Metabolic Syndrome in Kidney Transplantation: Management of Risk Factors

Donald E. Hricik

The metabolic syndrome is a constellation of clinical abnormalities related to insulin resistance and inflammation. The syndrome is now recognized as a risk factor for diabetes and cardiovascular disease in the general population. Recent studies suggest that the metabolic syndrome is common after kidney transplantation, also possibly being predictive of allograft loss and poor allograft function. The development or worsening of obesity plays a central role in the development of metabolic syndrome after kidney transplantation. Immunosuppression also plays an important role in the pathogenesis of the individual components of the metabolic syndrome. In fact, the overriding influence of immunosuppressive medications makes it unclear whether the metabolic syndrome has the same value in predicting outcomes as is true in the general population. However, recent studies suggest that the presence of metabolic syndrome before transplantation predicts the subsequent development of new-onset diabetes after transplantation, independent of other widely known risk factors. Aggressive management of the metabolic syndrome is warranted both before and after transplantation.


Introduction

The concept of metabolic syndrome was first described by Reaven (1) as a combination of central obesity, dyslipidemia, hypertension, and fasting hyperglycemia, all thought to be based on insulin resistance and inflammation as the common pathophysiologic disturbances. In the general population, the presence of metabolic syndrome is associated with a risk for overt diabetes and cardiovascular diseases (2-4). In addition, metabolic syndrome has been associated with proteinuria and reduced GFR (5,6), suggesting a link to chronic kidney disease. To the extent that diabetes (i.e., new-onset diabetes after transplantation), cardiovascular disease, and proteinuria are common complications of kidney transplantation, the role of metabolic syndrome in kidney transplantation recently has attracted a great deal of interest. However, the relevance of the syndrome in kidney transplantation 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 (7). In addition, it remains unclear whether the presence of metabolic syndrome is any better at predicting new-onset diabetes after transplantation than traditional risk factors such as age, ethnicity, family history of diabetes, and obesity (8). Finally, the pathophysiology of the syndrome observed in the general population is dramatically altered by the effects of immunosuppressive medications in kidney transplant recipients. Thus, for this review, management of risk factors focuses on the pathophysiologic role of immunosuppression in each component of the metabolic syndrome and on the role of manipulating immunosuppression for the sake of reducing risk in kidney transplant recipients.

Definitions of Metabolic Syndrome

Two slightly different definitions of metabolic syndrome have emerged from the literature, as shown in Table 1. In contrast to the definition proposed by the Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP) (9), the defining criteria proposed by the International Diabetes Federation (10) incorporate central obesity as an essential component of the syndrome. This is of interest because Armstrong et al. (11) showed that, among kidney transplant recipients, every individual element of the metabolic syndrome is most common in patients with a body mass index of >30 (Figure 1), suggesting a central role for obesity in the metabolic syndrome after kidney transplantation. Recently, Sharif et al. (12) measured insulin sensitivity and C-reactive protein concentrations (as a measure of inflammation) in their kidney transplant population and concluded that the International Diabetes Federation criteria were more closely associated with those putative pathophysiologic components than the NCEP criteria, once again emphasizing the predominant role of obesity in the metabolic syndrome observed after kidney transplantation.

Prevalence and Predictive Value of Metabolic Syndrome in Kidney Transplantation

A number of studies have investigated the prevalence and impact of the metabolic syndrome in kidney transplant recipients. de Vries et al. (13) reported a prevalence of 63% at a median of 6 years (2.6 to 11.4...
years) in a study of 606 renal transplant outpatients. Among 337 patients, Courivard et al. (14) reported a prevalence of metabolic syndrome of 32% 1 year after kidney transplantation. In another analysis of 230 consecutive renal transplant recipients who did not have diabetes and who had stable graft function at 1 year, Porrini et al. (15) noted a prevalence of metabolic syndrome of 22.6%, which increased to 37.7% at the 18-month assessment, suggesting that the prevalence of metabolic syndrome may increase over time. In the last study, transplant recipients with metabolic syndrome before transplantation more frequently developed posttransplantation diabetes during follow-up than those without metabolic syndrome. Of note, these three studies all were based on European populations in which a lower incidence of obesity may underestimate the prevalence and severity of metabolic syndrome in the US population.

