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Novel approaches to sarcopenic obesity and weight management before and after kidney transplantation

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Purpose of review
Although a widely recognized and complex pathophysiological condition, sarcopenic obesity remains less appreciated and may elude diagnosis and workup in both kidney transplant waitlisted candidates and kidney transplant recipients. The lack of consensus definition, and practical diagnostic tools for evaluating waitlisted candidates and transplant recipients are barriers to early detect and initiate therapeutic management for sarcopenic obesity. Although sarcopenia leads to poor clinical outcomes, posttransplant obesity yields conflicting results. Exercise and nutritional managements are common therapies for sarcopenic obese patients; however, surgery weight loss or bariatric surgery in both transplant candidates and potential living kidney donors shows promising benefits for kidney transplant access in waitlist obese candidates but may require to be selected for appropriate patients.

Recent findings
Pathogenesis and management for sarcopenia and obesity are interconnected. The benefits of exercise to improve muscle mass and function is clear in waitlist kidney transplant candidates and transplant recipients. However, there are several barriers for those to increase exercise and improve physical activity including patient, provider, and healthcare or environmental factors. The advantages of fat mass reduction to lose weight can promote muscle mass and strength. However, epidemiological data regarding the obesity paradox in dialysis-dependent patients when overnutrition provides survival benefits for this population should be taken into account when performing weight loss especially bariatric surgery.

Summary
Barriers in providing optimal care to kidney transplant waitlisted candidates and transplant recipients may partly result from underdiagnosis of sarcopenic obesity; notwithstanding that this entity has increasingly been more recognized. Mechanistic studies to better understand pathogenesis of sarcopenic obesity will help determine pathogenesis and clinical tools for diagnosis of this entity, which can facilitate further studies related to the outcomes and weight management to ultimately improve kidney transplant outcomes.

Keywords
epidemiology, kidney transplantation, obesity, obesity paradox, outcome, reverse epidemiology, sarcopenia, sarcopenic obesity, waitlist candidate

INTRODUCTION

Kidney transplantation is currently the treatment of choice of suitable advanced chronic kidney disease (CKD) or end-stage kidney disease (ESKD) patients [1]. Successful kidney transplantation provides a survival benefit compared with dialysis therapy. However, mortality risk in kidney transplant recipients still remains higher than the general population particularly death from cardiovascular disease which may be resulted from metabolic disturbances occurring from pre through posttransplant periods.

Sarcopenia and obesity are common metabolic disarrangements and can occur separately or

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KEY POINTS

- Kidney transplant recipients are at risk for sarcopenic obesity starting at the advanced chronic kidney disease stage, continuing throughout end-stage kidney disease while on a transplant waiting list, and extending after successful kidney transplantation.
- Pathogenesis of sarcopenia and obesity leads to the complexity of clinical aspects of sarcopenic obesity in kidney transplant recipients involving definition, epidemiology, diagnosis, and management.
- Although sarcopenia is one of the geriatric syndromes, it can be reversed with combined management strategies of exercise and nutrition.
- Obesity defined by BMI criteria is a common barrier for kidney transplantation, but fat mass reduction by bariatric surgery both pre and posttransplantation can extend the opportunity for waitlist candidates to enhance access for transplantation sooner and to receive the greater advantage of transplantation especially survival benefits compared with staying on the waiting list.
- Although weight loss for sarcopenic obesity decreases fat mass, cumulative evidence of the obesity paradox as commonly referred to reverse epidemiology showing survival benefit of overnutrition requires further investigation concerning outcomes and weight management in waitlist kidney transplant candidate and kidney transplant recipients.

simultaneously as the so-called sarcopenic obesity. They are consequences of aging but are in the opposite direction as shown in Fig. 1.

In this article, we review the epidemiology, pathogenesis, and evidence related to outcomes of sarcopenia and obesity after kidney transplantation. We also focus on weight management as potential therapeutic approach to sarcopenic obesity during pre and postkidney transplantation.

DEFINITION, DIAGNOSIS, AND EPIDEMIOLOGY OF SARCOPENIC OBESITY IN KIDNEY TRANSPLANTATION

Sarcopenia

Sarcopenic obesity is a complex condition involving multiple potential pathogenic pathways. Sarcopenia is generally defined as progressive generalized muscle disorders involving in a state of loss in muscle masses and strength which lead to adverse clinical outcomes [2]. Primary sarcopenia happens with aging, while secondary sarcopenia is in the context of disease states such as kidney disease. Whereas cachexia refers to unintentional weight loss from a pathologic condition and is often associated with sarcopenia, sarcopenia per se can happen without weight loss. Sarcopenia is part of frailty, which is a geriatric syndrome that becomes increasingly relevant during pretransplant evaluation. Sarcopenia and its severity are diagnosed by the 2018 revised European consensus on definition and diagnosis of sarcopenia from the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) as probable (low muscle strength), confirmed diagnosis (low muscle strength and low muscle quantity or quality), or severe (low muscle strength, low muscle quantity or quality, and low physical performance) [2,3▪▪–6▪▪,7].

