

## Glucometabolic disease in the kidney transplant patient

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### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Diabetes in the kidney transplant patient
  - 3.1. Pre-transplant Diabetes
  - 3.2. New onset diabetes after organ transplantation (NODAT)
    - 3.2.1. Risk factors for NODAT
    - 3.2.2. Associated morbidity and mortality of NODAT
  - 3.3. Management of diabetes after KT
4. Other related conditions
  - 4.1. Obesity
  - 4.2. Metabolic syndrome
5. Summary
6. References

### 1. ABSTRACT

The comprehensive care of the kidney transplant (KT) patient includes a broad clinical assessment to detect and stage metabolic disease both before and after transplantation. In this review, the metabolic consequences of KT in both the short and long term will be explored in the context of new data and a synthesis proposed based upon what has been studied for over two decades. A review of the changes in epidemiology introduces a discussion of the current state of the literature for the diagnosis and management of diabetes after KT, obesity and the metabolic syndrome.

### 2. INTRODUCTION

Solid organ transplantation has grown precipitously in the last few decades. Based on the Organ Procurement and Transplantation Network (OPTN), a total of 371,129 kidney transplants have been performed in the US alone from 1988 until May 1, 2015 (1). During this time, advances in immunosuppressive regimens have improved the success of transplantation significantly. However, in recent years the metabolic complications post-transplant are receiving increased attention. Prominent among these is New Onset Diabetes After Organ Transplantation (NODAT), which affects 20-50% of patients and appears to be an independent factor in both graft and patient survival. Given the high but variably reported incidence of NODAT, standardized screening and risk assessment for diabetes prior to kidney transplant

(KT) is increasingly important. Several organizations have published guidelines for standardizing screening and diagnosis of NODAT, with varying approaches (2, 3). For the patient with diabetes prior to KT, an increased risk of graft failure and death is compounded by management complexity with fluctuating insulin requirements. This is the result of concurrent events including post-transplant return of metabolic kidney function (i.e. insulin metabolism and renal gluconeogenesis), in addition to the diabetogenic effects of immunosuppressive agents and finally a liberalization of diet, increased appetite from corticosteroids and general improvement in health. The first section will discuss the expectations and management implications for KT patients with pre-transplant diabetes and the diagnosis and management of NODAT. The following section addresses the impact of obesity on organ transplantation outcomes, which is discussed in the contexts of both metabolic risk factors and potential immunologic disadvantages. The final section discusses cardiovascular risk modification in the context of a high prevalence of the metabolic syndrome. Recommendations for comprehensive pre-transplant metabolic assessment are then summarized in Table 1.

### 3. DIABETES IN THE KIDNEY TRANSPLANT PATIENT

The kidney plays a large role in metabolic stability, especially in the patient with diabetes, and this

**Table 1.** Comprehensive glucometabolic pre-transplantation assessment

Glucose tolerance (non-diabetes)	Fasting plasma glucose, 2 hour OGTT, A1c
Glycemic control (diabetes)	A1c, Fructosamine (if anemia is present)
BMI	Waist to hip ratio, waist to height ratio
Lipids	Total cholesterol, triglycerides, HDL, LDL

understanding ultimately guides the assessment of the patient with pre-transplant diabetes, and management of diabetes post-transplantation. It can be said that kidney function is second to the pancreatic beta cell in determining the overall state of glucometabolism, and it follows that kidney failure represents a complex interplay of defective glucometabolism (Figure 1). Not only is the kidney responsible for proteolyzing excess insulin to prevent hypoglycemia (about one-third of the total insulin produced), the kidney also contributes up to 25% of the fasting serum glucose via gluconeogenesis. This represents nearly half of all gluconeogenesis occurring in the human body (4). Conversely, uremia itself leads to peripheral insulin resistance, which may not be relieved post-KT due to other factors that create a diabetogenic environment as discussed below (5). Uremic insulin resistance has been established for over 20 years, and is likely due to a complex interplay of factors. Recently, several investigators have reported evidence to implicate specific protein bound uremic toxins (PBUTs). in the direct link between the uremic state and insulin resistance (6). PBUTs are produced by gut microbiota, are normally cleared by the kidney, and are elevated in the bloodstream in chronic kidney failure (7,8). They are poorly eliminated by hemodialysis, but have not been evaluated in the post-KT population. Finally, the recent development of a new class of anti-diabetes medication, the sodium-glucose cotransporter 2 (SGLT2). inhibitors has highlighted the renal modulation of glycemic control through glycosuria. This physiologic event is probably most important in the post-prandial state whenever glucose rises above the glycosuric threshold, between 180-220mg/dl in a patient with diabetes. Successful renal transplantation would restore this component of glucometabolism. However, compared with enhanced insulin clearance and restored gluconeogenesis, restoration of glycosuria has only a modest impact on overall insulin requirement and glycemic control (9,10). As a consequence, this complex set of renal metabolic defects generally manifests as an increased insulin requirement.

