

Prevalence of Metabolic Syndrome in Organ Transplantation: A Review of the Literature

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Abstract

The clinical features of the Metabolic Syndrome (MS) as risk factors for transplantation have been cited separately and extensively in the transplant literature. There are few studies in literature evaluating the prevalence of MS before and after solid organ transplantation.

MS puts transplant patients at risk in in two ways: 1) MS is one more risk factor to be considered in the pretransplantation workup; and 2) the combined risk of cardiovascular disease post-transplantation as a side effect of immunosuppressive medication together with the risk from cardiovascular disease stemming from the MS might put a post-transplantation patient at vastly increased risk for a cardiovascular event.

There are several reports on the treatment of MS expecially after transplantation; from lifestyle changes to drug therapies. However, to now, guidelines about management of these patients are lacking.

Keywords: Metabolic syndrome; Organ transplantation; Cardiovascular disease; Liver transplant

Introduction

The clinical features of the Metabolic Syndrome (MS) as risk factors for transplantation have been cited separately and extensively in the transplant literature. Examples are diabetes [1], obesity [2], and Non-Alcoholic Steatohepatitis (NASH) [3].

With the advent of the MS as a recognized entity, it is now realized that all these separate risk factors are most likely part of the same overall problem. The most important clinical sequel of the MS is coronary vascular disease. This puts transplant patients who have the MS at increased risk in two ways: 1) it is one more risk factor to be considered in the pre-transplantation workup, along with any other risk factors the patient may have; and 2) the combined risk of cardiovascular disease post-transplantation as a side effect of immunosuppressive medication together with the risk from cardiovascular disease stemming from the MS might put a post-transplantation patient at vastly increased risk for a cardiovascular event.

The aim of this review is to analyze the prevalence/recurrence of MS after solid organ transplantation. Attention was focused on kidney and liver transplant because of the volume of literature with respect to other solid organ transplantation.

The main findings found in literature refer to prevention and management of New-Onset Diabetes Mellitus (NODAT) and MS following kidney and liver transplantation.

For this purpose, the terms used in the PubMed research were: metabolic syndrome, liver transplantation, renal/kidney transplantation, new-onset diabetes mellitus, obesity and bariatric surgery.

Liver transplant: general considerations

Liver transplantation is a life-saving and life-changing procedure for patients with hepatocellular carcinoma and decompensated cirrhosis. The outcomes are excellent, with 1- and 5-year survival rates of 85–90% and 70–80% respectively [4-10]. Indications for LTx are reported in Table 1.

The transplant population has changed over the years with regard to indication and recipient characteristics. Hepatitis C is declining as an indication for transplant while Non-Alcoholic Fatty Liver Disease (NAFLD) is increasing, and the average age of transplant candidates is rising [11,12].

Improved survival after transplantation and the increasing numbers of transplants performed have increased the long-term consequences of transplantation. These include obesity, hyperlipidemia, diabetes mellitus, renal dysfunction, hypertension and bone disease [13]. The origin of these alterations, apparently related to Insulin Resistance (IR) and characterizing the MS, is under debate.

MS and its components are the main cardiovascular risk factors. In fact, cardiovascular complications arising post-transplant are an important cause of morbidity and mortality. Cardiovascular disease is the third most common cause of death in those recipients surviving the first year and accounts for up to 14% of deaths [14]. Johnston estimated that the incidence of ischemic heart disease events and mortality is 7.9% over 10 years, but this was probably an underestimation of the risk [15]. Others, however, have reported that the incidence of cardiovascular disease in patients surviving 5 years is similar to the general population [16].

Weight gain after liver transplantation has been widely reported, with about two-thirds of patients becoming obese soon after transplant [17]. There is much debate as to the cause of this weight gain, but several factors, including immunosuppressive drugs and a return of normal diet and appetite have been suggested.

However, only a few studies have systematically reported data on the markers of MS before and after transplantation in large liver transplantation series, and on risk factors for the development of metabolic alterations [18].

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Chronic non-cholestatic liver disorders
Chronic hepatitis C
Chronic hepatitis B
Autoimmune hepatitis
Alcoholic liver disease
Cholestatic liver disorders
Primary biliary cirrhosis
Primary sclerosing cholangitis
Biliary atresia
Alagille syndrome
Non-syndromic paucity of the intrahepatic bile ducts
Cystic fibrosis
Progressive familial intrahepatic cholestasis
Metabolic disorders causing cirrhosis
Alpha-1-antitrypsin deficiency
Wilson disease
Non-alcoholic steatohepatitis and cryptogenic cirrhosis
Hereditary hemochromatosis
Tyrosinemia
Glycogen storage disease type IV
Neonatal hemochromatosis
Metabolic disorders causing severe extrahepatic morbidity
Amyloidosis
Hyperoxaluria
Urea cycle defects
Disorders of branch chain amino acids
Primary malignancies of the liver
Hepatocellular carcinoma
Hepatoblastoma
Fibrolamellar hepatocellular carcinoma
Hemangioendothelioma
Fulminant hepatic failure
Miscellaneous conditions
Budd-Chiari syndrome
Metastatic neuroendocrine tumors
Polycystic disease
Retransplantation

Table 1: Indications for liver transplantation

The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [19] defined the components of the metabolic syndrome as follows; (1) impaired fasting glucose (\geq 100 mg/ dL); (2) Abdominal obesity (>102 cm in men, >88 cm in women); (3) hypertriglyceridemia (\geq 150 mg/dL or drug therapy for triglycerides); (4) low levels of High Density Lipoprotein (HDL) (< 40 mg/dL in men, < 50 mg/dL in women or drug treatment for low HDL); and (5) elevated blood pressure (\geq 130/85 mmHg or drug treatment for hypertension). The presence of 3 or more of these components defines the MS.

Complications of advanced liver disease can confound the diagnosis of the MS in the pre-transplant setting. The presence of ascites alters waist circumference. Vasodilatation and decreased effective circulating volume found with portal hypertension results in lowered systemic blood pressure. Synthetic dysfunction observed with end stages of liver disease immediately prior to transplant can result in lowered serum glucose and lipid values.

Review of the Literature

The literature contains several studies, reported in Table 2, analyzing the prevalence of MS in patients undergoing liver transplantation.

The results of these studies are not comparable, even though the aims are similar. First of all, the definition of MS differed among the studies. Some Authors define MS as the presence of 3 components [18-22] others chose 5 components [11].

Some studies investigated the prevalence of MS after LTx, while others did so both before and after LTx. Moreover, in some studies, only data about the single components of MS were reported and not of MS as a single entity (Table 2). All the studies found are retrospective; the data are often incomplete and obtained from clinical files. The only prospective study by Anastacio et al. [23] investigated the prevalence of single elements of MS only after LTx.

The weakness of the studies investigating the prevalence of MS only after LTx is the lack of data about possible metabolic disorders before surgery. There are several factors which must be considered before surgery, which are well known risk factors for MS development after LTx (see Paragraph below).

