Review

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Assessment of Muscle Mass and Diagnosis of Sarcopenia in Peritoneal Dialysis Patients

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Abstract

Sarcopenia is characterized by the progressive loss of muscle mass and function, and it represents a significant and prevalent condition in patients undergoing peritoneal dialysis (PD). However, limited research has been conducted to document techniques for the early detection of sarcopenia in PD patients. This review addresses the pathophysiology, prognostic implications, and various assessment techniques for sarcopenia, including creatinine kinetics, anthropometry, imaging techniques (computer tomography, magnetic resonance imaging, and ultrasound sonography), bioimpedance spectrometry, and the modified creatinine index. Each of these techniques presents unique strengths and limitations, necessitating careful consideration of the most appropriate assessment method based on specific clinical conditions. By synthesizing current knowledge, this review aims to evaluate the strengths and limitations of available muscle-assessment techniques and assist in the development of improved diagnostic strategies for sarcopenic PD patients.

Keywords: renal failure; malnutrition; frailty

1. Introduction

End-stage renal disease (ESRD) represents a significant and costly chronic illness. Globally, the number of PD patients has risen dramatically from 100,000 in 2000 to 450,000 in 2020 (1). Compared to traditional hemodialysis, PD offers several advantages, including better preservation of residual kidney function, increased lifestyle flexibility, cost-effectiveness, and an enhanced quality of life (1). However, various complications adversely impact clinical outcomes and diminish the quality of life of PD patients. Notably, malnutrition is a major concern for PD patients (2). Among PD patients, approximately 28% to 54% have malnutrition, which is associated with increased morbidity, mortality, heightened risk of infections, and a reduced quality of life (2).

Nutritional status is a multifaceted concept that encompasses several components, including muscle mass, visceral protein levels, and immune function. Recent findings, however, indicate that significant muscle loss can exist even in the absence of malnutrition, including among individuals with obesity (3). Sarcopenia, i.e. loss of skeletal muscle mass, significantly affects the well-being of the general population (4, 5) and patients undergoing dialysis (6). This review discusses the current methodologies for the assessment of muscle mass in PD patients.

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2. Sarcopenia

2.1. Definition

There are several commonly used defining criteria of sarcopenia. The definition proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) (7) was updated in 2019 as EWGSOP2 (8). The revised diagnostic criteria are an appendicular mass index below 7.0 kg/m^2 for men or 5.5 kg/m^2 for women, or a handgrip strength below 27 kg for men or 16 kg for women. The International Working Group on Sarcopenia (IWGS) proposes a definition that is based on a low muscle mass (≤7.23 kg/m^2 for men, ≤ 5.67 kg/m^2 for women) and a low gait speed (≤ 1m/s) (9). The agreement of sarcopenia defined by EWGSOP and IWGS was only fair, and the prevalence of sarcopenia varied considerably by using different muscle mass indices (10).

2.2. Prevalence

The global prevalence of sarcopenia among older adults is around 5% when using EWGSOP2 criteria and 17% with the IWGS definition (11). Among CKD patients, 43.4% have low muscle strength, 29.1% low muscle mass, and 38.6% low physical performance (3). Sarcopenic obesity was noted in 10.8% (3). In dialysis patients, the prevalence is 25.9% to 34.6% (12), with severe sarcopenia found in 26.2% of dialysis patients (3). The prevalence was higher in HD than PD patients (13). Sarcopenia was more common in male PD patients, those with longer PD duration, those with fluid retention, and varied by ethnicity (14-18). Older age and comorbidities like diabetes, cardiovascular disease, and dementia increased sarcopenia risk, though specific prevalence impacts in PD patients remain less reported (19-21).

2.3. Sarcopenia in Relation with Malnutrition and Frailty

Malnutrition and sarcopenia, while overlapping, are distinct conditions. Both involve nutritional factors, leading to muscle loss, decreased functional capacity, and lower quality of life. Malnutrition encompasses nutrient or energy intake imbalances, resulting in weight and muscle loss, visceral protein depletion, and weakened immunity (22). Sarcopenia, on the other hand, is characterized by age-related muscle deterioration, exacerbated by inactivity or chronic disease (23, 24). Malnutrition is a direct, though not exclusive, cause of sarcopenia due to insufficient nutrients needed for maintaining muscle mass and function. Despite their similarities, each condition presents unique challenges and manifestations.

