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Using Oral Challenge Testing to Assess Insulin Action and Secretion With Mathematical Modeling

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COMMENTARY

There is no optimal method to measure insulin resistance or insulin secretion in large clinical studies or in clinical practice. The convenient methods that have been proposed as suitable for large clinical studies have been subject to criticism for limitations when studying individuals with diabetes and with different etiologies of glucose dysregulation, or in populations of diverse racial and ethnic backgrounds (1–3). It has also been pointed out that some methods reflect only part of the complex relationships that define glucose-insulin homeostasis (3,4). There is broad consensus among the scientific community that with the euglycemic-hyperinsulinemic clamp, insulin resistance can be measured (5,6), and by hyperglycemia clamping, measurement of insulin secretion is possible (5,6). Additionally, scientific consensus is that the minimal model used with the frequently sampled intravenous glucose tolerance test (FSIVGTT) provides reliable measures of both insulin secretion and insulin resistance (7). However, these testing regimens required specially trained personnel and are labor intensive, limiting their use to specialized research centers and, for practical purposes, to application in limited numbers of subjects.

Standing somewhat in contrast to the sophistication of procedures like the glucose clamp or the FSIVGTT has been an unadorned oral glucose tolerance test (OGTT). An OGTT is a well-established clinical test with translatable diagnostic parameters and can be performed in most clinical centers, and indeed can be used in large clinical trials (8,9). Many investigators have worked to amplify the knowledge that can be garnered from the OGTT. An extensive body of data have been developed using glucose tracers to study splanchnic uptake and peripheral delivery of ingested glucose and the effect on endogenous glucose production and on systemic glucose disposal. Combining indirect calorimetry with an OGTT has enabled investigation of the partitioning of glucose disposal into oxidative and nonoxidative pathways. With measurement of plasma C-peptide, in addition to glucose and insulin, rates of insulin secretion can be determined. Thus, there is abundant precedent that with a layering of sophisticated methodologies, the complex physiology underlying glucose tolerance can be investigated and measured. These approaches have certainly enriched and informed the understanding of the pathophysiology of diabetes and shed light on the mechanisms by which interventions in diabetes and prediabetes improve glucose intolerance. Yet, for the most part, these elegant methodologies used as adjuncts to the OGTT, except for the C-peptide–based assessment of insulin secretion, are not feasible in large clinical studies. In this issue, Cobelli et al. (10) provide a review of their efforts over the last decade to bridge these gaps through development of a modeling-based approach that enables extraction of the richly complex and dynamic glucose-insulin homeostasis contained beneath the surface of the plasma glucose response to an OGTT (or a mixed-meal tolerance test [MTT]). Among the promising potentials of their efforts is a platform that can be used for small intensive investigations and yet is also scalable for large studies.

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An intuitive appeal of using an OGTT or an MTT as a basis for investigating diabetes and prediabetes is that these procedures more closely emulate daily habits of nutrient ingestion than do an intravenous bolus or continuous infusion of glucose (11,12). Further, these procedures evoke incretin and other gut hormone release that have a marked effect upon islet physiology, and in the contemporary context of treatments for type 2 diabetes, tests that include incretin physiology are clearly germane. Additionally, the MTT may have some advantage over the OGTT as it is better tolerated by subjects. Cobelli et al. describe their approach to model the data from an OGTT and an MTT into constituent components of insulin action, secretion, and hepatic extraction as an oral minimal model, paying deserved homage to the groundbreaking work of the FSIVGTT-based minimal model. One of the several important contributions of the minimal model has been the impetus and data it provided for the notion of the disposition index (DI). Understanding (and parameterizing) the reciprocity between insulin secretion and action that normally holds in governing glucose homeostasis has a lot of appeal in gauging responses to intervention, pharmacological or otherwise, and adds valuable mechanistic insights complementary to the glycemic and insulin responses.

Approaches to estimate insulin secretion and insulin action derived from an OGTT are not unprecedented, and the limitations of these parameters have been previously reported by others (1–4). At the crux of these limitations is whether insulin action can be deduced during the nonsteady conditions of an OGTT or MTT. In the past few years, Cobelli and colleagues (13–16) have modeled data obtained from oral stimulation tests to obtain estimates of insulin secretion and resistance and have reported that the values obtained are comparable to those obtained from either the FSIVGTT (17) or clamp (18). The correlations between oral minimal model estimation of insulin sensitivity with those of the FSIVGTT and clamp appear to be reasonably strong and this is quite encouraging. This is the aspect of the oral minimal model that will likely draw close scrutiny as the method becomes more broadly used, and especially so if its parameters of insulin sensitivity are foci of specific interest. The euglycemic-hyperinsulinemic clamp has stood the test of time as a gold standard ascertainment of insulin action and will not be easily dislodged, particularly in the context of detailed mechanistic studies of relatively small sample size. But arguably the findings emerging from the work on the oral minimal model open a potential for a new level of mechanistic sophistication that can be employed in large clinical studies.

Cobelli et al. (10) summarize the characteristics and benefits of using mathematical modeling of data obtained from an orally administered nutrient challenge, which could be either a mixed meal or glucose. The authors do an admiral job of explaining the assumptions behind the model, and for those willing to invest the time to understand each of the equations, these are clearly described and allow for deeper understanding of the parameters of insulin action and secretion. For those without the interest or time to dive into the equations provided, Figs. 2 and 3 provide an understanding of how the use of compartments minimizes the complexity of the system and allows for separate estimates of insulin sensitivity (from insulin and glucose levels), insulin secretory responsiveness (from glucose and C-peptide), and hepatic extraction of insulin (from glucose, insulin, and C-peptide). As all models have assumptions and thus do not provide precise measurements but only estimates, dividing the entire glucose-insulin homeostatic system into these three compartments reduces the error and bias in each compartment. The authors point out that the insulin secretory parameters are higher and those for insulin sensitivity lower with an MTT rather than with an OGTT, but despite these differences, for a given individual, the two challenges result in a similar DI.

The oral minimal model provides a welcomed, less invasive, and practical method for assessing insulin sensitivity and secretion in clinical studies. It will indeed be a major methodological advance if it can be affirmed that the oral minimal model provides estimations of insulin action and secretion that are considered with the same confidence as values obtained from the gold standards of the euglycemic or hyperglycemic clamp. Given the need for at least 3 h of testing (and for many patients with type 2 diabetes, 4 h of testing) and at least 8 to 10 time points for blood sampling, this is a methodology that will likely remain useful for subsets of subjects in larger clinical trials. Efforts are under way by others to evaluate even simpler sampling schemes with the use of widely available standard mixed-meal stimuli for use in larger scale trials. The β-Cell Function project sponsored by the Biomarkers Consortium is one such effort that is ongoing and only recently beginning to report results (19). Having an easy-to-perform, practical method of measuring insulin sensitivity and secretion remains a goal for the future. Such a tool will facilitate research, and ultimately one would hope it might help clinicians to target personalized medicine for patients. The development of the oral minimal model holds promise as an important step toward this goal.

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