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# Obesity and Kidney Transplantation

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## 1. Introduction

Worldwide, countries continue to face an epidemic of obesity, the number one risk factor for diabetes and hypertension. Obesity likely mediates, at least in part, the majority of kidney disease among industrialized societies. Due to the rising prevalence of obesity, the incidence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) will likely not decrease over the next several decades, but may in fact increase. The impact of obesity is especially important for kidney transplantation because many obese individuals are precluded from kidney transplantation due to concerns over the potential medical and surgical complications associated with their body habitus. Because higher BMI appears to be associated with decreased mortality among patients receiving dialysis, clinicians may be reluctant to counsel obese patients to lose weight. To understand the impact of obesity on transplantation, the discussion needs to begin with a review of how obesity impacts mortality in populations with CKD. This chapter will then discuss trends in obesity among adults receiving dialysis, controversies surrounding the preclusion of morbidly obese individuals from transplantation, and behavior modifications and surgical interventions and their respective risks and benefits for obesity management.

## 2. BMI and mortality in the general population

Body mass index (BMI) (the weight in kilograms divided by the square of the height in meters) has been widely used to estimate overweight and obesity. Weight indexed for height was first used by life insurance companies to estimate life expectancy in the early part of the twentieth century (1, 2). In 1997, the World Health Organization (WHO) created categories for underweight (BMI < 18.5 kg/m<sup>2</sup>), overweight (BMI 25.0-29.9 kg/m<sup>2</sup>), and obesity stages I (BMI 30.0-34.9 kg/m<sup>2</sup>), II (BMI 35.0-39.9 kg/m<sup>2</sup>), and III (≥ 40 kg/m<sup>2</sup>) (Table 1) (3). Controversy exists as to whether these BMI categories are applicable for assessing mortality risk in all age and racial/ethnic groups. However, in the general U.S. population, studies have consistently shown that a BMI ≥ 35 kg/m<sup>2</sup> heightens mortality risk in young and middle-aged individuals (4-6) but this risk declines with advancing age (7). A meta-analysis of studies limited to adults 65 years or older concluded that federal guidelines for ideal weight (BMI 18.7-25 kg/m<sup>2</sup>) may be too restrictive for populations over the age of 70 years due to lack of evidence that overweight in the elderly confers excess mortality risk (8).

BMI	<b>(kg/m<sup>2</sup>)</b>
Underweight	<18.5
Normal	18.5-24.9
Overweight	25.0-29.9
Class I Obesity	30.0-34.9
Class II Obesity	35.0-39.9
Class III Obesity	≥40
<b>Waist circumference</b>	<b>(cm)</b>
Increased risk	Men ≤ 102 Women ≤ 88
Decreased risk	Men >102 Women >88

\*Adapted from World Health Organization 1998 guidelines for obesity classification (3)

Table I. Classification of Underweight, Overweight, and Obesity by BMI and Waist Circumference\*

### 3. Abdominal obesity in the general population

The indexing of weight for height (BMI) includes fat mass and fat-free mass and provides no information about body composition or regional adiposity. Abdominal fat remains a strong predictor of mortality even after adjustment for sensitive measures of total body fat. In fact, the increased cardiovascular risk associated with obesity is mainly mediated by abdominal fat (9). Visceral adipose tissue produces cytokines including tumor necrosis factor alpha, which can cause insulin resistance by the suppression of adiponectin. Abdominal obesity can amplify this problem by the high influx of portal fatty acids, cytokines, and hormones into the liver from omental adipocytes, resulting in increased hepatic synthesis of apolipoprotein B and very low density lipids (10). Although abdominal fat can be measured directly by using dual-energy X-ray absorptiometry, computed tomography, or magnetic resonance imaging, waist circumference correlates highly with abdominal fat and can be measured easily and fairly reliably (11-13). The definition of abdominal adiposity (waist circumference ≥102 cm in men and ≥88 cm in women) is based on a Scottish study which found that this threshold for waist circumference effectively identified obese (BMI ≥30kg/m<sup>2</sup>) individuals in addition to adults with BMI < 30 kg/m<sup>2</sup> in the setting of a high waist/hip ratio (Table 1) (14). While waist circumference thresholds for abdominal adiposity may differ by racial/ethnic groups (i.e. > 87cm and > 83cm in Japanese men and women, respectively) (15), individuals with abdominal adiposity are more likely to have hypertension, diabetes, dyslipidemia, and the metabolic syndrome than individuals without abdominal adiposity, even after adjusting for BMI class (16, 17). Furthermore, abdominal adiposity is associated with increased mortality risk regardless of BMI or racial/ethnic group (16-18).