In PD patients, substantial weight gain after the initiation of dialysis often leads to sarcopenic obesity, characterized by concurrent sarcopenia and obesity (25). Without weight loss, sarcopenia may be present due to fluid overload and fat gain. This combination complicates the metabolic profile, heightening risks of mobility issues, insulin resistance, and inflammation (26).

Sarcopenia and frailty often coexist in older adults, sharing close epidemiologic, biological, and clinical links (27-29). Both conditions stem from factors like physical inactivity, chronic diseases, and inadequate nutrition, leading to impaired physical performance measured by tests such as walking speed and grip strength. Sarcopenia focuses on the musculoskeletal system—loss of muscle mass, strength, endurance (30, 31), while frailty encompasses broader issues like cognitive decline, cardiovascular problems, and inflammation (32). Frailty leads to reduction in physical activity and undernutrition, which may further worsen sarcopenia.

3. Techniques for the Assessment of Muscle Mass

Given that sarcopenia has considerable prognostic importance for PD patients, it is imperative to develop accurate methods for assessing and monitoring skeletal muscle mass. Currently, there are several readily available methods, but none is ideal.

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3.1. Creatinine Kinetics (CK)

The creatinine kinetic method (CK) is a traditional means to assess skeletal muscle mass in dialysis patients (33). The parameter is often referred to as lean body mass by creatinine kinetics (LBM-CK) in previous studies (34), but the term fat-free edema-free body mass (FEBM) was recommended by the Dialysis Outcomes Quality Initiative (DOQI) guidelines (35). Since creatinine is largely a metabolite of skeletal muscle, the FEBM is often considered to be equivalent to the skeletal muscle mass. FEBM has unique advantages as a muscle marker because it is a simple technique and can be easily integrated into routine small solute clearance (i.e. dialysis adequacy) tests. Unlike many other methods (36), the measurement of FEBM is independent of the hydration status of the patient (35). Several studies reported that the FEBM of PD patients had a reasonable agreement with the skeletal muscle mass measured by other techniques, such as bioimpedance spectrometry (BIS), anthropometry, or dual X-ray absorptiometry (DXA) but FEBM generally produced a lower value (37-40). As a result, the prevalence of muscle wasting tends to be higher when CK is used for muscle mass assessment (40). The discrepancy may be explained by the fact that CK measured the dry weight of skeletal muscle, while the other methods were affected by the hydration status of the patient (37, 38). On the other hand, Xu et al (41) suggested that CK might actually underestimate muscle mass, especially in male patients with larger muscle mass and higher residual renal function (41). FEBM may also be affected by dietary patterns and serum albumin levels (42, 43). More importantly, there is little data supporting FEBM as a prognostic marker in PD patients, which casts doubt on the value of FEBM in clinical practice.

3.2. Anthropometry

Anthropometric measurement is a traditional method for assessing muscle mass. The major advantages are being portable, inexpensive, and non-invasive. The anthropometric approach typically involves measuring the body weight, height, waist and hip circumferences, mid-upper arm circumference, and calf circumference (44). Among these measurements, the mid-upper arm and calf circumferences had good correlations with skeletal muscle mass, serving as effective proxy measures (45). The commonly used cut-off mid-upper arm circumference was <23.1 cm for females and <23.8 cm for males. However, their correlation with physical function, such as hand-grip strength, is less robust. A recent cohort study involving 283 HD patients found that an increase in mid-upper arm circumference and mid-arm muscle circumference over one year was associated with reduced risks of all-cause hospitalization and death (46). In contrast, changes in calf circumference showed no association with any clinical outcomes (46).

