Chapter 3

Body Composition and Its Clinical Outcome in Maintenance Hemodialysis Patients

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Additional information is available at the end of the chapter

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Abstract

Previous epidemiological cohorts demonstrated that higher body mass index (BMI) was associated with greater survival in patients treated by hemodialysis. Although BMI is a simple measure of adiposity in general population, it may be an inaccurate indicator of nutritional status, particularly among dialysis patients given that it does not differentiate between muscle mass and fat as well as body fat distribution. This problem might be aggravated in end-stage renal disease patients because of wasting or edema. In addition, individuals with higher BMI usually have both higher muscle and fat mass than those with lower BMI. Therefore, more sophisticated tool of body composition analysis is needed to address the query of which component is associated with mortality outcome among patients receiving hemodialysis. We summarized the current state of body composition, including lean and fat tissue evaluated by bioelectrical impedance analysis, dual X-ray absorptiometry, computerized tomography, or magnetic resonance imaging, and its association with clinical outcomes among hemodialysis patients. The studies using anthropometry for the estimation of muscle mass, either mid-arm muscle circumference as a proxy of muscle mass or skinfold thickness and waist circumference as a surrogate of body fat and visceral fat, respectively, were all included in this review.

Keywords: body composition, muscle, fat, nutrition, hemodialysis

1. Introduction

Dialysis-related malnutrition is prevalent among end-stage renal disease (ESRD) patients and may have important implications for mortality and other outcomes [1]. Various metabolic derangements occur during hemodialysis such as increased pro-inflammatory state, chronic

metabolic acidosis, and accumulation of uremic toxins that can negatively impair body protein anabolism and increase the rate of muscle degradation [2, 3]. In fact, the term "malnutrition" has been recently replaced by "wasting" in recognition that this disorder might not be corrected by appropriate supplementation of dietary intake. Consequently, the International Society of Renal Nutrition and Metabolism defined the term "protein energy wasting" (PEW) according to the presence of at least three out of the following four criteria: (1) abnormal low levels of serum albumin, prealbumin, or cholesterol concentrations; (2) low body mass or fat mass; (3) decreased muscle mass; and (4) inadequate protein or energy intake for more than 2 months with or without abnormal nutritional score [4]. However, individual with low muscle mass can be misclassified as not having PEW if there is a concurrently increase in non-muscle body weight, making a diagnosis of nutritional disorder difficult in such case.

While kidney disease wasting remains a concerning issue, obesity or excess body adiposity is also a debatable topic among dialysis community. Although increased body mass index (BMI) is one of the most common cardiovascular risk factors and other health problem-related risks in general population, some studies have reported that a low, rather than high, body fat is an independent predictor for poor survival in maintenance hemodialysis patients [5, 6]. One potential explanation is that although BMI is a key nutritional assessment tool recommended by both the Kidney Disease Outcomes Quality Initiative (KDOQI) [7] and European guidelines [8], it may not be a good representative of body fatness and cannot reflect the real nutritional status particularly in patients treated by hemodialysis [9].

This chapter aims to provide an updated current evidence describing the significance of body composition as a useful nutritional tool to detect as well as monitor the important outcomes associated with patients undergoing hemodialysis.

2. Body composition and its clinical outcomes among hemodialysis patients

2.1. Role of body mass index as a nutritional parameter in hemodialysis patients

BMI is defined as body weight in kilograms divided by the square of height in meters. BMI is currently considered as a useful nutrition risk stratification tool for obesity in the general population and undernutrition in developing countries because of its simplicity and ease of use [10]; however, its accuracy to assess the nutritional status in chronic kidney disease (CKD) patients is still questionable [11]. Observational studies have reported contradictory findings regarding the association between obesity and mortality in CKD population. Previous epidemiological studies in hemodialysis patients have demonstrated that patients with low BMI are at higher risk of mortality than those with normal BMI range, whereas high BMI is not associated with higher mortality as it is in general population, the phenomenon known as "obesity paradox" or "reverse epidemiology" [12–17]. Given that BMI has a significant correlation with percentage of body fat, although it does not differentiate fat from muscle compartments, this observation might suggest that being fatter accompanying with more nutritional reserve is protective against wasting particularly in the setting of acute illness or chronic inflammation.

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Obese individual with higher BMI usually has not only higher body fat, but also higher muscle mass, therefore which component of body composition-fat or lean-is more associated with survival is debatable topic since then. Other studies have suggested a U- or J-shaped association between obesity classified by BMI and mortality among dialysis patients, with a higher risk of death in underweight and morbidly obese categories compared with normal weight [18, 19]. Recently updated meta-analysis [20] has shown that for every 1 kg/m^2 increase in BMI, there was a reduction in the risk of all-cause and cardiovascular mortality by 3% (hazard ratio (HR) 0.97; 95% confident interval (CI) 0.96–0.98) and 4% (HR 0.96; 95% CI 0.92–1.00), respectively, in CKD stage 5 undergoing hemodialysis, whereas a similar association between BMI and risk of death was not observed in patients on peritoneal dialysis. Interpretation of these data should be aware of other limitations of using BMI as a single nutritional assessment tool among that population. Inaccuracy of measurement and misclassification may exist, causing an overrepresentation of individual with lower cardiovascular disease risk in higher BMI categories and inflating the observed protective effects in obese hemodialysis patients. In addition, BMI may underestimate the prevalence of obesity in ESRD population. A previous study among dialysis patients from Stockholm [21] found that obesity diagnosis using BMI cut point misclassified more than half of the patients with excess body fat as having normal BMI. This data emphasized the limitation of BMI as a reflection of body composition, and a BMI of more than or equal to 30 kg/m^2 has a high specificity but low sensitivity for excess body fat. In agreement with the Swedish cohort, analyses in prevalent hemodialysis patients from the United States Renal Data System (USRDS) database found that underidentification of obesity was more common by using BMI than waist circumference criteria (31.3% vs 15.2%, respectively) [22]. Furthermore, the agreement level of obesity by BMI was significantly lower than waist circumference (Cohen kappa of 0.4 vs 0.6, $p < 0.01$) compared to the reference standard (percent body fat criteria), highlighting the poor performance of BMI for excess adiposity. Moreover, BMI does not capture the differentiation in body fat distribution between subcutaneous and central fat deposit, which is more associated with inflammation, oxidative stress, insulin resistance, and so on [23, 24]. Lastly, extracellular volume expansion and fluid overload could probably yield falsely high BMI [25, 26].