### 4. Obesity trends in CKD stages 1-5

Rates of obesity worldwide have increased dramatically over the past 20 years. In the U.S., prevalence of obesity has doubled from 15 to 30% while morbid obesity prevalence

increased by four-fold (19). Overall, obesity trends in adults with ESKD mirror those in the general population. Not surprisingly, during years 1995-2002, the mean BMI among patients initiating dialysis increased from 25.7 to 27.5 kg/m<sup>2</sup> (20). The percentage of incident ESKD patients who had stage II obesity (BMI>35 kg/m<sup>2</sup>) during this timeframe increased from 9.4% to 15.4%. Likewise, the percentage of patients listed for kidney transplantation who were obese (BMI≥30kg/m<sup>2</sup>) increased from 11.6% to 25.1% between the years 1987 and 2001 (21).

## 5. Adiposity measures and mortality in adults with CKD

Using BMI measures as a proxy of adiposity in CKD patients may not account for differences in body composition or muscle wasting. Indeed, studies using BMI to study adverse outcomes in the CKD population have shown conflicting results from the general population (22-24). Similarly, in studies of adults with CKD who are not receiving dialysis, BMI has not been found to be an independent predictor of cardiovascular disease or all-cause mortality (25,26). To examine associations between abdominal adiposity as measured by the waist-hip ratio (WHR) and BMI with cardiovascular events, Elsayed et al pooled data from the Atherosclerosis Risk in Communities Study and the Cardiovascular Health (ARIC) Study (27). A total of 1,669 adults with CKD were followed for a mean of 9.3 years. Mean age was 70.3 years and mean estimated glomerular filtration rate (eGFR) was 51.1 ml/min/m<sup>2</sup>. The highest WHR group had a 36% increased hazard of cardiovascular events compared to the lowest WHR group. Obesity (BMI>30 kg/m<sup>2</sup>) was not associated with cardiovascular events when compared to those with an ideal BMI (18.5-24.9 kg/m<sup>2</sup>).

Among adults receiving dialysis, numerous studies have reported a survival benefit with higher BMI compared to BMI in the ideal (18.5-24.9 kg/m<sup>2</sup>) and low (< 18.5 kg/m<sup>2</sup>) range (28-31). It has been posited that fat may play a protective role in these patients who often suffer from protein-energy malnutrition and inflammation (28). However, BMI represents both muscle mass and abdominal and peripheral fat. Higher muscle mass reflects better physical functioning, which is extremely important for predicting mortality in patients with co-morbid conditions such as ESKD. An Italian study of 537 dialysis patients examined associations of waist circumference, waist-to-hip ratio (WHR), and BMI with cardiovascular and total mortality (32). The inverse relationship between BMI and mortality was reaffirmed whereas waist circumference and WHR were directly associated with increased cardiovascular and total mortality. After adjustment for cardiovascular risk factors, every 10-cm higher waist circumference conferred an excess 26% risk for death and an excess 38% risk for cardiovascular death (32). The association between BMI and mortality in patients receiving dialysis has also been shown to be modified by muscle mass as reflected by 24-hour creatinine excretion (33).

Few studies have examined the link between adiposity measures and mortality in adult kidney transplant recipients. Kovedsky examined BMI and waist circumference in 993 kidney transplant recipients in Hungary (34). Mean age was 50.9 years, 21% were diabetic, and mean eGFR rate was 50.9 ml/min/1.73 m<sup>2</sup>. Individuals with higher BMI or waist circumference were more likely to be diabetic, less likely to smoke, and more likely to have had delayed graft function. While risk of mortality declined with higher BMI, a 15 cm higher waist circumference was associated with greater than 2-fold increase in all-cause mortality after adjustment for BMI (34).

In summary, BMI may be inadequate by itself to assess mortality risk associated with adiposity. Waist circumference reflects visceral adiposity burden and is directly associated with mortality among individuals with co-morbid conditions such as ESKD while BMI appears to be inversely related to mortality (30-32, 34). Many centers currently exclude patients with BMI >35 kg/m<sup>2</sup> from kidney transplantation until they are able to lose weight (35, 36). Use of waist circumference in the evaluation of kidney transplant candidates may provide more accurate information regarding the pre- and post-transplantation risks associated with obesity.

