Review Article

Assessment of uremic sarcopenia in dialysis patients: An update

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Abstract

Uremic sarcopenia, which is highly prevalent in dialysis patients, leads to an increased risk of adverse outcomes, such as poor quality of life, falls, fracture, hospitalization, and even mortality. Therefore, early detection of uremic sarcopenia is crucial for administering quick and adequate multidisciplinary therapy to improve clinical outcomes. This review updates the current information about uremic sarcopenia assessment in chronic dialysis patients. We discuss the methods of assessing skeletal muscle mass, strength, and physical performance. We also discuss surrogate markers derived from serum and dialysate creatinine, in addition to emerging screening tools. The prevalence, clinical relevance, and impact of uremic sarcopenia on survival are reviewed and we discuss the limitations and challenges in applying the current working definition of sarcopenia based on the senior population to dialysis patients. The review shows that dialysis patients with skeletal muscle weakness or poor physical performance, either with or without low skeletal muscle mass, should undergo multidisciplinary therapy, included nutritional counseling, lifestyle modification, and exercise intervention, to mitigate the detrimental effects of uremic sarcopenia.

Keywords: Dialysis, Physical performance, Skeletal muscle mass, Skeletal muscle strength, Uremic sarcopenia

Introduction

Protein-energy wasting (PEW), a malnutrition status involving a progressive decline of the body’s stores of protein and energy fuels, is common in patients with chronic kidney disease (CKD) [1,2]. The prevalence of PEW increases progressively as renal function declines. Up to 75% of end-stage renal disease patients in the United States suffer from PEW [3]. In Taiwan, the estimated prevalence of PEW in dialysis patients ranges from 44% to 58% [1]. The development of PEW leads to a loss of skeletal muscle mass with skeletal muscle weakness or impaired physical performance. This condition is called uremic sarcopenia [4].

Sarcopenia is first described by Irwin Rosenberg in 1989 to define the process of age-related loss of skeletal muscle mass, which leads to poor quality of life and increased risk of adverse outcomes, such as falls, bone fractures, hospitalization, and death [5]. In Asian community-dwelling older adults, the prevalence of sarcopenia ranges from 7% to 12% [6-9]. In CKD patients, renal function deterioration is accompanied by skeletal muscle mass loss [10]. The prevalence of sarcopenia is 6%–14% in non-dialysis CKD [10,11], and this risk is markedly increased in dialysis patients with end-stage renal disease [12-14].

The pathogenesis of uremic sarcopenia is intricate and multifactorial. Beyond the factors commonly observed in older adults, such as the decline in exercise and protein intake, Vitamin D deficiency, growth hormone resistance, decreased sex hormones, and underlying comorbid conditions, dialysis patients are more susceptible to sarcopenia due to the loss of amino acids and other nutrients during dialysis [15]. In addition, metabolic acidosis, insulin resistance, inflammatory status, and overexpression of angiotensin II and myostatin in dialysis patients activate the ATP-dependent ubiquitin-proteasome system, the main pathway of skeletal muscle protein degradation in CKD [15-19]. Recently, indoxyl sulfate, a poorly dialyzable gut-derived uremic toxin, is also implicated in the pathogenesis of uremic sarcopenia through inducing mitochondrial dysfunction and overexpression of two muscle atrophy-related genes, atrogin-1, and myostatin [20-23].

There is a close link between uremic sarcopenia and mortality in dialysis patients. Compared to those without...
showed that the MAMC is well correlated with the 50th percentile of the reference body cell mass assessed by BIA [39-41]. In addition, several studies have confirmed its prognostic significance [42-44]. Moreover, phase angle, the phase difference between voltage and current sinusoidal waveforms, is regarded as an important indicator of cellular integrity and health [45,46]. A low phase angle is associated with increased mortality in both HD and peritoneal dialysis (PD) patients [47-49].

The 2020 National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative clinical practice guidelines recommend BIA’s clinical utility for monitoring the nutrition status [50]. Both single-frequency BIA and multi-frequency BIA show adequate accuracy in assessing the body composition compared to DEXA [51]. Although both of them are useful tools for longitudinal follow-up, multi-frequency BIA can provide more precise estimates of intracellular and extracellular fluid [52,53].

To avoid hydration effects in dialysis patients, it is recommended that measurements be performed after an HD session in HD patients and on an empty stomach in PD patients [54]. Since different devices might show significantly different measurements, the same device should be used for a patient [55].

