Obesity, metabolic syndrome and diabetes mellitus after renal transplantation: Prevention and treatment

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A B S T R A C T

The prevalence of the metabolic syndrome in dialysis patients is high and further increases after transplantation due to weight gain and the detrimental metabolic effects of immunosuppressive drugs. Corticosteroids cause insulin resistance, hyperlipidemia, abnormal glucose metabolism and arterial hypertension. The calcineurin inhibitor tacrolimus is diabetogenic by inhibiting insulin secretion, whereas cyclosporine causes hypertension and increases cholesterol levels. Mtor antagonists are responsible for hyperlipidemia and abnormal glucose metabolism by mechanisms that also implicate insulin resistance. The metabolic syndrome in transplant recipients has numerous detrimental effects such as increasing the risk of new onset diabetes, cardiovascular disease events and patient death. In addition, it has also been linked with accelerated loss of graft function, proteinuria and ultimately graft loss. Prevention and management of the metabolic syndrome are based on increasing physical activity, promotion of weight loss and control of cardiovascular risk factors. Bariatric surgery before or after renal transplantation in patients with body mass index > 35 kg/m^2 is an option but its long term effects on graft and patient survival have not been investigated. Steroid withdrawal and replacement of tacrolimus with cyclosporine facilitate control of diabetes, whereas replacement of cyclosporine and mtor antagonists can improve hyperlipidemia. The new costimulation inhibitor belatacept has potent immunosuppressive properties without metabolic adverse effects and will be an important component of immunosuppressive regimens with better metabolic risk profile. Medical treatment of cardiovascular risk factors has to take potential drug interactions with immunosuppressive medication and drug accumulation due to renal insufficiency into account.

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Renal transplantation is the treatment modality of end-stage renal disease offering the best improvement of life expectancy and quality of life. For many decades the effective prevention of acute and chronic rejection has been the main focus of interventions to prevent graft loss and ultimately patient death.

Although transplantation decreases the risk of cardiovascular disease as compared to patients on dialysis the annual risk of cardiovascular incidents and mortality remains ten to fifty-fold higher than in the general population [1]. With the increasing efficacy of immunosuppressive regimens and a lower incidence of early graft loss, long term graft and patient survival increasingly depends on the efficient prevention of cardiovascular morbidity and mortality [2].

1. Pathogenesis of the metabolic syndrome

In the general population the metabolic syndrome is a group of linked metabolic abnormalities that is strongly associated with the development of atherosclerotic cardiovascular disease (reviewed in [3–5]).

Although the pathophysiology of the metabolic syndrome is incompletely understood, upper body or central obesity, which is strongly associated with insulin resistance, plays a key role in its development. The large volume of upper body and particularly visceral fat in obese subjects generates increased amounts of circulating free fatty acids by lipolysis of triglyceride-rich lipoproteins. Circulating fatty acids cause insulin resistance by inhibition of downstream signaling from the insulin receptor. Insulin resistance in the liver is associated with overproduction of VLDL, hypertriglyceridemia, reduction in HDL cholesterol and increased amounts of atherogenic small and dense LDL. Insulin resistance also prevents the inhibition of hepatic neoglucogenesis and glucose uptake by muscle and adipose tissue. This results in impaired fasting glucose and glucose intolerance, which are predisposing factors for the development of type 2 diabetes. Obesity and insulin resistance are also associated with arterial hypertension by mechanisms that remain poorly understood [5].

Patients with the metabolic syndrome frequently have increased markers of inflammation such as C-reactive protein and interleukin-

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6 [6,7]. CRP has been associated with the development of cardiovascular complications [7,8]. In addition, CRP and IL-6 have been described as risk factors for the later development of diabetes mellitus [9].

In the US obesity prevalence has doubled in adults aged 20 years or more between 1980 and 2002, with currently more than half of the population being overweight or obese [10,11]. At the global scale mean BMI has also risen significantly every decade between 1980 and 2008 [12] with parallel rises in mean fasting plasma glucose and prevalence of diabetes [13].

Similar to the general population the prevalence of obesity and the metabolic syndrome has been on the rise in candidates for renal transplantation and renal transplant recipients. This is largely due to the increasing proportion of patients who develop ESRD due to metabolic diseases such as type 2 diabetes, renal vascular disease and arterial hypertension, which are linked with excessive weight, and also due to the increasing age of the dialysis population. USRDS data of more than 160,000 candidates for kidney transplantation effectively showed that the proportion of obese patients more than doubled from 12.3% to 25.8% between 1990 and 2003, whereas the proportion of morbidly obese (BMI > 35) increased from 3.5% to 8.4% in the same period [14].

2. Contribution of immunosuppressive medication to the metabolic abnormalities of the metabolic syndrome

In addition to the high prevalence of obesity as a classical risk factor for the metabolic syndrome the majority of immunosuppressive medications used in organ transplantation have a detrimental impact on one or several of the component criteria of the metabolic syndrome.