## **6. Access to kidney transplantation and barriers due to obesity**

Obesity is currently an important barrier keeping many individuals from being listed for kidney transplantation (37). A study of the UNOS database from 1995-2006 evaluated the association between BMI and time to transplantation (38). Individuals with severe obesity (BMI 35-40 kg/m<sup>2</sup>) and morbid obesity (BMI 40-60 kg/m<sup>2</sup>) at time of initial listing were 28% and 44% less likely, respectively, to receive a deceased-donor kidney transplant compared to individuals with an ideal BMI (18.5-24.9 kg/m<sup>2</sup>) (38). This study could not account for the number of obese individuals who were never listed at all due to their weight, and likely underestimates the impact obesity may have on access to transplantation. Indeed, 15% of transplant centers did not list a single severely obese (BMI 35-40 kg/m<sup>2</sup>) patient during the 11-year period of the study (38). While this study cannot prove causality, it seems likely that body habitus is a major deciding factor when determining whether a person may be listed for transplantation. Certainly, economic pressures favor kidney transplantation for "low-risk" non-obese patients in which complication rates and hospital stay may be lower. Moreover, obesity is considered a reversible risk factor, and losing weight prior to transplant is thought to be beneficial, especially considering how common weight gain is after kidney transplantation (37). Obese kidney transplant recipients are at increased risk for short-term complications including delayed wound healing, longer surgical times, and delayed graft function (39, 40). Data on whether obese transplant recipients are at higher risk for long-term adverse outcomes remains controversial, but the majority of larger studies suggest poorer long-term outcomes among obese individuals compared to non-obese individuals (40-42).

The decision by some transplant centers to use BMI thresholds for the exclusion of patients from kidney transplantation should consider both societal and individual level concerns. From an individual-level perspective, kidney transplantation offers a clear survival benefit over dialysis regardless of obesity status (43,44). Among obese adults receiving dialysis for ESKD during years 1995-1999, both living and deceased donor kidney transplant recipients had decreased mortality risk of 61% and 77%, respectively, compared to those remaining on the kidney transplant waiting list. Due to the excess surgical risks and graft failure among obese individuals, one option would be to limit opportunities for cadaveric kidneys. However, evidence for this is contentious. Excluding obese individuals due to increased risk ignores the fact that co-morbid conditions such as diabetes pose similar risk as obesity yet these conditions do not preclude transplantation (40). Transplantation centers should also consider the extra time an obese patient spends on dialysis while trying to lose weight in order to be listed for transplantation. Unfortunately, weight loss is usually unsuccessful for individuals with severe obesity (45).



## 7. Obese kidney transplant patients

### 7.1 Post-operative complications

For all surgical procedures, obesity can complicate the post-operative period with delayed wound healing, increased rates of ventral hernias, and longer operating times and hospitalizations. In transplant recipients, obesity is also associated with heightened risk of infections, and post-transplant diabetes (49-53). One single-center study which included 2013 adult kidney transplants performed between 1984 and 1998, superficial or deep wound infections occurred in 4.8%, whereas 3.6% developed either a fascial dehiscence or hernia of the wound (54). Those with BMI  $\geq 30$  kg/m<sup>2</sup> had a 340% increased risk for a wound infection and 182% increased risk for a fascial dehiscence or incisional hernia compared to those with BMI  $< 30$  kg/m<sup>2</sup>.

Delayed graft function (DGF), defined as the need for dialysis therapy in the first week after kidney transplantation, places a recipient at increased risk for chronic rejection and decreased graft survival. Only a minority of single-center studies have shown that obesity increases risk for decreased graft survival after kidney transplantation (46-53) but this may be due to small sample sizes in these single-center studies. In a large study which included 51,927 kidney transplant recipients, severe obesity (BMI  $> 35$  kg/m<sup>2</sup>) was associated with a 51% increased risk of DGF compared to the transplant recipients with a BMI between 22-24 kg/m<sup>2</sup> (41). These findings were supported by a study which included data from 27,377 kidney transplant recipients (40).

Overall mortality, regardless of obesity status, is substantially reduced with kidney transplantation (43,44). However, compared to non-obese kidney transplant recipients, obese transplant recipients appear to have an increased risk of graft loss although not all studies agree (39-56). Overall, BMI  $> 35$  kg/m<sup>2</sup> appears to increase graft failure risk by approximately 20-30% compared to recipients who are not obese while no excess risk is seen among transplant recipients with a BMI between 30-35 kg/m<sup>2</sup> (40,41). The magnitude of the association between morbid obesity and graft failure is similar to the increased risk of graft failure associated with diabetes (40). Overall mortality after kidney transplantation does not appear to be associated with obesity itself. However, obese patients may have co-morbid conditions which influence survival (40).

