New-onset diabetes is a common complication of renal transplantation. The appearance of this form of diabetes is associated with worsening cardiovascular risk and loss of renal allograft function.1–3 The most important modifiable risks for its appearance are obesity and the choice of immunosuppressant drugs. In a landmark study, Kasiske et al.2 used data from the US Renal Data System and Medicare billing to show the high incidence of diabetes after transplantation is associated with choice of initial maintenance immunosuppression, as well as race, ethnicity, obesity, and history of hepatitis C infection. More important, they found diabetes is a strong, independent predictor of graft failure and mortality. The incidence of new diabetes was higher in patients treated with tacrolimus, confirming an association seen in one of the earliest tacrolimus studies published in 1997.4 In that study, the initial incidence of diabetes (defined liberally as the use of insulin for ≥30 d in patients with no history of diabetes) was 19.9% in tacrolimus-treated patients and 4% in cyclosporine-treated patients. Of the 36 patients who developed diabetes, seven tacrolimus-treated patients and one cyclosporine-treated patient were able to discontinue insulin treatment within the first year. Five of the tacrolimus-treated patients were weaned from insulin without discontinuing tacrolimus or steroid therapy, and two patients discontinued insulin after crossover to cyclosporine. It is important to note that discontinuation of insulin is not the same as return to normoglycemia. As Crutchlow and Bloom5 pointed out, the term “transplant-associated hyperglycemia” encompasses all types of abnormal glucose homeostasis after transplantation.

In this issue of JASN, Johnston et al.6 analyzed data from >20,000 kidney transplant recipients in the US Renal Data System database for associations between particular drug regimens and diabetes. Using an analysis of multiple drug combinations, they found combinations that include sirolimus are also associated with more Medicare billing for diabetes than are drug combinations without sirolimus. The most diabetogenic combination on the basis of these results is the combination of sirolimus and a calcineurin inhibitor. The authors analyzed a subgroup of recipients (n = 16,861) who did not change their immunosuppressive regimen during the first posttransplantation year and found that regimens including sirolimus have an association with diabetes only in the presence of a calcineurin inhibitor. Their analysis did not address the role of induction therapy in the development of diabetes. These new data do not confirm clinical findings from initial sirolimus studies, and, as Johnston et al.6 points out, previous studies on sirolimus-induced diabetes were mixed in their results. Ordinarily this would cast some uncertainty as to the interpretability of all of these findings; however, a growing body of evidence suggests that chronic inhibition of mammalian target of rapamycin (mTOR) with sirolimus leads to exacerbation of hyperglycemia and insulin resistance. Normal sig-

References:


Diabetes after Transplantation and Sirolimus: What’s the Connection?

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New-onset diabetes is a common complication of renal transplantation. The appearance of this form of diabetes is associated with worsening cardiovascular risk and loss of renal allograft function.1–3 The most important modifiable risks for its appearance are obesity and the choice of immunosuppressant drugs. In a landmark study, Kasiske et al.2 used data from the
naling of insulin (and other growth factors) depends on insulin receptor substrate-1 (IRS-1) and mTOR in the IRS-1–AKT–mTOR–S6K cascade. Early in vitro studies suggested sirolimus inhibits IRS-1 degradation, thereby potentially rescuing acute insulin responsiveness in states characterized by chronic insulin stimulation; however, more recent studies showed that long-term mTOR inhibition impairs activation of IRS-1 and AKT and augments insulin resistance and β cell dysfunction in a unique rodent model for metabolic syndrome (Psammomys obesus). Finally, renal transplant patients tested for insulin sensitivity before and after conversion from a calcineurin inhibitor to sirolimus had a significant reduction in insulin sensitivity and β cell function.

Why did the previous article by Kasiske et al. fail to show the same increase in diabetes using a similar patient population and similar methods during a comparable period? The answer is likely that Kasiske et al. did not look at combinations of the medications but rather at single medications as separate risks. Exposure to tacrolimus by itself, for example, was associated with more diabetes, supporting the notion that tacrolimus is diabetogenic. They did not have evidence to implicate sirolimus in a similar manner. If one is to assume that sirolimus is associated with higher rates of diabetes, then the results of these two studies might be hard to reconcile. Alternatively, it is easier to reconcile the findings of Kasiske and Johnston when one assumes sirolimus is not, by itself, associated with diabetes, but rather combining it with tacrolimus makes the known diabetogenic effect of tacrolimus worse. This is the logical conclusion of the presented article, which does not contradict Kasiske’s findings.

For the clinician, the question is how to interpret and possibly use the results of this study to inform practice. It is generally accepted that retrospective analyses like this one serve well as hypothesis generators but have little to add to our knowledge of role of intervention or therapy selection; however, it seems only a very small number of retrospective data analyses are followed by interventional studies. In many cases, prospective clinical trials are simply impossible for the reasons of sample size, costs, or ethical considerations. Then it becomes the clinical judgment of the practitioner to decide whether retrospective data are persuasive enough to change clinical practice. This is where a clear understanding of the limitations of any published study is very important. Epidemiologic literature is saturated with general discussions of the limitations of retrospective studies.

Posttransplantation diabetes is a relatively frequent and unfortunate complication in patients carrying renal allografts. All available information regarding potentially modifiable factors associated with or leading to diabetes should be part of a thoughtful decision-making process regarding the optimal maintenance of immunosuppression. In particular, although diabetes is an important potential complication of transplantation, studies also suggest that graft survival has a more profound impact on patient survival than does the impact of developing diabetes. Many programs already minimize steroid use and provide counseling on weight management. It seems careful consideration of the metabolic condition of patients is needed in determining and monitoring any immunosuppression regimen, especially when using sirolimus and tacrolimus in combination.

DISCLOSURES
None.

REFERENCES