Another point is that the reasons for LTx were different in all the studies; just one study analyzed metabolic alterations following HCV recurrence after LTx [24]. It is well known that HCV infection is related to insulin-resistance, so it would be better to separately investigate all patients with HCV infection, who may already have metabolic alterations before LTx [25].

Another point concerns the time of follow up; this differs considerably from study to study, ranging from a few months to several years.

Pre-transplant MS risk factors

As mentioned before, the transplant population has changed over the years with regard to indication and recipient characteristics. With these changes, risk factors for the MS are becoming more common in liver transplant candidates and are important Predictors of Post-Transplant MS (PTMS) development. There are some small-size studies in the literature about risk factors for predicting PTMS, but certain factors identified were consistent across multiple series. A summary of the risk factors is presented in Table 3.

Obesity

Obesity before transplant is a key factor in predicting the MS after transplant. Both pre-transplant weight [21] and Body Mass Index (BMI) [18,20,24] were correlated with PTMS. The rate of obesity in wait-listed patients varies by transplant indication.

On the other hand, there are conflicting data in the literature about the effect of obesity as a risk factor for high mortality in the LTx population [2]. An analysis of the United Network for Organ Sharing database from 1988 to 1996 showed that liver transplant recipients with severe obesity (BMI > 35) had higher mortality, but only morbid obesity $(BMI \ge 40)$ was independently associated with higher mortality when other confounding factors were included [25]. The American Association for the Study of Liver Diseases considers morbid obesity a contraindication for LTx, and recommends weight loss in all patients awaiting LTx, especially if the patient's BMI is greater than 35 kg/m² [26]. Two studies have re-examined the effect of obesity on orthotopic liver transplantation and reported rather different results. Pelletier et al.. [27] found that obese patients, compared to patients with normal BMIs, have a similar risk of death while on the liver transplant waiting list, have similar mortality rates after liver transplantation, and have a similar reduction in the risk of death. Likewise, Leonard et al.. [28] found that corrected BMI is not independently predictive of patient or graft survival and concluded that obesity should not be considered a contraindication for liver transplantation in the absence of other relative contraindications.

On the contrary, single-center studies have shown that there are more postoperative complications and longer lengths of stay for obese patients [29-33].

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Author	Subjects (%)	Before LTx	After LTx	Indications for LTx	Time of follow-up	Adverse outcome related to MS
Laish [20]ª	252	221	252	various	6mths-15yrs	More CVD
Obesity		24 (10.8)	69 (27.5)			
Diabetes mellitus		32 (14.4)	100 (39.6)			
Hypertension		19 (8.6)	147 (58.3)			
Low HDL		87 (39.8)	123 (48.8)			
Abnormal TG		16 (7.2)	119 (47.2)			
MS		12 (5.4)	131 (51.9)			
Bianchi [18]ª	296			various	7mths-17yrs	Not studied
Obesity		111 (37.5)	170 (57.4)			
Diabetes mellitus		29 (9.8)	112 (37.8)			
Laryea [21] ^a	118			various	3-18mths	
Hypertension		12 (10)	72 (62)			
Dyslipidemia		4 (3)	54 (46)			
Diabetes mellitus		15 (13)	73 (61)			
MS			69 (58)			More CVD
Hanouneh [22]ª	82			HCV recurrence	1yr	Not studied
Hypertension		18 (19)	61 (64.2)			
Diabetes mellitus		21 (22)	49 (51.6)			
MS			41 (50)			
Anastacio [23] ^b	117				7yrs	
AO			51 (43.2)			
Hypertension			41 (34.7)			
Diabetes mellitus			29 (24.6)			
Low HDL			45 (44.6)			
Abnormal TG			34 (33.3)			

Legend: a: Retrospective study; b: Prospective study. TG: Triglycerides. AO: Abdominal Obesity. CVD: Cardiovascular Event.

Table 2: Studies examining the prevalence of MS before and/or after liver transplantation (numbers in parentheses are percentages)

Weight (21)
Body mass index (18,20,24)
Cryptogenic cirrhosis (20,21)
Alcoholic cirrhosis (21)
Hepatitis C cirrhosis [21]
Pretransplant diabetes (1820,24)
Age (20,21)
Miscellaneous (triglycerides, high density lipoprotein (20)

Table 3: Liver pre-transplant risk factors

Cryptogenic cirrhosis

Persons with cryptogenic cirrhosis awaiting transplant were found to be more commonly obese than age and gender matched controls [34].

NAFLD is seen worldwide and is the most common liver disorder in Western industrialized countries, where the major risk factors for NAFLD, central obesity, T2DM mellitus (T2DM), dyslipidemia and MS, are common [35]. Ethnic differences in the prevalence of NAFLD have been found [36]. NAFLD is characterized by fat accumulation within liver cells when no other etiologies for hepatic fat accumulation (*e.g.*, heavy alcohol consumption) are present. NAFLD is known to progress to cirrhosis and is likely an important cause of cryptogenic cirrhosis [37]. The development of the NAFLD fibrosis scoring system and the realization that NASH can progress to cirrhosis (in 8 to 10 years) has dramatically decreased the diagnosis of cryptogenic cirrhosis [38]. Therefore, endstage liver disease secondary to NAFLD is projected to become the most common indication for LTx by 2025 [38], given its increasing incidence and the steady decrease in frequency of hepatitis C infection and alcohol induced liver disease. The proportion of obese persons awaiting transplant will presumably increase with the indication for transplant changing to a higher proportion of recipients with NAFLD. Compounding the effect of obesity, transplant for NASH was found to be a risk factor for PTMS when controlling for other factors, including pre-transplant BMI [20,21].

Pre-transplant diabetes

Pre-transplant diabetes was found to predict PTMS in multiple series [18,20,24]. In fact, in one study, persons with pre-transplant diabetes had nearly 6 fold higher odds of having the MS after transplant [20].

Age

Age was additionally predictive of the MS after transplant [20,21]. This is particularly important as the recipient population in the United States is aging. In 2009, nearly 75% of transplant recipients were above the age of 50, compared to 1993 where only 42% of recipients were 50 years of age or older [39].

Miscellaneous

Other pre-transplant factors that were associated with the development of the metabolic syndrome after transplant in at least one series included hypertriglyceridemia [20], low HDL [20] and transplantation for hepatitis C or alcohol cirrhosis [21].

Post-transplant risk factors

As obesity prior to transplant is a risk factor for PTMS, it is intuitive that weight gain after transplant might predict the MS. However, data are mixed. The overall change in BMI after transplant was associated

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with the MS in one series [18] but not in another [20]. It is possible that pre-transplant ascites may result in the underestimation of weight gain post-transplant in the later series. Weight gain after transplant is well described, even if there are conflicting data in the literature. There is much debate as to the cause of this weight gain, but several factors, including immunosuppressive drugs and a return of normal diet and appetite have been suggested [40]. In one series, the proportion of overweight and obese persons after transplant was 57% compared to 38% prior to transplant [18]. In a large series of almost 600 liver transplant recipients, the median weight gain at 1 year and 3 years was 5.1 kg and 9.5 kg, respectively [40].