### 7.2 Weight loss interventions for obese adults with CKD

#### 7.2.1 Who should lose weight

The management of obesity requires identification of individuals who will benefit from weight loss. All obese patients (BMI  $\geq 30$  kg/m<sup>2</sup>) should be counseled to modify their lifestyles (diet and physical activity) to induce weight loss but goals must be individualized (57). In adults with CKD, abdominal obesity, measured by waist circumference should be considered an indication for weight loss considering the increased risk of cardiovascular and total mortality associated with increased waist circumference (27, 32, 34). Weight loss in patients with diabetic and non-diabetic kidney diseases has been shown to reduce proteinuria (58, 59). However, there is a paucity of data regarding the long-term outcomes of intentional weight loss in adults with CKD. Perhaps the strongest evidence supporting weight loss in this population comes from surgical intervention studies in the morbidly obese. Successful weight loss dramatically improves blood pressure, proteinuria, and in some cases, stabilizes GFR (60-63). However, surgical interventions for obesity carry significant risks as discussed later.

Regardless of the small survival benefits associated with obesity observed among patients receiving dialysis, kidney transplantation greatly improves longevity and survival is substantially higher among obese kidney transplant recipients compared to individuals remaining on the waiting list (38). In fact, obesity should be considered the most important modifiable mortality risk factor if a patient receiving dialysis is not listed for kidney transplantation solely due to obesity (45). Weight loss goals for obese patients receiving dialysis who are seeking kidney transplantation must be assessed individually and goals should account for the obesity-related co-morbid conditions and nutritional status of that individual. Moreover, interventions should also account for the patient's body composition because increasing muscle mass may improve overall fitness and survival (31, 45).

### 7.2.2 Weight gain after kidney transplantation

Weight gain after kidney transplantation is very common, with studies showing increased weight between 8-14 kg one year post-transplant (37, 39, 64). Johnson et al showed that a 10% weight gain correlated with increased serum cholesterol and triglyceride levels which may heighten cardiovascular risk (49, 65). In a study of 3,899 white Australian and New Zealand adults, weight gain of 10% to 19.9% during the first year after transplantation and stable weight (0% to 4.9% gain) during the second year after transplantation were associated with the best outcomes while weight loss over the first two years after transplantation was associated with the worst outcomes (66). A 20% weight gain above the pre-transplant weight during the first year with continued weight gain during the second year after transplantation was associated with increased graft loss and mortality compared to transplant recipients who maintained their weight after the second year.

Certain individuals may be at higher risk for excessive weight gain after kidney transplantation than others. Certainly the improved appetite and sense of well-being may lead to augmented caloric intake. A study of renal transplant recipients from a racially diverse center between 1983 and 1998 reported that African Americans were at higher risk for weight gain (67), and these results have been supported by several other studies (47, 49, 50, 64). Part of this race disparity may be due to socioeconomic status because accounting for income level attenuates the association between race and weight gain after kidney transplantation (64). Weight gain patterns after transplantation seem to mirror the general population as the majority of studies have shown that younger age, female sex and low income-status increase the probability of weight gain (47, 49, 50, 64). Patients who are obese at the time of kidney transplantation appear to have similar (67) or greater weight gain (47, 64) compared to non-obese kidney transplant recipients.

Immunosuppressant medications have varying adverse cardiovascular risk profiles. Corticosteroids can cause excessive weight gain and redistribution of fat to undesired areas (face and back) as well as worsen blood pressure, glucose and lipid metabolism (68). Overall, steroid doses used for kidney transplantation are much lower than in the past with some transplant protocols minimizing or avoiding steroid use. However, minimization or avoidance of steroid use in kidney transplantation must be counterbalanced with adequate immunosuppression, which often requires lymphocyte depleting agents or anti-IL2 strategies coupled with the use of other immunosuppressive medications (69). One study examined 95 kidney transplant recipients enrolled in National Institutes of Health clinical transplant trials (70). Regardless of therapy received, weight increased by 5 kg (not BMI) on average among all patients at one year post-transplant. Another small retrospective study

compared patterns of weight gain among 301 kidney transplant recipients receiving chronic corticosteroid therapy to patients who had early corticosteroid withdrawal (within 7 days post-transplant) (71). A 33% lower rate of weight gain among the early corticosteroid withdrawal group was observed. In contrast, a Dutch study which included 123 patients found no difference in one year post-transplant weight gain between patients who were and were not maintained on low dose steroids (72). In a study of 334 transplant patients at a single institution, average weight gain in patients treated with a steroid taper to 10 mg/day over the course of a year was 28.5% lower compared to the group in whom the steroid dose was tapered to 5mg/day at 6 months (73). The benefits of corticosteroid-sparing regimens on weight gain as well as long-term outcomes are yet uncertain and deserve further study.