### 3.1. Pre-transplant diabetes

Diabetes is the primary cause of end stage renal disease (ESRD). in 45% of patients who receive dialysis therapy and is known to be present in approximately 25% of KT recipients (11). Among those

without known diabetes pre-transplant, up to 50% develop some degree of significant glucose intolerance following transplant. Given the high, yet variably, reported prevalence of NODAT, it is likely that many patients have undetected pre-transplant diabetes for various reasons to be discussed. Nevertheless, the overall prevalence of diabetes-related ESRD is expected to rise with the obesity crisis, which will likely yield an increase in youth-onset type 2 diabetes (T2D). Recent studies confirm that the natural history of youth onset T2D is similar to adult onset T2D, so that affected children will develop ESRD and become KT candidates at an earlier age (12,13). Patients with preexisting type 1 diabetes (T1D). and T2D undergoing KT have significantly higher rates of mortality and graft loss. Studies have demonstrated a 1.3. to 3 fold increased risk of death and graft loss, respectively, (14-16). with most mortality (61%). attributed to cardiovascular events (15, 16). This risk appears to be highly modifiable by the use of standard multi-target treatment strategies (16), but it remains unclear how glycemic control impacts this risk. There are, for example, no clear data to show a unique pathophysiology of early graft loss in patients with diabetes, given the multitude of known risk factors for early graft loss that often overlap with diabetes. Classical diabetic nephropathy may be accelerated in transplant grafts, occurring within the first 6 years (17). However, in one retrospective study, classical diabetic nephropathy was an unusual cause of graft loss within the first 10 years post KT among patients with diabetes (18). Most studies aimed at identifying the role of glycemic control on graft function and death are of short duration and retrospective. Given this, the classic studies of glycemic control in prevention of microvascular disease, including diabetic nephropathy, may still be the most relevant in the long term protection of the transplanted kidney and KT patient. The DCCT (1993). (19,20). in T1D and the UKPDS (1999). (21). in T2D provided definitive evidence that good glycemic control, compared with less-well controlled glycemia, prevented diabetic nephropathy and death. When viewed as a complex condition with altered glucometabolism as just one of many defects, post-KT metabolic management requires a comprehensive approach to both glycemic control and cardiovascular risk factor modification.

### 3.2. NODAT

Historically, the reported incidence of NODAT was highly variable and underestimated, largely due to the lack of a standard definition. Other challenges included accurately identifying patients who had preexisting diabetes before transplantation, appropriate monitoring post-transplant, and particularly, the immunosuppressive regimens used post-transplant. In 2003, the International Consensus Guidelines for NODAT were published and recommended the standardization of diagnosis using the World Health Organization (WHO). and the American Diabetes Association (ADA). criteria. These guidelines established the use of fasting glucose  $\geq 126$  mg/dl,

random glucose  $\geq 200\text{mg/dl}$  with symptoms of diabetes, or oral glucose tolerance test (OGTT), with 2 hour glucose  $\geq 200\text{mg/dl}$  2 and were updated in 2005 (3). Current estimates of the incidence of NODAT at  $\geq 12$  months post-transplant are approximately 20-50% in kidney transplants, 9-30% in liver transplants (40-60% if Hepatitis C infection is present), 28-30% in heart transplants and 6-45% in lung transplants (22). As a group, 2-53% of all solid organ transplant patients develop NODAT (23). Therefore, NODAT is gaining increased focus in the management of all post-transplant patients.