2.1. Corticosteroids

Steroids cause a wide range of metabolic abnormalities that are instrumental in the post-transplant metabolic syndrome. Steroids directly inhibit insulin signaling in skeletal muscle and the liver which reduces postprandial glucose uptake and impairs inhibition of hepatic glucose production. Steroids enhance hepatic VLDL production and lipolysis in adipose tissues thereby increasing circulating triglycerides and free fatty acids, which further increases insulin resistance (reviewed in [15]). Steroid use has been shown to increase blood pressure and steroid withdrawal in transplant recipients is associated with a significant reduction in blood pressure [16]. In addition, steroid use has been associated with weight gain of 4%–8% [17,18] although this observation has not been consistent after organ transplantation. Overall, the pattern of metabolic abnormalities caused by steroids is very similar to that seen in patients with the metabolic syndrome.

2.2. Mtor antagonists

Similar to corticosteroids, mtor antagonists sirolimus and everolimus reproduce and reinforce key metabolic hallmarks of the metabolic syndrome. Hyperlipidemia with increased levels of both cholesterol and triglyceride is frequently observed in transplant recipients treated with these agents [19] and is related to an increase in ApoB100, a key component of triglyceride rich lipoproteins, presumably by reduced receptor mediated clearance [20,21]. Sirolimus also causes a marked increase in circulating free fatty acids in addition to triglycerides, which is compatible with increased lipolysis and a reduction of insulin-mediated peripheral storage of triglycerides [22]. Mtor is an integral part of the insulin receptor and recent studies have shown that sirolimus causes insulin-resistance by inhibiting the downstream signaling cascade after receptor binding [23,24].

Mtor antagonists are also strongly associated with post-transplant diabetes [25–30]. The mechanism is complex implicating both insulin resistance due to interference with receptor signaling [23,24] as well as inhibition of insulin secretion which prevents hyperinsulinemia in response to insulin resistance [24,31].

2.3. Cyclosporine

Cylosporine is known to cause hyperlipidemia with marked increases in total and LDL cholesterol as well as triglycerides [32–36].

Cyclosporine also causes arterial hypertension (Reviewed in [37]) [32]. The hypertensive effect has been observed in numerous clinical trials and was recently confirmed in the BENEFIT and BENEFIT-EXT trials [36].

2.4. Tacrolimus

Insulin secretion by pancreatic beta cells depends on the activation of a calcineurin/nuclear factor of activated T cells (NFAT) dependent signaling pathway [38]. The higher diabetogenicity of tacrolimus as compared to the other calcineurin inhibitor cyclosporine has been attributed to high levels of FK506 binding protein, the intracellular ligand of tacrolimus, in pancreatic beta cells [39]. The inhibitory effect of tacrolimus on insulin secretion in response to glucose load has been documented after renal transplantation [40,41].

3. Definition of the metabolic syndrome

There have been several definitions of the metabolic syndrome that have been progressively adapted over time, thus creating a degree of uncertainty and overlap when comparing data published in the literature [3]. Currently there are two main definitions based on clinical criteria and standard laboratory assessments that are easily applicable in clinical practice. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria [42] and the 2005 International Diabetes Foundation (IDF) criteria [4] are both based on the same set of 5 component criteria (central obesity assessed by waist circumference, impaired fasting glucose or diabetes, elevated triglycerides, reduced HDL cholesterol, elevated systolic and/or diastolic blood pressure). Three of the 5 component criteria are required for the diagnosis of metabolic syndrome (Table 1). The two classifications differ mainly in the mandatory requirement for central obesity, based on waist circumference, in the IDF criteria. The ATP III criteria allow the diagnosis of metabolic syndrome in the absence of

Table 1
Comparison of NCEP ATP III and IDF diagnostic criteria for metabolic syndrome.

	NCEP ATP III[a]	IDF[b]
Waist circumference		
Men	≥102 cm	≥94 cm[c]
Women	≥88 cm	≥80 cm[c]
Triglycerides	≥150 mg/dl	≥150 mg/dl
HDL cholesterol		
Men	<40 mg/dl	<40 mg/dl
Women	<50 mg/dl	<50 mg/dl
Blood pressure		
Systolic	≥130 mmHg	≥130 mmHg
Diastolic	≥85 mmHg	≥85 mmHg
Fasting glucose	≥110 mg/dl	≥100 mg/dl

[a] National Cholesterol Education Program Adult Treatment Panel III criteria. Metabolic syndrome defined by any three of the five component criteria.
[b] International Diabetes Foundation Criteria. Metabolic syndrome defined by increased waist circumference in combination with at least two out of any of the four remaining component criteria.
[c] Values for Europids. Country-specific values for waist circumference provided in [4].