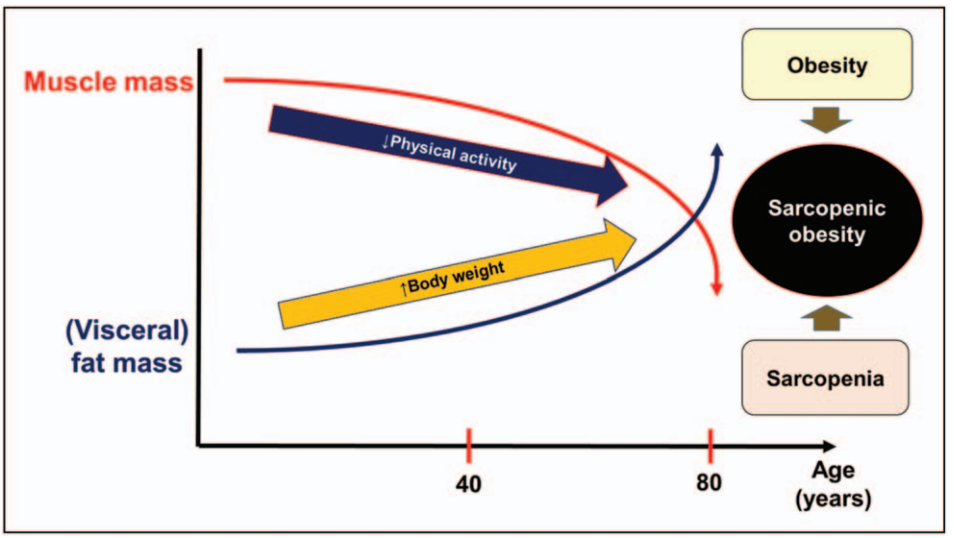

FIGURE 1. Natural course of muscle mass loss and visceral fat mass gain, which are due to aging process. Rates of muscle loss and visceral fat gain increase with the aging especially after around 40 years old, but in the opposite direction. These processes lead to sarcopenia and obesity as the so-called sarcopenic obesity.

Several investigations and tests are used to examine muscle quantity or quality, but most have limitations [8–18]. Some tests are not commonly used except for research. The results of some tests may vary by age, race, body size, and other characteristics and require validation. Therefore, identifying possible sarcopenic cases before proceeding with the further work-up is recommended [7].

The clinical symptoms or signs that suggest sarcopenia include falling, feeling weak, slow walking speed, difficulty rising from a chair, or weight loss/muscle wasting [2]. EWGSOP2 recommends SACR-F which is a 5-self-reported questionnaire as a case-finding tool and followed by further investigation to confirm the diagnosis [19,20]. Ishii's core is another tool to assist in the early detection of sarcopenic cases [21,22▪].

To determine the quantity of muscle mass, several tests and imaging modalities have been used both in clinical care and research (Table 1). Computer tomography scan is the gold standard due to its accuracy in assessing fat and muscle changes both quantitatively and qualitatively [23]. For muscle strength or quality, there is no standard measurement and future research is needed.

Overall examination of physical performance is a practical approach to be incorporated for kidney transplant evaluation and follow-up during post-transplant evaluation. Health-related quality of life should also be incorporated into the overall sarcopenic assessment. A sarcopenia and quality of life (SarQoL) questionnaire is a validated tool that can assess patients' perception of their physical and psycho-social aspects [24–27].

The prevalence of sarcopenia is uncertain because of its complex pathophysiology which partly contributes to different definitions and diagnostic criteria among different studies. Sarcopenia is commonly seen in the ESKD population with a prevalence of 20–44%; [28,29] although this is likely underestimated. The prevalence of sarcopenia in kidney transplant candidates, who are likely healthier than dialysis dependent patients, is 20% [30].

After successful kidney transplantation, sarcopenia may remain especially if allograft functions may be suboptimal and immunosuppressive medications especially glucocorticoids can perpetuate the sarcopenic process. Moreover, de-novo sarcopenia may occur in some kidney transplant recipients. The prevalence of sarcopenia in kidney transplant recipients range from 11 to 21% [31–33,34▪▪].

Obesity

Similar to sarcopenia, the pathogenesis of obesity is multifactorial. Obesity appears to be much more common in kidney transplant candidates and recipients due partly to well defined and universal BMI criteria to diagnose obesity [35].

Although BMI is not the reliable marker of obesity, it can still be utilized as a screening tool before pursuing further workup for visceral adipose tissue and muscle mass [36].

The prevalence of obesity in the ESKD population who initiated dialysis has been increased over the past 2 decades [37,38] same as those in the kidney transplant population [39]. This temporal trend of obesity in kidney transplant recipients likely reflects expanding criteria for accepting kidney transplant candidates.

