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Body composition in chronic kidney disease

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Abstract

Purpose of review—To summarize the latest information on body composition among patients with chronic kidney disease and its association with outcomes.

Recent findings—Obesity is increasing among patients with end-stage renal disease and is more prevalent when direct measures of adiposity are used rather than BMI. High BMI is not associated with better survival among patients with earlier chronic kidney disease or after kidney transplantation, suggesting that excess fat is most protective among the sickest patients. Despite the positive association between BMI and survival among patients with end-stage renal disease, visceral fat is associated with coronary artery calcification and adverse cardiovascular events. Muscle wasting is prominent among patients with chronic kidney disease, sometimes even in the setting of obesity. Obesity and muscle wasting are associated with worse physical functioning. Indicators of low muscle size and strength are associated with higher mortality. Some interventions can affect body composition, but whether they affect survival has not been determined.

Summary—Recent studies show that a high BMI is not protective for all patients with chronic kidney disease and is associated with poor physical functioning and frailty. Visceral adiposity is associated with adverse cardiovascular outcomes. Sarcopenia is common among patients with end-stage renal disease and is associated with worse physical performance and higher mortality.

Keywords

frailty; obesity; physical function; sarcopenia; visceral fat

INTRODUCTION

Both obesity and muscle wasting are common among patients with chronic kidney disease (CKD) and may have important implications for survival, physical function, and other outcomes. BMI, defined as body weight in kilograms divided by the square of height in meters, initially described in 1832 [1,2] but not called BMI until 1972 [3], is a useful screening tool for obesity in the general population and for undernutrition in developing countries [4]. The association of BMI with survival is usually described as having a J or U shape, with higher mortality at both extremes [4].

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Conflicts of interest

There are no conflicts of interest.

The examination of BMI among patients with CKD has demonstrated important associations with survival [5–8]. Patients with low BMI are at a higher risk of mortality than those with a BMI in the normal range, but high BMI is not associated with higher mortality among patients with end-stage renal disease (ESRD) as it is in the general population [5–8]. Recent studies have highlighted the limitations of BMI in the CKD population and have gone beyond BMI to further our understanding of the impact of body composition on survival and on other important outcomes, including physical function and quality of life. This review will focus on advances in characterizing body composition among patients with CKD and in understanding associations of body composition with outcomes.

A CLOSER EXAMINATION OF THE BMI–SURVIVAL ASSOCIATION

The mean BMI and prevalence of obesity among incident dialysis patients have been increasing steadily over the last 15 years (Figs 1 and 2) [9,10]. In 2002, almost one-third of all adult incident dialysis patients were obese [9], and by 2009 the mean BMI was almost in the obese range at over 29 kg/m² [10]. However, new evidence suggests that even these staggering numbers may underestimate the prevalence of obesity in the ESRD population. A recent study of 284 incident and 209 prevalent dialysis patients from Sweden compared the prevalence of obesity based on a BMI of more than 30 kg/m² with the prevalence based on anthropometry [11■]. Although only 9% of incident and 10% of prevalent patients met the traditional BMI definition of obesity, 65% of both incident and prevalent patients were obese based on percentage of body fat. These data highlight the limitations of BMI as a reflection of body composition, and the authors pointed out that a BMI of more than 30 kg/m² has a high specificity but low sensitivity for excess body fat. In addition, the authors noted that patients with a BMI of more than 30 kg/m² (overtly obese) had higher muscle and fat stores and appeared to be better nourished by subjective global assessment than nonobese patients, a finding that lends support to the idea that better survival among obese patients with ESRD could be related to protection against wasting in the setting of acute illness or chronic inflammation.

A study of a large cohort of veterans with non-dialysis-dependent CKD examined the association between BMI and outcomes across categories of estimated glomerular filtration rate [12■]. Overall, there was a U-shaped association, with higher mortality at both low and high BMI. The association of low BMI with higher mortality was fairly constant across categories of estimated glomerular filtration rate, whereas the association of high BMI with higher mortality was progressively attenuated at more advanced stages of CKD and was not present among patients with stage 4 or 5 CKD. The authors offered a potential explanation that the protective effects of a better nutritional reserve accompanying higher muscle mass or higher body fat may offer short-term advantages under conditions of duress. Such protection would be expected to be magnified among patients with the most advanced CKD, who also have more comorbidity burden and shorter life expectancy [12■].