Previous studies have shown that changes in body weight are more strongly associated with mortality than measurement of BMI at a single time point. Database from a large hemodialysis organization and the Scientific Registry of Transplant Recipients [27] revealed that patients with body weight loss of 3–5 kg and more than 5 kg had death hazards of 1.31 (95% CI 1.14–1.52) and 1.51 (95% CI 1.30–1.75), respectively, compared to those with minimal weight change (±1 kg) over the past 6 months. However, one of the limitations is that potential reasons of weight change could not be identified due to its observational nature, making confounded by intercurrent health status likely as more spontaneous weight loss among sicker patients. The Current Management of Secondary Hyperparathyroidism: A Multicenter Observational Study (COSMOS) [28] also evaluated the implication of weight loss and gain among obese patients undergoing hemodialysis and their nonobese counterparts. Assuming that weight changes were unintentional, weight loss (<1% of dry weight at baseline) was significantly associated with increased rate of mortality, whereas weight gain (>1%) was strongly associated with higher survival compared with stable weight (±1%). Interestingly, the associations of weight variation and death were attenuated after stratification by BMI categories.

There was no longer statistical significance of the association of weight loss with mortality (HR 0.98; 95% CI 0.74–2.14) as well as weight gain with survival benefit (HR 0.95; 95% CI 0.59–1.62) among obese individual. These data raise attentions to rapid weight differences as a potential clinical sign for health monitoring in hemodialysis patients.

On this basis, recent studies have gone beyond a solitary assessment of BMI to further characterizing the impact of a more diverse range of body composition measures on mortality and other dialysis-related outcomes among patients receiving hemodialysis.

2.2. Methods of body composition assessment

Body composition assessment is one of the objective methods used for nutritional assessment. The ability to identify the alteration of muscle or fat mass is absolutely important for the diagnosis of PEW and may offer opportunities for timely interventions to retard ongoing catabolic process. Because ESRD patients can accumulate significant amount of adiposity concurrently with muscle mass depletion [29], it is necessary to quantitate fat and lean mass independently. Recently, several tools are available targeting early detection of changes in body composition over time. These include anthropometric approaches, rate of creatinine generation or creatinine kinetics, equations to estimate muscle mass, bioimpedance-based evaluation of body composition: bioimpedance analysis (BIA) or spectroscopy (BIS), dual X-ray absorptiometry (DXA), computerized tomography (CT), magnetic resonance imaging (MRI), and other methodologies that less likely to be used in routine clinical practice such as whole body counting, neutron activation analysis, etc.

The human body is divided into two compartments consisting of fat tissue and nonfat tissue as shown in (**Figure 1**).

Body fat is the sum of adipose tissue and fat mass (mainly triglyceride). Adipose tissue is composed of collagenous and elastic fibers, fibroblasts, and capillaries. Body fat accumulates to around 33% in subcutaneous tissue, to about 4–10% in intramuscular depots, and approximately 8–12% in visceral thoracic and abdominal area [30]. The nonfat tissue can be defined using more complicated terminology that sometimes used incorrectly in the scientific literature: lean body mass (LBM) and fat-free mass (FFM). Lean body mass, may be used interchangeably with lean soft tissue, is the sum of total body water, skeletal muscle mass (SMM), and also the fat-free part of organs. Fat-free mass is the combination of lean body mass and bone mineral component [31]. By virtue of LBM, FFM, and SMM which designate as the different tissues of body compartments, choice of methods to determine specific body composition should be selected appropriately. For diagnostic purposes, SMM is the representative of ideal tissue to study for muscle abnormalities among dialysis population but frequently accompanied by higher cost and less portability [32]. Although methods that estimate FFM have greater clinical applicability, lower costs, and ease of use, they tend to have lower precision.

To assess body composition in dialysis patients, specific CKD-related factors should be considered such as hydration status. The accuracy for all methods for estimating body composition is affected. Thus, body composition assessment during 15–120 min after dialysis at midweek

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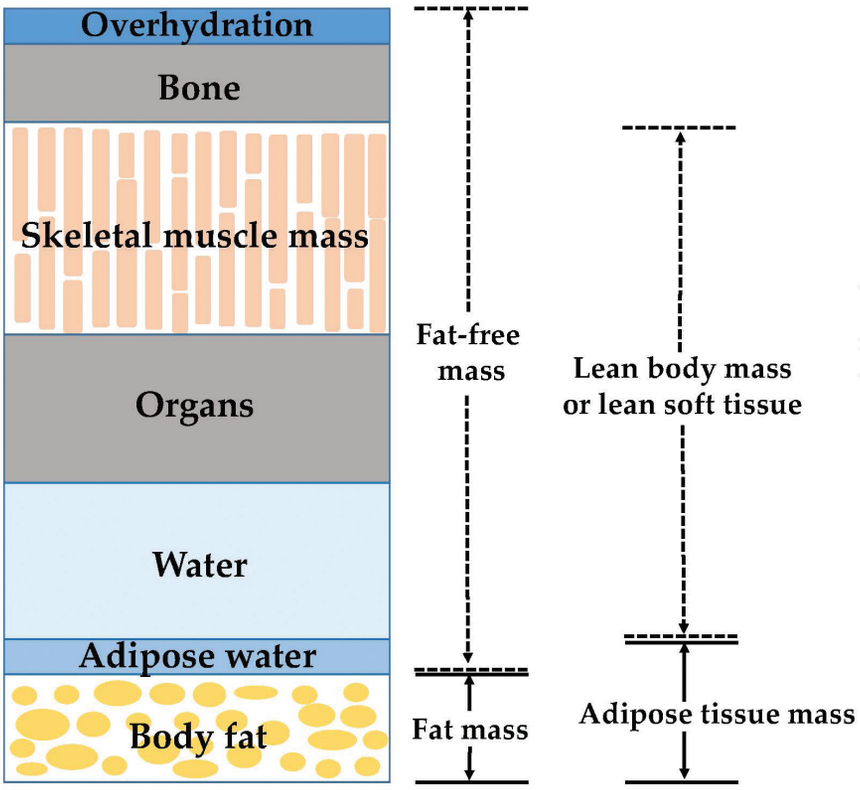

Figure 1. Compartments of body composition.

session, when patients are most closely to their dry weight, could lessen the impact of fluid overload. This recommendation should be cautious especially with instruments that cannot distinguish fluid between extra- and intracellular part, for example, single-frequency BIA or DXA. Standardized condition and procedure should be repeated when possible to allow reproducibility from time to time [33].

