Predicting Diabetes Using Measures of β-Cell Function

Adrian Vella[1] and Alan R. Zinsmeister[2]

Type 2 diabetes causes significant morbidity and mortality, making diabetes prevention a worthwhile goal. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have high rates of progression to type 2 diabetes. In Olmsted County, MN, 40% of people with a fasting glucose ≥110 mg/dL progressed to overt diabetes within a 10-year period, compared with 5% of those with fasting glucose <95 mg/dL (1). What explains why 60% of people with a fasting glucose ≥110 mg/dL did not progress to diabetes? One answer is that IFG encompasses individuals with differing glucose tolerance, some of whom might have normal glucose tolerance (NGT) whereas others have IGT (2). This is supported by the observation that postchallenge glucose concentrations are a better predictor of diabetes risk than fasting concentrations (3).

Maintenance of glucose tolerance is largely dependent on insulin secretion and insulin action—the ability of insulin to stimulate glucose uptake and suppress glucose release. Other parameters that may contribute to defects in glucose tolerance include hepatic insulin clearance, which determines systemic insulin bioavailability (4).

In this issue of *Diabetes*, Giannini et al. (5) examined the progression of glucose intolerance in obese adolescents, seeking to determine whether defects in insulin secretion and action are apparent within the normal range of glucose tolerance (based on 2-h glucose values). Fifty-five subjects with NGT and 20 with IGT were studied on two occasions, ~27 months apart. Insulin secretion was derived from the hyperglycemic clamp and glucose tolerance test (OGTT), whereas insulin sensitivity was measured using a hyperinsulinemic-euglycemic clamp and the OGTT. Glucose tolerance was evaluated at baseline and follow-up, and predictors of follow-up 2-h glucose values were identified (5).

The authors make several interesting observations. One is that there are demonstrable differences in $_{o}$DI (disposition index measured by OGTT) across groupings of individuals within the "normal" range of 2-h OGTT values. In addition, at least in terms of the DI calculated from clamp data ($_{c}$DI) and the dynamic component of insulin secretion (σ^1), no differences are apparent between individuals with IGT and those with a 2-h glucose value in the 120–139 mg/dL range. Finally, using a multiple stepwise regression analysis among subjects with NGT, age and $_{c}$DI were the best predictors of 2-h glucose and therefore of conversion to IGT.

Although the relative importance of changes in insulin secretion and action in the temporal progression from NGT to IGT and overt diabetes has been debated, there are few studies in which β-cell function and insulin action were measured longitudinally. As such, this article is a step in the right direction. Insulin secretion and insulin action are both impaired in people with prediabetes and decline in tandem across the spectrum of glucose intolerance (2,6). This is supported by OGTT data despite use of an insulin-based measure of insulin secretion, which correlates weakly with acute insulin response (7). Insulin in the systemic circulation has undergone hepatic extraction (8), a process altered by factors such as obesity (9,10) or β-cell function (2,11). Consequently, reliance on insulin-based measures of secretion when comparing subjects with differing hepatic extraction can introduce a systematic error into such comparisons.

Although data from a frequently sampled OGTT can be used to generate accurate indices of insulin secretion and insulin action (12), the indices in this study relied instead on 0, 30, and 120 min measures of glucose and insulin. Given this limitation, it is not surprising that $_{c}$DI performed a little better than $_{o}$DI (or 2-h glucose values at study entry) in predicting IGT. Giannini et al. do not provide the predictive usefulness of the models they evaluated (e.g., R^2 values), or the corresponding partial R^2 values for the variables included in each model. Thus, although it appears that DI values outperformed the predictive usefulness of the (study entry) 2-h glucose values, it is difficult to make an accurate assessment without these details (and corresponding partial regression plots).

As regards the lack of differences between subjects in the upper boundaries of NGT and those with IGT, it is important to point out the variability of 2-h glucose values in a given individual, which can result in reclassification of glucose tolerance status when using discrete categories of glucose tolerance (13). Subjects within a narrow band of glucose values (e.g., 140 ± 10 mg/dL) may not differ that dramatically in terms of β-cell function.

Testing the integrity or degree of abnormality of a feedback-control system where glucose concentrations are closely regulated by insulin is perhaps best accomplished by using methodology that allows simultaneous measurement of insulin action and β-cell responsivity (4). Moreover, an oral challenge is perhaps a better reflection of normal physiology since it captures the incretin contribution to insulin secretion that may be another source of variation in response to meal challenges. Nevertheless, at present there is no good evidence to suggest—at least for the hormonal component of the insulin response—that differences in incretin hormone secretion contribute to the pathogenesis of prediabetes or diabetes (14,15). Finally, the relationship of insulin secretion to insulin action as reflected in the DI may differ across categories of glucose tolerance, and this may need to be accounted for in cross-sectional comparisons (16).

In conclusion, functional tests ranging in complexity from fasting and postchallenge glucose concentrations to

From the [1]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minnesota; and the [2]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota.
Corresponding author: Adrian Vella, vella.adrian@mayo.edu.
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qualitative functional measures have been used to predict progression to diabetes. It remains to be ascertained if more sophisticated model-based measures of insulin secretion can help individualize diabetes risk and predict individual response to other secretagogues (including pharmacotherapy). The goal of using functional measures to characterize β-cell "integrity" and "mass" remains tantalizingly over the horizon. However, a systematic understanding of the limitations and the strengths of existing measures as well as the gaps in our knowledge base will enable us to chart a course to this destination.

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