Anthropometric measurements are commonly used for the estimation of appendicular muscle mass (AMM). Xu et al. (47) developed three prediction models: the limb-length circumference model, the height-circumference model, and the height-weight model. These models show strong correlations with AMM measurements obtained through DXA, confirming their reliability for assessing appendicular muscle. A recent study further confirmed that AMM measured via anthropometric methods is positively and significantly related to physical function in older adults (48).

In spite of its widespread use, anthropometric measurement has notable limitations. Most importantly, the measurement is subjective and exhibits considerable intra- and inter-observer variability, leading to reduced reliability (49). Furthermore, muscle mass estimates derived from this method tend to be imprecise (50), as it cannot reliably differentiate between muscle and fat mass (51). This issue is particularly pronounced in patients on PD. Previous studies showed that the accuracy of anthropometric measurement diminishes in PD patients who are obese or have fluid overload (52, 53). Additionally, there are currently no established cut-off values for anthropometric measurements to diagnose sarcopenia, which limits its use in clinical practice.

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3.3. Imaging Techniques

Imaging techniques, such as computed tomography (CT), magnetic resonance, and ultrasound sonography, have been widely used for the assessment of muscle mass. In general, they are accurate methods, but each has their own limitations.

CT scan is probably the most commonly used imaging modality for the assessment of muscle mass (54). Instead of measuring the total muscle mass in the body, CT usually uses derived parameters, such as skeletal muscle index (SMI), psoas muscle index (PMI), and skeletal muscle radiodensity (SMD), to represent muscle mass. SMI is the cross-sectional area of the whole L3 vertebral muscle normalised by the patient's height square, and has been used to diagnose sarcopenia (55). The recommended cut-off SMI value was <38.5 cm^2/h^2 in females and <52.4 cm^2/h^2 in males (55). Similarly, PMI is a focused measure of the psoas muscle size, which is computed by the cross-sectional area of the psoas muscle normalised to the body height squared (56). SMD, in contrast, reflects muscle quality based on the average Hounsfield Units (HU) (57), with a higher value indicating less fat infiltration and a healthier status.

The prognostic values of CT-measured muscle mass have been well validated. A recent retrospective cohort study has indicated that lower SMI and SMD were independently associated with all-cause mortality and risk of cardiovascular death in HD patients (58). In PD patients, PMI significantly correlated with BMI, serum creatinine, and serum albumin levels (59). Sarcopenia defined by psoas muscle mass was also an independent predictor of survival in PD patients (60).

Despite gaining popularity in recent years, CT scan has several limitations. The concern of high radiation exposure precludes its extensive clinical use for muscle mass assessment, particularly when repetitive measurements are required (61). Although the cost of CT scans has decreased over the years, it remains higher than most other muscle-assessment techniques. In addition, the lack of standardisation and the absence of solid, evidence-based cut-off values for diagnosing sarcopenia make CT unsuitable for routine clinical testing (62).

MRI is another non-invasive imaging technique often used for the measurement of skeletal muscle mass. It has high accuracy and reproducibility (63), and is often regarded as the reference method for skeletal muscle measurement (64). MRI typically measures the contractile cross-sectional area (CSA) and muscle fat infiltration (MFI), which have important prognostic values in dialysis patients. For example, HD patients had lower contractile CSA and higher MFI than healthy controls, despite similar absolute CSA values (65). A low CSA is associated with worse physical performance and functional status in HD patients (66). Published literature on PD patients, however, is limited. A small case-control study in pediatric PD patients found that CSA corrected for the body mass index (CSA/BMI) was not different between children on PD and healthy ones, whereas T2 signal intensity was significantly higher in PD patients than in the controls (67). In this study, physical functioning tests and quadriceps muscle strength significantly correlated with muscle CSA/BMI and with T2 signal intensity (67).

In addition to measuring muscle mass by CSA, sodium-23 magnetic resonance imaging (23Na MRI) allows direct measurement of muscle sodium concentrations, which is related to systemic inflammation and adverse metabolic effects in dialysis patients (68, 69). MRI is also commonly used for the diagnosis of diabetic muscle infarction, a common complication in dialysis patients with diabetes (70). As compared to CT, MRI has several advantages, such as clearer images and free from ionising radiation (61, 71). However, MRI is not suitable for routine measurement of muscle mass in clinical practice due to its high personnel and equipment costs (72), and it is not suitable for patients with pacemakers or metallic prosthetics (73).