Ultrasound
Another emerging tool for diagnosing sarcopenia is ultrasound, which is easily applicable at the bedside. Studies have shown the validity and reliability of ultrasound in older adults [56,57]. In HD patients, the quadriceps rectus femoris and quadriceps vastus intermedius thickness is significantly correlated with the nutritional status, as assessed by the body mass index, serum albumin, and malnutrition-inflammation score [58]. In addition, the quadriceps rectus femoris thickness is positively correlated with the phase angle and body cell mass assessed by BIA [59]. Beyond the skeletal muscle size, echo intensity can be used as a muscle quality index to predict physical performance in non-dialysis CKD patients [60]. Therefore, ultrasound is a promising assessment tool not only for measuring skeletal muscle mass but also for assessing skeletal muscle quality in dialysis patients. However, further studies are required to confirm these findings.

A comparison of different methods for the assessment of skeletal muscle mass is summarized in Table 1.

Measurement of Skeletal Muscle Strength and Physical Performance
A dialysis patient’s skeletal muscle strength and physical performance depend not only on his or her skeletal muscle mass but also on his or her cardiopulmonary function, overall nutritional status, anaemia degree, dialysis dose, underlying comorbidities and nervous system coordination, which can be considered a comprehensive manifestation of multiple organ systems. Compared to healthy individuals, dialysis patients show significant deficits in skeletal muscle strength and physical performance [15,61].
## Radiography

High showed that compared to Low, No, and Yes, High was the most effective in improving outcomes.

### Fat infiltration assessment

- Low: Yes
- No: Yes
- Moderate: Yes

### Clinical feasibility

- High: High
- Moderate: No
- Low: No

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**MRI:** Magnetic resonance imaging  
**MAMC:** Mid-arm muscle circumference  
**BIA:** Bioelectrical impedance analysis  
**DEXA:** Dual-energy X-ray absorptiometry  
**CT:** Computed tomography

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### Skeletal muscle strength

Handgrip strength measurement using a dynamometer is a simple, widely used tool for assessing skeletal muscle strength in dialysis patients, which is inversely correlated with the malnutrition-inflammation score [62]. Studies have consistently reported the correlation between low handgrip strength and increased mortality in dialysis patients [63-66]. A meta-analysis of nine prospective cohort studies by Hwang et al. showed that compared to the high-handgrip-strength group, the low-handgrip-strength group had 1.88 times higher risk of all-cause mortality, while a per kilogram unit increase in handgrip strength decreased the HR for mortality by 5% [67]. Vogt et al. established the best cut-off to predict mortality in dialysis patients is <22.5 kg in males and <7.0 kg in females [65]. Two studies compared the handgrip strength differences before and after HD sessions and reported a significant decrease in handgrip strength after HD sessions [68,69]. Therefore, handgrip strength assessment of HD patients should be performed before the HD session.

The isokinetic dynamometer is a gold standard for evaluating the skeletal muscle strength of lower extremities in the general population and also in dialysis patients with good accuracy [70,71]. However, the equipment is expensive and not widely available in clinical practice. An alternative is the portable hand-held dynamometer, whose results, which when used by well-trained operators, correlate well with those of isokinetic testing [72,73].

### Physical performance

Among various physical performance assessments, the simplest method widely used in clinical practice is the usual gait speed measurement during walking for 4-6 m in a straight path at the usual speed. Gait speed is not only closely correlated with quality of life but also strongly linked to the risk of falls, hospitalization, and mortality in dialysis patients [25,74-76]. Compared to HD patients with a gait speed of ≥0.6 m/s, the adjusted HRs for mortality are 2.17 and 6.93 for HD patients with a gait speed of <0.6 m/s and those unable to walk, respectively [75].

Other common tests for assessing physical performance and evaluating the effects of exercise on dialysis patients include the 6-min walk, repeated sit-to-stand, time-up-and-go, intermittent shuttle walk, stair climb, and short physical performance battery tests. The last comprises three tests: 4 m gait speed, five-time repeated sit-to-stand, and balance assessment in different standing positions. Painter and Marcus provided an excellent review of the evaluation of physical function in CKD patients [77].

### Working diagnosis of sarcopenia and related research in dialysis patients

Table 2 summarizes the current consensus for the operating definitions of sarcopenia. The skeletal muscle mass, measured by either DEXA or BIA, is usually divided by height squared or the BMI for adjustment. Diagnosis of sarcopenia is based on the presence of low muscle mass as an essential criterion, accompanied by either low HGS or slow gait speed.

