Transplant-Associated Hyperglycemia: Shedding Light on the Mechanisms

Peter P. Reese*†‡ and Roy D. Bloom*

*Department of Medicine, Renal Division, †Center for Clinical Epidemiology and Biostatistics, and ‡Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania

Clin J Am Soc Nephrol 5: 560–562, 2010. doi: 10.2215/CJN.01430210

Transplant-associated hyperglycemia (TAH) encompasses the full range of new-onset, posttransplantation glycemic abnormalities, including the prediabetic states of impaired fasting glucose and impaired glucose tolerance, as well as new-onset diabetes after transplantation (NODAT). TAH is a common transplant-related complication that leads to higher rates of cardiovascular events, death, and allograft loss (1,2). Numerous risk factors predispose patients to TAH; some, such as the use of calcineurin inhibitors (CNIs), impair pancreatic insulin secretion, whereas others, such as obesity, impair insulin sensitivity (3). The study by Hornum *et al.* (1) in this issue of *CJASN* aimed to elucidate the relative contributions of defects in insulin secretion *versus* insulin resistance in the development of TAH. Their results highlight the importance of insulin resistance.

Estimation of the cumulative incidence of TAH depends on the population studied and the surveillance method used. US registry data analysis suggests that 15% of kidney recipients develop clinically diagnosed NODAT by 1 year after transplantation (4). More sensitive methods, such as oral glucose tolerance testing, allow detection of impaired fasting glucose or impaired glucose tolerance that, similar to NODAT, are associated with adverse posttransplantation cardiovascular outcomes (4). Single-center reports using these methods indicate that, *in addition* to patients who are classified as having NODAT, the prediabetic states are present among 30 to 45% of kidney recipients at 1 year after transplantation (1,5,6). Evidence from meta-analyses and clinical trials confirms that TAH occurs in a substantial proportion of transplant recipients and should be a major cause for concern (7–9).

The greater risk for death and cardiovascular complications observed in patients with NODAT is similar to that seen in patients with diabetes in the general population (4). For example, in a single-center study with detailed information about the metabolic profile of kidney transplant recipients, Cosio *et al.* (10) reported an adjusted hazard ratio for mortality of 1.80 ($P < 0.01$) associated with NODAT. Notably, the metabolic milieu of patients with TAH is characterized not just by abnormal glucose homeostasis but also by deterioration in the lipid profile, higher BP, and elevated inflammatory markers. Even after multivariable adjustment for lipids, BP, and inflammation, however, TAH remains an independent risk factor for cardiovascular events (2). A recent analysis of US registry data suggested that for many patients with TAH, mortality becomes an important competing outcome, to the extent that TAH makes it more likely that a patient will die before the allograft fails (11).

An extensive literature on TAH has illuminated the many risk factors for development of TAH. Before transplantation, older age, obesity, hepatitis C infection, family history of type 2 diabetes, and metabolic syndrome increase the probability of subsequent glycemic abnormalities through insulin resistance (3). The association of black race with diabetes also seems to be mediated by insulin resistance, although studies of race-specific mechanisms of disease in TAH are lacking (12). After transplantation, corticosteroid use and weight gain may magnify insulin resistance further (13). Conversely, CNIs, particularly tacrolimus, as well as proliferation signal inhibitors (*e.g.*, sirolimus) impair insulin production from pancreatic β cells. Consistent with the role of medications, the incidence rate of TAH is highest in the early posttransplantation months, when corticosteroid and CNI dosages are usually highest (4). Attempts to decrease TAH risk through steroid-avoidance regimens have met with mixed success. As an example, a recent randomized, double-blinded, controlled, multicenter trial compared steroid withdrawal with long-term low-dosage prednisone (5 mg) in 386 renal transplant recipients who were treated with a tacrolimus and mycophenolate mofetil regimen. By 5 years, there was no significant difference in the rate of NODAT (21.5% in the steroid-withdrawal group *versus* 20.9% in the steroid group) (7).

