Metabolic syndrome, insulin resistance, and chronic allograft dysfunction

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Metabolic syndrome (MS) is a cluster of cardiovascular (CV) risk factors (hypertension, dyslipidemia, obesity, and glucose homeostasis alterations), and insulin resistance (IR) is suggested to be a common pathogenic background. In the general population, MS and IR have been proven to be risk factors for diabetes, CV disease, and chronic kidney disease. In the renal transplant setting, few studies have analyzed the relevance of MS and IR. According to the few data available, the prevalence of MS in renal transplant patients has been described as 22.6% at 12 months, 37.7% at 36 months, and 64% at 6 years after transplantation. Importantly, MS has been shown to be an independent risk factor for chronic allograft dysfunction (CAD), graft failure, new-onset diabetes, and CV disease. Also, persistent hyperinsulinemia during the first posttransplant year has been related to an increase in glomerular filtration rate, probably reflecting glomerular hyperfiltration as observed in prediabetes and early type 2 diabetes. Importantly, prediabetes (impaired fasting glucose and impaired glucose tolerance), a state hallmarked by IR, proved to be highly frequent among stable renal transplant recipients (30%), which is nearly three times its incidence in the general population. Posttransplant IR has been associated with subclinical atheromatosis as assessed by carotid intima-media thickness, and with chronic subclinical inflammation. In conclusion, MS and IR are important modifiable risk factors in renal transplant recipients, and prompt interventions to avoid its deleterious effects at the metabolic, CV, and graft function levels are needed.

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Metabolic syndrome (MS) is a cluster of 'classic' cardiovascular (CV) risk factors including obesity, hypertension, dyslipidemia, and alterations in glucose metabolism.[1] More recently, some 'non-classical' risk factors such as chronic subclinical inflammation,[2] microalbuminuria,[3] hyperuricemia,[4] and alterations in thrombosis and fibrinolysis[5] have been associated with MS. However, more important than the number or type of components is the fact that this clustering of risk factors may have a common pathogenic background, namely, insulin resistance (IR).[6]

Thus, MS may be considered as a practical approach to the more complex state of IR. As a consequence, MS has received an extensive acceptance in the medical community. In a short period of time, MS proved to be a risk factor for new-onset diabetes and CV disease in the general population.[7,8] This review will try to underscore the importance of both MS and IR in renal transplantation, mainly as a possible pathogenic factor for chronic allograft dysfunction (CAD).

RATIONALE FOR THE RELATIONSHIP BETWEEN MS AND CAD

Although both immunological and non-immunological risk factors for CAD have been described, the elucidation of its mechanisms remains incomplete.[9] From a temporal view, some risk factors have an early and others a late influence in CAD.[10] Importantly, some late non-immunological risk factors for CAD include hypertension, dyslipidemia, obesity, and new-onset diabetes, which proved to induce CAD separately[9,10] and not as forming a group of clustering elements. de Vries *et al.*[11] have to be acknowledged for the hypothesis that links MS to CAD in renal transplant patients, which is based on the following: (a) late risk factors for CAD (hypertension, obesity, dyslipidemia, alterations in glucose metabolism) are components of MS; (b) IR is highly frequent in renal transplant recipients; and (c) MS and CAD share common histological findings such as interstitial fibrosis, tubular atrophy, and arterial sclerosis.[11–13]

ARE IR AND MS HIGHLY PREVALENT IN RENAL TRANSPLANT PATIENTS?

Few studies have investigated this issue. In an elegant study, Ekstrand *et al.*[14] compared two groups of renal transplant patients with and without new-onset diabetes (NODAT) after transplantation with healthy subjects. The IR state was assessed by the euglycemic hyperinsulinemic clamp.

Interestingly, transplanted patients who did not develop NODAT proved to be more insulin resistant than healthy controls.

The prevalence of IR in kidney transplant recipients can also be derived from studies analyzing prediabetes (impaired fasting glucose or impaired glucose tolerance), a state highly related to IR.[15] A prospective and multicenter Spanish study showed that the prevalence of prediabetes at 3 and 12 months after transplantation was 36 and 33%, respectively.[16] In addition, in a cross-sectional study of 374 stable recipients with a mean of 4 years after transplantation, a prediabetic state was detected in one-third of them.[17] This figure is nearly three times the incidence in the general population.[18] Moreover, prediabetic recipients showed higher body mass index (BMI), more severe hypertension, higher levels of triglycerides, and lower levels of high-density lipoprotein-cholesterol, as expected from an IR state.[17]

On the other hand, the prevalence of MS in long-term kidney transplant recipients has ranged between 20 and 60%.[19–21] In a historic cohort study of 230 consecutive non-diabetic renal transplant patients, we observed a prevalence of MS of 22.6% at 12 months, which increased to 37.7% after 3 years of follow-up.[20]

WHAT INDUCES IR IN RENAL TRANSPLANT RECIPIENTS?