### 3.2.1. Risk factors for NODAT

The risk factors for NODAT are a combination of those traditionally identified for T2D in the general population as well as additional risk factors attributed to transplant medications and transplant-related infections. Traditional risk factors include: non-Caucasian ethnicity, age  $> 45$  years, family history of diabetes, obesity, dyslipidemia, hypertension, preexisting impaired fasting glucose or impaired glucose tolerance, hepatitis C infection, and male gender. Similar to its associated risk for the general population, an elevated hemoglobin A1c level also predicts NODAT, although it is unclear if a lower threshold should be used to identify pre-KT patients at higher risk for NODAT (24). Risk factors unique to a transplant setting include HLA subtypes A30, B27, B42, HLA DR mismatches, deceased donors, acute rejection, CMV infection and male donors (25). Immunosuppressive therapy has a significant impact on development of NODAT with a wealth of literature demonstrating the role of corticosteroids, calcineurin inhibitors (tacrolimus, cyclosporine), and, more recently, mammalian target of rapamycin (mTOR), inhibitors (sirolimus, everolimus), as well (26-30). These risk factors have been previously categorized as “non-modifiable,” “potentially modifiable” and “modifiable” by Pham and coauthors (31).

### 3.2.2. Associated morbidity and mortality of NODAT

NODAT has been demonstrated to negatively impact both graft and patient survival negating the significant advances made in transplant medicine. Complications related to infections, and particularly, adverse cardiovascular events are of major concern. Several studies have investigated the associated risk of NODAT on graft survival and patient survival in kidney transplantation with varying outcomes. However, it should be noted that the definitions of NODAT as well as the study designs vary among each of these studies. The largest published cohort is the U.S. Renal Data System (USRDS), study of 11,659 patients who underwent kidney transplantation between 1996-2000. In this population, NODAT was associated with a more than 60% increased incidence of graft failure and almost 90% increase in mortality rate (32). Prior to this study, Miles and coauthors performed a case-controlled study with 78 patients and found an adjusted relative risk of

graft failure of 3.72 ( $p=0.0.4$ ), but no significant difference in patient survival (33), while Cosio, *et al.* showed a relative risk of death of 1.88 (95% CI 1.0.7-3.3.0), in a retrospective review of 1811 patients (34). Other studies have similarly shown varying effects on graft and patient survival with one Canadian study reporting no difference in either outcome (35). The variation in mortality outcomes is likely due to several factors, including improved surgical and postoperative technique in the past decades, heterogeneous experience among centers referring large cohorts, variable sample size, and duration of the study period. Some groups have looked at specific glucose parameters and risk of mortality, for example, identifying the glucose level 2 hours after a glucose challenge to be the best predictor of mortality as compared with fasting glucose (36). Given these data, and similar data from prior studies in T2D (37, 38), it may be that post-meal glucose and/or glucose variability after KT may be independent predictors of poor outcomes, which could also explain heterogeneity in the literature on the relationship between NODAT, graft survival and mortality.

### 3.3. Management of diabetes after KT

The natural history of T2D involves both diminished insulin production (39), and excess gluconeogenesis, both of which are partially attenuated in the ESRD patient only to re-emerge after successful kidney transplantation. Clinically this is manifest as dramatic hyperglycemia occurring immediately after the onset of graft function despite very low insulin needs and good glycemic control preoperatively. Steroid therapy in the immediate postoperative period universally exacerbates this condition due to the action of corticosteroids impairing glucose disposal in the liver, muscle and fat (40). Given the potent glucometabolic effects of both a functioning graft and the corticosteroids, and the unpredictability of onset of graft function, subcutaneous insulin therapy can be less flexible compared with intravenous insulin and is generally unable to address the rapid increase in plasma glucose resulting from a functioning graft and anti-rejection therapies. When possible, patients should ideally be managed in a setting that allows for continuous, variable-rate insulin infusion therapy for the first 48-72 hours post-KT. While the optimal glucose range in the perioperative period has not been definitively established, it is recommended, based on several trials, that moderate glycemic targets (e.g. 140-180mg/dl), are superior to those that include normoglycemia as part of the range (e.g.  $<100\text{mg/dl}$ ). (41,42). In one randomized trial of 93 KT patients, tight control using intravenous insulin to achieve a target glucose of 70-110mg/dl was compared with subcutaneous insulin designed to achieve a target of 70-180mg/dl over three days post-KT (43). While there were no differences in delayed graft function, patients in the tight control IV insulin group had an increased rate of a rejection episode within the follow-up period of 1.5 years. This difference did not appear to be related to