In this issue of *CJASN*, Hornum *et al.* (1) studied TAH in a cohort of Danish, live-donor kidney recipients who did not have diabetes prior to transplant and who were treated with CNI-based regimens. Unlike most previous studies of TAH, the authors prospectively administered oral glucose tolerance tests before transplantation and 1 year afterward. This approach enabled them to exclude undiagnosed preexisting diabetes (recently reported to be present in approximately 8% of kidney candidates) and to examine changes in response to these oral glucose challenges within individuals during the first posttransplantation year (14). By 1 year, nearly one third of this transplant cohort had worsening of their glycemic status, and

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Roy D. Bloom, Renal Division, 1 Founders Pavilion, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. Phone: 215-662-2638; Fax: 215-349-5176; E-mail: rdbloom@mail.med.upenn.edu

ISSN: 1555-9041/504–0560

14% had NODAT (1). Using an insulin sensitivity index calculated from insulin and glucose levels measured while fasting and during the glucose tolerance test, the authors found that insulin sensitivity worsened after renal transplantation and concluded that insulin sensitivity is the primary mechanism that drives the development of TAH.

These results and their interpretation challenge evidence from animal and human studies suggesting that impaired insulin secretion, caused by CNIs, plays a key role in worsening of glycemic metabolism after transplantation. For example, in a study of rats that were treated with tacrolimus, insulin production declined as a result of decreased messenger RNA transcription (15). In another study of murine pancreatic β cells lines, tacrolimus and cyclosporine inhibited insulin gene transcription that occurs in response to glucose (16). Furthermore, Nam *et al.* (6) assessed insulin resistance among 144 kidney transplant recipients without diabetes by performing insulin tolerance testing before and after transplantation. The insulin tolerance test involves intravenous infusion of insulin and measurement of the slope of subsequent serum glucose decline. Kidney transplantation led to *improvement* in the insulin tolerance test in this cohort of Korean recipients, although comparisons across the cohort after transplantation showed that patients with worse insulin resistance had a greater likelihood of impaired glucose tolerance and posttransplantation diabetes.

The conflicting results of Hornum *et al.* (1) and Nam *et al.* (6) may be related to important differences in the cohorts studied and/or to methods. First, it is possible that the Danish cohort studied by Hornum *et al.* had more insulin resistance as a result of different genetic heritage or clinical characteristics such as a higher mean BMI (24.4 *versus* 20.0 to 21.0 in the Nam cohort). A second alternative seems more likely, which is that assessment of changes in glycemic metabolism after kidney transplantation is rendered problematic by the fact that renal function, insulin sensitivity, and insulin production all may change to varying degrees in different individuals. Specifically, the insulin sensitivity index used by Hornum *et al.* relies on serum glucose and insulin levels. After kidney transplantation, better renal function and faster renal metabolism of insulin would plausibly lead to lower insulin levels and higher glucose levels, but because both are in the denominator of the formula used by Hornum's group, it is unclear which change would be expected in this index even if insulin resistance and secretion remained unchanged. An additional methodologic challenge is that accurate assessment of pancreatic insulin secretory capacity might need confirmation with other methods, such as measurement of c-peptide degradation.

In our view, it is likely that insulin resistance does contribute to the development of TAH. Maintenance of euglycemia requires a balance between insulin secretion and insulin resistance. In new transplant recipients, it is likely that two or more "hits" occur simultaneously, with CNIs impairing insulin secretion at the same time that the many factors that are associated with insulin resistance come into play. The inability to compensate in one or the other direction results in TAH. The importance of insulin secretion is indirectly supported clinically by the well-documented increase in risk for TAH with tacrolimus over cyclosporine, which seems to be mediated by differential effects on pancreatic β cells (17,9). Understanding the relative contributions of insulin resistance and insulin secretory capacity remains a thorny problem whereby multiple factors—including preexisting metabolic syndrome, weight gain, multiple new medications, and resolution of uremia—change the biological milieu of the transplant recipient.

This study from Hornum *et al.* (1) indicates that a renewed focus on improving insulin sensitivity is warranted, especially in the early posttransplantation period. Therapeutic lifestyle change should be emphasized, whereas any minimization/modification of potentially diabetogenic immunosuppressants has to be very carefully counterbalanced by consideration of the risk for compromising allograft outcomes (18). The best way to make use of studies such as that by Hornum *et al.*, however, is to validate the findings in clinical trials. We need empirical evidence about the comparative efficacy of TAH prevention and treatment strategies. If during the next decade new immunosuppressive agents that have similar efficacy to currently used therapies emerge, then their widespread acceptance will likely hinge on a lower cardiovascular risk adverse effect profile. From a diabetes therapy standpoint, the past 5 years has witnessed an impressive expansion in the treatment arsenal; available medications make use of diverse mechanisms that have potential advantages. As an example, comparative studies that involve both thioglitazones, which increase insulin sensitivity, and meglitinides, which potentiate insulin secretion, should be performed. The even newer class of dipeptidyl peptidase-4 inhibitors further has the advantages of less weight gain and hypoglycemia than some other agents (3). Trials with contemporary diabetes agents, besides determining optimal therapy, could ideally lend clues as to the mechanisms of TAH that we can fix and ultimately guide us toward better patient care.