More recently, in a multicenter US study designed to assess the value of pretransplantation metabolic syndrome as a predictor of new-onset diabetes after transplantation, Bayer et al. (16) recruited 640 consecutive renal transplant recipients without diabetes and reported that 57.2% had metabolic syndrome before transplantation. Confirming results of the smaller study by Porrini et al. (15), this study reported that 31.4% of patients developed new-onset diabetes after transplantation and that pretransplantation metabolic syndrome was a risk factor for posttransplantation diabetes, independent of recipient age, ethnicity, and cumulative steroid dosage (16). Interestingly, using NCEP criteria, the only individual component of the metabolic syndrome that independently predicted new-onset diabetes was a low concentration of HDLs (16).

Porrini et al. (15) also showed that the presence of metabolic syndrome after transplantation adversely influenced allograft survival (Figure 2). De Vries et al. (13) also similarly showed that metabolic syndrome was associated with reduced long-term kidney function. Patients with metabolic syndrome had a creatinine clearance approximately 5 ml/min lower than the control group of patients after 7 years of follow-up. Among the components of the meta-

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
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<tr>
<td>Waist circumference</td>
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<td>≥135/80</td>
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<td>&gt;110 (recently lowered to &gt;100)</td>
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According to the NCEP Adult Treatment Panel III (9).

According to the International Diabetes Federation (10).

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**Table 1. Definitions of the metabolic syndrome**

*Any three of the five risk factors listed*¹

- Abdominal obesity
  - Men: >40 in
  - Women: >35 in
- Triglycerides (mg/dl)
  - Men: >150
  - Women: >110
- HDL cholesterol (mg/dl)
  - Men: <135/80
  - Women: <100
- BP (mmHg)
  - Fasting glucose (mg/dl)

*Central obesity plus any of the other two listed risk factors*²

- Abdominal obesity
  - Men: >37 in
  - Women: >31.5 in
- Triglycerides (mg/dl)
  - Men: >150
  - Women: >110
- HDL cholesterol (mg/dl)
  - Men: <135/80
  - Women: <100

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**Figure 1.** Incidence of metabolic syndrome (MS), hypertension (HTN), hypertriglyceridemia (Trig), and fasting hyperglycemia (FBG) on the basis of body mass index (BMI) in kidney transplant recipients. Adapted from reference 11.

**Figure 2.** Allograft survival rates in kidney transplant recipients with and without metabolic syndrome (MS). Adapted from reference 15.
bolic syndrome, systolic BP and hypertriglyceridemia had the most negative impact on long-term graft function (13).

**Risk Factor Management**

**Obesity**

Pretransplantation obesity, defined as a body mass index >30, independently increases the risk of graft loss and posttransplantation cardiovascular disease (17). After transplantation, weight gain is common and, in fact, occurs in the majority of kidney transplant recipients (18,19). In a study of 263 consecutive kidney transplant recipients, pretransplantation obesity (defined as >120% of ideal body weight) was associated with more posttransplantation weight gain than in nonobese patients (14.2 versus 2.2 kg after 1 year; P = 0.002) (20). One large, single-center study suggested that weight gain is particularly common in women, black individuals, and low-income patients (18). In addition to indirect effects on graft survival, obesity is associated with a higher incidence of surgical wound infections (20). 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 (19). 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 (21).

**Hypertension**

Elevated BP is extremely common after kidney transplantation and might independently contribute to graft loss (22). Rare forms of secondary hypertension, especially anastomotic renal artery stenosis or stenosis of the arterial tree above the level of the transplant stenosis, should always be considered, especially in patients with worsening hypertension and progressive allograft dysfunction. No single antihypertensive drug or combination of drugs has emerged as a first-line approach to treatment of posttransplantation 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 posttransplantation hypertension (23). Calcium channel blockers, compared with placebo or no treatment (plus additional agents in either arm as required) reduced graft loss (risk ratio 0.75; 95% confidence intervals [CI] 0.57 to 0.99) and improved GFR (mean difference 4.5 ml/min; 95% CI 2.2 to 6.7). Data on ACEIs versus placebo or no treatment were inconclusive for GFR (−8.1 ml/min; 95% CI −18.6 to 2.4) and inconsistent for graft loss, precluding meta-analysis. In direct comparison with calcium channel blockers, ACEIs decreased GFR (11.5 ml/min; 95% CI 7.2 to 15.8), proteinuria (0.28 g/d; 95% CI 0.10 to 0.47 g/d), and hemoglobin (11.5 g/L; 95% CI 7.2 to 15.8 g/L) and increased hyperkalemia (risk ratio 3.7; 95% CI 1.9 to 7.7). Graft loss data were inconclusive (risk ratio 7.4; 95% CI 0.4 to 140.0). These data suggest that calcium channel blockers may be preferred as first-line agents for hypertensive kidney transplant recipients (23). 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 calcineurin inhibitor (CNI) for immunosuppression and when the non-dihydropyridine 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 renoprotective effects of ACEIs in the renal transplant population, despite abundant data supporting this concept in the general population. A single-center retrospective study suggested that use of these agents was associated with improved allograft and patient survival but not death-censored graft survival (24). A larger registry analysis concluded that the use of these agents had no benefit on either patient or graft survival (25). Moreover, use of these agents might be associated with hyperkalemia and anemia (26), 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 reductase inhibitors are effective in lowering LDL cholesterol and in reducing the risk for cardiac events (27). 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 nonfatal 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 posttransplantation 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.
Role of Immunosuppression

