Point: HOMA—Satisfactory for the Time Being

HOMA: The best bet for the simple determination of insulin sensitivity, until something better comes along

There is no doubt that the cluster of clinical and metabolic features associated with insulin resistance predicts risk of developing type 2 diabetes and cardiovascular disease (CVD) (1); however, whether there is merit in defining a syndrome is less clear (2). There is also a lack of agreement regarding the value of measuring insulin sensitivity in clinical practice (3). The widely used criteria for defining the metabolic syndrome (those recommended by the World Health Organization [4] and the Adult Treatment Panel III [5]) includes a measure of insulin resistance in the definition of the syndrome. A very recent approach suggested by a group representing the International Diabetes Federation involves identifying individuals with central obesity and a range of clinical and metabolic parameters associated with insulin resistance; however, it does not include a direct measure of insulin sensitivity (6). It is argued that measures of insulin resistance do not predict CVD when other more easily measured components of the metabolic syndrome cluster are present, and these measures based on fasting insulin are unreliable (3). However, measurement of insulin sensitivity has greatly enhanced the understanding of the pathophysiology of diabetes and relationships to cardiovascular outcomes (7). Dismissing the assessment of insulin sensitivity because its measurement is too variable or difficult (3) is understandable, but hardly desirable, as one major dimension of altered metabolism will be omitted from research and clinical assessments. It may prove to be much the same as assessing cardiovascular risk without serum cholesterol. A truly reliable simple measure may prove to be more appropriate than an aggregation of surrogates in predicting subsequent development of diabetes and CVD and in further explaining disease progression and response to treatment.

Several reviews (8,9) describe some of the numerous methods for measuring or estimating insulin sensitivity. The different methods do not necessarily measure the same effect, even if they correlate well with accepted accurate methods. The euglycemic insulin clamp, which provides highly reproducibly (coefficient of variation [CV] 6–10%) (8) steady-state estimates of insulin-mediated glucose clearance in peripheral tissues, is generally regarded as the gold standard. The test uses very high-dose infusions of glucose and insulin to almost completely suppress hepatic glucose uptake and pancreatic insulin secretion. The euglycemic insulin clamp may be criticized on the grounds that it is an assessment in a nonphysiological state and that the test yields different results if performed at different infusion rates, suggesting saturable peripheral glucose uptake; hence, there is underestimation of actual insulin sensitivity. As a result, studies using very different insulin infusion rates cannot be compared (10). Non–insulin-dependent glucose uptake, such as the constant uptake by the brain and central nervous system, are not separately accounted for and included in the final measure of insulin sensitivity. In addition, the procedure is time consuming, expensive, reasonably difficult to perform, and not suited to population studies, large intervention trials, or clinical practice.

The intravenous glucose tolerance test, using Bergman's minimal model, has been extensively used in relatively small research studies and compares favorably with the euglycemic insulin clamp, although it is considerably less reproducible (CV 14–30%) and is just as arduous to undertake (8,11,12). Various modifications have been made in an attempt to improve its reliability. These modifications include the infusion of tolbutamide to trigger a pancreatic response, an injection of insulin 20 min after glucose administration, the addition of glucose tracers to separate the effects of glucose production and utilization, and several different methods to enhance the minimal model (13–15). Overall, its use is limited to small research studies as an alternative to the euglycemic insulin clamp (16,17).

The continuous infusion of glucose with model assessment involves relatively low-dose infusion of glucose over 60 min to mimic a postprandial state. It is physiologically and relatively simple and safe, but the high CV (17–21%) and relatively poor correlation with the euglycemic insulin clamp ($r = 0.66–0.87$) (18,19) explain why continuous infusion of glucose with model assessment is no longer used. Measurements of insulin sensitivity based on the oral glucose tolerance test were developed to avoid the requirement of intravenous procedures. Whereas all the oral methods are less invasive, they are inherently less reproducible due to the variability of entry of oral glucose in circulation, which is determined by the rate of gastric emptying and splanchnic glucose uptake.

The remaining surrogate methods rely on fasting blood samples (9). The appreciable number of such tests suggests that none are ideal. Homeostasis model assessment (HOMA), based on fasting glucose and insulin, is the oldest (developed in 1985) (20) and most widely used and published test. For this reason alone, it offers some advantage over other methods in that it permits comparisons among studies that use this metric. HOMA has the additional advantage of providing an assessment of β-cell function, in addition to insulin sensitivity. Its calculation is based on a simplified solution of a physiologically based structural model. It is based on the relationship of basal glucose and insulin levels, which reflect the balance between hepatic glucose output and insulin secretion and is maintained by a feedback loop between the liver and β-cells (21). HOMA has been most extensively used in descriptive epidemiological studies, e.g., comparisons of insulin sensitivity in different racial groups (22–24), and in those with different genetic polymorphisms (25). The approach has also been used to examine changes in insulin