Sarcopenic obesity

Sarcopenic obesity (or obese sarcopenia) is the concurrent existence of sarcopenia and obesity in the same person and is characterized by an imbalance between muscle and fat masses [40]. There are several proposed definitions of sarcopenic obesity; however, there is a lack of consensus definition and there are some limitations of certain definitions (Table 2) [41–46]. Therefore, detection and diagnosis of obese sarcopenia can be easily missed and the

Table 1. Clinical tools and investigations to screen and diagnose sarcopenia

Clinical tools/Investigations	Comments
Case finding instrument	
SARC-F	5 Self-reported questionnaires [2,19,20] Strength Walking ability Rising from a chair Stair climbing Experiences with falls
Ishii's screening tool	An equation-derived score based on three variables [21] Age Grip strength Calf circumference

Table 1 (*Continued*)

Clinical tools/Investigations	Comments
Sarcopenia parameter measurement	
Muscle strength	
Muscle grip strength	Limited in patients with hand disability e.g., stroke, arthritis
Isometric torque methods	Lower extremity strength evaluation [8]
Chair stand test	Quadriceps muscle strength evaluation
Muscle quantity	
CT scan MRI	Noninvasive gold standards
DXA	Total body lean tissue mass or ASM Correlated with body size [(ASM/height^2), weight (ASM/weight) or BMI (ASM/BMI)] [9] Interfered by hydration status
BIA	Derives an estimate of muscle mass based on whole-body electrical conductivity No direct muscle mass measurement
Anthropometry	Reflect nutritional status in older adults Not a good measure of muscle mass [10]
Physical performance	
Gait speed	Testing for muscles, central and peripheral nerve function, and balance [11] All associated with outcomes including mortality Limited in patients with dementia, gait disorder, or a balance disorder [2]
Short physical performance battery	
Timed-up and go test	
400-m walk test	
Alternative tests	
Lumbar 3rd vertebra imaging by CT scan	Correlated with whole-body muscles [12,13] Prediction equations using single abdominal CT images have poor accuracy and are not surrogates for DXA [14]
Mid-thigh muscle measurement	A good predictor of whole-body skeletal muscle [12]
Psoas muscle measurement with CT scan	The argument as nonrepresentative of sarcopenia given psoas is a minor muscle [15,16]
Muscle quality measurement	
CT scan MRI	
Muscle strength to appendicular muscle mass ratio	
Muscle volume	
BIA-derived phase angle measurement	
Creatine dilution test	Estimate whole-body muscle mass (for research)
Ultrasound assessment of muscle	Assess muscle quantity, identify muscle wasting, and muscle quality Detect a decrease in muscle thickness and cross-sectional area, fascicle length, pennation angle, and echogenicity (quality) [17] Valid to estimate muscle mass as compared with DXA, MRI, and CT
Biomarkers markers of the neuromuscular junction Muscle protein turnover Behavior-mediated pathways Inflammation mediated pathways Redox-related factors Hormones or other anabolic factors [18]	A panel rather than a single biomarker given the complex pathophysiology of sarcopenia
SarQoL questionnaire	Validated Assess patients' perception of their physical, psychological, and social aspects of health

ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; CT, computer tomography; DXA, dual-energy X-ray absorptiometry; SARC-F, strength, assistance with walking, rise from a chair, climb stairs and falls; SarQoL, Sarcopenia and Quality of Life.

Table 2. Limitation of definitions characterizing sarcopenia and sarcopenic obesity

Limitations of definitions	Characteristics	Comments
Loss of muscle mass	No threshold of muscle mass loss that correlates with clinical outcomes such as disability, morbidity, or mortality [41]	
Obesity	The lack of the most appropriate indices and the cutoff for obesity in the elderly [42]	
Muscle quality	Progressive deterioration of muscle quality Fatty infiltration in the muscles	Obese elderly Poorer muscle quality assessed by force per unit of cross-sectional muscle area ↓Functional status, aerobic capacity, strength balance, and walking speed compared frail nonobese elders [43] Sarcopenia regardless of total fat-free muscle mass quantity [42] ↑Intramuscular triglycerides with aging ↑Mid-thigh low-density lean tissue [44] ↑Age-related visceral abdominal adipose tissue and intermuscular fat [45] Muscular dystrophy and in disuse atrophy [46]

prevalence of sarcopenic obesity is likely underestimated. Generally, the prevalence of sarcopenic obesity range from 4 to 12% [47].

PATHOGENESIS OF SARCOPENIC OBESITY IN KIDNEY TRANSPLANTATION: THE INTERCONNECTION BETWEEN MUSCLE LOSS AND ENERGY IMBALANCE

Sarcopenia in kidney transplantation

Given the overlap in the pathogenesis between sarcopenia and obesity and both immunological and nonimmunological alterations after kidney transplantation, the pathogenesis of sarcopenic obesity in kidney transplant recipients is complex and not elucidated.

Sarcopenia is an aging process of loss in muscle quantity and quality. Muscle mass and strength are at a maximum level in adults around the age of 40. Thereafter leg muscle mass declines 1–2%/year [48] and muscle strength decreases 1.5–5%/year after the age of 50 [49].