Although the definition of sarcopenia is well established in the older population [34-37], there is no consensus on the working diagnosis of uremic sarcopenia in dialysis patients. Most research on uremic sarcopenia applies the geriatric definition to dialysis patients, which leads to heterogeneity in the prevalence of uremic sarcopenia. For example, in older maintenance HD patients, the prevalence of uremic sarcopenia by applying different criteria widely ranges from 3.9% to 63.3% [79]. In addition, the best indices for adjusting the skeletal muscle mass in dialysis patients are unclear. In HD patients, while adjustment by height squared is commonly adopted, the prevalence of uremic sarcopenia using four different indices for low skeletal muscle mass ranges from 3.9% to 15.9%. There is a risk of underestimating the prevalence of low muscle mass if the skeletal muscle mass is normalized to height squared, especially in overweight and obese patients. Adjustments for body size, such as the BMI and body surface area, might better define uremic sarcopenia in these patients with low muscle mass [80].

Table 3 summarizes some of the recent studies on dialysis patients. Compared to HD patients, two studies showed that PD patients have a lower prevalence of sarcopenia [83,85]. This discrepancy could be largely explained by different characteristics between HD and PD patients. Regarding the difference risk of sarcopenia between diabetes mellitus (DM) and non-DM dialysis patients, Mori et al. showed that DM has a 3.11-fold odds ratio to have sarcopenia [12].

### Relevance of skeletal muscle mass and strength in dialysis patients: dilemma regarding uremic sarcopenia diagnosis

Although low skeletal muscle mass is well-established to be associated with poor clinical outcomes in dialysis patients, few previous studies evaluated its impacts together with muscle

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| Tools     | Accuracy | Cost | Radiation | Fat infiltration assessment | Operator-dependent | Clinical feasibility |
|-----------|----------|------|-----------|----------------------------|--------------------|----------------------|
| MAMC      | ++       | Low  | No        | No                         | Yes                | High                 |
| BIA       | +++      | Low  | No        | No                         | No                 | High                 |
| DEXA      | +++      | Moderate | Low      | No                         | No                 | High                 |
| CT        | ++++     | High | High      | Yes                        | No                 | Low                  |
| MRI       | ++++     | High | No        | Yes                        | No                 | Low                  |
| Ultrasound| ++       | Low  | No        | Yes                        | Yes                | High                 |

MAMC: Mid-arm muscle circumference, BIA: Bioelectrical impedance analysis, DEXA: Dual-energy X-ray absorptiometry, CT: Computed tomography, MRI: Magnetic resonance imaging
strength and physical performance. Isoyama et al. showed in 330 incident dialysis patients that low skeletal muscle mass alone does not increase the risk of mortality, while patients with low skeletal muscle strength are at increased risk of mortality regardless of skeletal muscle mass [13]. Similarly, in our chronic HD patients with normal skeletal muscle mass, those with skeletal muscle weakness or slow gait speed remain at high risk of hospitalization and mortality [84]. Kittiskulnam et al. showed that, in HD patients, slow gait speed and weak handgrip strength are independently associated with mortality, but low skeletal muscle mass is not, regardless of normalization to height squared, body weight, BMI, or body surface area [25]. Altogether, compared to skeletal muscle mass, skeletal muscle strength and physical performance are more closely correlated with the risk of mortality in dialysis patients.

Notably, the prevalence of skeletal muscular dysfunction is considerably higher compared to low skeletal muscle mass in dialysis patients [14,83-85]. Therefore, the diagnosis of uremic sarcopenia in dialysis patients by applying geriatric criteria is mainly driven by skeletal muscle mass, which is the prerequisite for diagnosing sarcopenia. This approach might overlook patients with only skeletal muscle weakness. In addition, during the muscle wasting process, the loss of skeletal muscle strength could occur earlier and be more rapid than the loss of skeletal muscle mass [86]. Accordingly, dialysis patients diagnosed as having sarcopenia, with concurrent low skeletal muscle mass and strength, may implicate the late stage of muscle wasting. In this regard, skeletal muscle strength and physical performance measurement should be the initial step in uremic sarcopenia assessment. Dialysis patients with skeletal muscle weakness or poor physical performance should be encouraged to modify their lifestyle, diet, and exercise, even with preserved skeletal muscle mass.