To date, there are several available methods for body composition assessment including SMM, LBM, and also FFM as shown in **Table 1**.

Anthropometric measurements of mid-arm circumference (MAC), mid-arm muscle circumference (MAMC), calf circumference, or adductor pollicis muscle thickness are valid for screening of low muscle mass, whereas triceps skinfold thickness using high-precision calipers can estimate subcutaneous fat deposit. Anthropometric research over the previous 40 years established that skinfold thickness measured at up to seven sites in various areas of trunk and legs by a caliper provides reliable information for estimating body fat and that measurement made at least three sites may be sufficiently informative in most clinical settings. Waist circumference (WC) and waist-to-hip ratio (WHR) render a reliable indicator for the amount of visceral fat. These relatively simple anthropometric methods have been shown to be good proxies of muscle or fat mass, but most of them are subject to inter- and intraobserver variability, particularly skinfold thickness [34]. Nuclear-based methods (i.e., total body nitrogen or body potassium content) are considered the reference methods for body composition, but scarce studies were conducted in dialysis patients [35, 36].

Modality	Methods	Body compartment assessed	Advantages	Disadvantages
1. Anthropometry	- MAMC, calf circumference, APMT	- SMM	Moderate accuracy, widely available, low cost, and quick	Low reproducibility, high inter- and intraobserver variations, needs well-trained personnel
	- Skinfold thickness	- Subcutaneous fat		
	- Waist circumference and waist-to-hip ratio	- Central/ abdominal fat		
2. Estimating equations	- Various	- SMM	Usually low cost and readily available	No validation studies in ESRD population
3. Creatinine kinetics	- Urinary creatinine excretion	- SMM	Low cost and allow routine assessment in dialysis patients	Largely influenced by dietary creatine and protein consumption
	- Serum creatinine	- LST		
4. Bioelectrical impedance	- BIA	- FFM	- Widely available and medium cost	- Not a direct measure of lean mass and affected by hydration status
	- BIS	- LST or SMM	- Low inter- and intraobserver variations, portable and less impacted by fluid overload	- Relatively high cost and cannot be used in patients with metal implants, pacemakers, and limb amputation
5. Whole body counting	- Total body potassium	- Body cell mass	High precision and not influenced by fluid status	High cost and low clinical applicability
6. Neutron activation analysis	- Total body nitrogen	- Body protein store	High precision and not influenced by fluid status	High cost and low clinical applicability
7. Imaging techniques	- DXA	- LST (total and appendicular)	- Readily available in most hospitals and research centers	- Radiation exposure, high cost, affected by hydration status Orthopedic implants can cause artifacts
	- CT scan	- Muscle cross-sectional area and muscle density yielding an estimate of SMM	- High precision of muscle cross-sectional area and volume Theoretically not affected by fluid status	- Intermachine variability, provides regional (not total) estimates of muscle size, radiation exposure, and high cost
	- MRI	- Same as CT scan	- Same as CT scan	- Highest cost, estimates regional muscle size, and cannot be used in patients with metal products

APMT, adductor pollicis muscle thickness; BIA, bioelectrical impedance analysis; BIS, bioelectrical impedance spectroscopy; CT, computerized tomography; DXA, dual X-ray absorptiometry; ESRD, end-stage renal disease; FFM, fat-free mass; LST, lean soft tissue; MAMC, mid-arm muscle circumference; MRI, magnetic resonance imaging; SMM, skeletal muscle mass.

Table 1. Objective methods for body composition assessment in hemodialysis patients.

Equations to calculate muscle mass have been originally developed in non-CKD population and are often used to estimate appendicular skeletal muscle mass using body weight, height, hip circumference, and handgrip strength [37] as well as total muscle mass from BIA measurements [38]. One promising study among hemodialysis cohort [39] reported the estimation of total body muscle mass using intracellular volume derived from the BIS machine as described: SMM (kg) = 9.52 + 0.331 × intracellular volume (L) + 2.77 (if male) + 0.180 × weight (kg) − 0.113 × age (years). This equation was also validated against muscle mass assessment by MRI with R^2 value of 0.94, $p < 0.001$. Previous studies have continually attempted to develop equations to estimate FFM among CKD patients based on 24-h urinary creatinine excretion, serum creatinine concentration, or the amount of creatinine in dialysate [40, 41]. Even though these equations are in the acceptable agreement with reference methods, they have under- or overestimated the true FFM in some circumstances because of the absence of consideration on creatinine degradation or daily creatinine excretion [42]. Owing to the lack of reference ranges of serum creatinine and urinary creatinine excretion, this method would be inappropriate for monitoring of body composition changes.

Imaging techniques have higher precision and accuracy for skeletal muscle mass assessment but are time-consuming and expensive. CT and MRI can assess the quantity of the muscle in a specific region of the body in ESRD patients [43]. CT allows the calculation of muscle density and the degree of intramuscular fat infiltration as well [44].

Evaluation of body composition by DXA is probably the most popular used imaging technique in kidney researches. It emits two different energies of X-ray beams throughout the body to detect thickness, density, and chemical composition of the tissue. This information is then applied through different equations to calculate fat mass, LBM, and bone mineral density by assuming a constant hydration status in the derivation of FFM [45]. Therefore, altered fluid status can result in over- or underestimation of LBM content by DXA. However, the ability to evaluate appendicular skeletal muscle mass (the sum of lean mass of both arms and legs but excluding trunk) is the outstanding characteristic of DXA. Recent consensus from expert around the world [46–49] currently pays attention on the estimation of appendicular, instead of total, muscle mass because it has a higher correlation with muscle strength and physical function. Additionally, DXA provides precise assessment of fat mass and is sometimes regarded as the gold standard. Pitfalls of this machine are high cost, need specialized personnel, and may yield limited ability to separate muscle mass from fluid overload.