**Table 2.** Effects of common immunosuppressants on glucose metabolism, lipid derangements, blood pressure

Immunosuppressant	Diabetes	Dyslipidemia	Hypertension	Dose dependence
Corticosteroids	++++	+++	+++	Yes
Tacrolimus	+++	+	+	Yes
Cyclosporin A	++	+++	+++	Yes
Sirolimus/Everolimus	+/-	++++	-	Yes
Mycophenolate mofetil	-	-	-	No
Azathioprine	-	-	-	No
Polyclonal Antibodies: Antithymocyte globulin (ATG)	*	*	*	No
Monoclonal Antibodies: basiliximab	*	*	*	No
+ Known to be associated, - Not known to be Associated, *May have an indirect beneficial effect by reduction in the intensity of other immunosuppressive agents such as corticosteroids, calcineurin inhibitors. However a direct effect is not described. (Adapted from references 26-28)				

hypoglycemia. Based on these other data in the medical and surgical ICU populations, perioperative glucose management of the KT patient should follow best practice for the surgical ICU population, which supports IV insulin therapy to maintain a glucose goal that is higher than the normal range but lower than 180mg/dl. The guiding principles for glucometabolic control immediately following KT therefore include the following: 1). monitor glucose every 2-4 hours, 2). any glucose  $\geq$  180mg/dl, initiate insulin therapy within a validated variable-rate intravenous protocol or scheduled subcutaneous insulin to achieve a target glucose between 120-180mg/dl (or a different target within this range). 3). patients receiving intravenous insulin, once food intake is established, should be transitioned to a combination of long-acting basal insulin and rapid acting bolus subcutaneous insulin regimen using a planned 2-hour overlap of the subcutaneous dose prior to discontinuation of the IV infusion.

Transition from IV to subcutaneous insulin has not been specifically studied after KT, but several analogous studies can provide guidance in this scenario. The overnight fasting insulin requirement during insulin infusion is used to extrapolate a total daily insulin dose (TDD). (44, 45). This dose can also be used to determine the other components of a standard hospital insulin program, namely the nutritional and correction scale. Half or two-third of the TDD may ideally be given as two doses of Neutral Protamine Hagedorn (NPH). insulin separated by twelve hours to accommodate the glucocorticoid effect (40). Depending upon the patient's expected food intake, the other half of the TDD can be used to guide nutritional insulin therapy, given as three divided doses of rapid-acting insulin (e.g. lispro, aspart or glulisine). prior to breakfast, lunch and dinner. Generally, patients will have higher prandial than fasting insulin needs due to the predominant postprandial hyperglycemia caused by glucocorticoids.

Monitoring long term glycemia in the KT patient is best done by measuring the percent hemoglobin A1c (A1c). every 3 months per international guidelines, with a particular emphasis on achieving and maintaining recommended goals to prevent recurrent nephropathy in the graft (46). In many patients, the pre-KT A1c may be inaccurate due to various concurrent factors that are resolved by a functioning kidney graft. These include increased carbamylated hemoglobin, reduced red blood cell life span, blood transfusion, iron deficiency and metabolic acidosis (47). For this reason, pre-KT A1c may be unhelpful in predicting post-KT glycemic control.