The pathogenesis of sarcopenia can be divided into primary and secondary processes. The muscle mass loss as a primary aging process can be followed

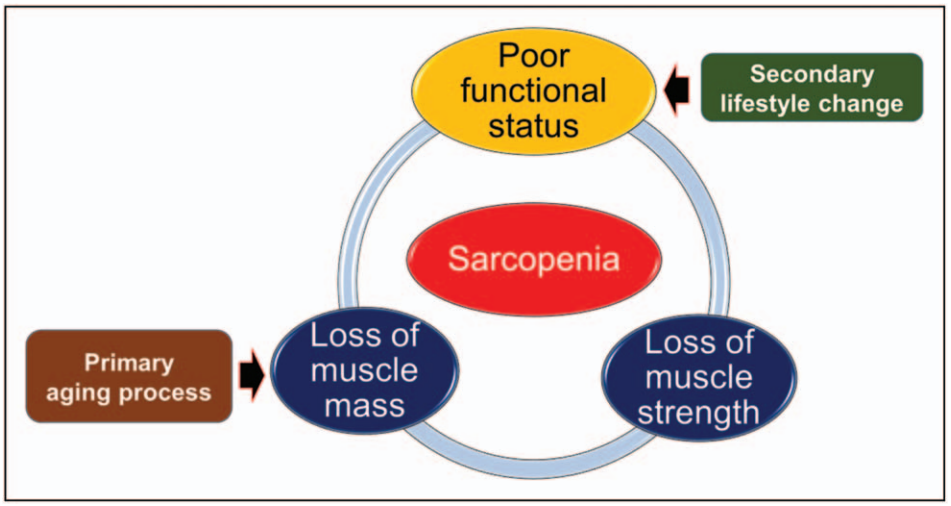

FIGURE 2. Pathogenesis of sarcopenia involving in both loss of muscle mass and strength primarily as an aging process. However, loss of muscle quantity and quality can be a barrier to physical activity, which in turn becomes a secondary cause of sarcopenia.

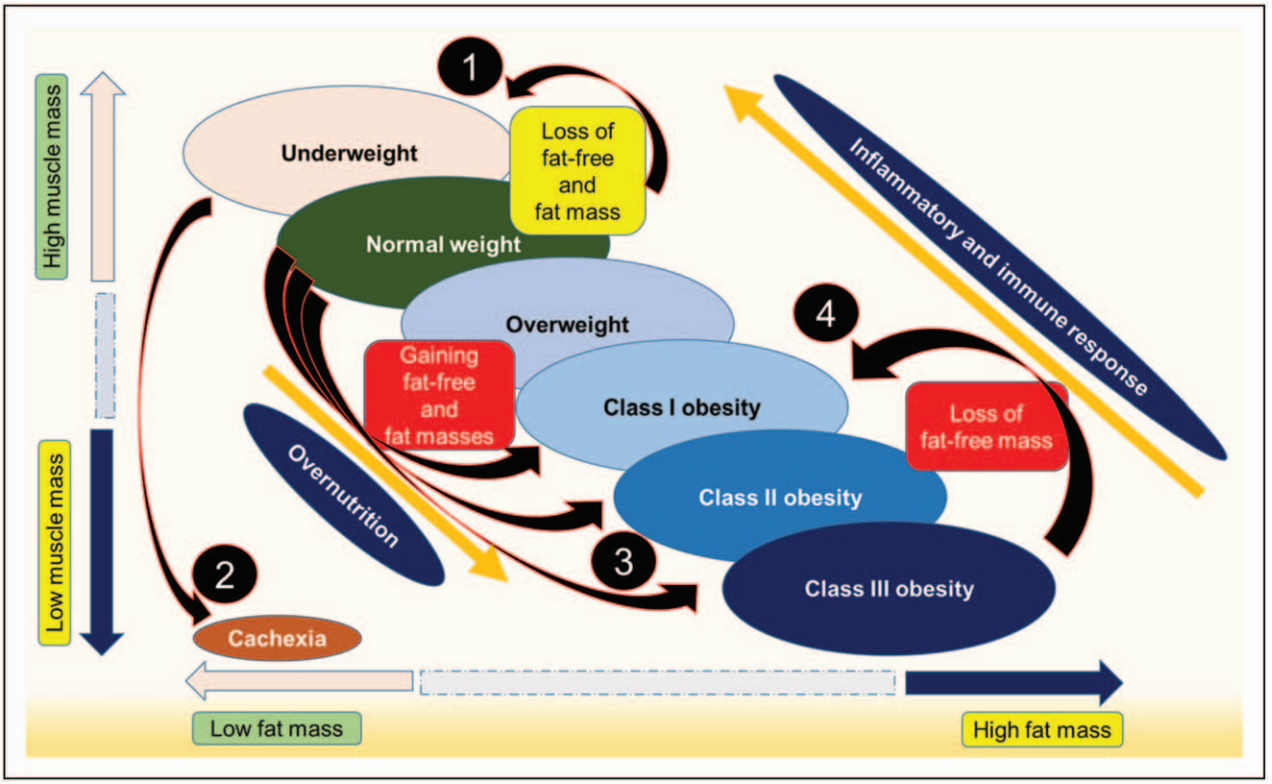

FIGURE 3. Dynamic change between losing and gaining fat-free and fat masses, respectively, during pre and posttransplant periods. Normal weight waitlist kidney transplant candidates may (1) lose their fat masses and gain muscle masses, and then develop pretransplant underweight, (2) lose their muscle masses and/or fat masses, and then develop pretransplant cachexia, or (3) lose their muscle masses and gain fat masses, and then develop pretransplant sarcopenic obesity. After successful kidney transplantation, obese kidney transplant recipients may gain their muscle masses and if they successfully lose weight, sarcopenic obesity may reverse (4).

by loss of muscle quality and strength. The lack of muscle strength subsequently leads to decreased physical activities and poor functional status, which in turn become secondarily contributing factors of loss of muscle mass and strength. These primary and secondary factors can lead to a vicious cycle (Fig. 2).