There are three categories of bioimpedance devices available commercially: single-frequency BIA (SF-BIA), multiple-frequency BIA (MF-BIA), and BIS. Regardless of the device specification, principles of bioimpedance-based evaluation of body composition involved the administration of a weak, alternating electrical current at one or more radiofrequencied through leads attached to surface electrodes for characterizing the conductive and nonconductive tissue and fluid compartment of the body [50]. The current electrical flow is well conducted by water- and electrolyte-rich tissues, for example, blood and muscle, but poorly conducted by fat, bone, and air-filled spaces. The reduction of voltage of the current occurs as it passes over the body and is detected through the current-sensing electrodes, and then the impedance data are recorded by the bioimpedance device [51]. In brief, impedance (Z) is the frequency-dependent opposition by the conductor (body) to the flow of electrical current. Geometrically,

impedance is the vector composed of resistance (R) and reactance (Xc). Resistance is the opposition to the flow of current when passing through the body. Reactance is the delay in conduction caused by cell membrane, tissue interfaces, and nonionic substances. Capacitance is a function of reactance that arises when cell membranes stores a portion of the current for a short time. This temporary storage of charge creates a phase shift or "phase angle" described as the ratio of the arc tangent of reactance to resistance. At very low (or near zero) frequencies, no conduction occurs because a higher cell membrane capacitance permits the current to only pass through and quantify the extracellular water (ECW). In contrast, at very high frequencies approaching infinity, total conduction occurs through cell membranes, therefore allowing the quantification of total body water (TBW) [52]. The difference between TBW and ECW determines intracellular water (ICW), which theoretically can be used to estimate body cell mass based on the assumption that cells are composed of 73.2% water [53, 54].

By using a single frequency at 50 kHz, SF-BIA can calculate FFM, fat mass, and TBW without differentiating ECW from ICW. This machine based on the assumption that the body is a uniform conductor with constant geometry is not physiologically accurate. MF-BIA devices typically apply the current at one very low frequency (i.e., 50 kHz) and several higher frequencies (i.e., 50, 10, 200, 500 kHz). Therefore, MF-BIA is able to differentiate between the ECW and ICW compartments [55, 56]. Furthermore, MF-BIA can evaluate segmental BIA, to provide more accurate whole body estimates, by recognizing the body as having five distinct cylinders (2 arms, 1 trunk, 2 legs) with different resistivities over which impedances are measured separately.

In general, BIS has more advantages over SF-BIA and MF-BIA in which BIS measures impedance over an entire range of frequencies, does not depend upon population-specific prediction equations to generate whole body volumes and masses, and does not assume that ECW and ICW are uniformly distributed [57, 58]. The three-compartment (3C) BIS model (fat mass, LBM, and water) incorporates TBW in its assessment, hence controlling for interindividual variation in lean tissue hydration and being more accurate for body composition analysis in ESRD population. Using equations based on the 3C model, BIS is the bioimpedance method of choice to distinguish lean tissue mass, adipose tissue mass, ICW, and TBW in both routine patient care and research [59]. More recently, this technique has largely replaced SF-BIA and MF-BIA. As mentioned above, for a more reliable and reproducible assessment of body composition, it should be done post dialysis session. Alternatively, if predialysis BIS is used instead, there is a recommendation to focus on ICW per kilogram concurrent with the interpretation of LBM.

Finally, the appropriateness of each method of body composition assessment should depend on availability, practicality, medical purposes, the trained personnel, and most importantly patient' risks and benefits. For clinical routine practice, the method chosen should be simple with low risk of complications.

2.3. Association of body adiposity and fat distribution with clinical outcomes

Obesity is increasing worldwide not only in the general population but also ESRD patients. In the USA, the incidence and prevalence rate of obesity among those on dialysis is far exceeding in the contemporary estimates in the general population [60]. Apart from BMI, other

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measures of obesity are skinfold thickness, metrics of central (abdominal) obesity, and percentage of body fat. All of which have been reasonably well validated against established gold standards and provide estimates of fat mass superior to BMI [61]. Central obesity, recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), was defined as WC of more than 102 (Caucasian) or 90 (Asian) cm in male and 88 (Caucasian) or 80 (Asian) cm in female [62]. According to the World Health Organization (WHO), WHR should not exceed 0.90 in men and 0.85 in women [63]. WC should be measured over the unclothed abdomen at the midpoint of lower thoracic cage and iliac crest at the midpoint of midaxillary line using a nonstretchable standard tape measure. Hip circumference should be assessed at the level of the widest diameter around the buttock according to the WHO recommendation [63]. Despite the lack of cut points of percentage of total body fat according to the WHO to define obesity, the diagnosis of obesity, as abnormal or excessive fat accumulation that may impair health, can be made when body fat exceeds 25% in male and 30–35% in female [64].

A study of 30 clinically stable hemodialysis patients indicated that skinfold measurements made in triplicate at four sites (biceps, triceps, subscapular, and suprailiac region) by the well-trained personnel on the opposite site of vascular access as well as BIA performed relatively well in which DXA was used as the gold standard with interclass correlation coefficient of 0.94 and 0.91, respectively [65]. Skinfold thickness measurement at single site (triceps level) also demonstrated a good agreement with fat mass content derived by DXA [66]. However, given the lack of validation of single-site measurement in CKD population, it is preferable to use skinfold measurement made at least three sites, if dedicated well-trained personnel are available, rather than single site. The performance of BIA for estimating body fat content has been formerly validated against the DXA as a gold standard method. The validity of MF-BIA has been specifically assessed in a series of 53 hemodialysis patients with body weight ranging from 35 to 111 kg. Tetrapolar BIA overestimated total fat mass by only 157 g (95% CI 937–1251 g) versus DXA [67]. In another study, SF-BIA obviously provided a satisfactory agreement with the gold standard (DXA), among 118 hemodialysis patients [66].

Fat is not uniformly beneficial or that not all fat is good. Measures of fat distribution and central obesity such as WC and WHR maintain a direct association with mortality both in general population and dialysis patients. Visceral adipose tissue is more closely related with metabolic syndrome than is subcutaneous adipose tissue [68, 69]. A strong association between WC, WHR, and cardiovascular mortality has been confirmed in a prospective cohort of 537 end-stage renal disease patients. The prognostic power of waist circumference per 10 cm increase for all-cause (HR 1.23; 95% CI 1.02–1.47, $p = 0.03$) and cardiovascular mortality (HR 1.37; 95% CI 1.09–1.73, $p = 0.006$) remained significant after adjustment for other cardiovascular comorbidities and traditional and emerging risk factors. WHR was also found to be related to all-cause mortality in which a 0.1 unit increase in WHR was significantly associated with a 1.24-fold increased risk of all-cause mortality in multivariable Cox regression analysis (HR 1.24; 95% CI 1.06–1.46, $p < 0.001$) but not cardiovascular mortality (adjusted HR 1.21; 95% CI 0.98–1.50) among dialysis patients [70]. Another study in an Asian hemodialysis cohort found that central obesity (≥90 cm in men and ≥80 cm in women) was predictive of increased risk of cardiovascular events (HR 4.91; 95% CI 1.30–18.9, $p = 0.02$) and all-caused