### **7.3 Weight management before and after kidney transplantation**

#### **7.3.1 Lifestyle modifications**

A multidisciplinary approach to weight management is necessary to maximize weight loss. This approach should utilize all members of the kidney transplant or CKD team including dietitians, nurses, psychologists, social workers and physicians. These members should work together to identify specific needs, motivations, and barriers for each individual patient who requires weight loss. For most patients, a combined approach including diet, exercise and behavior modifications, similar to methods used in the general population, should be applied. Preclusion of kidney transplantation due to obesity generally focuses on BMI thresholds > 35 kg/m<sup>2</sup>. Patients with this level of obesity will frequently fail traditional methods for weight loss and surgical interventions should be considered after a trial of lifestyle changes. In the following paragraphs, we describe traditional dietary changes for weight loss and the benefits of exercise in patients with CKD. This is then followed by a discussion of the risks and benefits of weight loss drugs and bariatric surgery.

#### **7.3.2 Dietary interventions for patients not receiving dialysis**

Dietary modification remains the most important component of any weight loss intervention and dietary interventions have been shown to be effective in ameliorating weight gain after kidney transplantation (74-76). As weight gain is quite common after kidney transplantation, dietary counseling prior to kidney transplantation with frequent follow-up after transplantation should be done. To aid in developing a plan, a diet history should be obtained and patients can take part in this plan by keeping a food diary for several days. Review of medications that may contribute to weight gain should be completed. While numerous diets exist, none can be universally recommended for patients with CKD including the kidney transplant recipient (77). A conservative approach is to restrict caloric intake by approximately 500 kcal/day, which in the absence of physical activity changes, will lead to a weight loss of 1 pound per week (74). More restrictive diets (<1,200 kcal/day) require more intensive monitoring of the nutritional status and well-being of the patient.

With the exception of protein intake, there are no exact recommendations for specific nutrient and dietary composition for patients with CKD. The American Heart Association guidelines for a healthy lifestyle provide no specific recommendations for diet and state that the exact percentage of carbohydrates, proteins, and fat within a given meal will not in itself influence weight management (78). Addressing portion size and reducing energy intake to less than energy expenditure is the only reliable way to facilitate weight loss (78). High protein diets for weight loss are quite popular and can be successful for some individuals,



but data on long-term safety is lacking (79). High protein diets should be avoided in adults with CKD due to concerns that higher protein intake can accelerate loss of GFR (80). Accordingly, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines recommend that protein intake not exceed 0.8g/kg/day with 50 to 75% of the protein derived from lean poultry, fish, and vegetables (81). This level of protein intake is substantially lower than the average protein intake in many individuals in the U.S. and other countries where protein intake may exceed 1.2 gm/kg/day. Diets such as the Dietary Approaches to Stop Hypertension (DASH) diet emphasize the consumption of fresh fruits and vegetables, whole grains, and low dairy while minimizing red meat intake, sodium intake and processed foods. The DASH diet may provide additional benefits beyond those associated with weight loss (82). However, the DASH diet contains higher levels of protein (1.4 g/kg/d), potassium (4500mg/d), and phosphorus (1.7g/d) than recommended by the NKF-KDOQI guidelines for the CKD patient (74). Specific nutritional recommendations for CKD and kidney transplant recipients remain poorly defined, and more research needs to be done to better define an optimal diet before making specific recommendations. Thus, diet interventions for the CKD patient must be individualized and focus should be on portion size reduction. Identification of excess snacking times (e.g. night time) and intake of nutrient poor yet high calorie foods will help the individual patient reduce their caloric intake. In general, the weight loss goals should not exceed 1 pound per week.

### **7.3.3 Dietary interventions for patients receiving dialysis**

Studies to support dietary recommendations for patients receiving dialysis to promote weight loss are substantially limited. Current guidelines for patients receiving dialysis recommend protein intake of 1.2g/kg/day and 30 to 35 kcal/kg/day for stable patients (81). However, in order to lose weight, obese patients must reduce caloric consumption to less than caloric expenditure. Nutritional plans should be individualized to ensure that the unique nutritional requirements of patients receiving dialysis are met. Food diaries and dietary histories can be used to help identify sources of empty calories. There is no strong evidence to suggest any particular dietary intervention to promote weight loss in patients receiving dialysis. One conservative approach is to start with 25 kcal/kg/d based on the adjusted body weight (ideal body weight - [dry total body weight - ideal body weight]/4) and then adjustments can be made based on the patient's weight loss (45). However, this method is not as reliable as using direct measures of resting energy expenditure to determine caloric needs. Additional research is needed to determine safe and effective interventions for weight loss in this patient population.