One of the greatest challenges following hospital insulin management post-KT is to select an appropriate treatment regimen for discharge. The safety of most anti-diabetes agents in the setting of immunosuppressive therapy and fluctuating GFR are unknown (Table 2). Insulin and meglitinide secretagogues (short-acting sulfonylurea-type agents). have the lowest post-transplant risk as they have robust clinical experience and pose no known risks to the kidney itself. However, these agents are associated with some of the highest rates of hypoglycemia. This risk is mitigated by patient education and thoughtful dosing, and is generally acceptable given the unknown potential risks of many other agents. The biguanide metformin is solely eliminated by the kidney, and in the setting of acute kidney injury, can accumulate and potentially cause clinically significant lactic acidosis. This is more likely to occur in patients also taking ACE-inhibitors and/or patients with other causes of acidosis (e.g. diarrhea); hence it is best avoided in the early months after kidney transplantation. Sulfonylurea agents can be problematic in renal insufficiency as they cause glucose-independent insulin secretion and require adequate renal metabolic function for normal clearance and avoidance of hypoglycemia. However, shorter acting sulfonylureas known to be cleared mostly by the liver,



e.g. glipizide, can be safe in small doses administered prior to meals. Glitazones (e.g. pioglitazone), have been studied in kidney transplant patients and shown to be effective (48,49), but their potential for volume expansion, heart failure, and reports of post-exposure bladder cancer should be considered. The alpha glucosidase inhibitors are generally avoided postoperatively due to predictable gastrointestinal (GI) side effects and have not been studied in the transplant setting. Inhibitors of the renal tubule transporter SGLT2 belong to the newest class of oral hypoglycemia agents, but due to both the potential for genitourinary infection and lack of data these agents are not preferred after transplant. Agents that modulate incretin physiology for glycemic control have potential for use in the post-KT setting. Short term studies of dipeptidyl peptidase-4 (DPP-4) inhibitors suggest vildagliptin (48) and sitagliptin (50) are safe post-transplant, and linagliptin is reassuring as it is metabolized by the liver and is safe in ESRD (51). Glucagon-like peptide-1 (GLP-1) receptor agonists have not yet been as well described in KT patients. Their effects include increased glucose dependent insulin secretion, decreased glucagon production, and central appetite suppression. This makes them a potentially ideal class to directly counteract the decreased insulin production, beta cell apoptosis, peripheral insulin resistance and weight gain caused by the immunosuppressive drugs (52). Some concerns include altered absorption of immunosuppressive medications due to the known delayed gastric emptying effect of this class, though two small studies have demonstrated that there was no change in serum immunosuppressive drug levels (53,54). Additionally, these drugs have GI side effects that are similar to other immunosuppressive agents such as diarrhea, nausea and vomiting. Nevertheless, the GLP-1 receptor agonists are effective glucose lowering agents with the added benefit of appetite suppression and weight loss and may be good choices when considered weeks to months following transplantation.

For the above reasons, most often, insulin is the mainstay of therapy post-KT. In general, the patient who was receiving insulin prior to transplantation will need 30-50% more insulin than their pre-transplantation doses. This dose adjustment varies depending upon the degree of glucocorticoid use in the immunosuppression regimen, which ideally is limited to the greatest extent possible in patients with pre- or immediate post-operative hyperglycemia. Although insulin requirements decrease as glucocorticoid doses are tapered, total daily insulin requirement typically remains higher than pre-transplantation doses. Given the potentially rapid changes in insulin requirement in the weeks post-discharge, early follow up, ideally within 1-2 weeks, with a provider experienced in the diabetes regimen is imperative. Patients also need to leave the hospital with contact information of this provider as some patients may be discharged on more complex insulin regimens with more involved guidelines for use and titration.