hospitalization (HR 1.83; 95% CI 1.10–3.10, $p = 0.03$) [71]. These abovementioned data suggested that the distribution of fat mass is important among patients with ESRD and the negative metabolic consequences of excess visceral fat are preserved despite the association of higher BMI with better survival in those populations. Nonetheless, the agreement between the absolute changes in WC and visceral fat over time was relatively poor in CKD patients [72]. Therefore, WC may not be an inadequate tool for monitoring changes in visceral fat in this population. The conicity index, the emerging surrogate of abdominal fat deposition that models central obesity as the deviation of body shape from a cylindrical toward a double-cone shape (i.e., two cones with a common base at the waist level), predicts mortality independently of a series of age, sex, comorbidities, and dialysis vintage in hemodialysis patients (HR 1.93; 95% CI 1.06–3.49) [73]. Moreover, as increasing the tertiles of the conicity index, patients were significantly older and fatter, reduced handgrip strength, and lower serum creatinine. Even though the result of the association of conicity index and hard outcome is promising, but one should keep in mind that conicity index has never been formally validated as a measure of visceral fat against gold standard methods like DXA, CT, or MRI, particularly among ESRD patients. Therefore, further confirmation studies in other hemodialysis populations are required to establish the validity of conicity index in this population.

Some studies have reported that a low, rather than a high, body fat mass is an independent risk factor of poor survival in maintenance hemodialysis patients owing to more difficulty to cope with the chronic catabolic stress. The summary of studies evaluating the effect of body adiposity with various clinical outcomes is shown in **Table 2**.

A multicenter longitudinal observational study of hemodialysis patients in Europe reported that the lowest tertiles of fat tissue index (fat mass normalized by the square of height (kg/m^2)), performed 30 minutes before midweek dialysis session using BIS machine, was significantly associated with lower survival rate during a 12-month follow-up period (HR 3.25; 95% CI 1.33–7.96, $p = 0.01$) after adjustment for traditional and nontraditional risk factors [74]. The authors speculated that the reduction in total body fat may be associated with decreased humoral immunity in recognition that adipose tissue can secrete not only inflammatory but also anti-inflammatory adipokines such as adiponectin. Therefore, adipose tissues might have some beneficial functions related with energy storage which may exceed the harmful effects in hemodialysis patients. Likewise, percentage of total body fat of less than 15% measured by single-frequency BIA after the end of dialysis treatment significantly predicted the overall mortality in 149 prevalent hemodialysis patients [75]. Besides that, hemodialysis patients with percent body fat, measured by the use of near-infrared (NIR) interactance via light emission by using NIR spectroscopy, of less than 12% had a death hazard ratio four times higher than that of those patients with body fat content between 24 and 36% after multivariate adjustment for demographics and surrogates of muscle mass and inflammation (HR 4.01; 95% CI 1.61–9.99, $p = 0.03$) [6]. In a subset of 411 patients whose fat loss was reevaluated after a 6-month period, a fat loss (≤−1%) was significantly associated with mortality risk two times that of patients who gained fat (≥1%) after adjusting for covariates (HR 2.06; 95% CI 1.05–4.05, $p = 0.04$). On the other hand, there was a trend toward a significantly worse (or lower) physical health score domain of quality of life, assessed by short form of health-related quality of life scoring system (SF-36) in patients with percent body fat ≥36% compared to those remaining three categories (<12%, 12–23.9%, and 24–35.9%).

Authors	Study population	Age (years)	Method of body composition assessment	Outcomes
Kalantar-Zadeh et al. [6]	535 maintenance HD patients divided into four categories by body fat (<12%, 12–23.9%, 24–35.9%, and ≥36%)	Ranged from 41 ± 15 to 58 ± 14	Total body fat measured by near-infrared interactance with a coefficient of variation of 0.5% (Futrex 6100, Gaithersburg, MD)	- Low baseline body fat (<12%) had a higher death HR [4.01; 95% CI 1.61–9.99, $p = 0.003$] - Fat loss (≤−1%) over time was associated with higher risk of death [HR 2.06; 95% CI 1.05–4.05, $p = 0.04$]
Segall et al. [75]	149 HD patients (55.0% men) with mean follow-up of 13.5 ± 1.5 months	53.9 ± 13.7	Percent body fat and phase angle by SF-BIA within 30 minutes after dialysis session	Percent body fat <15% and phase angle <6° were significantly associated with increased death risk [adjusted HR 4.14; 95% CI 1.09–15.53, $p = 0.036$]
Postorino et al. [70]	537 ESRD patients in 36 dialysis units	63 ± 15	WC and WHR by anthropometry	- A 10-cm increase in WC was associated with higher all-cause [HR 1.49; 95% CI 1.26–1.77] and CV mortality [HR 1.55; 95% CI 1.25–1.93] - A 0.1 unit increase in WHR was related to overall [HR 1.24; 95% CI 1.26–1.46] but not CV mortality [HR 1.21; 95% CI 0.98–1.50, $p = 0.07$]
Cordeiro et al. [73]	173 HD patients (57.8% men) with median follow-up of 41 (25–47) months	65 (51–74)	Conicity index to assess abdominal fat accumulation: WC (m) divided by 0.109 × square root of weight (kg)/height (cm) - WC by anthropometry	Mortality was increased in the highest tertiles of conicity index (HR 6.07; 95% CI 2.51–14.64) and the highest tertiles of WC [HR 2.87; 95% CI 1.29–6.40]
Wu et al. [71]	91 HD patients (54.9% men) with dialysis vintage of 25 (6–30) months	58.7 ± 12.5	WC by anthropometry (≥90 cm in men and ≥80 cm in women indicate the presence of abdominal obesity	Abdominal obesity was significantly a predictor of cardiovascular-related events [HR 6.25; 95% CI 1.65–23.6, $p = 0.007$ and adjusted HR 4.91; 95% CI 1.30–18.9, $p = 0.02$]

Authors	Study population	Age (years)	Method of body composition assessment	Outcomes
Caetano et al. [74]	697 HD patients with 12 months of follow-up	67 (55.5–76)	Fat tissue index (fat tissue/height^2) by midweek pre-dialysis BIS	The lowest fat tissue of index tertiles was a significant predictor of mortality [adjusted HR 3.25; 95% CI 1.33–7.96, p = 0.01]

Data are shown as mean standard deviation, median (interquartile range).