Longitudinal data have shown that most weight gain occurs within the first year after liver transplant [41-43].Weight gain after transplant should be viewed in the context of persons returning to health after illness. Aggregate data from three studies that measured the rate of an elevated waist circumference after transplant totaled 36.9% [18,20,44]. Although the populations are not matched, the absolute number is strikingly similar to the 38.6% rate reported for the United States population [44]. In a study comparing rates of obesity, the prevalence was not significantly higher in persons after liver transplant compared to the general United States population [45].

Despite the weight gain over time after transplant, time since transplant was not associated with the prevalence of PTMS [18,20,21]. This finding suggests that factors resulting in PTMS develop soon after transplant and that factors in addition to obesity require further studies. Immunosuppression is one such factor. The overall contribution of immunosuppression to the development of the MS after transplant is difficult to measure, since immunosuppression is unavoidable.

Immunosuppressive treatment

Different immunosuppressive agents have been shown to increase risk for various components of the MS, although the choice of Calcineurin Inhibitor (CNI), mainly cyclosporine and tacrolimus, was not associated with the development of the MS [18,22].

With regard to weight gain after transplant, one series found more weight gain with cyclosporine in the first year [21]. However, the effect was not seen at 2 years. Another study found a higher overall BMI in cyclosporine treated patients, but no difference in rates of elevated waist circumference [18]. Weight loss occurred in a majority of liver transplant recipients after switching to tacrolimus from cyclosporine [46]. Although corticosteroids are often associated with weight gain, this effect after transplant was found in some [42,47] but not all series [41,43].

The effect of immunosuppressive therapy on metabolic alterations will be discussed below.

Kidney transplantation

Kidney Transplantation (KTx) has become a great success story overall [48], mainly because kidney transplant recipients benefit from increased survival rates [49-54] and higher quality of life compared with dialysis patients [55-58]. To ensure that post-transplant outcomes may continue to improve in aging end-stage renal disease populations, the transplant community is undertaking considerable efforts [59-61]. Furthermore, the search for optimal immunosuppression is undergoing constant review [62-65].

MS has been associated with proteinuria and reduced GFR [66,67] suggesting a link to chronic kidney disease. To the extent that New Onset Diabetes Mellitus After Transplantation (NODAT), cardiovascular disease, and proteinuria are common complications of KTx, the role

of MS in KTx has recently attracted a great deal of interest. However, the relevance of the syndrome in KTx is confounded by the fact that the incidence of cardiovascular disease actually declines after successful transplantation compared with that observed in dialysis patients on the transplant waiting list [68]. In addition, it remains unclear whether the presence of MS is any better at predicting NODAT than traditional risk factors such as age, ethnicity, family history of diabetes, and obesity [69]. Finally, the pathophysiology of the syndrome observed in the general population is dramatically altered by the effects of immunosuppressive medications in kidney transplant recipients.

The literature contains fewer studies about the prevalence of MS in KTx than in LTx. Most studies are retrospective and include a small number of subjects. Moreover, as in LTx, data about the prevalence of MS before transplantation are lacking. However, all Authors agree that MS is a prominent risk factor for chronic graft dysfunction, graft loss and patient death in KTx.

In all these studies, there is no mention about the reason for transplantation and the time of follow up is quite different, ranging from 6 months to several years, as in LTx studies. There is also no mention about the immunosuppressive treatment and the relationship between metabolic alterations and the dosage of therapies. Among the components of the MS, systolic BP and hypertriglyceridemia had the most negative impact on long-term graft function [70-75].

Pre- and post-transplant MS risk factors

Differently to what happens for liver transplantation, there are no strong data in literature about either pre- or post-transplant risk factors [76]. There are a few studies focalizing attention on obesity, hypertension and hyperlipidemia as risk factors for impaired graft function or graft loss.

Obesity

Pre-transplantation obesity, defined as a BMI > 30, independently increases the risk of graft loss and post-transplantation cardiovascular disease [77]. However, after transplantation, weight gain occurs in the majority of patients [78-80] particularly in women, black individuals, and low-income patients [78]. In addition to indirect effects on graft survival, obesity is associated with a higher incidence of surgical wound infections [80]. Although sustained weight loss through conservative intervention is difficult to achieve, prevention of weight gain is a more feasible goal that should be addressed routinely. In addition to encouragement of lifestyle modification, pharmacologic and surgical options should be reviewed with appropriate patients [79]. Finally, the benefits of exercise should be emphasized. A review of 21 studies that examined the role of physical activity in kidney transplant recipients concluded that habitual physical activity level was positively associated with quality of life and aerobic fitness and negatively associated with body fat [81].

Hypertension

Elevated blood pressure is extremely common after kidney transplantation and might independently contribute to graft loss [82]. No single antihypertensive drug or combination of drugs has emerged as a first-line approach to the treatment of post-transplantation hypertension. Because of the high prevalence of cardiovascular disease before and after transplantation, many Centers prefer the cardioprotective β -blockers as the first line of therapy. Recently, the Cochrane Group published a meta-analysis of randomized studies comparing calcium channel blockers with placebo, calcium channel blockers with Angiotensin-Converting Enzyme Inhibitors (ACEIs),

and ACEIs with placebo for post-transplantation hypertension [83]. Calcium channel blockers, compared with placebo or no treatment reduced graft loss. These data suggest that calcium channel blockers may be preferred as first-line agents for hypertensive kidney transplant recipients [84].

The results of this meta-analysis should be interpreted with caution for several reasons. First, only 60 of 1025 studies reviewed met inclusion criteria for the analysis. Second, most studies included in the analysis were performed in an era when cyclosporine was the favored CNI for immunosuppression and when the non-di-hydropyridine calcium channel blockers were often used to decrease the metabolism of cyclosporine. As tacrolimus has gradually replaced cyclosporine as the CNI of choice, the relevance of these interactions has decreased, in part because tacrolimus is less often associated with hypertension than cyclosporine. Finally, the incorporated studies were performed in an era when the use of ACEIs in kidney transplant recipients was limited compared with the modern era.

It has been difficult to confirm the putative reno-protective effects of ACEIs in the renal transplant population [84], despite abundant data supporting this concept in the general population. A larger registry analysis concluded that the use of these agents had no benefit on either patient or graft survival [85]. Moreover, use of these agents might be associated with hyperkalemia and anemia [86] and these risks may outweigh any putative benefits in some patients. Most transplant physicians use these agents in transplant recipients with proteinuria. However, in the absence of large randomized trials, the benefits of using ACEIs or angiotensin receptor blockers in kidney transplant recipients must be weighed against their associated risks.

