Obesity, Chronic Kidney Disease, and Kidney Transplantation: An Evolving Relationship

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Summary: Obesity has a fundamental role in driving the global kidney disease burden. The perplexing relationship of obesity with chronic kidney disease remains debated. However, a thorough understanding of the interplay of obesity in conjunction with chronic kidney disease and appropriate management options is lacking, leading to further increases in morbidity and mortality. Moreover, underutilization of bariatric procedures and unrealistic expectations of weight reduction based on body mass index, leading to poor access to kidney transplantation, are fueling the fire. In this review, we summarize the available data related to the obesity and chronic kidney disease association and its novel management options.

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According to current estimates, 40% of the adult US population (132 million) is obese and every 1 in 10 adult Americans is severely obese.[1] The growing understanding of obesity as a systemic inflammatory disease has revealed its adverse effects on widespread organ systems in accelerating the disease process and reducing overall survival.[2] However, a large body of evidence indicates that obesity has an evolving relationship in the context of kidney disease. Obesity plays a dual role called "Obesity Paradox/Reverse Epidemiology," where on one hand it acts as a modifiable risk factor for the development of chronic kidney disease (CKD) and on the other hand it has been associated consistently with better survival outcomes in patients with end-stage renal disease (ESRD).[3-5]

Furthermore, obesity is associated with decreased access to deceased donor kidney transplantation, especially when performance metrics of transplant centers (TCs) are focused on 1-year post-transplant survival and ignore long-term survival, pretransplant outcomes, and processes of care.[6,7] Transplant recipients with obesity defined as increased body mass index (BMI) have been shown to experience more surgical complications such as surgical site infections (SSIs), lymphocele formation, delayed graft function (DGF), prolonged hospitalization, and increased health care costs when compared with transplant recipients with a normal BMI.[8-10] These complications do not adversely affect the long-term survival of transplant recipients.[11,12] In contrast, they are marked as a red flag on the performance of the TC, creating a bias against selecting obese patients for a kidney transplant (KT).

This article reviews the role of obesity in various phases of CKD, pretransplant and post-transplant, respectively, and focuses on different management options to reduce the barriers to KT access and improve the overall short-term and long-term clinical outcomes in obese patients with CKD.

DEFINITION OF OBESITY

The definition of obesity changes in the context of overall health and internal milieu for an individual. The Obesity Medicine Association defines obesity as "a chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial Health consequences."[13] Different metrics can be used to define obesity, such as the following.

BMI is used by the Centers for Disease Control and Prevention (CDC) and the World Health Organization, and is a person's weight in kilograms divided by their height squared in meters. It categorizes weight as follows: underweight, 18.5 kg/m^2 or less; normal weight, 18.5 to 24.9 kg/m^2; overweight, 25.0 to 29.9 kg/m^2; class I obesity, 30.0 to 34.9 kg/m^2; class II obesity, 35.0 to 39.9 kg/m^2; and class III obesity, 40.0 kg/m^2 or more (severe obesity).

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BMI should not be considered as the only indicator of a person's overall metabolic disease risk.[14,15] Although it is easy to calculate, low cost, and reproducible, it does not account for sex, race, the proportion of total muscle mass, and body fat. BMI often is confounded by fluid retention in CKD patients.[16,17]

Waist circumference (WC) is associated strongly with all-cause and cardiovascular (CV) mortality, with or without adjustment for BMI.[18] It is simple, easy to measure, and acts as a surrogate marker for abdominal adiposity, but must be interpreted with its limitations. In the United States and Canada, a WC of 102 cm or greater (in men) or 88 cm or greater (in women) indicates an increased risk of developing cardiometabolic comorbidities. For adults with a predominant Asian ethnicity, a lower cut-off measurement for WC (≥85 cm in men and ≥75 cm in women) is recommended.[15]

Several other methods for measurement of obesity such as bioelectrical impedance analysis and dual energy X-ray absorptiometry have been developed. However, there is a common consensus that BMI, WC, and waist-to-hip ratio are easily available, are the least expensive, and are handy methods for measurement of obesity in a clinical set-up, provided they are interpreted in view of clinical limitations and the patient's overall health status.[18]

Epidemiology of Obesity and Kidney Disease

Nearly 1 in 10 Americans is severely obese, with a BMI of 40 kg/m^2 or greater, based on recent data released by the CDC from 2017 to 2018.[1] The prevalence of obesity increased from 30.5% to 42.4% from 1999 to 2000 through 2017 to 2018, and the prevalence of severe obesity increased from 4.7% to 9.2%, which gives us an idea about the trend of increasing obesity rates across the United States.