Disclosures

None.

References

1. Hornum M, Jorgensen KA, Hansen JM, Nielsen FT, Christensen KB, Mathiesen ER, Feldt-Rasmussen B: New-onset diabetes mellitus after kidney transplantation in Denmark. *Clin J Am Soc Nephrol* 5: 709–716, 2010
2. Ducloux D, Kazory A, Chalopin JM: Posttransplant diabetes mellitus and atherosclerotic events in renal transplant recipients: A prospective study. *Transplantation* 79: 438–443, 2005
3. Crutchlow MF, Bloom RD: Transplant-associated hyperglycemia: A new look at an old problem. *Clin J Am Soc Nephrol* 2: 343–355, 2007
4. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ: Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 3: 178–185, 2003
5. Cosio FG, Kudva Y, van der Velde M, Larson TS, Textor SC, Griffin MD, Stegall MD: New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int* 67: 2415–2421, 2005
6. Nam JH, Mun JI, Kim SI, Kang SW, Choi KH, Park K, Ahn

CW, Cha BS, Song YD, Lim SK, Kim KR, Lee HC, Huh KB: Beta-cell dysfunction rather than insulin resistance is the main contributing factor for the development of postrenal transplantation diabetes mellitus. *Transplantation* 71: 1417–1423, 2001
7. Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P: A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation *versus* long-term, low-dose corticosteroid therapy. *Ann Surg* 248: 564–577, 2008
8. Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC: Posttransplantation diabetes: A systematic review of the literature. *Diabetes Care* 25: 583–592, 2002
9. Vincenti F, Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, Uchida K, Pescovitz MD, Marchetti P, Tuncer M, Citterio F, Wiecek A, Chadban S, El-Shahawy M, Budde K, Goto N: Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant* 7: 1506–1514, 2007
10. Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, Ferguson RM: Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. *Kidney Int* 62: 1440–1446, 2002
11. Cole EH, Johnston O, Rose CL, Gill JS: Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. *Clin J Am Soc Nephrol* 3: 814–821, 2008
12. Hyatt TC, Phadke RP, Hunter GR, Bush NC, Munoz AJ, Gower BA: Insulin sensitivity in African-American and white women: Association with inflammation. *Obesity (Silver Spring)* 17: 276–282, 2009
13. Hjelmesaeth J, Hartmann A, Kofstad J, Stenstrom J, Leivestad T, Egeland T, Fauchald P: Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. *Transplantation* 64: 979–983, 1997
14. Bergrem HA, Valderhaug TG, Hartmann A, Hjelmesaeth J, Leivestad T, Bergrem H, Jenssen T: Undiagnosed diabetes in kidney transplant candidates: A case-finding strategy. *Clin J Am Soc Nephrol* 5: 616–622, 2010
15. Tamura K, Fujimura T, Tsutsumi T, Nakamura K, Ogawa T, Atumaru C, Hirano Y, Ohara K, Ohtsuka K, Shimomura K, *et al.*: Transcriptional inhibition of insulin by FK506 and possible involvement of FK506 binding protein-12 in pancreatic beta-cell. *Transplantation* 59: 1606–1613, 1995
16. Oetjen E, Baun D, Beimesche S, Krause D, Cierny I, Blume R, Dickel C, Wehner S, Knepel W: Inhibition of human insulin gene transcription by the immunosuppressive drugs cyclosporin A and tacrolimus in primary, mature islets of transgenic mice. *Mol Pharmacol* 63: 1289–1295, 2003
17. van Duijnhoven EM, Christiaans MH, Boots JM, Nieman FH, Wolffenbuttel BH, van Hooff JP: Glucose metabolism in the first 3 years after renal transplantation in patients receiving tacrolimus *versus* cyclosporine-based immunosuppression. *J Am Soc Nephrol* 13: 213–220, 2002
18. Desai NM, Schnitzler M, Jendrisak MD, Brennan DC: Maintenance steroid therapy for kidney recipients: Not ready for relegation. *Am J Transplant* 9: 1263–1264, 2009

See related articles, "Undiagnosed Diabetes in Kidney Transplant Candidates: A Case-Finding Strategy," on pages 616–622, and "New-Onset Diabetes Mellitus after Kidney Transplantation in Denmark," on pages 709–716.