According to this explanation, one might expect obesity to be more ‘harmful’ among transplant recipients, who represent the healthiest subset of patients with ESRD, and a recent study examined this question among just over 30 000 kidney recipients using data from the United Network for Organ Sharing database [13■]. Morbidly obese patients (BMI 35–40

kg/m²) had slightly higher crude 3-year mortality that was not independent of diabetes and functional dependence, both of which were more common among morbidly obese individuals. In a meta-analysis on this topic [14[■]], the authors identified 10 studies, of which four had sufficient numerical data for meta-analysis. The three smaller studies included in the meta-analysis did not find an association between obesity and higher mortality, but the largest study, accounting for 94% of the patients in the meta-analysis, did find a significant association, as did the meta-analysis overall. Thus, the jury is still out on whether obesity is associated with higher mortality after kidney transplant.

Several studies have shown that changes in body weight are more strongly associated with mortality than single measures of BMI, with higher mortality among patients who lose weight or fat and lower mortality among those who gain [15,16]. However, these observational studies suffered from a key limitation in that intentional and unintentional weight loss could not be distinguished, making confounding by health status likely as sicker patients are more likely to lose weight. A recent article from a large European multinational observational study examined the association between changes in dry weight over 6 months and survival [17[■]]. Weight loss (>1% decline) and weight gain (>1% increase) were compared with stable weight ($\pm 1\%$). Although weight loss was associated with higher mortality and weight gain with lower mortality in the whole cohort, the association of weight loss with mortality was attenuated and no longer statistically significant among obese patients [hazards ratio 1.28, 95% confidence interval (CI) 0.74–2.14]. In addition, there was no survival benefit of weight gain (hazards ratio 0.98, 95% CI 0.59–1.62) among obese patients. These data may also lend support to the ‘nutritional reserve’ explanation for the better survival among ESRD patients with higher BMI.

ASSOCIATION OF OBESITY WITH PHYSICAL FUNCTION

The greater-than-expected body fat relative to BMI observed among many patients with ESRD [11[■]] can also be thought of as less-than-expected muscle mass, a condition that is not unique to dialysis patients and has been termed ‘sarcopenic obesity’ [18,19]. Thus, the increasing BMI in the dialysis population does not exclude concurrent muscle wasting, which, in conjunction with higher body fat, may exert a negative effect on physical functioning among patients with ESRD.

Martinson *et al.* [20[■]] examined the associations of body size and composition with physical performance and quality of life among prevalent hemo-dialysis patients. They obtained estimates of mid thigh muscle area and intra-abdominal fat area by magnetic resonance imaging among 105 patients and reported that patients with higher BMI had higher muscle area and higher abdominal fat. BMI was negatively correlated with the distance participants walked in 6 min without adjustment for muscle area, and the association became more pronounced after adjusting for the larger muscle area among obese patients. Higher fat mass and waist circumference were also negatively correlated with physical performance. Conversely, higher muscle area was associated with better function.

Two other studies took a similar approach, examining the associations between body fat and lean mass estimated by bioelectrical impedance spectroscopy (BIS) and frailty [21[■],22]. Among 638 prevalent 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 [21[■]]. Patients with higher fat mass were more likely to be frail, as well as to have the weakness and slow gait speed components of frailty, whereas those with more muscle were less likely to be frail. Similar associations were observed among 80 well characterized clinical trial participants [22]. Taken together, these studies suggest that higher BMI is associated with both higher fat and higher muscle mass but that the overall impact of high BMI on physical function is negative. These associations of higher fat mass with higher odds of frailty and worse physical performance seem contrary to the better survival associated with higher BMI in dialysis patients and suggest that fat is not uniformly beneficial or that not all fat is good.