CI, confident interval; CV, cardiovascular; HD, hemodialysis; HR, hazard ratio; MF-BIA, multifrequency bioelectrical impedance analysis; SF-BIA, single-frequency bioelectrical impedance analysis; BIS, bioelectrical impedance spectroscopy; WC, waist circumference; WHR, waist-hip ratio.

Table 2. Summary of recent studies in the effects of adiposity and outcomes in patients undergoing hemodialysis.

2.4. Magnitude of low muscle mass and sarcopenia with associated outcomes

As the consequences of studies regarding the "obesity paradox," there is an emerging topic discussion on the importance of muscle mass over fat mass and vice versa in the nephrology community. Fat is good but the muscle is better described that fat cells are not metabolically active as muscle cells and fat mass can decrease or expand its size depending upon the balance between energy intake and expenditure. In contrast, muscle mass is tightly regulated because excess protein is not stored and the muscle is broken down when proteins or amino acids are needed. As the turnover of cellular proteins is estimated to be 1–1.5 kg of the muscle [76, 77], a decrease in protein synthesis or an increase in protein degradation can have substantial effects on muscle mass or size. Despite the high prevalence of obesity among ESRD patients, protein energy wasting or muscle wasting is not uncommon [78]. The increasing BMI in the dialysis population does not exclude concurrent muscle wasting. Excess energy intake concurrent with physical inactivity, low-grade inflammation, or insulin resistance, all of which are common among ESRD patients, may result in muscle mass loss, even in the setting of excess adiposity known as "sarcopenic obesity" [79–81]. Recently, sarcopenia is currently defined as a generalized loss of skeletal muscle mass combined with reduced muscle strength or physical performance according to the European and International Working Group on Sarcopenia in Older People based on rationale that muscle strength does not depend solely on muscle mass [46, 48, 82]. As would be expected, sarcopenia has been associated with multiple clinical outcomes including physical disability, hospitalization, and overall mortality in community-dwelling older adults [83–85]. A cross-sectional data from National Health and Nutrition Examination Survey (NHANES) [86] demonstrated a higher prevalence of sarcopenia with lower estimated glomerular filtration rate suggesting that muscle wasting progresses as renal function deteriorates. Several studies have reported a prevalence of sarcopenia or low muscle mass, based on estimates of muscle mass indexed to body size and used thresholds for low muscle mass that were based on sex-specific norms, among patients with ESRD from 4 to 60% [87–89]. The broad range in the prevalence of sarcopenia is mainly due to the lack of consensus criteria on the definition of low muscle mass to allow comparison across populations. Frailty, on the other hand, represents a syndrome resulting from cumulative deterioration in multiple physiological system, leading to impair

homeostatic reserve and reduced capacity to withstand stress [90–92]. Therefore, frailty is partly overlapped with sarcopenia but sometimes can occur with non-skeletal muscle-related conditions.

Body composition is significantly associated with physical functioning and quality of life. The longitudinal study in 105 prevalent hemodialysis patients [93] reported that higher muscle area, measured by mid-thigh muscle area by CT scan, was associated with better physical function assessed by 6-minute walk distances, whereas higher intra-abdominal fat area was inversely correlated with physical performance. Each increment per 1 standard deviation of muscle area was also associated with higher physical (HR 3.78; 95% CI 0.73–6.82) and mental health component score (HR 3.75; 95% CI 0.44–7.05) of SF-12, a short-form survey with questions selected from the SF-36 health survey. In agreement with western communities, lean tissue index was moderately associated with better physical health assessed by short version of WHO quality-of-life scoring system ($r = 0.46$, $p = 0.007$) in Asian patients receiving hemodialysis [94]. Similarly, other studies examined the associations between body composition estimated by BIS and frailty. Among approximately 650 hemodialysis patients, frailty was defined as having at least three of the following characteristics: weight loss, exhaustion, low physical activity, weakness, and slow gait speed. Patients with higher ICV, representing higher muscle mass, were less likely to be frail, while those with higher fat mass were associated with higher odds of frailty [95]. Likewise, the same associations were observed among another group of 80 well-characterized hemodialysis participants that performance-based frailty was associated with smaller muscle size as estimated using cross-sectional area of quadriceps muscle by MRI, and this association was of greater magnitude than that of 10 years of age in multivariate analysis (-30.3 cm^2 vs -6.6 cm^2, $p < 0.001$) [96].

Well-preserved amount of muscle mass, as shown by both direct and indirect methods of assessments, represents one of the strongest nutritional indicators for survival among ESRD population. Report from a large dialysis organization database, transplant-waitlisted hemodialysis patients with the highest serum creatinine as a muscle mass surrogate, had significantly lower death hazard (HR 0.57; 95% CI 0.49–0.66) compared to the lowest creatinine quintiles [27]. Similar associations were observed with serum creatinine change over time. Interestingly, de Oliveira and colleagues explored the alternative simple method of anthropometric estimates of adductor pollicis muscle thickness (APMt), performed at the opposite hand of vascular access, to predict mortality in hemodialysis patients [97]. APMt was modestly correlated with MAMC ($r = 0.5$, $p < 0.001$), and the value of APMt ≤ 10.6 mm was significantly associated with 3.3 times (95% CI 1.13–9.66) greater risk of hospitalization on the following 6-month follow-up. At the time of dialysis initiation, nonobese patients with MAMC adequacy (more than percentile 90th of normal population from NHANES distribution tables as a reference) showed that the best survival and reduced MAMC was independent predictor of death in incident hemodialysis patients ($p = 0.008$) [98]. Huang and colleague [99] revealed in a post hoc analysis of the Hemodialysis (HEMO) cohort that hemodialysis patients with higher MAMC (representing muscle mass) together with higher triceps skinfold thickness (representing body fatness) showed a consistency toward lower mortality rates during a follow-up period of 2.5 years, independently of each other. Another post hoc analysis from the HEMO study [100] evaluated the prognostic implications of changes in anthropometric measurement.