In the large study by Oterdoom *et al.*, age, BMI, corticosteroid dose, and creatinine clearance were the predominant determinants of IR.[22] The use of β-blockers has also been related to both IR[23] and prediabetic states.[17] Importantly, steroid reduction and withdrawal are associated with an improvement in IR.[24] Thus, the proportion of kidney transplant recipients receiving a steroid-free immunosuppression at discharge is increasing every year.[25]

Renal dysfunction-associated IR is a mechanism not so well studied in the general and renal transplant populations. The kidney is supposed to have an important role in insulin and glucose homeostasis.[26] Therefore, renal function impairment may favor an IR state. In fact, Becker *et al.*[27] have observed that chronic kidney disease patients were more IR than healthy controls and this difference was evident even in patients with minimal renal dysfunction. This finding is relevant, as the majority of transplant recipients are in stages II–III of chronic kidney disease.[28]

EVIDENCE LINKING MS AND CAD

In a cross-sectional study including patients with a mean of 6 years after transplantation, MS was independently associated with lower graft function.[19] Interestingly, when replacing MS by its components, only systolic blood pressure and triglyceride levels were associated with renal dysfunction. Finally, the authors suggest that not all MS components contribute equally to CAD.[19]

In a historic cohort study, 230 non-diabetic renal transplant patients were studied 1 year after transplantation and then followed up for 3 years.[20] The primary outcome was graft dysfunction defined as a 30% decrease in baseline 1/creatinine, an early marker of future graft failure.[29] The outcome was more frequent among recipients with MS at baseline as compared with those without MS (26.9 vs 12.4%; $P = 0.013$). Further, in the multivariate analysis, MS at 12 months more than doubled the risk of graft dysfunction (hazard ratio 2.6, 95% confidence interval 1.3–5.1). As a consequence, graft survival was lower among recipients exhibiting MS 12 months after transplantation.[20] Finally, as previously noted, a different contribution of MS components to graft dysfunction was observed. Only BMI and diastolic blood pressure predicted graft dysfunction when replacing MS by its components.[20]

The reasons why not all elements of MS have the same influence on renal dysfunction are more elusive. It may be speculated that this is reflective of the diverse prevalence of IR in each component. In other words, IR may cluster MS components, but not all patients with a single MS component exhibit IR. In fact, 50% of hypertensive patients and 25% of obese patients are insulin resistant.[30] This is why more accurate and still practical approaches to detect IR in the setting of renal transplantation are needed.

Finally, these data are in agreement with several studies in the general population showing that MS and IR are prominent risk factors for chronic kidney disease.[31,32] In the study by Kurella *et al.*,[32] a Homeostasis Model Assessment for Insulin Resistance test of >2.5 predicted future development of chronic kidney disease, with similar results obtained when replacing Homeostasis Model Assessment for Insulin Resistance by MS.

HOW CAN MS OR IR CAUSE RENAL DAMAGE?

It has been hypothesized that the resistance to the action of insulin typically observed in muscle and adipose tissues is not present in the kidney.[33] As a consequence, the kidney in this situation is exposed to the effects of hyperinsulinemia, and this may contribute to renal dysfunction. Several *in vitro* and *in vivo* studies have observed that insulin stimulates mesangial cell proliferation and production of mesangial matrix.[34] Furthermore, insulin induces the synthesis of insulin-like growth factors, endothelin, and transforming growth factor-β, which favor the synthesis of collagen by mesangial cells and renal interstitial fibrosis.[12,34] Moreover, the renin–angiotensin system, systemic or renal, shows diverse relationships with IR. These include the stimulation by insulin of the hepatic synthesis of angiotensinogen, and a synergistic effect between insulin and rennin–angiotensin system on mesangial cells and vascular contraction at kidney tissue level.[34,35] Further, diverse markers of oxidative stress and endothelial dysfunction are increased in IR.[36] Finally, hyperglycemia, advanced glycation end products, and dyslipidemia (excess of free fatty acid and hypertriglyceridemia), which are common in IR, may induce nephrotoxicity by diverse mechanisms.[37]

Further, IR may induce glomerular and vascular hemodynamic changes. Hyperinsulinemia rends the tubuloglomerular feedback dysfunctional because of an increase in sodium absorption at proximal tubules and in the loop of