COMMENTS AND RESPONSES

Comment on: Chakkera et al. Can New-Onset Diabetes After Kidney Transplant Be Prevented? Diabetes Care 2013; 36:1406–1412

"To a man with a hammer, everything looks like a nail" is a popular metaphor attributed to Mark Twain, also known as the "law of the instrument" and presented in Maslow's *The Psychology of Science: A Reconnaissance* (1). Being ourselves guilty or not of "using only one hammer, and seeing nothing but nails," we would like to comment on the recent review of Chakkera et al. on new-onset diabetes after transplantation (NODAT) (2).

The authors have described our prior proof-of-concept study on early posttransplant insulin administration (3), which has become the basis for currently ongoing NODAT prevention trials exploring strategies of insulin administration (clinical trial reg. nos. NCT01683331 and NCT01680185). Contrasting with the existing guidelines, early insulin administration fits perfectly into the context that impaired insulin secretion, mediated by β-cell dysfunction, could be the predominant pathophysiological feature after renal transplantation, with recent data provided by us and others (4,5), but further, perhaps unrecognized evidence previously available (rev. in 6).

In the past, NODAT development has more strongly been attributed to insulin resistance, which is the hallmark of the metabolic syndrome and thereby type 2 diabetes. The association between metabolic syndrome components and NODAT has undoubtedly been demonstrated. Thus, the hypothesis of Chakkera et al. that NODAT principally results from the same metabolic risk factors as type 2 diabetes, merely altered and enhanced by transplantation and "tipping" patients with seemingly normal glucose homeostasis before transplant, cannot be rejected on reasonable grounds.

However, the intricate relationship of insulin secretion versus resistance in renal transplant patients might be overshadowed by too much emphasis on analogies to type 2 diabetes. We have recently summarized aspects in which NODAT and type 2 diabetes are pathophysiologically different (6).

1. Type 2 diabetes develops slowly, while early posttransplant NODAT has a sudden onset. This is why prevention may be so rewarding, and even more warranted after transplantation than in the general population.
2. Glucose profiles are dissimilar between type 2 diabetic patients and NODAT patients, with NODAT patients displaying a characteristic afternoon peak, not uncommonly followed by normal fasting glucose. Thus long-acting insulin formulations with a "flat" 24-h profile may be less ideal than intermediate-acting insulin formulations, and sulfonylureas, which increase insulin secretion at a constant rate, might not be ideal at all. Besides, the fasting glucose thresholds that define type 2 diabetes are likely too high for NODAT patients.

By clinical logic, transplant patients should therefore self-monitor glucose, especially afternoon and evening blood glucose. Treatment of severe hyperglycemia is probably mandatory. Active lifestyle interventions are superior to passive lifestyle modification advice (7) and ought to be studied more extensively, but we fully agree that they should be incorporated into any structured NODAT prevention program (6). Surpassing the approach proposed so far, we posit that NODAT prevention should be promoted for all patients who become overtly hyperglycemic after transplantation, regardless of their metabolic history. If we focus on patients with type 2 diabetes–related risk factors, we run the risk of missing many hyperglycemic cases and may not become successful in changing the current watch-and-wait approach. NODAT and type 2 diabetes should therefore not be equalized anymore.

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DOI: 10.2337/dc13-1277

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

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