USG (ultrasound sonography) is a non-invasive imaging technique that can assess muscle mass at a lower cost than CT and MRI. The muscle thickness (MT) measured by USG correlated significantly to the cross-sectional area (CSA) measured by CT in ICU patients, with an average difference of 2 cm^2 (74). A systemic review concluded that USG was reliable in determining muscle mass in the elderly population, especially for the measurement of vastus lateralis, rectus femoris,

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upper arm anterior, and trunk muscles (75). However, inter- and intra-observer variability is considerable with USG (76).

The reliability of USG has been validated in CKD and dialysis patients (77). Consistent reductions in muscle thickness, as measured by USG, have been observed in HD patients following the initiation of dialysis (78). Compared to non-sarcopenic HD patients, those with sarcopenia exhibited significantly lower rectus femoris CSA, and a threshold of 4.61 cm^2 can independently predict sarcopenia and malnutrition (79). Zhang et al (80) utilized USG to propose a model for predicting sarcopenia in HD patients, achieving an area-under-curve of receiver operating characteristic (ROC) at 0.902, underscoring its potential utility in this context. As a simplified method, the quadriceps CSA alone has high sensitivity and specificity in diagnosing sarcopenia (81). A recent study further showed that, when combined with low hand-grip strength, a low quadriceps muscle thickness by USG was an independent predictor of all-cause mortality in HD patients (82). In PD patients, muscle thickness assessed by USG had an excellent correlation with the MRI measurements (83), but the prognostic relevance has not been studied specifically. Another major limitation of using USG for the diagnosis of sarcopenia is that no generally accepted cut-off values have been established (84), and it remains uncertain which muscle parameter should be used.

3.4. Bioimpedance Spectroscopy

Bioimpedance spectroscopy (BIS), also known as bioimpedance analysis (BIA), is a non-invasive and convenient method for measuring skeletal muscle mass. In essence, BIS assesses the impedance of electrical currents at various frequencies, employing a three-compartment model to determine the amounts of extracellular water (ECW) and intracellular water (ICW). From these measurements, it calculates the lean tissue mass (LTM) of the patient, and the parameter is commonly considered as the muscle mass (85). In addition to muscle mass evaluation, BIS also evaluates the patient's hydration status simultaneously, which makes it an attractive tool for clinical use.

BIS demonstrates several advantages that render it suitable for clinical application. In comparison to other methodologies, BIS is less expensive, less time-intensive, and does not necessitate highly specialized personnel. Furthermore, the three-compartment model utilized in BIS allows for the estimation of ATM and overhydration, both of which are pertinent to clinical outcomes. A decrease in LTM and an increase in overhydration by BIS have been associated with elevated risks of frailty, hospitalization, and mortality (86). The reliability of BIS can be influenced by several variables, including the device itself (such as the electrodes), the operators, the subject being tested, and the environmental conditions during testing (87). The technique of BIS is predicated on assumptions that may not consistently align with reality, such as representing the body as primarily composed of cylinders and assuming that LTM comprises all body water and conducting electrolytes. Given the multitude of equations developed for calculating muscle mass, it is crucial to take into account the characteristics of the patients to ascertain the appropriate equation for use (87).

In patients without kidney disease, multiple studies have assessed the validity of BIS for the measurement of skeletal muscle mass, usually using computed tomography (CT) as the reference standard. Although Kim et al (88) demonstrated a significant correlation between the skeletal muscle mass by BIS and CT, supporting the potential of BIS measurement as a prognostic marker, most studies showed that BIS underestimates the prevalence of low muscle mass and can exhibit biases in certain patient populations. Specifically, in critically ill patients and those with chronic obstructive pulmonary disease (COPD), BIS has shown variable performance, with a tendency to overestimate skeletal muscle mass, especially in those with higher muscle mass or severe edema (89, 90), as compared to CT scans, BIS tended to underestimate the prevalence of low muscle mass in patients with colorectal cancer (91). Similarly, Zuo et al (92) reported that in patients with gastric cancer, BIS overestimates the value of the skeletal muscle index, especially in malnourished individuals. Amongst different equations for calculating muscle mass by BIS, the Talluri equation provided the strongest correlation with CT, although biases were noted across all examined equations (90).