Regardless of the methods and criteria used, periodic and longitudinal monitoring of the body composition,
### Table 3: Prevalence rates of uremic sarcopenia among different studies

| Author         | Population | Age (years) | Definition            | Prevalence | Main findings                                                                 |
|----------------|------------|-------------|-----------------------|------------|-------------------------------------------------------------------------------|
| Kim et al.,    | 95 prevalent HD patients | 63.9±10.0   | EWGOSP, 2010          | 33.7%      | Sarcomenia is associated with subjective global assessment, inflammatory markers, beta2-microglobulin, depression and cognitive dysfunction. |
| 2014 [81]      |            |             |                       |            | Low muscle strength was more closely associated with aging, protein-energy wasting, physical inactivity, inflammation, and mortality than low muscle mass. |
| Isoyama et al.,| 330 incident dialysis patients | 53±13       | EWGOSP, 2010          | 20%        | 1. The prevalence of sarcopenia increased with age.                         |
| 2014 [13]      |            |             |                       |            | 2. Dialysis duration, diabetes, serum phosphorus level and malnutrition are the predisposing factors for sarcopenia. |
| Ren et al.,    | 131 prevalent HD patients | 49.4±11.7   | EWGOSP, 2010          | 13.7%      | 3. The 1-year mortality risk of sarcopenic patients was higher than that of non-sarcopenic patients. |
| 2016 [82]      |            |             |                       |            | 1. Skeletal muscle mass normalized to height square may underestimate the prevalence of low muscle mass, particularly among overweight and obese patients. |
| Kittiskulnam et al., 2017 [80] | 645 prevalent HD patients | 56.7±14.5   | Low SMI:               |            | 2. Valid detection of sarcopenia among obese patients receiving HD requires adjustment for body size. |
| Bataille et al., 2017 [14] | 111 prevalent HD patients | 77.5 (70.8-84.8) | (A) muscle mass/height<sup>2</sup> (kg/m<sup>2</sup>):<br> < 7.89 in men and 6.05 in female<br> (B) muscle mass/weight (%): 32.68 in men and 27.85 in female<br> (C) muscle mass/BSA (kg/m<sup>2</sup>): 14.31 in men and 11.64 in female<br> (D) muscle mass/BMI (m<sup>2</sup>): 0.97 in men and 0.72 in female | (A) 3.9% | Regarding the low muscle strength in the large majority of HD patients, the diagnosis of sarcopenia was mainly driven by muscle mass measurement. |
| As’habi et al., 2018 [83] | 79 prevalent PD patients | 18 to 40 years: 21.5%<br> 41 to 64 years: 52.0%<br> ≥ 65 years: 26.5% | EWGOSP, 2010 | 11.5% | 1. Dynapenia was associated with age, physical activity level, and the presence of diabetes mellitus. |
| Giglio et al., 2018 [24] | 170 prevalent HD patients | 70±7 | EWGOSP, 2010 | 36.5% | 2. Male patients had a significantly higher prevalence of sarcopenia than female patients. |
| Mori et al., 2019 [12] | 308 prevalent HD patients | 54.4±11.0 (non-sarcopenic patients)<br> 63.5±11.0 (sarcopenic patients) | AWGS, 2014 | 40% | 1. Reduced muscle mass was strongly associated with poor nutritional status, while low muscle strength was associated with worse quality of life. |
| Lin et al., 2020 [84] | 126 prevalent HD patients | 63.2±13.0 | EWGOSP, 2010<br> Taiwanese criteria | 13.5%<br> 8.7% | 2. Low muscle strength alone and sarcopenia were independently associated with higher hospitalization, and sarcopenia was a predictor of mortality. |

Contd...
skeletal muscle strength, and physical performance changes in dialysis patients could provide a more comprehensive assessment of uremic sarcopenia, which may be more closely associated with prognostic significance compared to single measures [87,88].

**Surrogate markers of sarcopenia**

Creatinine is a breakdown product of creatine phosphate from skeletal muscle tissue and is a well-known serum surrogate for skeletal muscle wasting in dialysis patients. Low serum creatinine levels (pre-HD levels for HD patients), which indicate low skeletal muscle mass, increase the risk of mortality for dialysis patients without residual renal function [89,90]. Creatinine kinetics, which estimates the skeletal muscle mass from pre-HD serum creatinine, 24-h dialysate, and urinary creatinine excretion with a steady status, is significantly correlated with skeletal muscle mass measured by BIA and DEXA in both HD and PD patients [91,92].

Given the complexity of creatinine kinetics, Noori et al. and Canaud et al. developed formulas for estimating the skeletal muscle mass of HD patients using pre-HD serum creatinine levels and routine clinical parameters [93-95]. The skeletal muscle mass estimated by the two formulas had a good correlation with the skeletal muscle mass measured using multifrequency BIA and near-infrared interactance. Table 4 summarizes the skeletal muscle mass estimation formula using creatinine kinetics, the Noori formula, and the Canaud formula.