Hyperlipidemia

The Assessment of LEscol in Renal Transplantation (ALERT) trial was a large study in which stable kidney transplant recipients were randomly assigned to receive treatment with either fluvastatin or placebo to determine whether hepatic Hydroxymethyl Glutaryl-CoA (HMG-CoA) reductase inhibitors are effective in lowering LDL cholesterol and in reducing the risk for cardiac events [87]. After 5 years of follow-up, patients who were assigned to fluvastatin exhibited significantly lower total and LDL cholesterol levels than the control group, and achieved a reduction in important secondary end points such as cardiac death and non-fatal myocardial infarction. The incidence of clinically significant rhabdomyolysis, once a concern in transplant recipients, was negligible. On the basis of this study, "statins" have become the drugs of choice for management of post-transplantation hypercholesterolemia that is resistant to lifestyle modifications. Treatment of hypertriglyceridemia has been more problematic. Ezetimibe, fibric acid derivatives, and fish oil have been used anecdotally with some success, but large-scale, randomized trials are lacking.

New-onset diabetes mellitus after solid organ transplantation

NODAT may increase the risk of morbidity and mortality after solid organ transplantation, reduced graft function and patient survival [88-90]. While previously referred to as "post-transplantation diabetes mellitus", NODAT is the preferred current term. An international expert panel consisting of experts from the solid organ transplantation and diabetes fields published consensus guidelines in 2003 indicating that the definition and diagnosis of NODAT should be based on American Diabetes Association or the World Health Organization guidelines for diabetes mellitus and impaired glucose tolerance (Table 4) [91,92]. The pathophysiology of NODAT has not been clearly defined and may resemble that of T2DM. Insulin resistance is a predominant feature, but defective insulin secretion may also prevail, or both may be present [89].

The incidence of NODAT has continued to be a concern following solid organ transplantation. It has been reported to occur in 4-25% after kidney transplantation, 2.5-25% after liver transplantation and 2-53% after all kinds of solid organ transplantation [89]. The variation in the reported incidence may partly be due to the variable criteria used for the diagnosis of NODAT, before the publication of the International Expert Panel Consensus Guidelines [88]. Risk factors for development of NODAT are reported in Table 5.

NODAT shares several features with Type 2 diabetes. Insulin resistance and relative insulin deficiency are involved in the pathogenesis of both disorders [93]. The impact of insulin deficiency and insulin resistance may vary in the presence of different risk factors; among these, the type of immunosuppressant accounted for 74% of the variability in the 12-month cumulative incidence of NODAT [94].

Therefore, attention will be focused on the mechanisms causing NODAT by glucocorticoids, calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors and on the role of HCV and CMV infections.

Glucocorticoids

Glucocorticoids (GC) are associated with the greatest risk of developing NODAT. An early study showed that 46% of 114 renal transplant recipients treated with high dose prednisone developed NODAT with a follow up of at least 1 year [95]. The diabetogenic effect of GC is dose dependent, and a 0.01 mg/kg/day increase in prednisolone dose has been associated with a 5% risk of developing NODAT [96]. It has been shown that the rapid decrease of steroid dose after solid organ transplantation resulted in an average increase in insulin sensitivity [97].

The precise mechanisms of GC-induced insulin resistance are not well understood; however, they largely depend on dosage and time of exposure. The predominant underlying mechanism is increased insulin resistance based on OGTTtest (OGTT) [93]. In vivo and in vitro animal studies have demonstrated that GC interfere at several steps in the insulin signaling cascade in skeletal muscles, resulting in reduced glucose uptake and glycogen synthesis [98]. Skeletal muscle biopsies in renal transplant recipients exposed to long-term high-dose glucocorticoids showed reduced glycogen synthesis [89]. Increased endogenous glucose production may also be involved [98]. Moreover, glucocorticoid-induced insulin resistance is associated with its indirect adverse effects, such as weight gain, increased appetite and redistribution of body fat [93].

High-dose oral prednisolone may acutely impair insulin secretion during glucose infusion in healthy volunteers, suggesting an acute inhibitory effect on β -cells [96]. However, GC may simultaneously cause other systemic metabolic abnormalities, such as an increase in nonesterified fatty acids [98]. GC were shown to reduce the expression of GLUT2 and glucokinase, thereby impairing glucose-stimulated insulin secretion [96]. Moreover, dexamethasone was reported to stimulate the transcription of serum and glucocorticoid-inducible kinase 1, up regulating the activity of voltage-gated K⁺ channels resulting in reduced Ca₂⁺ entry through voltage-gated Ca₂⁺ channels and decreased insulin release [99]. In isolated rat islets, dexamethasone decreases the activation of protein kinase C through inhibition of the diacylglycerolphospholipase C pathway [100]. GC also increased expression of α 2adrenergic receptors leading to reduced cAMP and protein kinase A

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Criteria for the diagnosis of DM

Any one of the following:

1. Classic symptoms of DM^a + random PG concentrations ≥ 200 mg/dL (11.1 mM) 2. FPG ≥ 126 mg/dL (7.0 mM). Fasting is defined as no caloric intake for ≥ 8 hours 2-hour PG ≥ 200 mg/dL (11.1 mM) during an OGTT^b 4. A1C° ≥ 6.5% In the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation, criteria 2-4 must be confirmed by repeat testing on another day. Criteria for normal FPG and IFG or IGT FPG WHO criteria FPG < 110 mg/dL (6.1 mM) = normal fasting glucose FPG ≥ 110 mg/dL (6.1 mM) and <126 mg/dL (7.0 mM) = IFG 2003 ADA consensus FPG < 100 mg/dL (5.6 mM) = normal fasting glucose FPG ≥ 100 mg/dL (5.6 mM) and <126 mg/dL (7.0 mM) = IFG OR OGTT 2-hour PG < 140 mg/dL (7.8 mM) = normal glucose tolerance 2-hour PG ≥ 140 mg/dL (7.8 mM) and < 200 mg/dl (11.1 nM) = IGT Prediabetic states based on A1C level 2010 ADA consensus: 5 7%-6 4% International expert committee: 6.0%-6.4%

Notes: a: Classic symptoms of DM include polyuria, polydipsia, and unexplained weight loss; bOGTT: the test should be performed as described by WHO, using a glucose load containing equivalent of 75 g anhydrous glucose dissolved in water; cA1C should be performed using a method certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) reference assay.

Abbreviations: (WHO) World Health Organization; (ADA) American Diabetes Association; (DM) Diabetes Mellitus; (PG) Plasma Glucose; (FPG) Fasting Plasma Glucose; (IFG) Impaired Fasting Glucose; (IGT) Impaired Glucose Tolerance; (OGTT) OGTTtest.