Likewise, a CDC report from 2019 shows that 1 in 7 US adults have CKD, and 9 of 10 individuals who have CKD are not aware of it. Moreover, 20% of adult patients with ESRD are morbidly obese.[19] Together, these reports show that almost every 14 individuals in 1,000 adult Americans are severely obese with CKD. Obesity is a significant contributory factor to the development of hypertension (HTN) and diabetes mellites type 2, which are the main reported causes of ESRD in the US adult population.

Furthermore, every day more than 240 people on dialysis die in the United States without getting a KT. An open compartmental simulation model showed that trends of obesity, diabetes mellitus (DM), and lifestyle are the prime determinants of the increase in the burden of ESRD in the US population through 2030, and obesity is one of the major reasons that TCs decline these patients for KT.[6,20] Huang et al[21] has supported the fact by using Organ Procurement and Transplantation Network/United Network for Organ Sharing data from 2006 to 2012, including 1,679 adult kidney candidates with a BMI of 30 kg/m^2 or greater, of whom 49% were converted to active status, 15% died before conversion, and 21% were delisted. Higher BMI was associated strongly with a decreased chance of activation (BMI, ≥45 versus 30-35; subhazard ratio, 0.2; 95% CI, 0.16-0.3). Weight gain is a well-known phenomenon after KT predominantly in the first year[22,23]; however, there is a paucity of data on the current prevalence of post-KT obesity across the United States.[24,25] Nohre et al[26] described a 20% prevalence of obesity at 4 years after KT in a German cohort.

OBESITY PARADOX

The association between the presence of obesity and the risk of death are different in patients with CKD, ESRD, and after KT (Fig. 1). The terminology ''reverse epidemiology'' was first proposed by Kalantar-Zadeh et al[5] in 2003 as a phenomenon in which obesity and other risk factors for CV disease such as HTN, high levels of serum cholesterol, creatinine, uric acid, and homocysteine counterintuitively serve as protective factors and reduce mortality in certain population groups such as patients with CKD. The concept of the obesity paradox, although well described in other chronic conditions such as congestive heart failure, is still a topic of debate in patients with CKD.[27-29] It has been challenged in the past as a fallacy, an observational bias confounded by other factors such as terminal illness, other chronic conditions, smoking, and as a methodologic artifact[27,30] Obesity defined by BMI has been shown to reduce the all-cause mortality in predialysis and hemodialysis (HD) populations, but not in peritoneal dialysis or KT recipients.[31] This relationship, however, is unlikely to be linear, with the highest risk of death occurring in extreme

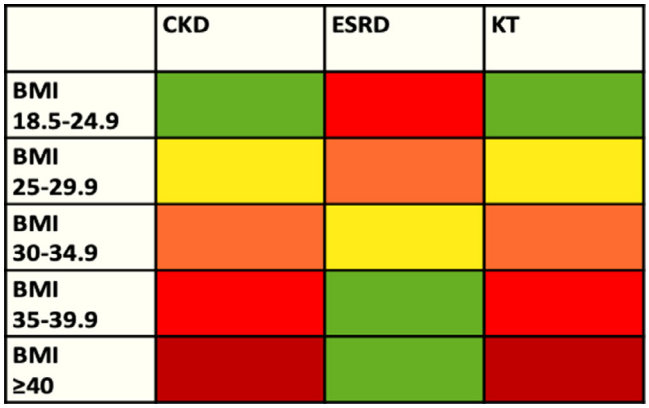

Figure 1. Reverse heat map of obesity paradox. Abbreviations: BMI, body mass index (in kg/m^2); CKD, chronic kidney disease; ESRD, end-stage renal disease; KT, kidney transplantation.

BMI categories. The nutritional and metabolic hypotheses explain the obesity paradox in patients with ESRD in many ways.[4,28,32] According to the bioimpedance theory, vasculature in fat tissue acts as an in-series circuit, thereby preventing hypotensive episodes during hemodialysis. The adiposity particularly in subcutaneous tissue serves as a subsistent energy reserve, delaying protein-energy wasting (PEW). Anti-inflammatory cytokines and a better nutritional profile all can contribute to better short-term survival. Although poorly understood, favorable alterations in the microbiome of obese patients also could be a likely contributor to better clinical outcomes in advanced kidney disease.[33,34] The practical implication of the obesity paradox has not been proven long term because of the overall shorter life span in patients on dialysis unless they receive a KT. Table 1 summarizes the explanation provided by supporters of the obesity paradox across different stages of kidney disease.