Sarcopenic obesity in kidney transplant recipients may occur as a continuing process involving factors from pre through posttransplant periods (Fig. 3 and Table 3).

During the pretransplant period, fluid-electrolyte and metabolic disturbances, and uremic milieu from advanced CKD and ESKD increase risk or worsening sarcopenic states from decreased nutritional intake, low physical activity, endocrine disorders, mitochondrial dysfunction, neurodegenerative diseases, and comorbidities [2]. Apart from age, the duration of pretransplant dialysis was associated with sarcopenia in kidney transplant recipients [32]. Moreover, underlying chronic inflammation including altered gut microbiome may perpetuate sarcopenia [50▪▪]. Physical stress and catabolic state during the peritransplant period as well as immunosuppressive medications for the treatment of underlying disease inevitably aggravate muscle loss.

For the posttransplant period, both immunological and nonimmunological factors are involved in the continuation of sarcopenia. These include suboptimal kidney allograft function, glucocorticoid administration, and physical inactivity.

Obesity in kidney transplantation

Obesity results from the overall imbalance between caloric intake and energy expenditure, which in turn leads to increased visceral fat mass [51].

During the pretransplant period, known risk factors are patient-related conditions, lifestyle, and environmental factors. A meta-analysis of genome-wide association studies of phenotypic variation demonstrated variance for BMI at the fat mass and obesity-associated (FTO) locus approximately 7% [52]. There is an association between obesity and lifestyle risk factors including an increase in carbohydrate intake, [53] sucrose (glucose and

Table 3. Common causes of sarcopenia and obesity during pretransplant, peritransplant, and posttransplant periods

Sarcopenic obesity components	Pretransplant	Peritransplant	Posttransplant
Sarcopenia (loss of muscle mass and strength)	Age Duration of dialysis Uremic milieu Leading to Decreased nutritional intake, endocrine disorders, mitochondrial dysfunction, neurodegenerative diseases Chronic inflammation including the altered gut microbiome	Physical stress and catabolic state High-dose glucocorticoids	Immunological factors Suboptimal kidney allograft function Long-term glucocorticoid use Nonimmunological factors ↓Physical inactivity
Obesity (overall imbalance between caloric intake and energy expenditure)	Patient Genetic Lifestyle ↑Carbohydrate, sucrose (glucose and fructose) intake ↑Energy-dense food with high-glycemic index and high-fructose corn syrup e.g., soft drinks ↓Physical activity Immunosuppressive therapy Environments Immunosuppressive therapy for the underlying native kidney diseases	Suboptimal kidney allograft function e.g., delayed graft function High-dose glucocorticoids Water weight gain	Positive energy balance leading to an increase in visceral fat mass from ↑Dietary intake and ↓Physical activity

fructose) intake, [54] energy-dense food with high-glycemic index and high-fructose corn syrup in soft drinks, [55] and a decrease in physical activity, [53,56] and immunosuppression [53].

During the peritransplant period, suboptimal allograft function for example delayed graft function and high-dose glucocorticoids contribute to weight gain which is from volume overload and gaining fat mass.

Throughout the posttransplant period, apart from the effects of immunosuppressive medications positive energy balance from increased dietary intake and decreased physical activity can increase visceral fat mass and obesity. Obesity during the posttransplant period can lead to decreased growth hormone, testosterone secretion, thyroid hormone responsiveness, leptin resistance, free fatty acid, insulin resistance [57].

Sarcopenic obesity in kidney transplantation

Sarcopenic obesity combines the pathogenesis and clinical features of both sarcopenia and obesity, which are causally interconnected and leads to the overall decreased physical activity and subsequently poor functional status, which we define as a state of inadequate or ineffective ambulatory performance for biological-appropriate and physical-appropriate conditions (Fig. 3).

Declined functional status is one of the common reasons that may affect transplant candidacy. It can not only lead to the vicious cycle as a secondary cause of sarcopenia but also leads to a lower energy expenditure than energy intake during pre and post-transplant periods. Moreover, decreased muscle mass and mitochondrial function lead to fat accumulation in muscles and the body as the so-called ectopic lipid deposition [58]. In addition, amelioration of anorexia after a successful kidney transplantation may lead to higher dietary energy intake.

Despite excellent graft function, many long-term kidney and liver transplant recipients exhibit a phenotype of sarcopenic obesity, which cannot be explained by overeating and hypermetabolism [59]. On the other hand, hormonal disturbances from obesity and intramuscular fat can lead to resistance to growth factors, other hormones, amino acids, and effect of physical exercise, also known as the so-called anabolic resistance, which contributes to sarcopenia. Moreover, immunosuppressive milieu and chronic inflammation can induce muscle protein catabolism [60].