Table 4: WHO and ADA criteria for the diagnosis of diabetes mellitus

	Non modifiable	Potentially modifiable	Modifiable
	Older age	HCV infection	Obesity
	Genetic background	IFG and/or IGT	
Pre-transplant	Family history of diabetes		
	Ethnicity (non- Caucasian)		
	Specific disease		
		CMV infaction	Obosity
Post-transplant			Obesity
		MS	Corticosteroids
			Tacrolimus
			Sirolimus

Legend: (CMV) Cytomegalovirus; (HCV) Hepatitis C virus; (IFG) Impaired Fasting
Glucose; IGT, Impaired Glucose Tolerance; (MS) Metabolic Syndrome
Table 5. Disk fasters for the development of NODAT

 Table 5: Risk factors for the development of NODAT

activity, and decreased insulin release [101]. Moreover, GC may reduce islet mass, by inducing apoptosis in mouse islets or INS-1 cells [99].

Hyperglycemia

All the above-mentioned mechanisms lead to hyperglycemia, which is, by itself, a recognized stressor for β -cells, suppressing insulin secretion and/or leading to β -cell apoptosis in vitro [102-104] via oxidative stress [105]. B-cell failure appears to play a major role in T2DM development [106,107] and is thus very likely to play a key role in NODAT development as well. Additional general mechanisms contribute to hyperglycemia in the post-transplant are: a) perioperative stress of surgery and anesthesia may result in hyperglycemia through a variety of mechanisms such as increased secretion of catecholamines [108,109] and inflammatory cytokines exerting antagonistic effects on insulin [110-112]; b) unhealthy dietary habits and deficient aerobic

exercise are well known to increase the risk of developing T2DM [113-118]; c) physical inactivity is an inevitable consequence of early postoperative rehabilitation, but simultaneously a major contributor to T2DM [119,120]. The inability to perform physical exercise will most probably contribute to postoperative hyperglycemia and NODAT development.

Calcineurin inhibitors

CNI, mainly cyclosporine and tacrolimus, have greatly improved the outcomes of solid organ transplantation. Unfortunately, both have been implicated in the development of NODAT. Several studies have shown a 15-30% striking incidence of NODAT with CNI use [89]. The mechanisms are not well understood.

Effects on β-cell survival and replication

Animal studies have shown that enhanced proliferation of surviving β -cells plays a major role in spontaneous recovery from a diabetogenic injury; however, tacrolimus abolishes β-cell regeneration [121,122]. Calcineurin and its downstream signaling pathways are ubiquitous molecules with biological relevance in multiple tissues. In β-cells, the phosphatase activity of calcineurin has two well-described molecular targets: nuclear factor of activated T cell and cAMP response element-binding transcriptional co-activator, a transducer of regulated cAMP response element-binding activity-2 (TORC2). Tacrolimus and cyclosporine bind to their respective cognate intracellular binding immunophilins FK506-binding protein 1B, and cyclophilin before docking with the calcineurin binding site, thus inhibiting calcineurin and its downstream pathways [123]. Experiments in transgenic mice demonstrated the importance of these two pathways in maintaining β -cell function and growth [123]. Administration of tacrolimus to male Sprague Dawley rats led to a time-dependent decrease in insulin transcription in islets which resolved upon drug cessation [93].

Therefore, inhibition of calcineurin may underlie NODAT caused by cyclosporine and tacrolimus by direct toxic effect through nuclear factor of activated T cell and/or CREB pathway(s). However, the underlying molecular mechanism is complicated and needs to be further elucidated. Plaumann et al. [124] demonstrated that cyclosporine mediated inhibition of calcineurin activated the dual leucine-zipper-bearing kinase possibly through the cAMP response element-binding pathway, leading to β -cell apoptosis.

Tacrolimus was reported to decrease Akt phosphorylation, suggesting that calcineurin could regulate replication and survival via the PI3K/Akt pathway in both rodent and human islets. Its upstream regulator insulin receptor substrates (Irs)2 mRNA and protein were also decreased, which may be mediated by both nuclear factor of activated T cell and/or cAMP response element-binding [125].

Effects on insulin secretion and action

In vitro and in vivo studies have demonstrated that pharmacological CNI impairs insulin secretion and may be dose dependent [93]. A clinical study revealed that the inhibitory effect of tacrolimus on insulin secretion may be caused by high blood trough levels, and that lowering of trough levels is associated with improved pancreatic b-cell function [126]. β -cell secretory capacity was normal in pancreas-kidney and kidney transplant recipients receiving low-dose GC (5 mg daily) and modern doses of tacrolimus (standard targets of 12-h blood trough levels were 6-10 ug/l) [127].

Whether insulin secretion is directly affected by tacrolimus inhibition is unclear. Calcineurin binding site-deficient mice have

markedly impaired glucose-stimulated insulin secretion; however, this may be an effect of reduced β -cell insulin content instead of an insulin secretory pathway defect [124]. Other pathways have been implicated to explain impaired insulin secretion caused by calcineurin inhibitors. Mitochondria play a key role in insulin secretion by both providing energy (ATP) and synthesizing metabolites that can couple glucose sensing to insulin exocytosis. Cyclosporine was found to bind readily to cyclophilinD in the mitochondrial permeability transition pore and block the opening of this channel, thus diminishing insulin release from mouse islets [128]. Pharmacological doses of tacrolimus significantly decrease mitochondrial content and respiration in INS-1 cells, probably at the level of gene transcription and translation [129]. Moreover, both tacrolimus and cyclosporine were reported to induce defective glucose-stimulated insulin secretion by inhibiting the closure of the ATP-sensitive potassium channel [130]. Tacrolimus may also reduce glucokinase activity and affect insulin exocytosis downstream of the rise in intracellular Ca,⁺, resulting in decreased glucose-stimulated insulin secretion [129-132].

Although the literature is sparse, some studies have suggested that CNI impair peripheral insulin action. Wahlstrom et al.. [133], by using clamp studies in dogs, demonstrated that cyclosporine may inhibit insulin release and induce insulin resistance and that cyclosporine withdrawal resulted in a reversal of these changes. An in vitro study showed that addition of cyclosporine to skeletal muscle cells from mice results in a significantly lower insulin-induced glucose uptake compared with controls, and blockade of calcineurin activity promotes the transformation from type I slow-twitch skeletal muscle fibers to the less insulin sensitive type II fast-twitch skeletal muscle fibers in rat soleus muscle [93]. However, detailed pathways need to be further defined. Conversely, a clinical study reported that patients with NODAT treated with prednisolone and CI were more likely to have defects in insulin secretion, both at baseline and after 1 year of follow up, indicating that defects in insulin release at baseline are more predictive of future NODAT and impaired glucose tolerance than insulin resistance [96].