How Obesity Increases the Risk of CKD?

There is a large amount of literature available showing a common consensus on the contribution of obesity as a significant independent risk factor for the development and progression of CKD.[35] This independent effect is above and beyond the role of obesity in driving the diabetes pandemic, burden of HTN, and CV disease.[35] What remains unclear is why all obese patients do not develop CKD in their lifetime? This leads to the idea of metabolically healthy obesity, suggesting that increased weight alone is not sufficient to trigger and propagate kidney damage, and there may be other metabolically adverse factors acting as an additional hit to trigger the cycle.[37] Even though metabolically healthy obese individuals may not develop full-blown CKD, there is still evidence of a decline in renal function.[37] The visceral fat, if not burnt, accumulates and creates a fat on fire type of situation by acting as a self-generating factory of micromolecules such as leptin and resistin, leading to a state of inflammation.[35] This inflammatory state leads to oxidative stress, abnormal lipid metabolism, activation of the renin-angiotensin-aldosterone system, and insulin resistance (IR) (Table 1). Glomerular hypertension, hyperfiltration, glomerulomegaly, ectopic lipid accumulation, increased deposition of renal sinus fat, and focal or segmental glomerulosclerosis (obesity-related glomerulopathy) are lesions reported in obese patients with kidney disease. An increase in perirenal visceral fat by itself is shown to be associated with adverse cardiometabolic risk factors in CKD by increasing the physical pressure, renin-angiotensin-aldosterone system activity, endothelial damage caused by the micro-inflammatory state, IR, and sympathetic response akin to the Page kidney.[38,39]

OBESITY IN ESRD

Larger body size accounts for either a gain in solid mass (fat and muscles), fluid mass (water), or both because bones and viscera do not expand significantly in adults. It is well established that gains in fluid mass have adverse CV consequences in patients with kidney disease,

Table 1. Role of Obesity Across Different Stages of Chronic Kidney Disease

CKD	ESRD	KT	Post-KT
Obesity serves as a key factor for the development and progression of CKD Direct effects[103,104] Injury to podocytes, PTC, mesangial cells ↑Endocannabinoid tone ↓FA oxidation ↑Inflammation and fibrosis Hyperfiltration podocyte injury Indirect effects causing HTN, DM, CVD[35,103] ↑IR ↑RAAS ↑Oxidative stress ↑Adipokines (leptin, resistin) ↓Adiponectin ↑Hepatic de novo FA synthesis—metabolic syndrome Abnormal lipid metabolism	Obesity increases the survival and sustainability in patients of advanced kidney disease on dialysis by[29] Decreasing Hypotension on HD Myocardial stunning Increasing Muscle and fat reserve Nutritional reserve Infection resistance Circulating lipoproteins against endotoxins Overall fitness Longevity Subcutaneous fat Anti-inflammatory cytokines Resistance to cachexia and PEW[105]	Obesity adversely affects eligibility for KT due to the fear of[106,107] Increased SSI Hospital LOS Duration and complexity of surgery Wound dehiscence Surgical re-exploration Cost of health care DGF rates Lymphatic complications Incisional hernias Re-admissions	Untreated obesity reduces the overall patient and graft survival and is associated with poor post-KT outcomes due to[10,26,108-110] Increased risk of: IR and NODAT CV mortality Rejections Infections Fractures Post-transplant depression Noncompliance Hepatic steatosis AVN

Abbreviations: AVN, avascular necrosis; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DGF, delayed graft function; DM, diabetes mellitus; ESRD, end-stage renal disease; FA, fatty acid; HD, hemodialysis; HTN, hypertension; IR, insulin resistance; KT, kidney transplant; LOS, length of stay; NODAT, new-onset diabetes after transplantation; PEW, protein energy wasting; PTC, peritubular capillaries; RAAS, renin-angiotensin-aldosterone system; SSI, surgical site infection.

particularly in patients on dialysis, whereas gains in solid mass "muscle better, fat good" increases longevity.[29,40,41] Dialysis is a catabolic state owing to increasing amino acid loss in dialysate and reduced protein synthesis, whereas muscle and fat mass act as a protein and energy reserve.[35,42] In the landmark report by Kalantar et al,[32] they showed that both all-cause and CV mortality rates were strictly decreased in patients with advanced categories of BMI. Patients with stable weight on dialysis had better survival rates than patients gaining weight, but weight loss on dialysis was the worst for all.[32,43]