### **7.3.4 Dietary interventions for kidney transplant recipients**

Several studies have examined dietary interventions to ameliorate weight gain after kidney transplantation. One single-center study gave 11 consecutive kidney transplant recipients individualized, intensive dietary advice for the first 4 months after transplantation (76). These individuals were then compared to 22 patients who received kidney transplants 4 years prior to the study and had not received dietary advice post-transplantation. Baseline characteristics of the two groups were similar with mean BMI of about 24 kg/m<sup>2</sup> in both groups. The group who received dietary advice showed no statistically significant change in weight four months after transplantation compared to their pre-transplant weight. In contrast, the group with no dietary intervention had a significant weight gain of 7kg four months after transplantation and

11.8 kg at one year after transplantation (76). Another study enrolled 34 overweight and obese (mean BMI 33 kg/m<sup>2</sup>) kidney transplant recipients who were highly motivated to lose weight in a weight loss program (83). During the initial visit, the negative impact of obesity after kidney transplantation was discussed and participants wrote down and reviewed a detailed 3-day history of their own dietary habits but no dietary advice was given. After six months of follow-up, only 27% of those in the weight loss program had weight gain compared to 80% of controls (83). While these two studies were not randomized controlled clinical trials, the study results support a beneficial role for dietary counseling after kidney transplantation. Transplant centers should utilize an approach whereby all potential kidney transplant recipients receive some individualized counseling on lifestyle (diet and physical activity) both before and after kidney transplantation. The use of dietary histories and food diaries are encouraged because it will enable the patient to participate in the development of plans to facilitate changing their own dietary habits.

## 8. Exercise

Increasing physical activity may promote modest weight loss and improve physical functioning. Patients with CKD are overall a sedentary population with markedly reduced peak maximal oxygen and reduced physical functioning compared to individuals with normal kidney function (84, 85). A study of ambulatory patients new to dialysis found that physical activity scores for these patients were below the 5<sup>th</sup> percentile of healthy individuals and estimated that 95% of patients initiating dialysis have very low fitness levels (84). Decreased physical activity is associated with excess mortality in adults with CKD (85, 86). Exercise in patients with CKD improves functional aerobic capacity, muscular strength, and blood pressure (87, 88). However, currently there is insufficient evidence to make specific exercise recommendations for patients with CKD. In addition, the co-existence of multiple co-morbid conditions in this patient population limits the capacity to exercise. In any case, considering the poor physical functioning demonstrated in the majority of patients receiving dialysis, exercise should be encouraged if possible (84). Low-to-moderate-intensity aerobic exercise three times per week should be recommended to all patients able to do so, just as it is recommended for the general population (89). The risk of cardiac events during exercise has not been quantified in patients with CKD, but the risks are likely no greater than those occurring during diagnostic tests for cardiovascular disease (3.6 myocardial infarctions per 10,000 tests) (90, 91).

## 9. Pharmacologic agents for weight loss

Dietary change remains difficult for the majority of individuals and some patients may request weight loss medications to augment weight loss. It should be noted that weight loss medications will only modestly improve weight loss and these drugs are frequently accompanied by substantial side effects. These possible risks and benefits must be discussed with the patient when considering the use of weight loss medications. Moreover, the safety of any weight loss drug should be strongly scrutinized given that two weight loss medications, sibutramine and rimonabant, were removed from the U.S. and European markets due to concerns about heightened risk of cardiovascular disease and suicide, respectively (92, 93). This illustrates the need for extreme caution with any weight loss medication.

In the U.S., the only medication currently approved by the FDA for long-term use is orlistat, which can promote modest weight loss but is accompanied by frequent gastrointestinal side effects. Short-term agents that are FDA-approved such as phentermine or diethylpropion should be avoided in kidney transplant recipients or individuals with CKD due to associated conditions such as hypertension, and cardiovascular disease risk. Thus, the only weight loss medication that potentially could be safe in populations with CKD is orlistat. Orlistat reversibly inhibits gastric and pancreatic lipases and blocks approximately 30% of gastrointestinal absorption of triglycerides. Only a small amount of orlistat is systemically absorbed with 800 mg of orlistat daily yielding minimal plasma concentrations of the drug (94). A small non-randomized trial of orlistat was conducted among patients with stages 3-5 CKD (95). These participants followed a low-fat renal-specific diet, and exercise was encouraged (95). Orlistat was given at the standard dose of 120 mg three times daily and patients were followed for two years. An average of 8.3 kg weight loss was noted and this loss occurred mostly during the initial six month period of the study. However, the weight loss was maintained after two years of follow-up. Gastrointestinal adverse events were common including flatulence, diarrhea, and fatty stools, with 43% reporting at least one side effect in the initial month of therapy. After six months of orlistat use, only 10% reported side effects (95). Thus, orlistat augments weight loss, but only modestly.