Tacrolimus vs cyclosporine

Tacrolimus has been described as being more diabetogenic than cyclosporine [88]. In a meta-analysis, a higher incidence of NODAT was reported in patients receiving tacrolimus compared with cyclosporine (16.6% *vs* 9.8%) in all solid organ transplantations [96]. Similarly, an open-label, randomized, multicenter study (DIRECT) in kidney transplant patients showed higher NODAT or impaired fasting glucose in tacrolimus-treated patients than in cyclosporine-treated patients (33.6% and 26%, respectively, P = 0.046) [88].

The reasons for the differences between these two medications need to be evaluated in more detail. One possible explanation could be the expression of FK506-binding protein 1B preferentially in β -cells, thus leading to a strong concentration of the drug in these cells, while cytochrome P450 is mainly located in the heart, liver and kidneys [96]. Furthermore, it has been demonstrated that tacrolimus and cyclosporine may act on different pathways except for the common effect of inhibiting calcineurin activity (Table 6). Only tacrolimus acutely inhibited basal insulin release from INS-1E cells, while cyclosporine decreased the transcription of several essential β -cell genes [133]. The insulin resistance induced by these two drugs may also be different. A clinical study showed that tacrolimus-based therapy led to higher peripheral insulin resistance and hyperinsulinemia than cyclosporine -based immunosuppression in kidney allograft recipients [96].

Mammalian target of rapamycin inhibitors

Sirolimus is a macrolide that inhibits T cell activation by linking with FK506 binding protein 1B; the complex inhibits mTOR. Sirolimus is a potent immunosuppressive agent that is associated with superior graft function, and comparable acute rejection, graft loss or mortality to CI.

Mammalian target of rapamycin, a conserved Ser/Thr kinase, which exists in two complexes (mTOR Complex1 (mTORC1) and mTOR Complex2 (mTORC2), has a key role in the regulation of cellular response to nutrients by integrating extracellular and intracellular signals originating from growth factors, hormones, and nutrients. Sustained activation of mTORC1 is a major cause for nutrient-induced obesity and insulin resistance [134]. So, theoretically, sirolimus could be useful in the management of obesity or T2DM through the deactivation of the negative-feedback loop of the mTOR pathway in adipose tissue, liver and muscle [135-137]. However, data in the literature are controversial and a growing body of evidence suggests that sirolimus may also be diabetogenic.

Data from the United States Renal Data System showed the association between sirolimus use and NODAT among renal transplant recipients [135]. Compared with patients treated with cyclosporine and either mycophenolate mofetil or azathioprine, sirolimus-treated patients were at increased risk for NODAT, whether used in combination with cyclosporine, tacrolimus or an antimetabolite (mycophenolate mofetil or azathioprine). However, Araki et al.. [136] did not find the increased risk of NODAT with de novo sirolimus use and sirolimus-based immunosuppression therapy in renal transplant recipients.

Conclusions about the effects of sirolimus alone on the function and survival of β -cells are also paradoxically based on animal studies, studies with cell lines or human islet investigations.

Sirolimus at therapeutic concentrations was reported to significantly increase insulin secretion in both basal (50%) and stimulated (40%) states in mini pigs in vivo [131]. Sirolimus also increases insulin content in human islets [134]. However, a down-regulation of insulin secretion in human islets at supra-therapeutic concentrations of sirolimus has also been reported. One study showed that, like CI, sirolimus may also impair insulin secretion by inhibiting the closure of ATP-sensitive potassium channels [130]. A study in rat pancreatic islets showed that sirolimus suppresses glucose-stimulated insulin secretion by reducing mitochondrial ATP production through suppression of carbohydrate metabolism in the Krebs cycle [137].

In summary, the effects of sirolimus on insulin secretion may depend on serum levels, the experimental animal species evaluated, nutrient status and whether the study is in vivo or in vitro. However, there is convincing evidence that sirolimus may disrupt islet regeneration and proliferation [134]. Sirolimus treatment almost completely inhibited β -cell proliferation induced by pregnancy in mice by inhibiting the mTORC1 signaling pathway, which regulates protein translation through downstream effectors such as ribosomal S6 kinase (S6K) and eukaryotic translation initiation factor 4EBP1. This pathway is critical for optimal cell growth, cell cycle progression and regulation of organ size. Further, Balcazar et al.. [137] demonstrated that sirolimus treatment inhibited cyclin-dependent kinase 4 activity through mTORC1 signaling by reducing cyclin D2 and D3, which are critical regulators of b-cell cycle, proliferation and mass [134].

Further, mTORC2 is also potentially important for the regulation of b-cell mass and function, by phosphorylation/activation of Akt at

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Author	Subjects (%)	Before KTx	After KTx	Indications for KTx	Time of follow-up	Adverse outcome related to MS
Courivaud [73] ^a	337			Not specified	1 yr	More atherosclerotic events
MS		67 (20)	107 (32)			
Elkehili [74]°	91			Not specified	6 mths	Not studied
Central obesity			46 (50)			
Hypertension			58 (64)			
Abnormal TG			44 (48)			
Low HDL			33 (36)			
Hyperglycemia			29 (32)			
MS			26 (29)			
Ozdemir [75]°	112			Not specified	1 yr	higher CVD morbidity and decreased graft function
MS		50 (17)				
Luan [76] ^b	203		97 (48)		7yrs	reduced transplant renal function
MS			98 (48)			
AGM						
Kishikawa [77] ^₀	94			Not specified		Not studied
MS			14 (15)		1-106 mths	
de Vries [78] ^b	606			Not specified		impaired renal allograft function
MS			383 (63)		2.6-11.4 yrs	
Porrini [79] ^a	230				18 mths	chronic graft dysfunction, graft loss
MS		87 (38)		Not specified		

Legend: a: retrospective study; b: prospective study. C: not specified. TG: Triglycerides. AO: Abdominal Obesity. CVD: Cardiovascular Event, AGM: Abnormal Glucose Metabolism.

Table 6: Studies examining the prevalence of MS before and/or after kidney transplantation (numbers in parentheses are percentages)

Ser473, which plays a pivotal role in cell survival [138]. However, its role in the pathogenesis of sirolimus-induced b-cell toxicity is still debated. One study reported that sirolimus treatment had no effect on mTORC2 and Akt activity in a controlled activation of Akt signalling murine islet cell line [137].

Hepatitis C virus and Cytomegalovirus

Epidemiologic analyses have demonstrated strong associations between HCV infection and hyperglycemia in the general population. Pre-transplant HCV infection represents a significant risk for NODAT after liver transplantation and kidney transplantation [88]. The risk of NODAT was increased fivefold in HCV(+) recipients compared to HCV(-) patients, but the pathogenesis remains poorly understood. Liver biopsies in patients with NODAT revealed more severe histological activity and fibrosis compared with controls without diabetes [93]. A significantly higher insulin resistance in the HCV (+) group during the first year after liver transplantation has been attributed to a direct effect of virus on insulin resistance [89]. This effect may be explained by down-regulation of Irs1 and Irs2 by the virus [139,140]. Hepatitis C virus induced immune mediated or direct b-cell damage may also play a role in the development of NODAT [93].