In the past 2 decades, scientists have had a hard time explaining the pathophysiology of the obesity paradox and survival benefit in ESRD because of the lack of perfect animal models and controlled large population-based studies with long-term follow-up evaluation in the setting of a unique and complex environment of uremia, dialysis, and difficult-to-measure body compartments. Nutritional theory suggests that fat and muscle mass act as a surrogate marker of the overall nutritional reserve and prevents PEW in the state of surge of inflammatory micromolecules (dialysis), in which interleukin 6 and tumor necrosis factor α suppress the appetite, promote muscle proteolysis, and cause direct endothelial damage, increasing CV mortality.[3,29,35,44] It also explains the "Paradox in Paradox," that despite a higher loss of proteins and amino acids from the peritoneal dialysate, patients on peritoneal dialysis with increased dextrose content of dialysate show attenuated benefits from their higher solid mass.[4] Sequestration of uremic toxins in muscles and fat and release of protective cytokines is another explanation for better short-term survival in obese ESRD patients.[4] In addition, it also has been proven that obesity provides a survival advantage only in patients with inflammation.[45] Obesity also imparts short-term hemodynamic stability during fluid removal on hemodialysis as a result of higher blood pressure, as explained earlier by the bioimpedance theory, and prevents transient hypotension-induced myocardial stunning in uremic patients.[46] This may be the result of a lower degree of bioimpedance-measured fluid overload of dialysis patients because every 10% increase in body fat translates to a decrease of overhydration of approximately 1.2 L ($r = -0.52$; $P < .0001$).[47]

It also is known that body composition changes longitudinally over time in advanced kidney disease by gaining fat mass and losing muscle mass.[36,44] The exact mechanism is not clear, but different plausible explanations suggest that dialysis is a state of chronic stress, and a gain in fat mass often dominates in states of allostatic stress, recovery after a hypercatabolic event, or acute illness and higher calorie intake with relatively low physical activity.[29,49,50] Hyperlipidemia particularly elevated triglyceride levels are seen in patients with ESRD owing to a reduced amount and impaired function of lipases secondary to increased levels of the hepatically derived factors called enzyme inhibitors angiopoietin-like protein 3, 4, and 8, most of which are not eliminated by dialysis. The use of heparin during HD releases lipases (lipoprotein and hepatic) from endothelial binding sites into circulation where they are rapidly degraded by the liver and never repleted as 100%, leading to less total reserve of lipases, resulting in fat deposition.[51] Uremic toxins, superimposed illnesses, resistance to anabolic hormones, oxidative stress, acidemia, loss of proteins in dialysate, and physical deconditioning are all the more reasons to explain lesser muscle mass in patients with ESRD.[51] Taken together, it is reasonable to assume all ESRD patients are sarcopenic unless proven otherwise.

Obesity reduces access to KT in ESRD patients.[6] A local study conducted in Georgia showed that of 3,532 ESRD patients with a BMI greater than 35 kg/m^2 only 959 (27%) were referred to a transplant center within 1 year after starting dialysis and only 138 (4%) were waitlisted for KT.[52] In July 2019, the US Department of Health and Human Services launched former President Donald Trump's visionary Executive Order on Advancing American Kidney Health to change the model of care in patients with kidney disease. This model will incentivize dialysis centers for early referrals of ESRD patients to transplant units and definitely will boost up the overall referral process for obese patients in the future.[53-55] Once referred to a transplant center, it is extremely challenging for an obese ESRD patient to get waitlisted.[6] They are given unrealistic high achievement goals for weight reduction to get on the waitlist (WL), which are exactly in contrast to the nutritional and metabolic hypothesis of the obesity paradox.[56] Rapid healthy weight reduction is almost impossible in ESRD patients by dietary modifications only. Most of these patients are used to sedentary lifestyles, and there are no intradialytic muscle-strengthening programs in the United States, as in other countries.[57] Eventually what happens is either loss of follow-up evaluation by the patient or achievement of Status 7 on the WL.[58] Unfortunately, all of these complexities lead to an increase in mortality of obese patients on the WL.[6] Moreover, there are a lack of data about what is happening with those patients who intentionally lost weight to be on the WL and then never received a transplant.