**Clinical approach of uremic sarcopenia**

A proposed algorithm for the evaluation of uremic sarcopenia is shown in Figure 1. We suggest measurement of handgrip strength and physical performance as the initial approach. Patients with preserved handgrip strength and physical performance, who are not at increased risk of adverse outcomes, should be regularly re-evaluated, while those with either low handgrip strength or poor performance should be further evaluated through BIA or DEXA to determine the skeletal muscle mass volume. If BIA and DEXA are not available, it is reasonable to estimate skeletal muscle mass through creatinine kinetics, Noori formula, and simplified creatinine index. Multidisciplinary management should be provided for any patients with low handgrip strength or poor performance, either accompanied by low skeletal muscle mass (sarcopenia) or not (poor muscle quality).

**Potential tools for screening uremic sarcopenia: SARC-F and SARC-CalF questionnaires**

To our knowledge, no tool has been validated for screening uremic sarcopenia. SARC-F, an easy-to-apply, semi-reported questionnaire, is recommended for initial screening of geriatric sarcopenia by the Asian Working Group for Sarcopenia and the European Working Group on Sarcopenia in Older People (EWGSOP)[9,78]. The SARC-F questionnaire contains five items: Sluggishness, assistance in walking, rise from a chair, climb stairs, and falls. Each item is scored as 0 (no difficulty), 1 (some difficulty), or 2 (many difficulties or inability). The total score ranges from 0 to 10, and SARC-F ≥4 is considered an increased risk of sarcopenia [96]. Table 5 shows details of the SARC-F questionnaire.

However, despite its high specificity for diagnosing sarcopenia, the SARC-F questionnaire yields low sensitivity in the geriatric population. To overcome this issue, the SARC-CalF questionnaire was developed, which includes an additional item, calf circumference measurement. In the SARC-CalF questionnaire, 10 points are added to the original SARC-F score if the calf circumference is ≤34 cm for males and ≤33 cm for females. SARC-CalF ≥11 is considered an increased risk of sarcopenia [97].

In HD patients, Yamamoto et al. first reported the use of the SARC-F questionnaire and showed good accuracy in identifying HD patients with physical limitations [98]. However, further studies are required to determine whether the SARC-F or SARC-CalF questionnaire can be a useful tool for initial screening of dialysis patients and what the best cut-off in this population should be.

**Management of uremic sarcopenia**

In addition to optimal dialysis delivery and treatment of comorbidities that accelerate muscle loss (such as infection, DM, cardiovascular disease, chronic wounds, gastrointestinal disorders, depression, and malignancy), nutritional supplementation and physical exercise are the cornerstones of uremic sarcopenia management [99]. Adequate energy (30-35 kcal/kg/day) and high protein intake (daily protein intake 1.2 g/kg/day) should be achieved to overcome the devastating process of muscle wasting [100]. Aerobic and resistance exercise, which are feasible and safe in dialysis patients, is not only shown to improve functional capacity and

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**Table 3: Contd...**

| Author          | Population | Age (years) | Definition | Prevalence (%) | Main findings |
|-----------------|------------|-------------|------------|----------------|---------------|
| Abro et al., 2020 [85] | Prevalent PD patients | 63.0±14.9 | FNIH       | 11.0-15.5      | 1. The prevalence of sarcopenia in PD was much lower compared to studies in HD patients. 2. There was similar prevalence of sarcopenia using EWGSOP, FNIH, AWGS definitions. |

EWGOSP, 2010: low ASMI: <7.23 kg/m² in men and<5.67 kg/m² in women or low SMI: <10.76 kg/m² in men and<6.76 kg/m² in women; low HGS: <30 kg for men and<20 kg for women; slow GS: ≤ 0.8 m/s . AWGS, 2014: low ASMI: <7.0 kg/m² in men and<5.7 kg/m² in women; low HGS: <26 kg for men and<18 kg for women; slow GS: ≤ 0.8 m/s . Taiwan criteria: low SMI: <8.87 kg/m² in men; <6.42 kg/m² in women (≥ 2 SD below the means of healthy young Taiwanese adults); low HGS: <26 kg for men and<18 kg for women; slow GS: ≤ 0.8 m/s.
Some other emerging and promising treatment strategies included vitamin D, androgens, growth hormone, anti-myostatin antibody, and AST-120, as well as novel strategies targeting myogenic satellite cells, epigenome, and pro-inflammatory cytokines [103-105]. However, more trials are warranted before firm conclusions can be drawn.

**Conclusion**

This review highlighted the importance of uremic sarcopenia assessment in clinical practice, which should be incorporated into the general nutritional assessment for dialysis patients. Given the relevance and clinical effects of skeletal muscle mass and function, dialysis patients with skeletal muscle weakness or poor physical performance, either with or without low skeletal muscle mass, should be identified early for nutritional counseling, lifestyle modification, and exercise intervention to mitigate the detrimental effects of uremic sarcopenia.

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**Conflicts of interest**

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