Association of Pre-Transplant C-Peptide with Post-Transplant Diabetes: A New Approach to Identifying High-Risk Patients?

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In the modern era of kidney transplantation, posttransplant diabetes (PTDM) is a major cause of morbidity and mortality for kidney transplant recipients. Studies estimate that 10%–40% of kidney transplant recipients will be diagnosed with PTDM, making it one of the most common complications after transplant, and is associated with increased risk of cardiovascular events and mortality (1–3).

Patients who receive a kidney transplant often have risk factors for developing diabetes common to the general population, including obesity, older age, and family history. However, they also have unique risk factors, including immunosuppressive medications with known adverse metabolic risks, and post-transplant weight gain with subsequent exacerbation of underlying metabolic syndrome (4). Studies have demonstrated that additional risk factors for PTDM include degree of HLA match, cytomegalovirus infection, episodes of rejection, and hypomagnesemia. Although instructive, these risk factors are often challenging to predict pre-transplant and may be difficult to modify.

In this issue of Kidney360, Vinson et al. publish their study examining the association of pre-transplant fasting C-peptide levels with the development of PTDM at 1 year post transplant (5). In their cohort of 132 adult patients without diabetes who underwent a kidney transplant between 2016 and 2021, 25 (19%) patients developed PTDM in their first year after transplant. The authors dichotomized the C-peptide status around the median in their population, at 3000 pmol/L, with patients in either the low or high C-peptide groups. Interestingly, 24 of the 25 patients who developed PTDM were in the high C-peptide group. However, there was no association between pre-transplant C-peptide level and hyperglycemia in the first 2 weeks post transplant nor in the nadir magnesium level.

This study provides evidence that pre-transplant fasting C-peptide may be valuable in identifying kidney transplant recipients who are at high risk of developing PTDM. A similar study in patients with allogeneic stem cell transplant (SCT) also demonstrated that elevated C-peptide levels pre-transplant were associated a higher risk of PTDM at 100 days post SCT (6). Compared with using the currently recommended 2-hour oral glucose tolerance test as a measure of a potential recipient’s glucose metabolism (7), C-peptide is more easily obtained, relatively inexpensive, and can be obtained at the time of transplant or even be monitored serially pre-transplant. Although pre-transplant HbA1c may also be more easily assessed in patients, concomitant anemia and use of erythropoietin-stimulating agents in patients with kidney disease often makes it difficult to use HbA1c as an accurate measurement of glycemic status (8).

The goal of identifying patients at risk for PTDM is to provide early intervention for modifiable risk factors in order reduce the incidence of PTDM and its complications. Using C-peptide as a marker of pre-transplant insulin resistance may allow more targeted interventions to the highest-risk patients.

Pretransplant weight is a known risk factor for PTDM, and weight loss has been shown to reduce this risk (9), with some patients requiring bariatric surgery to improve their candidacy for transplant. Although bariatric surgery clearly leads to weight loss, it is not without risk, and thus patients who will benefit the most from this intervention need to be identified. Vinson et al. demonstrated that in their subset of patients with a BMI of 20–35 kg/m², C-peptide was the only factor that was independently associated with PTDM, making C-peptide attractive as a potential tool to stratify patients with higher BMI who may benefit from targeted weight loss, although further studies demonstrating this would be needed.
Post-transplant immunosuppression also remains a major modifiable risk factor in the development of PTDM. Multiple studies have shown that tacrolimus has an increased diabetogenic risk profile compared with cyclosporine, and that minimizing or avoiding calcineurin inhibitors can reduce the odds of developing PTDM (10,11). However, there is an increased risk of acute rejection in patients maintained on cyclosporine or belatacept instead of tacrolimus. The use of C-peptide to risk stratify patients could allow discussion of the risks and benefits of immunosuppression regimens with patients who have a high risk of PTDM.

Although the use of C-peptide is promising, there are certain limitations to this study. The C-peptide levels of patients were not performed at the same time of day, and as the authors point out, C-peptide varies throughout the day, with highest C-peptide levels in the morning (12). Although the authors did repeat their analysis with C-peptide levels corrected for the potential that all of the elevated levels were obtained in the morning, it did not alter their conclusions. Additionally, C-peptide is cleared by hemodialysis and partially renally cleared, and not all patients had C-peptide obtained pre-hemodialysis, nor was the residual renal function of patients assessed. Finally, this was a small study, with a predominantly White population. Thus, the generalizability of these results in other populations should be assessed.

In summary, in their study of adult kidney transplant recipients without diabetes, Vinson et al. showed pre-transplant C-peptide levels >3000 pmol/L were highly associated with an increased risk of PTDM. Given the increased risk of cardiovascular disease and mortality in kidney transplant recipients with PTDM, early identification of patients at high risk is of paramount importance so that targeted interventions may be employed. Further studies will help clarify the role of C-peptide as a predictor of developing PTDM, which has the potential to be a powerful tool in the evaluation and management of a significant complication in the post-transplant population.

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Author Contributions
E. Joachim wrote the original draft and reviewed and edited the manuscript.

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