Recurrent CMV infection is highly prevalent after solid organ transplantation and dramatically affects patient morbidity and mortality [93]. The association of CMV infection with NODAT was first seen in a kidney transplantation recipient in 1985 [89]. Up to now, available data indicate that both asymptomatic CMV infection and CMV disease may be independent risk factors for NODAT, but the mechanism is unknown. Some studies have shown that CMV disease may be associated with insulin resistance and impaired insulin secretion after kidney transplantation [93]. Cytomegalovirus-induced

Endocrinol Metab Synd ISSN: 2161-1017 EMS, an open access journal pro-inflammatory cytokines leading to apoptosis or functional disturbances of the b-cell have also been reported [89]. Notably, the independent link between CMV infection and NODAT is difficult to confirm in human studies, as other factors may increase the risk of CMV infection, such as the degree of therapeutic immunosuppression.

Interestingly, CMV infection may change the natural history of HCV infection in renal and liver transplant recipients [96], but whether co-infection of CMV and HCV modifies the risk for NODAT needs further study.

NODAT treatment

Pre-transplant baseline evaluation

The 2004 updated International Consensus Guidelines on Newonset Diabetes after Transplantation suggest that a pre-transplant baseline evaluation should include a complete medical and family history, including documentation of glucose history [140]. Fasting Plasma Glucose (FPG) should be tested at regular intervals, and a 2-hour OGTT should be performed in those with normal FPG. The use of an OGTT is recommended for screening purposes because it is more predictive of increased cardiovascular disease risk and mortality than FPG testing, particularly in individuals with Impaired Glucose Tolerance (IGT). Furthermore, it has been suggested that OGTT diagnostic criteria may be more sensitive in identifying patients with IGT than those set for FPG [141]. Patients with evidence of IGT or an abnormal OGTT before transplantation should be counseled on lifestyle modifications including weight control, diet, and exercise. Pre-transplant treatment of HCV-infected renal transplant candidates should be considered. Selection of an immunosuppressive regimen should be tailored to each individual patient, weighing the risk of diabetes after transplantation against the risk of acute rejection.

Management of established NODAT

The management of NODAT should follow the conventional approach for patients with T2DM. Further intervention may include an adjustment or modification in immunosuppressive medications and pharmacologic therapy to achieve a target hemoglobin A1C level of less than 6.5%. Corticosteroid dose reduction has been shown to significantly improve glucose tolerance during the first year after transplantation [142]; however, any dose reduction should be weighed against the risk of acute transplant rejection. A steroid sparing regimen or steroid avoidance protocol should be tailored to each individual patient. Tacrolimus to cyclosporine conversion therapy in patients who fail to achieve target glycemic control or in those with difficult to control diabetes has yielded variable results. When lifestyle modification fails to achieve adequate glycemic control, medical intervention is recommended. Orally administered agents can be used alone or in combination with other oral agents or insulin. Although oral hypoglycemic agents may be effective in many patients with corticosteroid or cyclosporine or tacrolimus-induced NODAT, insulin therapy may be necessary in as many as 40% of patients [143], particularly in the early post-transplant period.

The choice of pharmacologic therapy is based on the potential advantages and disadvantages associated with the different classes of oral agents. Although metformin is the preferred agent for overweight patients, its use should be avoided in patients with impaired allograft function owing to the possibility of lactic acidosis. Care should also be taken when the sulfonylurea derivatives are prescribed to patients with impaired allograft function or to elderly patients due to the increased risk of hypoglycemia. In general, it is best to start with a low dose and to titrate upward every 1 to 2 weeks. The "non-sulfonylureas" meglitinides are insulin secretagogues with a mechanism of action similar to that of the sulfonylureas.

Nonetheless, they have a more rapid onset and shorter duration of action and seemingly lower risks of hypoglycemia and weight gain [144,145]. These agents are best suited for patients whose food intake is erratic, for elderly patients, and for patients with impaired graft function.

The thiazolidinedione derivatives are insulin sensitizers that may allow for a reduction in insulin requirement. Potential adverse effects of these agents include weight gain, peripheral edema, anemia, pulmonary edema, and congestive heart failure. The incidence of peripheral edema is increased when thiazolidinedione derivatives are used in combination with insulin [145].

More recently, during the A Diabetic Outcome Progression Trial (ADOPT) conducted to compare glycemic control in patients on rosiglitazone, metformin, or glyburide, a higher incidence of fractures in the upper arm, hand, and foot was noted among female patients treated with rosiglitazone [146,147]. Subsequently, pioglitazone was also recognized to be associated with a similar increased risk of fracture in women but not in men, although further studies are needed [147]. The risk of fractures associated with use of the thiazolidinedione derivatives in the transplant setting is currently not known. Nonetheless, thiazolidinedione derivatives should be used with caution, particularly in female transplant recipients who are also receiving steroid immunosuppressive therapy. Drug-to-drug interactions should also be carefully considered. The meglitinide derivatives repaglinide and, to a lesser extent, nateglinide are metabolized through the cytochrome P-450 isozyme CYP 3A4; therefore, glucose levels should be monitored closely when the patient also receives a strong inhibitor (e.g., cyclosporine, gemfibrozil, or the azole antifungal) or inducer (e.g., rifampin, carbamazepine, phenytoin, or St. John's wort) of the CYP 3A4 system [144]. The use of gemfibrozil, a CYP 3A4 inhibitor, and repaglinide combination therapy has been shown to dramatically increase the action of the latter, resulting in prolonged hypoglycemia. Coadministration of cyclosporine and repaglinide has also been shown to enhance the blood glucose lowering effect of repaglinide and increase the risk of hypoglycemia [147]. In contrast, rifampin, a strong inducer of CYP 3A4, considerably decreases the plasma concentration of repaglinide and also reduces its effects [148]. Although tacrolimus is also metabolized via the CYP 3A4 system and should be susceptible to many drug interactions similar to those of cyclosporine, these interactions are not as well documented.

Monitoring of patients with post-transplant diabetes mellitus should include measuring the hemoglobin A1C level every 3 months and screening for diabetic complications, including tests for microalbuminuria, regular ophthalmologic examinations, and regular foot care. The hemoglobin A1C level cannot be accurately interpreted within the first 3 months post transplantation due to various factors, including a history of blood transfusion in the early post-transplant period and the presence of anemia or impaired allograft function.

The former may render the test invalid until new hemoglobin is formed and the latter (anemia and kidney impairment) can directly interfere with the A1C assay.

The fasting lipid profile should be measured annually. In transplant recipients with multiple risk factors for cardiovascular disease, more frequent monitoring of the lipid profile should be performed at the discretion of the clinician.

Statins or the HMG-CoA reductase inhibitors are the most widely used lipid lowering agents in the non-transplant and transplant settings.