The main reason why transplant centers have a BMI cut-off value for candidate selection is the increased risk of surgical complications, higher re-intubation rates, prolonged hospital stays, increased medical expenditure, higher re-admission rates, DGF, and CV mortality in obese candidates.[59] Medicare, the principal insurer for KT, pays a set amount for the surgery regardless of a patient's overall health, the difficulty of the surgery, length of stay, postoperative care, and complications, all of which may increase significantly with obese patients.[60] Moreover, previous studies have shown increased death-censored graft loss in patients with a

BMI greater than 30 kg/m^2.[61] A key study by Sheetz et al[62] compared the clinical outcomes for obese ESRD patients (BMI, >30 kg/m^2) receiving bariatric surgery (BarS) with a matched cohort of nonsurgical patients receiving usual care. Bariatric surgery was associated with a lower adjusted risk of all-cause mortality (mainly driven by CV mortality) at all periods (3, 5, and 7 years) except at 1 year after BarS and an increased incidence of KT at 5 years. These data clearly suggest that patients with ESRD benefit from BarS. However, there is no detailed analysis available to show whether this survival advantage is solely owing to BarS or attributable to the increased incidence of KT. Researchers have attributed higher 1-year mortality rates to some up-front risks associated with BarS, or a potentially unreasonable selection of patients.[62]

POST-KT OBESITY

Previous studies showed that KT recipients, whether obese or nonobese, had a tendency to gain weight after transplant.[26,63] The incidence rate of post-KT obesity among pretransplant nonobese patients is higher in overweight than normal weight recipients, and higher in older age groups and female patients.[26,64] The potential factors for weight gain after KT are the end of dietary restrictions, increased caloric intake, increased appetite, lack of physical activity, antirejection medications including steroids, increased insulin requirements in diabetic patients, and IR.[24] Higher WC and BMI are associated independently with increased inflammatory markers in KT recipients.[65] Interestingly, a higher BMI and WC display opposite associations with all-cause mortality after KT. WC appears to be a better prognostic marker for obesity because of its surrogate ability to reflect visceral adiposity than BMI, which accounts for both visceral and nonvisceral adiposity and muscle mass.[25] Overall, it now has been well established that unlike the protective effect of obesity in the ESRD phase, post-KT obesity is a known factor for graft dysfunction, graft loss, and all-cause mortality.

Management of Obesity in CKD

It has been well established that the obesity pandemic and kidney disease should be dealt with a broad population-based approach. However, in this section we discuss how a nephrologist should approach an obese patient with kidney disease.[35]

A modified 5A's model for obesity management should be adapted as a structured approach to patients with kidney disease, ultimately directing toward management options, as follows[66,67]:

1. ASKING for permission to discuss obesity and explore readiness.
2. ASSESSING type of obesity (sarcopenic versus nonsarcopenic), related risk versus survival benefit (with respect to the stage of kidney disease), and root causes.
3. ADVISING on health risks and treatment options specific to the patient's status (CKD, ESRD, or post-KT).
4. AGREEING on health outcomes including candidacy for KT and behavioral goals.
5. ASSISTING in accessing appropriate resources and providers.

Lifestyle Modification

Lifestyle modifications including diet, exercise, smoking and alcohol cessation, and behavioral modification is an integral part of management of obese individuals with kidney disease. A low-protein diet of 0.6 to 0.8 g/kg per day mitigates proteinuria, likely owing to reduced intraglomerular pressure, and also helps by reducing the generation of urea, and therefore should be used in moderate-to-advanced kidney disease (estimated glomerular filtration rate [eGFR], <45 mL/min per 1.73 m^2 of body surface area) and for the management of substantial proteinuria (urinary protein excretion, >0.3 g/d).[68] Once there is progression to ESRD, when uremia is no longer a concern and can be cleared by efficient dialysis, the appearance of declining muscle mass and risk of PEW becomes a major concern in which increased protein intake (ie, 1.2 g/kg per day protein intake) is recommended.[44]

A Low Physical Activity Questionnaire can be used to assess and monitor physical activity in patients with kidney disease.[69] The Kidney Disease Improving Global Outcomes guidelines recommend a full integration of exercise (a combination of aerobic strength and flexibility exercises) in the daily life of CKD patients (at least 30 min/day, 5 times/wk), taking into consideration their cardiovascular health and level of tolerance, as increasing physical activity levels slow the rate of decline of eGFR in patients with CKD.[70-73] Unfortunately, there are no clear guidelines for intradialytic exercises in HD patients spending an average of 12 h/wk being sedentary on dialysis; thus it is a good opportunity to integrate intradialytic exercises to improve functionality, CV reserve, and muscle mass.[74]