Among kidney transplant recipients, orlistat use may complicate the immunosuppressant regimen. Orlistat interferes with cyclosporine absorption because cyclosporine is highly lipid-soluble. To prevent this issue, orlistat should not be taken within a two-hour window of taking cyclosporine and cyclosporine levels should be closely monitored (96, 97). Another concern is the increased risk of oxalate nephropathy with this drug. Although rare, acute kidney injury due to renal oxalosis has been reported in an adult with CKD taking orlistat for weight loss (98). Patients should also be advised that fat intake must be limited to less than 30% of total calories otherwise the patient may experience fecal incontinence. Fat-soluble vitamin deficiencies can also occur with use of orlistat and it is recommended that patients be supplemented with fat-soluble vitamins when taking orlistat (99).

Other pharmacologic agents such as serotonin reuptake inhibitors and bupropion are not approved for long-term use of weight maintenance in the general population, and have not been well-studied in adults with CKD. Over-the-counter dietary supplements should also be discouraged due to a dearth of evidence regarding efficacy, safety, and possible interactions with immunosuppressive medications.

## 10. Surgical options

Surgical options for weight management should only be considered after lifestyle interventions fail to yield adequate weight loss. These surgical options include procedures that divert food from the stomach into lower parts of the gastrointestinal tract to limit food absorption and reduce the size of the stomach leading to early satiety (Roux-en-Y diversion) and gastric banding (100). An adjustable gastric band placed around the upper part of the stomach may be inflated or deflated by injecting or removing saline through a port underneath the skin (100). Given the procedure is performed by an experienced surgeon, mortality risk is < 2% with gastric banding and approximately 3% with gastric diversion procedures. However, mortality risk may be higher in patients with a BMI  $\geq$  50 kg/m<sup>2</sup> (101, 102). Regardless of the type of procedure, the majority of weight loss occurs during the first year after surgery with greater weight loss consistently occurring with gastric diversion

procedures (70.1%) vs. gastric banding (47.5%) (101, 102). Advantages of gastric banding include less hospitalization time and fewer short-term complications (see Table 2) (103). However, long-term complications of gastric banding are higher than gastric diversion procedures albeit less severe. For instance, intragastric band erosion is caused by chronic ischemia of the gastric wall due to the constrictive effects of the band. The gastric band can also migrate and lead to severe abdominal pain and vomiting. A recent report of long-term followup at a center in Belgium reported that approximately 1 out of every 3 patients who underwent gastric banding experienced gastric band erosion with almost half required band removal (104).

	Roux-en-Y Gastric Bypass	Laparoscopic Adjustable Gastric Banding
Mortality	<1%	<1%
Resolution of type 2 diabetes	++	+
Maintenance of weight loss after 2 years	+++	+
Length of hospitalization	2-8 days	1-3 days
Short-term complications	More common	Less common
Long-term complications	Less common, but more serious (i.e. bowel obstruction, marginal ulcer, incisional hernia, nutrient deficiency)	More common, but less serious (i.e. band slippage with pouch dilation, band erosion, port problems)
Reoperation rates§	10-20%	20-60%
Vitamin deficiencies (B vitamins, fat soluble vitamins)	++ (may require substantial supplementation)	+ (often corrected with multivitamin supplement)

\*Adapted from Tice et al. (102)

§Reoperation rates from studies with long-term follow-up >24 months (102, 121-123)

Table 2. Comparison of Roux-en-Y Gastric Bypass and Laparoscopic Adjustable Gastric Banding\*

Patients receiving dialysis may obtain substantial weight loss allowing for kidney transplantation (105-107), but information on risk and long-term benefits remains limited. Using Medicare claims data during years 1991-2004 linked with the United States Renal Data System, investigators evaluated post-bariatric surgery mortality risk and outcomes (108). On average, patients lost 30-60% of their total pre-surgery body weight. Overall 30-day mortality risk was similar for patients listed for a kidney transplant and for kidney transplant recipients (3.5%). Allograft failure was reported in a patient 30 days after the kidney transplant (108). The largest single-center series of kidney transplant patients reported outcomes for 10 kidney transplant recipients who underwent gastric bypass surgery for excessive weight gain leading to morbid obesity after transplantation (109).