The authors observed that the decline in MAC (per cm) and sum of the three sites skinfold thickness including subscapular, biceps, and triceps (per mm) significantly increased the hazards of infection-related hospitalization, cardiovascular events, and overall death. A prospective hemodialysis cohort with longer follow-up period of 5 years reported that higher MAMC was associated with better SF-36 mental health scale and lower death hazards after adjustment for case-mixed, malnutrition inflammatory markers [101]. In addition, patients with high MAMC quartiles combined with either high or low TSF exhibited the greater survival when using median values of MAMC and TSF for dichotomizing (death HRs of 0.52 and 0.59, respectively). The authors pointed out that both compartments (muscle and fat) likely have complex roles in the maintenance of body homeostasis and equally perform as important nutritional parameters among patients receiving hemodialysis. Also, results from the large international MONitoring Dialysis Outcomes (MONDO) among over 30,000 participants [102] confirmed that both lean and fat tissue masses, as determined by whole body BIS, are important predictors of survival in chronic hemodialysis patients. Mortality rates were significantly higher at the lower lean and fat tissue index extreme (HR 3.37; 95% CI 2.94–3.87, $p < 0.001$). The summary of studies exploring indicators of muscle mass with outcomes among maintenance hemodialysis patients is shown in **Table 3**.

A relatively large hemodialysis cohort of 960 participants with 54-month follow-up demonstrated that patients with muscle wasting, defined as height-normalized lean tissue mass less than 10% of normal value by BIS, contributed significantly to the Cox regression model to predict mortality (HR 1.66; 95% CI 1.10–2.44) compared to those with normal nutrition status [103]. Similarly, body composition analysis among 6395 patients from Spain showed that hemodialysis patients with lean tissue index lower than percentile 10th had a higher relative risk of death than those patients with higher values [104]. Moreover, data from a prospective observation cohort of 299 hemodialysis population suggested that for every 1 kg gain in lean tissue during the first year of dialysis, there was a 7% reduction in all-cause mortality [105].

To address the associations between muscle mass and mortality, some relevant factors such as muscle strength or physical performance should be taken into account. Isoyama and coworkers [106] examined the association between low muscle mass and strength with mortality among 330 Swedish incident dialysis patients. Both low muscle mass (based on appendicular skeletal muscle mass by DXA indexed to the square of height) and muscle weakness, determined by handgrip dynamometer, were independently associated with higher death rate. However, when the two were included in the same analysis, muscle weakness was more strongly associated with overall mortality than low muscle mass (HR 1.79; 95% CI 1.09–2.49, $p = 0.02$ vs 1.17; 95% CI 0.73–1.87, $p = 0.51$, respectively). Report from prospective hemodialysis cohort using the United State Renal Data System (USRDS) indicated that patients with BIS-derived low muscle mass by different indexing methods (height^2, percentage of body weight, body surface area, and BMI) were associated with higher risk of death in the unadjusted analysis [107]. However, the significance of these associations was disappeared after adjustment for covariates. In contrast, functional limitations in muscle strength or gait speed were associated with mortality even after adjusting for confounders. Taken together, the abovementioned findings underscore the additional potential contributors to be concerned along with the interpretation of the associations of muscle mass

Authors	Study population	Age (years)	Method of body composition assessment	Outcomes
Araujo et al. [98]	344 HD patients (60.5% men, 26% diabetes)	50.4 ± 16.0	MAMC and triceps skinfold thickness by anthropometry	Patients with BMI ≤25 kg/m^2 but having MAMC adequacy showed the best survival. An increase in MAMC was associated with decrease death risk by 3% [HR 0.97; 95% CI 0.96–0.99, p = 0.008]
Huang et al. [99]	Post hoc analysis of 1709 HD patients (44% men) with mean follow-up of 2.5 years	57.7 ± 14	MAMC and triceps skinfold thickness by anthropometry	The HR per 1 SD increase were 0.84 [95% CI 0.76–0.92] for triceps skinfold thickness and 0.93 [95% CI 0.86–1.00] for MAMC
Noori et al. [101]	792 maintenance HD patients (53% men, 31% black) with 5-year survival follow-up	53 ± 15	MAMC and triceps skinfold thickness by anthropometry	The highest quartiles of MAMC, but not triceps skinfold thickness, were associated with death after adjusting for case-mixed and MICS (p for trend 0.04 and 0.15, respectively)
Molnar et al. [27]	14,632 wait-listed HD patients without KT (60% men) with 6-year follow-up	52 ± 13	Pre-dialysis serum creatinine concentration (mg/dL) as a surrogate of muscle mass	Patients with >1 mg/dL decrease of serum creatinine had 38% higher adjusted death risk [HR 1.38; 95% CI 1.23–1.56, p < 0.001], whereas those patients whose serum creatinine increased more than 2.4 mg/dL reported 13% better survival [HR 0.87; 95% CI 0.75–0.99, p = 0.045].
de Oliveira et al. [97]	143 HD patients (58% male)	52.2 ± 16.6	APMt measurement was performed using a Lange caliper on the contralateral arm of vascular access	APMt ≤ 10.6 mm was associated with hospitalization risk within 6 months [HR 3.3; 95% CI 1.13–9.66, p = 0.03] but not associated with higher risk of death within 6 and 12 months

Authors	Study population	Age (years)	Method of body composition assessment	Outcomes
Su et al. [100]	Post hoc analysis of 1846 HD patients (43.6% men) with mean follow-up of 2.8 ± 1.8 years	58	MAC and sum of skinfold thickness (subscapular, biceps, and triceps) by anthropometry to the nearest 0.1 cm	- Among participants with BMI≤25 kg/m^2, decline in MAC per 1 cm, but not skinfold thickness, was associated with higher mortality [HR 1.14; 95% CI 1.09–1.19, $p < 0.001$] - Baseline MAC (per 1 cm lesser) was associated with higher cardiac hospitalization [HR 1.07; 95% CI 1.02–1.11, $p = 0.002$] and infection-related death [HR 1.21; 95% CI 1.10–1.34, $p < 0.001$]
Yongsiri et al. [94]	34 HD patients (47.1% men)	61.1 ± 15.5	Lean and fat tissue (indexed to height^2) was obtained by BIS after dialysis session	Among HD patients, there was a positive correlation between lean, but not fat, tissue index and physical health ($r = 0.46$, $p = 0.007$)
Isoyama et al. [106]	330 incident HD patients (61.5% men) with mean follow-up of 29 (1–48) months	53 ± 13	- ASM measurement by DXA and cutoffs for low muscle mass were ASM/height^2 of ≥2 SD below the sex-specific mean of young adults - Handgrip strength cutoffs were <30 kg in men and <20 kg in women	- Muscle mass (per 1 SD increase) was associated with lower mortality [HR 0.21; 95% CI 0.06–0.73, $p = 0.01$] - Low muscle mass was not significantly associated with higher mortality [HR 1.17; 95% CI 0.73–1.87, $p = 0.51$] compared with appropriate muscle mass - Low muscle strength was associated with increased risk of death [HR 1.79; 95% CI 1.09–2.94, $p = 0.02$]
Keane et al. [105]	299 HD patients at six dialysis units (62% men, 42% diabetes)	63 ± 15	Lean and fat tissue index was obtained by BIS (indexed to height^2)	A 7% reduction in mortality for every 1 kg gain in lean tissue during 1 year after dialysis initiation [HR 0.93; 95% CI 0.99–0.98, $p = 0.01$]