OUTCOMES OF SARCOPENIA AND OBESITY IN KIDNEY TRANSPLANTATION

Sarcopenia in transplant recipients is associated with poor transplant outcomes including allograft

loss and mortality [61,62]. However, several epidemiological studies showed conflicting data regarding pretransplant obesity and mortality in kidney transplant recipients [63].

Over the past decade, there was evidence showing that even overweight with a BMI more than 28 kg/m^2 was associated with increased posttransplant mortality [64], and pretransplant BMI was associated with cardiovascular events, but not mortality [65]. Overweight and obesity were also associated with delayed graft function, graft loss, or mortality [66–69]. Among transplanted patients at least 75 years old, obesity was associated with greater mortality compared with nonobesity [69].

However, BMI is not a good marker for fat mass. The association between obesity and poor transplant outcomes were conflicted with several studies that showed no relationship between pretransplant BMI or obesity and posttransplant mortality [62,70–73].

One study showed a nonsignificant trend of higher combined graft loss and mortality among under and normal-weight groups compared with the overweight group after adjusted for the nutrition-inflammation complex. Moreover, a lower 3-month average pretransplant serum creatinine, which may be a surrogate of muscle, was associated with greater risk for the combined outcomes [62].

Weight gain after posttransplant was found to be associated with poor transplant outcomes. BMI at 1-year posttransplant and weight gain was related to mortality and death-censored graft loss [74]. Compared with nonobese patients, obesity class I, but not class II and III, was associated with lower mortality [75].

Other anthropometric parameters were found to be related to mortality in kidney transplant recipients. Kovesdy *et al.* [76] found that higher waist circumference was significantly associated with higher mortality; whereas, greater BMI was associated with lower mortality in kidney transplant recipients.

Given lack of clear consensus of definitions and diagnosis for sarcopenia notwithstanding attempts for unifying definitions and classification including by the Society of Sarcopenia and Wasting Disorders (www.society-scwd.org) [7], limitations of using BMI as a marker of fat mass, and the majority of previous outcome data resulted from of cross-sectional with some prospective longitudinal studies, temporal relationship is lacking and further clinical trials are required to test a potential causal relationship between sarcopenic obesity and transplant outcomes particularly short-term and long-term mortalities.

NOVEL THERAPEUTIC APPROACH FOR SARCOPENIC OBESITY DURING PRETKIDNEY AND POSTKIDNEY TRANSPLANT PERIODS

Given the interaction between sarcopenia and obesity, management for sarcopenic obesity needs to take factors contributing to both diseases into consideration.

The main interventions are exercise and nutrition. In the future, electronic health (eHealth) tools like mobile applications and wearables may be of added value in reducing food intake and increase exercise. Another potential approach to improve outcomes for patients with sarcopenic obesity is to develop tailored prehabilitation programs before kidney transplantation. Novel therapy in kidney transplant candidates and recipients are surgical intervention including bariatric surgery. These interventions provide advantages and disadvantages and risks of complications (Table 4).

Physical exercise

Exercise to maintain physical fitness serves as anabolic stimuli which subsequently leads to the synthesis of muscle protein [77]. It can be one of the important factors that regulate energy balance to avoid high-energy intake over energy expenditure which subsequently causes fat mass loss [78].

The goal of the exercise is to improve elasticity, strength, and muscular endurance. However, transplant-specific factors contribute to the lack of exercise in kidney transplant candidates and recipients including patients' underlying medical comorbidities and attitude, transplant providers, and the healthcare system [79]. Uremia and postdialysis syndrome as well as volume overload from suboptimal allograft function can physically limit their exercise. Exercise restriction during the early posttransplant period or immunosuppressive medications may also one of the contributing factors. Transplant providers may prioritize other transplant aspects of care and healthcare systems may not promote exercise referral. Exercise apps alone or in combination with wearables are widely used in the general population, but data on their utility for chronically ill patients are sparse. Although data from rigorous clinical trials are missing it is conceivable, that such interventions are also beneficial for patients on the waitlist or after kidney transplantation.

Types of exercise are generally categorized into resistance, eccentric, aerobic, concurrent, and electro exercise [80]. Multicomponent exercise intervention can improve muscle power, muscle strength, the total and high-density muscle cross-

Table 4. Advantages and disadvantages of different intervention for sarcopenic obesity

	Pros	Cons
Exercise	Fat mass loss Improved physical functioning parameters	Concomitant muscle mass loss
Diet		
Hypocaloric	Fat mass loss	Concomitant muscle mass loss
Protein (≥1–1.2 g/kg BW/day) Animal protein High leucine	Anabolic stimuli Avoid muscle mass loss	? Glomerular hyperfiltration
Micronutrient supplement Whey protein Vitamin D Omega-3 Spread protein intake for more meal/day (instead of pulse diet)	Prevention for sarcopenia	
Hypocaloric high-protein diet		Not for treatment for sarcopenia
Exercise and diet strategies		
Hypocaloric diet, protein intake, and exercise	Fat mass loss Improved physical functioning parameters Prevent muscle mass loss	
Surgical weight loss	Weight control	Surgical-related complications Wound infection Hospitalization
	Increase the opportunity to be active on kidney transplant waitlist and become kidney transplant candidates	Electrolyte imbalance
		Hormonal imbalance

BW, body weight.

sectional area, balance, and decrease the risk of falls [81]. Each type provides different effects on sarcopenic obesity [80] but it is beyond the scope of the review.