DISTRIBUTION OF BODY FAT MAY BE IMPORTANT

In the general population, adipose tissue is now understood to be an important endocrine organ, producing proinflammatory cytokines, such as interleukin-6, tumor necrosis factor- α , and leptin, as well as a more limited number of anti-inflammatory cytokines, such as adiponectin [23,24]. Both leptin and adiponectin accumulate in ESRD, but studies in the ESRD population have produced conflicting results about the association of adiponectin with outcomes [25–27]. Recent data confirm that visceral fat is negatively correlated with serum adiponectin concentration among patients treated with both hemodialysis [28] and peritoneal dialysis [29]. Furthermore, Zoccali *et al.* [28] made an interesting observation that waist circumference modifies the relationship between serum leptin and adiponectin concentrations and all-cause and cardiovascular mortality such that mortality associations parallel those in the general population among patients with large waist circumference but are opposite among patients with small waist circumference. These data suggest that adipokines may exert the expected effects unless they are indicating the presence of protein energy wasting (PEW), and may provide an explanation for the previously divergent findings.

Visceral adipose tissue is more closely associated with complications of obesity such as the metabolic syndrome than is subcutaneous adipose tissue [30]. Several recent studies have examined the association of the amount of visceral adipose tissue with outcomes [31,32[■], 33[■]]. In a study that enrolled 65 patients with stages 3 and 4 CKD from Brazil [31,32[■]], visceral and subcutaneous fat areas were calculated from abdominal computed tomography. Patients were considered to have visceral obesity if the ratio of visceral to subcutaneous adipose area was greater than the median, and the presence of visceral obesity was associated with higher coronary artery calcification (CAC) score [31] and higher risk of cardiovascular events [32[■]]. A follow-up analysis with a larger number of patients confirmed that greater amounts of visceral adipose tissue were associated with clinically significant coronary calcification and showed that waist circumference as a surrogate for visceral adiposity was also associated with coronary calcification [33[■]]. These data suggest that the distribution of fat mass is important among patients with ESRD and the negative metabolic consequences of excess abdominal fat are preserved despite the association of higher BMI with better survival in the ESRD population.

PREVALENCE OF SARCOPENIA

Despite the high prevalence of obesity among patients with ESRD, PEW [34] and muscle wasting [35] are also common. Sarcopenia was originally defined as age-related loss of muscle mass [36,37]. However, more recently, the European Working Group on Sarcopenia in Older People recommended using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia based on the rationale that muscle strength does not depend solely on muscle mass [38]. Recent studies have examined the prevalence of sarcopenia among patients with CKD using defined thresholds [39–42,43[■]] (Table 1). A cross-sectional study demonstrated a higher prevalence of sarcopenia with lower estimated glomerular filtration rate among participants in the National Health and Nutrition Examination Survey III [39], suggesting that muscle wasting progresses as kidney function declines.

Consistent with this possibility, several international studies in the past year have reported a prevalence of sarcopenia or muscle wasting among patients with ESRD ranging from 20 to 44% [40–42,43[■]] (Table 1). All of these studies used estimates of muscle mass indexed to body size and used thresholds for low muscle mass that were based on sex-specific norms, and all reported a prevalence of sarcopenia that was higher than is typically observed among patients with earlier stages of CKD or among healthy populations. Nevertheless, there was substantial variation across these cohorts. Differences among patient populations, such as country of origin, age ranges, treatment with hemo-dialysis or peritoneal dialysis, and duration of dialysis likely explain some of the variations in the observed prevalence of sarcopenia. However, methodological differences also may be an important explanation, and a better understanding of the impact of methodology on observed prevalence is important to allow comparison across populations and to better address the potential association of sarcopenia with outcomes. To that end, Lamarca *et al.* [44[■]] set out to examine the differences in prevalence of sarcopenia introduced by varying the definitions employed. They assessed 102 Brazilian hemodialysis patients for sarcopenia using criteria for low muscle mass based on dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis, skinfold thicknesses, and midarm muscle circumference [44[■]]. Eighty-five percent of the patients were weak, and the prevalence of sarcopenia varied from 4 to 63%, depending on the method and cutoff limit used to designate muscle mass as low (Table 1).