Authors	Study population	Age (years)	Method of body composition assessment	Outcomes
Castellano et al. [104]	6395 HD patients (62.7% men, 28.5% diabetes)	67.6 ± 14.7	Lean and fat tissue (indexed to height^2) was obtained by BIS before dialysis session	Lean tissue index lower than percentile 10th had a higher relative risk of death [HR 1.57; 95% CI 1.13–2.20, $p < 0.05$]
Kittiskulnam et al. [107]	645 prevalent HD patients (58.6% men, 61.5% black, 43.9% diabetes) with mean follow-up of 1.9 (0.1–3.2) years	56.7 ± 14.5	- TBMM was derived by pre-dialysis BIS and indexed to height^2 body weight, BSA, and BMI - Cutoffs for low muscle mass were ≥2 SD below the sex-specific mean of young adults using NHANES by each indexing strategy - Handgrip strength cutoffs were ≤26 kg in men and ≤16 kg in women - Slow walking speed was defined as ≤0.8 m/s	- Low muscle mass by all indexing methods was associated with significantly higher mortality compared with normal muscle mass, but these associations were not remained significant in multivariable analysis - Low grip strength was associated with increased risk of death [HR 1.68; 95% CI 1.01–2.79, $p = 0.04$] - Slow walking speed was associated with higher mortality risk [HR 2.25; 95% CI 1.36–3.74, $p = 0.002$]

Data are shown as mean standard deviation, median (interquartile range).

APMt, adductor pollicis muscle thickness; ASM, appendicular skeletal muscle; BIS, bioelectrical impedance spectroscopy; BMI, body mass index; BSA, body surface area; CI, confident interval; CV, cardiovascular; DXA, dual X-ray absorptiometry; HD, hemodialysis; HR, hazard ratio; KT, kidney transplantation; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; MICS, malnutrition inflammation cachexia syndrome; MF-BIA, multifrequency bioelectrical impedance analysis; NHANES, National Health and Nutrition Examination Survey; SF-BIA, single-frequency bioelectrical impedance analysis; TBMM, total body muscle mass.

Table 3. Selected articles evaluating low muscle mass, sarcopenia, and sarcopenic obesity with outcomes among maintenance hemodialysis patients.

and survival among patients undergoing hemodialysis because risk factors for the loss of muscle mass may not be similar to those for the loss of muscle functionality.

2.5. Strategies to preserve body composition in patients receiving maintenance hemodialysis

Intervention to preserve muscle mass and reduce excess body fat is an ultimate goal for improving outcomes among ESRD population. However, a major limitation in the development of effective therapies against muscle loss is the imprecision of the available methods

to assess changes in muscle mass during intervention. One alternative approach is serum biomarkers to determine the anabolic and catabolic balance within muscular structure. For example, serum creatinine may be a suitable surrogate of muscle mass in ESRD patients with no residual renal function and the novel biomarker N-terminal propeptide of type III procollagen (P3NP) that plays an important step during collagen synthesis [108]. At present, prevention and treatment of uremic muscle wasting should be initially based on optimal nutrition support and correction of acidosis [109, 110]. Other established therapies for prevention of muscle loss are physical exercise and supraphysiologic dose of anabolic steroid.

Recent observational data uncovered the benefit of increased physical activity with higher estimated muscle mass. In hemodialysis patients, aerobic exercise was positively associated with skeletal muscle mass volumes after adjustment for age, sex, and dialysis vintage [111]. Data from randomized controlled trials have demonstrated that intradialytic resistance exercise training can improve muscle volume and enhance muscle strength [112] or physical performance [113, 114] among hemodialysis patients. The use of resistance exercise combined with anabolic steroid (nandrolone decanoate) has been shown to increase muscle mass and decrease body fat among patients with ESRD [115, 116]. Furthermore, an oral androgen, oxymetholone, has significantly shown an anabolic effect to increase amount of FFM and handgrip strength, but this drug raised concerns about liver toxicity [117], suggesting that intramuscularly or transdermally administered androgens are better choices for further studies in ESRD population.

Another treatment strategy of preventing muscle mass loss includes active vitamin D administration [118]. Hemodialysis patients receiving either alfacalcidol or calcitriol experienced increase in the total amount of muscle mass assessed by BIA and a favorable effect on maintaining in physical functioning. Recombinant human growth hormone (rhGH) administered at a pharmacological dose may simultaneously improve net muscle protein synthesis and decrease muscle protein breakdown [119, 120]. Nonetheless, analysis from hemodialysis participants in a large GH supplementation trial suggested that rhGH was linked to adverse cardiovascular disease risk [121]. Currently, rhGH is thus not recommended to treat muscle wasting among CKD patients. Lastly, targeting pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrotic factor as well as manipulation of myogenic stem (satellite) cell or transforming growth factor-β superfamily members are all the potential future treatments to preserve body composition changes [122].

In conclusion, body composition is usually altered among patients undergoing maintenance hemodialysis. Sarcopenia, sometimes might occur in the setting of obesity, is a significant predictor of mortality outcome among patients receiving maintenance hemodialysis. Despite the positive association of higher BMI with greater survival in hemodialysis patients, visceral adiposity is associated with adverse cardiovascular outcomes. Additionally, changes in body composition over time might be informative as a predictor of clinical outcome. Interventions to preserve muscle mass and function or reduce excess body adiposity, particularly visceral fat, may have potentially beneficial effects on important clinical outcomes.

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