Nutrition and diet

Exercise alone without appropriate and adequate nutritional and dietary intakes can lead to muscle mass loss. Therefore, nutritional management is required to avoid worsening sarcopenia from exercise. Three main nutritional components to be considered are calories, protein, and micronutrient since an inadequate intake of these are associated with sarcopenia.

Hypocaloric diet

Dietary energy restriction by a hypocaloric diet can help fat mass loss; however, it can also lead to muscle mass loss. Up to 25% of weight loss from energy restriction is due to muscle weight loss [82]. Moreover, hypocaloric diets may cause inadequate micronutrient [83].

In ESKD patients who are on the kidney transplant waiting list and transplant recipients, the recommended daily calorie intake is 30–35 kcal/kg/day (adjusting for age and level of physical activity) [84–86]. Given the risk of muscle mass loss, a hypocaloric diet is not ideal for sarcopenic obese kidney transplant recipients.

Adequate dietary protein intake

Adequate protein intake is crucial to avoid loss of muscle mass in sarcopenic obese patients by providing appropriate essential amino acid. In addition to exercise, protein intake also one of the stimuli of protein muscle synthesis [87–89]. In the obese elderly population, protein intake up to 1–1.2 g/kg/day have been recommended. Recommendation for protein intake is 1–1.2 g/kg/day for ESKD both hemodialysis and peritoneal dialysis and up to 1.3–1.5 g/kg/day for kidney transplant recipients at the first-month posttransplant [84–86]. However, it is important to note that patients with stable CKD Stage 3b that is, estimated glomerular filtration rate less than 45 ml/min/1.73 m^2 or any CKD with substantial albuminuria more than 0.3 g/g including kidney transplanted patients with these specifications are recommended to target a dietary protein intake of 0.6–0.8 g/kg/day with more than 50% of it from plant-based sources [90▪▪]. This so-called Plant-Dominant (PLADO) low-protein diet has now been

widely recommended for all CKD patients, be it with native or transplanted kidneys included stable transplanted patients after the first 3 months postsurgery [91]. Dietary energy intake of 30–35 cal/kg/day and low-sodium of less than 4 g/day (or <3 g/day with those with hypertension or edema) are recommended to all PLADO taking persons. Plant sources of protein should be at least 50% or even higher, given data that animal-based proteins can deleteriously affect native and transplant kidneys [92▪▪].

It is important to note that for patients with advanced CKD and long-term kidney transplant recipients, a high-protein diet can cause physiologic glomerular hyperfiltration and hypertrophy initially [90▪▪]. Glomerular hyperfiltration can later lead to pathological glomerular hypertension, podocyte injury, and secondary focal segmental glomerulosclerosis. These can lead to progressive worsening kidney or kidney allograft function [93,94▪▪].

As stated above, not only the quantity, but the quality of protein also affects muscle protein synthesis. In elderly men, animal protein promoted postprandial muscle protein synthesis [95]. It is generally suggested that animal protein, not plant-based protein, increases protein muscle synthesis [96]. Indeed, there is a lack of evidence to suggest animal protein over plant-based protein in sarcopenic obese patients, advanced CKD, or kidney transplant recipients. Hence, a PLADO diet should be recommended for all stable transplanted patients [90▪▪], and the dietary energy intake of 30–35 cal/kg/day using ideal body weight will almost invariably lead to weight loss in obese patients.

It is important to note that in some studies, combined hypocaloric high-protein intake was associated with muscle mass preservation and enhanced fat mass loss in elderly men compared with hypocaloric and low-protein intake [97]. However, some other studies showed no benefits of a hypocaloric high-protein diet on preserving muscle mass or muscle strength [98,99]. Studies to address the appropriate amount and types of protein intake in sarcopenic obese CKD patients or kidney transplant recipients to balance between preventing sarcopenia and preserving kidney/kidney allograft function are required.

Micronutrient supplementation

In addition to the risk of inadequate protein intake, a hypocaloric diet may lead to micronutrient deficiency, which is associated with the risk of sarcopenia in older adults [100]. On the other hand, obesity is also associated with micronutrient deficiency. Vitamin D deficiency is very common in kidney transplant candidates and transplant recipients. It is associated with sarcopenia [101]. Sarcopenic parameters were found to be improved by a vitamin D supplement of 800–1200 IU/day [102]. In addition to 25-hydroxyvitamin D, other micronutrient deficiencies such as vitamin B6, vitamin C, vitamin E, selenium, magnesium, and zinc are more common in obese patients [103–105] and is associated with declined muscle mass, strength, and physical performance [106,107]. Given that inadequate nutritional intake of the three macronutrients and some micronutrients may increase the risk of sarcopenia, nutritional strategies should focus on adequate quantity and quality of calories, protein, and micronutrients.

