Frändin, K. (2012). Investigation into the reliability and validity of the measurement of elderly people's clinical walking speed: a systematic review. Physiotherapy theory and practice, 28(3), 238–256. https://doi.org/10.3109/09593985.2011.601804

66. Kittiskulnam, P., Carrero, J. J., Chertow, G. M., Kaysen, G. A., Delgado, C., & Johansen, K. L. (2017). Sarcopenia among patients receiving hemodialysis: weighing the evidence. Journal of cachexia, sarcopenia and muscle, 8(1), 57–68. https://doi.org/10.1002/jcsm.12130

67. Lin, Y. L., Liou, H. H., Wang, C. H., Lai, Y. H., Kuo, C. H., Chen, S. Y., & Hsu, B. G. (2020). Impact of sarcopenia and its diagnostic criteria on hospitalization and mortality in chronic hemodialysis patients: A 3-year longitudinal study. Journal of the Formosan Medical Association = Taiwan yi zhi, 119(7), 1219–1229. https://doi.org/10.1016/j.jfma.2019.10.020

68. Kittiskulnam, P., Chertow, G. M., Carrero, J. J., Delgado, C., Kaysen, G. A., & Johansen, K. L. (2017). Sarcopenia and its individual criteria are associated, in part, with mortality among patients on hemodialysis. Kidney international, 92(1), 238–247. https://doi.org/10.1016/j.kint.2017.01.024

69. Ikizler, T. A., Burrowes, J. D., Byham-Gray, L. D., Campbell, K. L., Carrero, J. J., Chan, W., Fouque, D., Friedman, A. N., Ghaddar, S., Goldstein-Fuchs, D. J., Kaysen, G. A., Kopple, J. D., Teta, D., Yee-Moon Wang, A., & Cuppari, L. (2020). KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. American journal of kidney diseases : the official journal of the National Kidney Foundation, 76(3 Suppl 1), S1–S107. https://doi.org/10.1053/j.ajkd.2020.05.006

70. Fahal, I. H., Bell, G. M., Bone, J. M., & Edwards, R. H. (1997). Physiological abnormalities of skeletal muscle in dialysis patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 12(1), 119–127. https://doi.org/10.1093/ndt/12.1.119

71. Pereira, R. A., Cordeiro, A. C., Avesani, C. M., Carrero, J. J., Lindholm, B., Amparo, F. C., Amodeo, C., Cuppari, L., & Kamimura, M. A. (2015). Sarcopenia in chronic kidney disease on conservative therapy: prevalence and association with mortality. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 30(10), 1718–1725. https://doi.org/10.1093/ndt/gfv133

72. Stam, S. P., Eisenga, M. F., Gomes-Neto, A. W., van Londen, M., de Meijer, V. E., van Beek, A. P., Gansevoort, R. T., & Bakker, S. J. L. (2019). Muscle mass determined from urinary creatinine excretion rate, and muscle performance in renal transplant recipients. Journal of cachexia, sarcopenia and muscle, 10(3), 621–629. https://doi.org/10.1002/jcsm.12399

73. Oterdoom, L. H., Gansevoort, R. T., Schouten, J. P., de Jong, P. E., Gans, R. O., & Bakker, S. J. (2009). Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population. Atherosclerosis, 207(2), 534–540. https://doi.org/10.1016/j.atherosclerosis.2009.05.010

74. Lien Y. H. (2017). Looking for Sarcopenia Biomarkers. The American journal of medicine, 130(5), 502–503. https://doi.org/10.1016/j.amjmed.2017.01.018

75. Lin, Y. L., Wang, C. H., Chang, I. C., & Hsu, B. G. (2022). A Novel Application of Serum Creatinine and Cystatin C to Predict Sarcopenia in Advanced CKD. Frontiers in nutrition, 9, 828880. https://doi.org/10.3389/fnut.2022.828880

76. Baczek, J., Silkiewicz, M., & Wojszel, Z. B. (2020). Myostatin as a Biomarker of Muscle Wasting and other Pathologies-State of the Art and Knowledge Gaps. Nutrients, 12(8), 2401. https://doi.org/10.3390/nu12082401

Author contribution. Acquisition of data: ZŠ, DM
Administrative, technical or logistic support: ZŠ, DM
Analysis and interpretation of data: ZŠ, DM
Conception and design: ZŠ, DM
Critical revision of the article for important intellectual content: ZŠ, DM
Drafting of the article: ZŠ, DM
Final approval of the article: ZŠ, DM
Guarantor of the study: ZŠ, DM