DRUG THERAPY

Weight loss medication may be used as adjunctive therapy with diet and exercise for additional modest weight loss. Several drugs are used for the treatment of obesity, but most of them have not been tested adequately in adults with stages 3 to 5 CKD.[75] Orlistat, a reversible inhibitor of gastric and pancreatic lipases, may be safe to

Table 2. Literature Review of Recent Studies Conducted to Review the Role of Bariatric Surgery in Obese Patients With Advanced Kidney Disease

References	**Number of patients (N) with BMI (kg/m^2)**	Exposure	Primary Outcome	Other Outcomes	Conclusions
Sheetz et al[62]	Group 1=1,597 ESRD patients with BMI >35 kg/m^2 BMI = 45.6 (± 6.7) kg/m^2 Group 2 = 4,750 ESRD patients with BMI >35 kg/m^2 BMI = 44.6 (± 6.8) kg/m^2	Group 1 had BarS	BarS was associated with a lower cumulative incidence of all-cause mortality at 5 years compared with usual care Group 1 = 16% Group 2 = 40% HR, 0.7 (95% CI, 0.6-0.8)	The adjusted risk of all-cause mortality associated with BarS was higher at 1 year (aHR, 1.45; 95% CI, 1.1-1.8); however, BarS was associated with a lower adjusted risk of all-cause mortality at all other times up to 7 years Bariatric surgery also was associated with an increase in KT at 5 years compared with nonsurgical control patients (cumulative incidence, 33% versus 20%; aHR, 1.82; 95% CI, 1.6-2.1)	BarS was associated with lower all-cause mortality, CV mortality, and increased cumulative incidence of KT compared with a matched cohort of nonsurgical obese ESRD patients
Kassam et al[111]	N = 243 ESRD: 198 CKD (stages 1-4): 45 BMI = 44 ± 6 kg/m^2	SG	BMI decreased from 44 ± 6 to 37 ± 7 ($P < .01$)	SG reduced HTN (86% versus 52%), antihypertensive medication use (1.6 versus 1.0) ($P < .01$ each), incidence of DM (60% versus 32%, $P < .01$) and mortality rate of 1.8 per 100 patient−years, compared with 7.3 for non−SG Patients with stage 3a or 3b CKD showed improved eGFR (43 versus 58 mL/min; $P = .01$) 71 ESRD patients were wait−listed for KT	SG safely improves KT candidacy while providing significant sustainable effects on weight loss, reducing medical comorbidities, and possibly improving renal function in CKD stage 3 patients
Montgomery et al[92]	Group 1 = ESRD N = 1,244 BMI = 44 (41-49) kg/m^2 Group 2 = no kidney disease N = 418,647 BMI = 44 (40-49) kg/m^2	SG Group 1 = 1,049 (84%) Group 2 = 300,380 (72%) RYGB group 1 = 195 (16%) Group 2 = 117,023 (28%)	30-day surgical complications were higher in ESRD patients: Unplanned reoperation (3% versus 1%) Endoscopic intervention (2% versus 1%) Transfusion (1.5% versus 1%) Sepsis (0.4% versus 0.2%) 30-day medical complications were higher in ESRD patients: Unplanned ICU stay (1.5% versus 1%) Pneumonia (1% versus 0.2%).	Absolute rate differences did not exceed 4% for any individual or composite outcome The risk-adjusted rate of perioperative death was rare among patients with ESRD, occurring in an estimated 3.1 per 1,000 cases	ESRD was associated with increased rates of surgical and medical complications, and death after BarS when compared with patients with normal kidney function However, the absolute rate differences were 4% or less for each individual and composite outcomes
Cohen et al[91]	Group 1 = ESRD N = 43 BMI at KT =	Group 1 = BarS before KT Group 2 = BarS after KT Compared outcomes with	There was no significant difference in BMI in the 5 years after BarS among patients	Compared with matched controls, BarS before and after KT was associated with a	BarS before and after KT resulted in similar maintenance of weight loss and

(*continued on next page*)

Table 2 (*Continued*)