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BIS has been specifically validated in patients with CKD. The relationship between lean tissue mass derived from BIS and anthropometric measures has been studied in patients with CKD. Romejko et al. (93) reported a good correlation between ASM from BIS and anthropometric parameters, such as weight, height, and BMI, in pre-dialysis CKD patients. However, the correlation between BIS and mid-upper arm circumference or mid-arm muscle circumference, which are specific anthropometric parameters of skeletal muscle mass, has not been shown. Longitudinal BIS assessments further showed that a decline in lean tissue mass (LTM) over the first two years of dialysis was associated with an increase in mortality rate, independent of initial baseline values (94). In addition to the conventional LTM, several indices derived from the BIS measurement have also been explored. For example, a recent study showed a good association between low lean tissue index (LTI, expressed as LTM/height^2) and an increased risk of all-cause mortality and adverse clinical outcomes (95). Visser et al. (96) proposed that employing fat-free mass (FFM) rather than lean tissue mass (LTM) can mitigate the bias of measurement because BIS-derived FFM does not have significant discrepancies when compared to CT-derived FFM, although individual variations may still occur (96). Besides, it has been reported that FFM is significantly lower in sarcopenic than non-sarcopenic HD patients, indicating its potential for screening sarcopenia (81). Lin et al. (97) developed a stepwise multiple regression equation for the calculation of appendicular skeletal muscle mass (ASM):

ASM = -1.838 + 0.395 × total body water (L) + 0.105 × body weight (kg)

Notably, this equation exhibited no significant bias when compared to ASM derived from the dual-energy X-ray absorptiometry (DXA).

BIS has limitations, particularly as its accuracy can be influenced by the patient's hydration status. Fluid overload, which is common among patients undergoing PD, may result in an overestimation of muscle mass, which can impede the early diagnosis of sarcopenia (36). While expressing muscle mass as a percentage of total body mass may help mitigate the effects of overhydration, the clinical significance of muscle percentage in dialysis patients has not been established. Additionally, different brands of bioimpedance machines may produce significant variances in measured LTM (98, 99), and different devices use various equations to perform the calculation (99), which poses challenges for the use of BIS in cross-center studies.

In addition to the calculation of ASM or LTM, assessing the raw parameters of BIS may provide further insights into the patients' body built. Notably, phase angle (PhA) is calculated from the body reactance and resistance (100), and the value is significantly associated with the nutritional status and other biochemical markers in PD (101). However, the utility of PhA may be context-specific. In critically ill patients, reduction in PhA had good agreement with the reduction in LTM (102), but a study in HD patients reported that PhA could not reliably identify patients with malnutrition (103). Another approach of analysis that has been tested is bioelectrical impedance vector analysis (BIVA), which uses PhA to construct a vector that indicates the muscle and hydration status (104). BIVA may provide a detailed assessment of body built, and distinguish well-nourished from malnourished elderly (105, 106). However, it was sufficiently accurate in assessing muscle mass as compared to ultrasound measurement in critically ill patients (107). Other impedance parameters, including resistance and reactance normalised for height (R/H and Xc/H), are related to hand grip strength, and may be used as surrogate markers of muscle function (not muscle mass) when a formal functional assessment is not possible (108, 109).