## **4. OTHER RELATED CONDITIONS**

### **4.1. Obesity**

The obesity epidemic pervades every medical specialty so it should not be surprising to find that obese (defined as body mass index (BMI) in  $\text{kg/m}^2$   $>30$ ), or overweight (BMI  $>25$ ), individuals in the US already constitute over 60% of transplant recipients with ESRD (55). Cardiovascular disease (CVD), remains the leading cause of death in individuals with KT and much of the clinical relevance of obesity, as it relates to KT, lies in the link between obesity and CVD (56). Obesity is no longer regarded as a benign adaptation to caloric energy excess. Adipose tissue is an active endocrine organ mediating various pro-inflammatory cytokine pathways involved in complex immune modulation, resulting in a chronic metabolic inflammatory state (57). Mortality rates in obese KT patients are increased in comparison to their lean comparators. This increase correlates with markedly increased rates of cardiovascular atherosclerotic disease (58,59). However, it is difficult to separate the direct effect of the obesity *per se*, from the associated co-morbid conditions like type 2 diabetes, hypertension and dyslipidemia, which are well known risk factors for CVD. Further research efforts are required to investigate the specific impact obesity holds as an independent factor in CVD outcomes in KT.

Obesity has been associated with an increased risk of acute graft rejection in a large database registry, (60), but not all studies are supportive of the association (61). USRDS data, however, do support an association between long term graft survival and BMI with both the highest (BMI  $>28$ ), and lowest (BMI  $<18$ ). BMI thresholds associated with poorer graft survival outcome (58). More recent smaller studies support this relationship for those with a BMI  $>35$  (62-64). Mechanistically, there is some evidence that dysfunctional vascular endothelium may play an important role in both the pathogenesis of graft rejection and CVD, through various adipocytokine signaling pathways. 64 More recently, *ex vivo* studies of lymphocyte function in obese patients suggest that there may be defects in B lymphocyte immune function, which could provide a direct link to graft survival (65, 66).

Wound infections in KT patients are strongly correlated with obesity and a BMI  $>30$  has been reported as the most significant risk factor for superficial or deep wound infection (67). Longer operating room times and longer length of stay (68), among other significant adverse outcomes have been reported in obese individuals undergoing KT.

Despite the aforementioned concerns, USRDS data suggest that KT may hold a survival benefit for most obese individuals. However, similar benefit for morbidly obese individuals (BMI  $>40$ ), is less clear (69). Obese individuals may wait longer for KT and certain KT

**Table 3.** Joint ATP III-IDF criteria for the metabolic syndrome

Waist circumference	
Men	>102 cm
Women	>88 cm
Triglycerides	≥150 mg/dl
HDL	
Men	<40 mg/dl
Women	<50 mg/dl
Blood pressure	≥130/≥ 85 mmHg
Blood glucose	≥100 mg/dl
Three out of 5 abnormal findings qualifies a person for the diagnosis of metabolic syndrome. (Adapted from reference 78)	

programs have regarded obesity as a contraindication to surgery (70). Recent research efforts have focused on weight loss in obese individuals with CKD, prior to KT, as a means to potentially improve access to KT, with the added potential to improve outcomes post KT. The drug orlistat was safe and effective in inducing weight loss in a small open-label prospective nonrandomized study of CKD patients. The authors conclude that a weight management program may enable obese patients with CKD to undergo KT (71). Bariatric surgery is an increasingly popular weight loss option in the general population (72). The bulk of the rather limited literature on the topic relates to Roux en Y gastric bypass (RYGB) procedures in CKD. The published data indicates that while early 30-day mortality may be slightly higher, (73), sustained weight loss leads to improvement in associated co-morbidities with reduced BMI and many patients who were initially denied KT access are assigned to wait lists after bariatric surgery (74). It is important to note though that gastric bypass surgery (RYGB, specifically), may affect the absorption and efficacy of many of the immunosuppressive drugs including cyclosporine and the calcineurin inhibitors such that increased doses may be required (75,76).

There is limited data on medical options for weight loss in transplant patients. Drugs such as orlistat, lorcaserin, phentermine, topiramate extended release, and naltrexone/bupropion are all considerations. Challenges include drug interactions with immunosuppressive medications, prophylactic antibiotics and antiviral medications. Of major interest is the safety and efficacy of GLP-1 receptor agonists after KT, as discussed above in the diabetes management sections. This class of injectable agents improves glucose metabolism and induces weight loss in most patients, but use in the transplant population is limited by lack of data. In addition, there is a theoretical concern

that since the injectable GLP-1 agonists reduce gastric emptying time, their use could impair the absorption of other medications.