Hecking et al. recently published a review [149] of the literature about NODAT and kidney transplantation and, after analyzing all studies, concluded that the stepwise approach even for NODAT treatment in stable KTx (not just for NODAT prevention) is not correct, for the following reasons:

(i) During the crucial period up to 6 months post-transplantation when hyperglycemia is prominent and subsequent incidence of overt (or full-blown) NODAT is highest [69,150,151], the disease does not begin insidiously, as T2DM, but has a much faster onset, even if hyperglycemia may have been overlooked early after transplantation. Thus, the treatment should be more aggressive, and not solely focused on lifestyle interventions, in order to restore normal glucose metabolism. The 'TIP-study' (Trial of Basal Insulin in Post-transplant Hyperglycaemia) [152] demonstrated that injection of relatively high daily doses of basal insulin early after transplantation induced very favorable metabolic outcomes (73% lower odds of NODAT) and significantly lower HbA1c in the basal insulin treatment group compared with the standard-of-care control group throughout 1 year of follow-up. In addition, significantly improved β -cell function in this exemplary case and in the entire treatment group, in comparison to the control group [152], suggests that early insulin therapy may genuinely protect β -cells against the deleterious NODAT-causing factors (ii) In view of the reported evidence indicating that NODAT is predominantly an insulin secretion problem, oral agent monotherapy - especially with sulphonylureas - may even aggravate beta-cell decline via islet cell exhaustion. (iii) Even in T2DM, β-cell preservation is becoming a major focus [153-155]. In hyperglycemic KTx, as well as stable KTx with full-blown NODAT, insulin can be more easily administered than in type 2 diabetics because glucose levels are likely higher early on, patients are used to complex medications and have frequent control visits.

Authors suggest novel recommendations for intermittent insulin therapy first, potentially even for treating overt NODAT in stable KTx. They suggest avoiding sulphonylureas, due to the risk of β -cell exhaustion. DPP-4 inhibitors (gliptins) and biguanides (metformin) may be more reasonable alternatives in view of their specific advantages and adverse effects [156,157]. Alpha-glucosidase inhibitors and thiazolidinediones (TZDs) are not irrational choices, but these agents seem harder to endorse, due to the public debate concerning TZD safety [158] and knowing that many patients will not accept acarbose because of frequent diarrhea and flatulence.

There is currently an ongoing debate regarding the safety of metformin in the complicated transplantation milieu and polypharmacy of KTx [159].

Obesity treatment

The World Health Organization categorizes obesity according to body mass index (BMI) ranges (overweight, 25-29.9 kg/m²; class I obesity, 30-34.9 kg/m²; class II obesity, 35-39.9 kg/m²; and class III obesity, ≥ 40 kg/m²) and has affirmed that the worldwide prevalence of obesity has doubled since 1980. Between 1986 and 2000, the prevalence of class III obesity quadrupled, and the prevalence of BMIs ≥ 50 kg/m² quintupled [160]. The 2008/2010 World Health Organization statistics determined that more than 1.5 billion adults are overweight and more than 200 million men and nearly 300 million women were found to be obese. It is even more worrisome that 43 million children less than 5 years old were found to be overweight.

Obesity is a serious health concern because it is a major risk factor for many diseases, including diabetes, hypertension, hyperlipidemia, cardiovascular diseases, chronic liver disease and cirrhosis, musculoskeletal disorders, renal disease, and malignancies.

Anorexia and wasting accompanies chronic liver disease and traditionally has required pre-transplant nutritional strategies aimed at maintaining or increasing body weight. However, the current epidemic of obesity has also impacted patients with end-stage liver disease, and may be either the primary cause of liver disease or at least a contributing factor in the patient's liver disease [160,161]. As mentioned before, NASH is the most rapidly rising indication for LTx in the United States and is projected to become the most common indication [162]. While obese patients may be transplanted with medium-term outcomes similar to non-obese patients [160-163], the long-term impact of obesity on post-LTx outcomes including recurrence of NASH and HCV is becoming increasingly evident [164-166]. Additionally, obesity is strongly associated with diabetes, heart disease and cancer which are leading causes of morbidity and mortality post-LTx [167].

Options for weight reduction for obese patients in need of organ transplant include a non-invasive approach of rigorous dietary and behavioral modification employed both pre and post-transplantation.

However, the non-invasive approach may not be successful for all patients, particularly those with long-standing severe obesity.

Concurrently, bariatric surgery has emerged as a successful treatment modality for morbid obesity [168]. Little evidence exists to support an optimal treatment pathway for morbid obesity in transplant recipients.

From a review of literature, there are many case-reports describing bariatric surgery performed before, after or in combination with organ transplant [169-177]. The bariatric surgical techniques used are various: gastric banding, sleeve gastrectomy, gastric bypass. All of these reported cases had minimal complications, and patient outcomes

appeared satisfactory. However, these studies enrolled a maximum of 3 patients and the time of follow up was different.

There are 3 studies, enrolling seven to thirty obese subjects, analyzing the effect of bariatric surgery performed at different times with respect to transplant (Table 6). All the studies found a reduction of BMI and of MS comorbidities, but the complications were very different, including re-intervention and death.

The main points that need to be addressed are: a) surgical technique (gastric bypass, gastric banding or sleeve gastrectomy) to be used; b) the time-table of intervention with respect to organ transplantation; c) eligibility criteria for obesity-surgery or specific contraindications in organ related pathology requiring transplantation.

Gastric bands may limit access to the GI tract for postoperative complications such as biliary stricture, though gastric bands are usually adjustable so there may not be a limitation to endoscopic access. In addition, there may be a theoretical increased risk of erosion of the band through the gastric wall in a patient on long-term immunosuppression as well as a decreased efficacy in achieving weight loss compared to gastric bypass.

In liver transplantation, the operations (Roux-Y-bypass and biliopancreatic diversion) were technically demanding procedures due to the altered surgical field from the prior LTx.

A sleeve gastrectomy is a procedure that does not interfere with future access to the biliary system should post-transplant complications arise. The effect on immunosuppressant medication absorption is presumably less than the mal-absorptive procedures, but there are no data about this topic. In addition, the weight loss experienced is generally more gradual, since it is only a restrictive procedure and not a mal-absorptive procedure, thus avoiding the rapid weight loss that may be a risk for liver injury. The benefits of combined surgery are that it involves a single operation and recovery for the patient, and thus avoids a potentially more hostile re-operative field, as well as avoiding other barriers to weight loss surgery such as delays due to complications like rejection, infection or disease recurrence [178-181]. The disadvantage is the potential for increased complications. The role of bariatric surgery in the context of solid organ transplantation continues to evolve. Combined liver transplant plus sleeve gastrectomy appears technically feasible in selected patients, though it is not without risk. Careful follow-up to avoid malnutrition and excessive weight loss is necessary. Long-term outcomes regarding durability of weight loss, impact on MS and other unanticipated complications must also be addressed.

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