Surgical management

Pretransplant bariatric surgery

Although there are conflicting data regarding transplant and patient outcomes of obese patients undergoing kidney transplantation, the majority of kidney transplant centers worldwide still use BMI as one of the criteria to determine the candidacy for kidney transplantation. Since there are several barriers for weight loss to meet BMI criteria for ESKD patients mainly due to their poor functional status, psychological factors, and environments, exercise and nutritional interventions may not be effective or sustainable. Pharmacological weight loss can be limited. Therefore, surgical weight loss or bariatric surgery is one option to increase access to the transplant waitlist with a caveat to those obese patients without sarcopenia who is also a candidate for bariatric surgery.

Two primary methods of surgical weight loss are Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy, which are restrictive/malabsorptive and restrictive procedures, respectively [108▪▪]. A retrospective study comparing transplant outcomes of kidney transplant recipients who underwent pre or posttransplant bariatric surgeries to those of kidney transplant recipients without bariatric surgery from Scientific Registry of Transplant Recipients by using 1 : 10 propensity score matching revealed better long-term allograft survival in the former group, but similar maintenance of weight loss [109▪]. Although bariatric surgery showed a long-term survival benefit, 30-day mortality after bariatric surgery in waitlist kidney transplant candidates or kidney transplant recipients was up to 3.5%, which was higher than nonkidney disease patients who had bariatric surgery [110].

A recent study reported prospectively long-term benefits of laparoscopic gastric sleeve (LGS) in ESKD and CKD patients. BMI was decreased to 40 kg/m^2 or less in two-third and to 35 kg/m^2 or less in half of the

study populations. Among ESKD patients whose BMI became 40 kg/m^2 or less, 63% were on the waiting list and received kidney transplantation and 14% remained on the waitlist. Moreover, patients with stage 3a or e3b CKD had significantly improved glomerular filtration rate. Hypertension and antihypertensive requirement were decreased as same as the incidence of diabetes. Mortality was lower among patients undergoing LGS compared with those who did not have LGS [111▪▪].

Indirectly, bariatric surgery in potential living kidney donors who are obese can provide survival benefits for their kidney transplant recipients from early access to kidney transplantation with a well functioning kidney allograft. In addition, it should benefit the donors themselves compared with donors without weight loss before the donation both in the short and long terms. These benefits include decreased risk for kidney function decline or developing ESKD and lowered risk of metabolic diseases such as diabetes, hypertension, and hyperlipidemia [112▪▪].

Whether pursuing bariatric surgery to lower BMI in obese, but otherwise candidates for kidney transplantation will always provide survival benefit is unclear since rebound weight gain may occur. Particularly, obese ESKD patients, who are anticipated to have a long waiting time such as those without any potential living kidney donor or residing in the areas with a long waiting time, may have better survival than their nonobese counterparts due to the protective effects of overnutrition in the former group as the so-called obesity paradox [113].

More studies about the benefits and risks of bariatric surgery in waitlist transplant candidates, kidney transplant recipients, and potential living kidney donors, particularly taking both sarcopenic and obese components into the consideration are warranted to justify bariatric surgery to become widely practiced.

CONCLUSION

Kidney transplant candidates and recipients are at risk of both muscle mass loss and fat mass gain, which is generally referred to as sarcopenic obesity. The complex and yet elucidated pathogenesis of sarcopenic obesity, which is a constellation of both sarcopenia and obesity, leads to no consensus definition and subsequently clinical tools for early case detection and diagnosis. This also causes limitations in conducting research especially those that are related to outcomes. Exercise and nutrition are generally considered as the mainstay of sarcopenic obesity management. Specific prehabilitation programs or novel eHealth applications and wearables may be helpful to reduce dietary intake and increase physical activity, but solid evidence is needed before those interventions can be recommended. Bariatric surgery can be one of the potential weight management strategies for appropriate obese kidney transplant candidates and recipients as well as potential living kidney donors. Further studies are warranted to elucidate pathogenesis and investigate outcomes related to therapeutic strategies for sarcopenic obesity to improve kidney transplant outcomes.

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Conflicts of interest

K.B. has received research funds and/or honoraria from Abbvie, Alexion, Astellas, Bristol-Myers Squibb, Chiesi, Fresenius, Genentech, Hexal, Novartis, Otsuka, Pfizer, Roche, Shire, Siemens, and Veloxis Pharma. K.K.-Z. has received honoraria and/or grants from Abbott, Abbvie, Alexion, Amgen, DaVita, Fresenius, Genzyme, Keryx, Otsuka, Shire, Rockwell, and Vifor, the manufacturers of drugs or devices and/or providers of services for CKD patients. K.K.-Z. serves as a physician in a US Department of Veterans Affairs medical centers with part-compensation and is a part-time employee of a US Department of Veterans Affairs medical centers. Opinions expressed in this article are those of the authors and do not represent the official opinion of the US Department of Veterans Affairs.

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- ▪ of special interest
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