3.5. Modified Creatinine Index (MCrI)

The creatinine index has been used as a surrogate of muscle measure for decades and is a reliable prognostic indicator of mortality, malnutrition, and CVD (cardiovascular disease) in HD patients (110-112). However, although it is reliable for assessing muscle mass, its computation is complicated and requires 24-hour urine collection to determine the creatinine generation rate (110). To simplify the calculation and facilitate routine clinical use, Canaud et al. constructed a simplified formula that only required demographic parameters, pre-dialysis serum creatinine concentrations, and a single-pooled Kt/V for urea (113). This parameter is now called MCrI. Similar to the traditional creatinine

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kinetic method, MCrI offers a convenient, non-invasive, and easy way to assess muscle mass (114). In a cross-sectional study, Tian et al showed that MCrI was accurate in identifying sarcopenia, with a receiver operating characteristic (ROC) curve area under the curve (AUC) of 0.804 (115). In this study, the optimal cut-off values were 21.1 mg/kg/day in male and 19.6 mg/kg/day in female HD patients (115).

The prognostic value of MCrI has been extensively studied in HD patients. A low MCrI was found to be an independent predictor of bone fracture (116). More recently, Yamamoto et al showed that every standard deviation increase of MCrI was independently associated with a 37% reduction in the lower all-cause mortality rate in HD patients (117). In PD patients, however, the clinical value of MCrI has not been extensively studied. Since total weekly Kt/V rather than a single-pooled Kt/V is used in PD for assessing small solute clearance, the application of MCrI in PD may result in a systemic bias. An observational study on patients who converted from PD to HD found an average bias of 0.76 mg/kg/day when the same formula was used for the calculation of MCrI (118), and the MCrI quartile was significantly associated with the one-year mortality in a separate cohort of PD patients (118). Further studies are required to validate the results.

4. Challenges and Further Directions

Commonly used techniques for the assessment of muscle mass are summarized in Table 1. Although muscle mass could be assessed by numerous methods reviewed above, each has its own limitations and there is no ideal technique. Furthermore, it may not be appropriate to diagnose sarcopenia solely by muscle mass measurement because muscle function is an equally important parameter. In this regard, hand-grip strength by a dynamometer is the best method. The EWGSOP2 recommended the cut-off levels at 16 kg for women and 27 kg for men (8), while AWGS proposed cut-off values as 18 kg for women and 28 kg for men for the diagnosis of sarcopenia (5). Unfortunately, although the dynamometer is objective, easy to use, and reproducible (119), its application in routine clinical practice is limited (120). The Chair Stand Test (CST), in which the patient is asked to transit from sitting to standing using a 40 cm high chair as many times as possible in 30 seconds, has been proposed as an alternative (121). The CST has the advantage of not requiring any specific equipment, and its reliability has been validated (122). However, CST is not suitable for patients with lower limb pathology (121). Taken together, each technique presents distinct advantages and limitations, which must be carefully evaluated based on the clinical context. Moreover, it is crucial to develop specific cut-off values tailored to each method to ensure accurate sarcopenia diagnosis. In clinical practice, these values would facilitate early intervention and inform treatment planning.

Table 1. Comparison of different available techniques for muscle mass assessment.

Method	Advantages	Disadvantages	Cost-Effectiveness	Convenience	Validated Prognostic Significance
Creatinine Kinetics	Simple, suitable for routine clinical tests	Rely on creatinine generation, so its accuracy may be affected by the patient's diet, residual renal function, and serum albumin levels	★★★	★★	★★
Anthropometry	Simple, and non-invasive, sutable for routine clinical tests	Limited accuracy due to subjective nature. Can't distinguish fat and muscle very well	★★★	★★★	★
Bioimpedance spectroscopy	Quicky, simple, non-invasive, suitable for routine clinical tests	Its accuracy may be affected by the patient's hydration status and different devices may yield inconsistent results	★★	★★★	★★
Computated tomography	Highly accurate for muscle mass assessment	Expensive, radiation exposure, requires special personnel and facilities. Not stuitable for routine clinical tests	★	★	★★★

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Megnestic resonance imaging	Highly accurate and no radiation exposure	Very expensive, requires special personnel and facilities. Not suitable for routine clinical tests	★	★	★★★
Ultrasound	Non-invasive, more cost-effective than other imaging technique	Inter- and intra-observer variability. No established cut-off and uncertain which muscle parameter shall be used.	★★	★★	★★
Modified creatinine index	Simple, suitable for routine clinical tests. More reliable than traditional CK	May still be affected by dietary intake and renal function.	★★	★★	★★

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