ASSOCIATION OF MUSCLE INDICATORS WITH OUTCOMES

Isoyama *et al.* [43[■]] examined the association between low muscle mass and strength with mortality among 330 Swedish patients beginning dialysis. Both low muscle mass (based on appendicular skeletal muscle by DXA indexed to the square of height) and weakness were individually associated with higher mortality, but when the two were included in the same analysis, weakness was more strongly associated with mortality (hazards ratio 1.79, 95% CI 1.09–2.94, $P = 0.02$) than low muscle mass (hazards ratio 1.17, 95% CI 0.73–1.87, $P = 0.51$). These findings highlight the associations of muscle mass with survival among patients on dialysis and underscore the possible independent contributions of other factors related to strength and physical performance, which might include neural activation or muscle architecture [45].

A recent study by Wilson *et al.* [46] uncovered additional evidence that muscle quality may be as important or more important than muscle quantity. They examined 24-h urine creatinine excretion and fat-free mass (FFM) estimated by single-frequency bioelectrical impedance analysis as estimates of lean body mass using appendicular lean mass (ALM) by DXA as the gold standard among participants in the Chronic Renal Insufficiency Cohort study [46] and found a stronger correlation between FFM and ALM ($\rho = 0.91$) than between urine creatinine excretion and FFM ($\rho = 0.50$) or ALM ($\rho = 0.47$). However, FFM was not associated with mortality, whereas higher urinary creatinine (UCr) excretion indexed to height was associated with lower mortality (hazards ratio 0.93 per 1-SD higher UCr excretion indexed to height, 95% CI 0.72–0.97). On the basis of their observation that UCr and the ratio of UCr to FFM were lower among patients with lower glomerular filtration rate, the authors speculated that the UCr and the UCr–FFM ratio may reflect muscle quality as well as mass.

CAN WE ADDRESS MUSCLE WASTING OR EXCESS BODY FAT?

Strategies to preserve muscle mass and function or to reduce excess body fat, especially visceral fat, might be of great benefit in the CKD population. Recent observational data has linked higher level of physical activity with higher estimated muscle mass among patients on dialysis [21■,47], highlighting the potential benefit of exercise. Indeed, several recent studies of intradialytic resistance exercise training [48–50] have all reported increases in muscle size and strength or physical performance, in agreement with prior studies utilizing this strategy [51–53].

A recently published randomized controlled trial (RCT) compared the effects of 12 weeks of aerobic exercise training in a fitness center or at home with no exercise on body composition and physical performance among 27 men with CKD stage 3 or 4 [54■]. Visceral fat, measured by abdominal computed tomography, decreased in both exercise groups compared with the control group. In addition, both exercise groups improved their performance on a sit-to-stand test, and the in-center exercise group increased muscle mass in the legs. Thus, aerobic exercise may be a promising strategy to decrease visceral fat as well as to build muscle and improve physical functioning. In addition, an RCT of intradialytic cycling is currently underway to evaluate its effects on PEW [55].

Supraphysiologic doses of androgens have been shown to increase muscle mass and decrease body fat among patients with ESRD [51,56,57]. Studies have recently shown a direct correlation between serum total testosterone and muscle mass among men on hemodialysis [58,59] or with earlier stages of CKD [60], suggesting that even variations in testosterone concentration within the physiologic range might affect muscle mass. An RCT recently assessed the effects of an oral androgen, oxymetholone, among men and women on hemodialysis [61■]. Anabolic effects were observed, with increases in FFM and handgrip strength, but liver toxicity, manifest as transient increases in serum aspartate aminotransferase and alanine transaminase concentrations, was a concern. Thus, intramuscularly or transdermally administered androgens are better choices for the further study of the long-term safety and longer-term anabolic effects of these agents.

Additional studies are needed to assess whether implementing strategies to modify body composition, including intentional weight loss among obese patients, translate into long-term improvements in quality of life, physical function, and survival.