References	Number of patients (N) with BMI (kg/m^2)	Exposure	Primary Outcome	Other Outcomes	Conclusions
	32 (28-36) kg/m^2 Group 2 = ESRD N = 21 BMI at KT = 34 (33-37) kg/m^2	individuals (controls) from national registry data who did not undergo BarS and performed 10:1 propensity score matching	who underwent BarS before versus after KT (36 versus 32 kg/m^2; P = .814)	decreased risk of allograft failure (HR, 0.3; 95% CI, 0.29-0.33 and HR, 0.85; 95% CI, 0.85-0.86 for pre-KT and post-KT, respectively) and mortality (HR, 0.57; 95% CI, 0.53-0.61 and HR, 0.8, 95% CI, 0.79-0.82 for pre-KT and post-KT, respectively)	improved long-term allograft survival compared with matched controls BarS appears to be a safe and reasonable approach to weight loss both before and after KT

Abbreviations: aHR, adjusted hazard ratio; BarS, bariatric surgery; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellites; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; HTN, hypertension; ICU, intensive care unit; KT, kidney transplant; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

use in CKD with caution because there are reports of acute kidney injury caused by renal oxalosis.[75] Because of interference with cyclosporine absorption, it should not be prescribed to patients taking calcineurin inhibitors. Liraglutide, a glucagon-like peptide-1−receptor agonist used to treat DM, is shown to reduce modest weight in diabetic patients with ESRD after dose adjustment.[76]

BARIATRIC SURGERY

Table 2 summarizes the recent studies performed to improve the understanding of surgical management of obesity in kidney disease. Nonsurgical interventions are cost effective and may result in short-term weight reduction, but, unfortunately, the desired goal and pattern of weight reduction solely by these measures remain elusive.[77] It has been well established over the past 2 decades that nonsurgical weight loss is associated with a reduction in proteinuria, HTN, hyperlipidemia, cardiovascular (CV) mortality, and reversibility of IR in obese patients with CKD, but no clear change in GFR was documented.[78,79] Surprisingly, several recent observational studies reported improvements in eGFR, and prognostic risk reduction for CKD with BarS.[80,81] In fact, slower progression to a composite end point (ESRD, stage 5 CKD, or doubling of serum creatinine level) also has been reported in recent studies.[82,83] The benefits of BarS are more pronounced in patients with or at risk for diabetic kidney disease.[84] There are some reports that BarS improves diabetic kidney disease markers such as albuminuria independent of weight loss and glycemic control. The exact mechanism is unknown but it is postulated based on the complex interplay of mechanisms, including modified adipokine balance, signaling pathways of fat tissue and gut hormones, and systemic inflammation, and the actual degree of weight loss seems to play a lesser role than expected.[85] However, Friedman et al[86] reported no weight-independent effect of Roux-en-Y gastric bypass (RYGB) on GFR, or an association between circulating glucagon-like peptide-1 levels and GFR.

There also is evidence that markers of tubular injury such as Kidney Injury Molecule-1 (KIM-1) are reduced after BarS in patients with acute and chronic kidney disease.[87] A decision analytic Markov state transition model was created by the researchers to simulate the life of 30,000 obese patients with CKD stage 3b as they progressed to ESRD, KT, and death. It was found that patients who underwent RYGB gained 10.6 months of life and gained 8.3 months of life after sleeve gastrectomy, compared with the patients undergoing nonsurgical measures.[88] There also is evidence that BarS with adjuvant exercise therapy, particularly resistance exercises, can help to attenuate muscle mass loss in obese patients without ESRD.[89,90] These findings, if confirmed

in larger studies involving ESRD patients with sarcopenic obesity, will help steer future research in this area.

Nutritional deficiencies, bone demineralization, higher fracture risk (particularly after the duodenal switch), nephrolithiasis, dumping syndrome, weight regain, and lack of adherence to diet and exercise are some of the challenges after BarS.[15] Alterations in immunosuppressive pharmacokinetics have been observed in patients who underwent RYGB, but not with purely restrictive procedures such as sleeve gastrectomy, which can explain acute rejections in some studies.[91]

One of the key aims of BarS is to improve access to KT. However, Montgomery et al[92] showed that not every post−BarS patient was waitlisted and underwent KT. Of the 198 ESRD patients, 71 were waitlisted and only 45 of these patients received KT (15 living-donor KT).