#### 4.2. Metabolic Syndrome

The metabolic syndrome (MetSyn), first described by Gerald Reaven in 1988 (77), is a constellation of five known cardiovascular risk factors that are more likely than by chance alone to exist together in an individual patient. The MetSyn is a precursor of T2D and cardiovascular disease. There are four published definitions of MetSyn. Each set of criteria includes central obesity, dyslipidemia, elevated blood pressure and elevated fasting blood glucose. The WHO definition requires a measure of insulin resistance, which thus endows most T2D patients with the MetSyn. Subsequent criteria from ATP III and the IDF do not require inclusion of insulin resistance/glycemic measures as a component of the MetSyn but the IDF definition necessitates the inclusion of central obesity (adjusted for ethnicity), as one of the criteria. The ATP III criteria are the most commonly used in recent literature (Table 3), and were merged with the IDF criteria in 2009 (78). Although the relevance of identifying the syndrome is debated,(79), it has been shown that the combination of multiple risk factors is synergistic in increasing risk of cardiovascular events and death and therefore may have a unifying pathophysiology (80). The prevalence of metabolic syndrome in post-KT patients is 23 to 60 percent (81, 82). This variability in the literature is best explained by two factors. First, the definition of MetSyn has changed over time and not all features are required for each definition. Second, the prevalence appears to increase with time after KT, thought to be related to development of abdominal obesity and NODAT. Patients with MetSyn do appear to have an increased risk of rejection and death post-KT, confounded by considerable overlap with diabetes and obesity which cluster together in the same patient.<sup>83</sup> For this reason, targeting MetSyn itself as a preventive strategy before or after KT is of unclear value. Based on the literature, the most useful reason to diagnose the metabolic syndrome in the KT population is to identify which patients are at highest risk of cardiovascular disease and diabetes (83-85).

The value of diagnosing MetSyn in the post-KT patients depends on ease of diagnosis and availability of specific treatments. There is a lack of a unifying hypothesis and validated single biomarker of MetSyn. However, the adipocytokine adiponectin may be a reliable blood biomarker of MetSyn (lower levels are predictive, higher levels are less associated), and has been found to correlate negatively with NODAT risk (86). Treatments known to increase adiponectin such as thiazolidinediones and significant weight reduction, may be uniquely effective in reducing post-KT cardiovascular risk, although this has not been specifically studied.

Post-KT patients should receive therapy with established risk-reduction medications, including HMG-CoA reductase inhibitors or statins, to achieve recommended cholesterol levels. Given that cardiovascular disease is the most common cause of death post-transplantation, elucidating a unified pathophysiology to explain the increased MetSyn post-KT and to guide treatment strategies would likely make a significant impact on KT outcomes.

## 5. SUMMARY

There are several glucometabolic effects of restored renal metabolic health after kidney transplantation that impact patients with pre-transplant diabetes, T2D probably more so than T1D: 1). increased insulin clearance and lower insulin availability; 2). increased renal gluconeogenesis and consequent higher insulin needs in the fasting state; 3). resolution of uremia-induced impaired insulin action in muscle; 4). restored glycosuria. While the latter two effects improve post-meal glycemic control post-KT, the first two perturbations generally result in increased insulin requirements and the need for glucose-lowering therapies. Consideration of obesity will continue to play an increasing role in the pre-transplant selection and preparation of obese individuals for KT as well as in efforts to minimize subsequent prevalent post-operative complications, including wound infections, graft rejection and overall increased post-KT CVD mortality. Further research efforts are required to better define the specific contribution of obesity as an independent risk factor for CVD, as well as the role of improved medical and surgical options in the obese pre-KT patient. As transplant medicine advances in immunosuppression and surgical techniques to improve immediate post-transplant outcomes, the need to address metabolic complications will become more pressing to ensure patient and graft survival in the long term. Periodic comprehensive metabolic evaluation after KT and timely and effective interventions from expert providers (such as a transplant endocrinologist). are essential to the success of any transplant program.

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