CONCLUSION

Body composition is frequently altered among patients with CKD, with obesity and muscle wasting common and sometimes occurring simultaneously. BMI does not accurately reflect overall adiposity and does not distinguish visceral fat, which is associated with adverse outcomes, from subcutaneous fat, which may be protective against wasting and catabolism in the setting of ESRD, particularly when intercurrent illnesses occur. Exercise and anabolic steroids have been shown to have potentially beneficial effects on body composition and to positively impact physical performance, but long-term data are lacking.

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KEY POINTS

- High BMI is not protective for all patients with CKD and is associated with poor physical functioning and frailty.
- Visceral adiposity is associated with adverse cardiovascular outcomes.
- Sarcopenia is common among patients with ESRD and is associated with worse physical performance and higher mortality.

FIGURE 1. Mean BMI among incident dialysis patients and the general population from 1995 to 2002. ESRD, end-stage renal disease. Reproduced with permission from [9].

FIGURE 2.

Mean BMI among incident dialysis patients and transplant recipients from 1995 to 2009. Reproduced with permission from [10].

Table 1

Summary of recent articles on the prevalence of sarcopenia

References	Population ^a	Measurement technique	Cutoff	Prevalence (%)
Foley <i>et al.</i> [39]	13 770 Adult NHANES participants from USA, 45.8% aged 20–39 years	Single frequency BIA	Skeletal mass indexed to total body mass (%) <2 SD below young adult values	4.5
	8923 Individuals with eGFR 90 ml/min/1.73 m ²			3.8
	4338 Individuals with eGFR 60–89 ml/min/1.73 m ²			5.3
	509 Individuals with eGFR <60 ml/min/1.73 m ²			9.4
Kim <i>et al.</i> [40]	95 Hemodialysis patients from Korea; age 63.9 ± 10 years, 57.2% women	Bioelectrical impedance spectroscopy	Lean tissue mass indexed to body surface area (kg/m ²) 2 SD below sex-specific means for young Persons + handgrip strength <30 kg for men or <20 kg for women	33.7
Rosenberger <i>et al.</i> [41]	748 Hemodialysis patients from the Slovak Republic; age 63 (54, 73) years, 46% women	Bioelectrical impedance spectroscopy	Lean tissue indexed to the square of height (kg/m ²) <10% of normal value	42.5
Kang <i>et al.</i> [42]	534 CAPD patients from Korea; 53.2 ± 14.1 years; 46.4% women	DXA	Appendicular skeletal muscle indexed to the square of height (kg/m ²) 2 SD below mean of young sex-specific reference groups	43 ^b
Isoyama <i>et al.</i> [43]	330 Incident dialysis patients from Sweden; age 53 ± 13 years, 38% women	DXA	Appendicular skeletal muscle indexed to the square of height (kg/m ²) 2 SD below the sex-specific mean from a young reference population + handgrip strength <30 kg for men or <20 kg for women	20
Lamarca <i>et al.</i> [44]	102 Hemodialysis patients from Brazil; 70.7 ± 7 years; 26.5% women	Single frequency BIA	LBMI to the square of height (kg/m ²) <20th percentile from NHANES + low HGS	51
	49 Hemodialysis patients	Single frequency BIA	LBMI <2 SD below means of young individuals from NHANES + low HGS	13.7
	49 Hemodialysis patients	DXA	ALMI to the square of height (kg/m ²) 20th percentile from NHANES + low HGS	73.5
	102 Hemodialysis patients	DXA	ALMI <2 SD below means of young individuals from NHANES + low HGS	32.7
	102 Hemodialysis patients	Skinfold assessment	LBMI <20th percentile of young individuals	44.1
	102 Hemodialysis patients	Skinfold assessment	LBMI <2 SD below means of young individuals	3.9
	102 Hemodialysis patients	MAMC	MAMC <90% of standard values + low HGS	34.7

ALMI, appendicular lean mass indexed; BIA, bioelectrical impedance analysis; CAPD, continuous ambulatory peritoneal dialysis; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; HGS, handgrip strength; LBMI, lean body mass indexed; MAMC, midarm muscle circumference; NHANES, National Health and Nutrition Examination Survey.

^a Age presented as mean ± standard deviation (SD) or median (25th, 75th percentile) according to the data in the original publication.

^b Estimated from information provided in the manuscript as percentage not reported.