Mean age was 44 years and the gastric bypass surgeries occurred on average 5.3 years after transplantation. In this group, there were no fatalities within the first 30 days after bariatric surgery and patients on average lost 70.5% of their excess weight above ideal weight (109). Clearly, the substantial weight loss after bariatric surgery can lead to resolution of diabetes and less need for blood pressure lowering medications in adults without CKD. In fact, 98% and 48% of adults with obesity and diabetes no longer have type 2 diabetes two years after undergoing gastric diversion and gastric banding, respectively, for obesity management (102). Other obesity related co-morbid conditions may resolve as well such as fatty liver, hypercholesterolemia and sleep apnea (101). These long-term benefits likely apply to patients with CKD, but the surgical risks may be heightened in this population. Gastric band erosion has been reported in a kidney transplant recipient treated with gastric banding for weight management (110). While these surgical complications are not unique to the transplant population, the presence of immunosuppressant agents could worsen the side effects of bariatric surgery.

Nutritional deficiencies are common after bariatric surgery for weight loss and this may be complicated by poor nutritional choices of the individual patient. Patients may become deficient in iron, calcium, B vitamins and fat soluble vitamins (101). An important complication of gastric bypass surgery includes increased oxalate absorption due to decreased intestinal absorption of fatty acids, and this could lead to kidney stones, renal oxalosis, acute kidney injury, allograft loss and even oxalate-induced anemia (111-115). The Roux-en-Y surgery results in a smaller gastric pouch which may not produce as much acid, and as a result, the higher stomach pH and the smaller surface area of both stomach and small intestine may impact the absorption of some drugs (116, 117). It should be noted that increased cyclosporine dosing may be required after gastric diversion procedures (117). The pharmacokinetics of tacrolimus, mycophenolate, and sirolimus may also change after gastric diversion, and higher doses of several immunosuppressants may be needed after gastric bypass (116). Obese patients often require lower doses of cyclosporine per body weight compared to lean recipients (118, 119) and dosing for cyclosporine based on ideal body weight is recommended (118-120). Given the excessive weight loss which occurs rapidly after bariatric surgery, levels of immunosuppressant drugs including mycophenolate mofetil, should be followed closely after gastric bypass surgery, especially during the first 18 months after bariatric surgery.

Due to the lack of information on long-term consequences of bariatric surgery, no specific recommendations can be made for patients with CKD or kidney transplant recipients. Thus, the decision to utilize bariatric surgery for weight management needs to be individualized. Most importantly, clinicians must ensure that these patients are informed of the associated risks before they proceed with surgical interventions for obesity management.

Regardless of obesity status, kidney transplantation is associated with improved survival and decreased morbidity compared to dialysis. Thus, obesity may be viewed as the most important modifiable mortality risk factor for patients precluded from kidney transplantation due to obesity status. Weight management should include a multi-disciplinary approach with dietary advice on caloric restriction and encouragement to increase physical activity. Patients should actively take part in the development of the obesity management plan (e.g. keep food diary). If lifestyle interventions fail to yield adequate weight loss, then surgical options should be considered. Clinicians should discuss frankly the potential risk of bariatric surgery for weight management. Transplant centers should also incorporate dietary counseling both before and after kidney transplantation to



ameliorate weight gain after transplantation which may heighten cardiovascular risk. Future research should address the use of both BMI and waist circumference to improve risk stratification and obesity interventions for patients before and after kidney transplantation.

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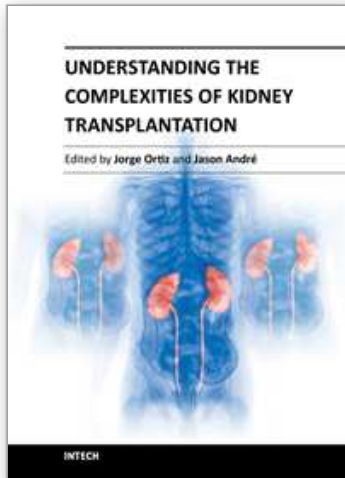
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## **Understanding the Complexities of Kidney Transplantation**

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Kidney transplantation is a complex field that incorporates several different specialties to manage the transplant patient. This book was created because of the importance of kidney transplantation. This volume focuses on the complexities of the transplant patient. In particular, there is a focus on the comorbidities and special considerations for a transplant patient and how they affect kidney transplant outcomes. Contributors to this book are from all over the world and are experts in their individual fields. They were all individually approached to add a chapter to this book and with their efforts this book was formed. Understanding the Complexities of Kidney Transplantation gives the reader an excellent foundation to build upon to truly understand kidney transplantation.

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