Immunosuppressive agents increase the incidence and severity of traditional cardiovascular risk factors and thus have expected effects on components of the metabolic syndrome after kidney transplantation. Corticosteroids negatively affect BP, lipid metabolism, and glucose metabolism and, at least at high dosages, may stimulate appetite and promote weight gain. Older randomized trials demonstrated improvement in all of these parameters with implementation of steroid withdrawal or steroid-free immunosuppression (28). A recent meta-analyses of 34 randomized trials of steroid-free immunosuppression concluded that elimination of steroids was associated with improvements in hypertension, hyperlipidemia, and the incidence of new-onset diabetes after transplantation (29). The last two reports are flawed by their inclusion of older trials in which immunosuppression was dominated by the use of cyclosporine and relatively high dosages of maintenance corticosteroids. Moreover, virtually every meta-analysis performed in the past two decades (spanning several eras of immunosuppression) concluded that elimination of steroids is associated with an increase risk for acute rejection. In a more recent large, placebo-controlled trial in which kidney transplant recipients were randomly assigned to either early steroid withdrawal or steroid maintenance while being treated with induction antibody therapy, tacrolimus, and mycophenolate mofetil, there was also a statistically significant increase in the cumulative incidence of acute rejection in the steroid withdrawal group (30). Importantly, the control group received only 5 mg/d prednisone by the third posttransplantation month. At the end of the 5-year study, there were no significant differences in the incidence of hypertension, hyperlipidemia, or new-onset diabetes (30). On balance, it seems that reduction in steroid dosages might have a beneficial effect on components of the metabolic syndrome. In the case of complete elimination of steroids, the risk for acute rejection may outweigh any additional benefits.

CNIs have a number of adverse effects, including nephrotoxicity that may indirectly promote cardiovascular disease. Compared with tacrolimus, cyclosporine is more commonly associated with hypertension and hyperlipidemia. However, tacrolimus is more commonly associated with glucose intolerance or overt new onset of diabetes (8). In patients who received cyclosporine in combination with mycophenolate mofetil or sirolimus, cyclosporine withdrawal or reduction resulted in improved BP and reduced antihypertensive medication usage (26). In addition, some small studies or anecdotal observations suggested that switching from cyclosporine to tacrolimus improved cardiovascular risk without impairing glucose metabolism (28). Complete withdrawal of either of the CNIs for the sake of improving metabolic parameters is clearly associated with a risk for rejection as has been observed in a number of trials (31–33). Conversion from one CNI to the other for the sake of metabolic benefits has not been tested adequately in large-scale, randomized trials.

The mammalian target of rapamycin inhibitors sirolimus and everolimus are recognized as a major cause of posttransplantation hyperlipidemia (28,34). Sirolimus is also independently associated with new-onset diabetes in kidney transplant recipients (35). Conversion from a target of rapamycin inhibitor to another immunosuppressive agent is a common practice, largely because of the adverse effects of this class of agents, including intractable hyperlipidemia. The adverse effect profiles of sirolimus and everolimus are very similar, and conversions between these agents thus are rarely performed for the sake of improving metabolic adverse effects.

Conclusions

The metabolic syndrome is common after kidney transplantation. The prevalence of this syndrome increases in concert with posttransplantation weight gain. In kidney transplant recipients, the metabolic syndrome is associated with cardiovascular disease, new onset of diabetes, deteriorating graft function, and graft loss. Immunosuppressive medications have an overriding effect on the pathophysiology of the metabolic syndrome, raising questions about its relevance to the syndrome in the general population. In transplant patients, it is not clear whether the metabolic syndrome is any more worthy of study than its individual components.

Disclosures

None.

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