Robotic-Assisted Kidney Transplantation

Over the past 2 decades, major advances in robotic surgery have encouraged transplant surgeons to use this approach in morbidly obese ESRD patients to reduce early postoperative complications. Tzvetanov et al[93] recently published their center's 10-year experience with a large robotic-assisted kidney transplantation (RAKT) cohort of 248 obese ESRD patients. Overall 3-year graft and patient survival were comparable with United Network for Organ Sharing patients receiving a transplant over the same time period, with minimal risk of SSIs. Warm ischemia time was increased moderately and was correlated positively with BMI and DGF (11%). Another retrospective study published by Prudhomme et al[94] involving RAKT from 8 European centers compared the surgical outcomes between obese and nonobese compared the surgical outcomes between obese and nonobese recipients with a mean follow-up period of 1.2 years. There was no significant difference in minor and major surgical complications between obese and nonobese patients. Serum creatinine values on the third postoperative day were higher in obese recipients owing to an increased DGF rate (15.4%), but eGFR was similar in both groups at the end of 6 months. Furthermore, the strengths of single-port RAKT are a smaller incision, less SSI, reduced postoperative morbidity, fewer incisional hernias, shorter length of hospital stay, faster recovery, and an earlier return to normal activities of daily living.[93,95,96] An extraperitoneal approach provides easy access for transplant biopsy and less intraperitoneal complications.[95,97] Successfully performed dual kidney transplant for marginal donors also have been reported.[95,98] Patients with type 1 DM and a higher BMI can benefit from a simultaneous robotic pancreas kidney transplant.[99,100] The main limitations of RAKT is the expensive infrastructure, requirement of specially trained personnel, and lack of widespread availability across the United States.

In summary, these studies support the notion that RAKT can increase the chances of morbidly obese patients receiving a timely transplant and can act as a savior to reduce overall WL mortality.[101,102] On the other hand, it is important to use this as a bridge and not to forget the importance of weight loss to improve long-term graft survival. Figure 2 summarizes the authors' approach and personal opinion for managing obese

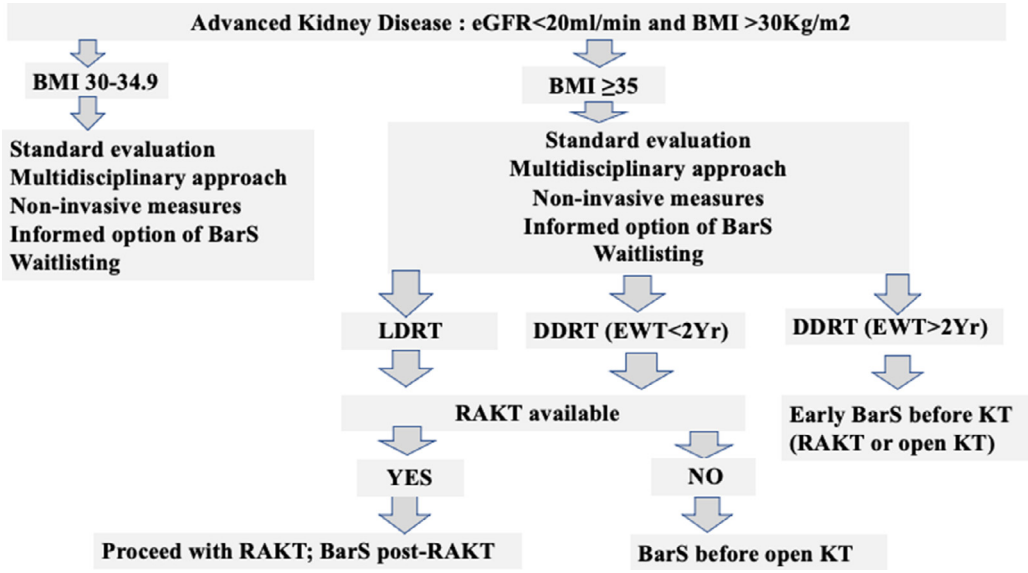

Figure 2. Modern management algorithm for obese patients with advanced kidney disease. Abbreviations: BarS, bariatric surgery; BMI, body mass index (in kg/m^2); DDRT, deceased donor renal transplantation; eGFR, estimated glomerular filtration rate; EWT, expected waiting time; KT, kidney transplant; LDRT, living donor renal transplantation; RAKT, robotic-assisted kidney transplantation.

patients with ESRD, incorporating novel therapeutic modalities including RAKT in the form of a modern management algorithm.

CONCLUSIONS

Obesity is very common in patients with kidney disease. Obesity itself plays a role in the development and progression of CKD and access to KT. The association of obesity, type of obesity, and outcomes are different in patients with CKD, ESRD, and transplant recipients. The barrier to transplantation based on obesity is highly questionable, and new therapeutic approaches can help to overcome these barriers.

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