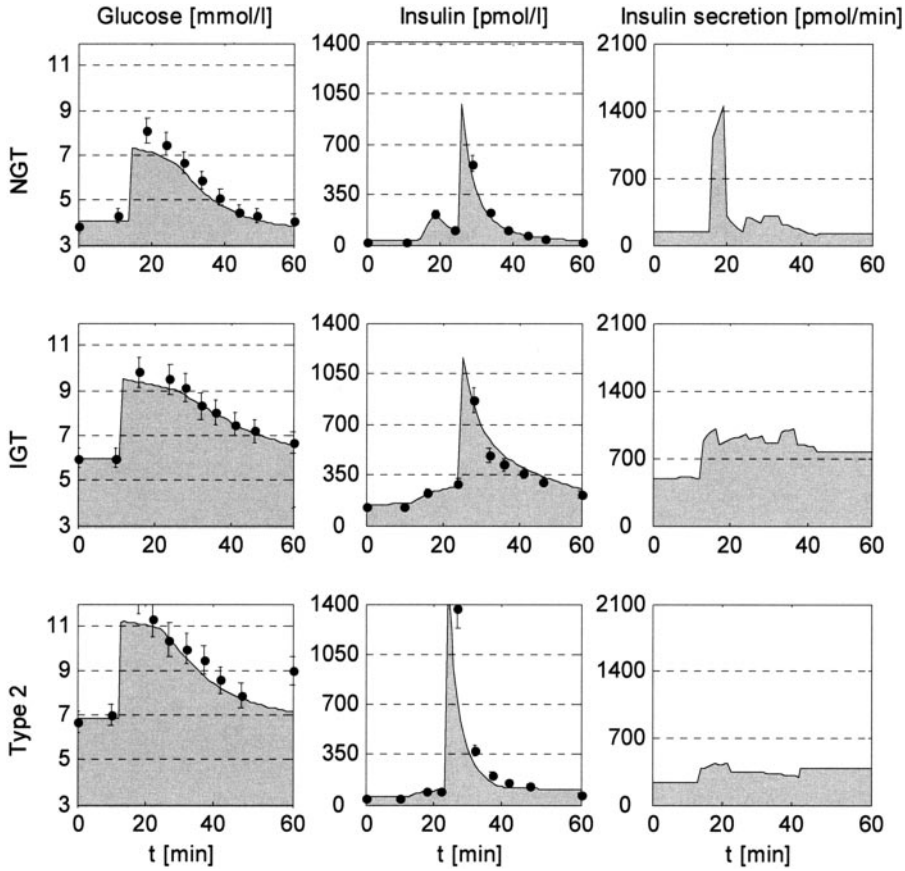

Figure 1— *Examples of three profiles from the proposed new test in an individual with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes (type 2). The individual with NGT has an insulin sensitivity value of 16.9 × 10^{-5} l · $pmol^{-1}$ · min^{-1}. The first-phase β-cell response to a bolus of glucose is very distinct and large, releasing 4,840 pmol insulin during the first 10 min after glucose administration. The first-phase release is 5–10 min, and the insulin secretion rate drops immediately back to its basal rate. The individual with IGT has an insulin sensitivity value of 4.6 × 10^{-5} l · $pmol^{-1}$ · min^{-1} and fasting glucose and insulin levels are increased. After a glucose bolus, the first-phase insulin secretion is no longer distinct, and high amounts of insulin are secreted for the duration of the test. Blood glucose levels drop slowly. The individual with type 2 diabetes has an insulin sensitivity value of 9.7 × 10^{-5} l · $pmol^{-1}$ · min^{-1} (higher than the individual with IGT). Basal insulin secretion is elevated, but not as high as the person with IGT, and it increases only slightly in response to the glucose bolus (1,576 pmol of insulin released during first-phase secretion), consistent with β-cell exhaustion. Black circles indicate measured glucose and insulin, with the respective assay error bars, and the shaded area represents glucose and insulin profiles calculated using the proposed model equations.*

sensitivity and β-cell function as the disease state progresses in longitudinal studies and to determine effects of treatment (26). HOMA has been inappropriately used to assess β-cell function in isolation or after relatively short interventions.

A recent review of the methods estimating insulin sensitivity on the basis of a simple fasting sample compared fasting insulin, glucose-to-insulin ratio, insulin-to-glucose ratio, HOMA of insulin resistance, quantitative insulin sensitivity check index, Belfiore glycemia, Belfiore free fatty acids, and the McAuley Index. Their performance was compared in normal-weight and overweight individuals, in those with type 2 diabetes, and in the group as a whole. It would appear from this review (9) that no one method outshines another. Whereas this review concluded that the methods were generally comparable, there may be situations when one of the surrogates has advantages over the others. For example, the McAuley Index, based on fasting insulin and triglyceride (27), was developed to determine insulin sensitivity in those with no detectable abnormalities of glucose metabolism with an aim of identifying and treating those at risk of the consequences of insulin resistance at the earliest detectable stage of the disease process. In this respect, the McAuley Index appeared to outperform HOMA of insulin resistance (27). However, HOMA may indeed remain the preferred method in large epidemiological studies.

More recently, we have attempted to develop an improved physiological simple measure that includes basal and dynamic components to provide a clear indication of glucose and insulin metabolism in individuals and groups. The test can be completed in 30–45 min, requires a simple intravenous cannula and small amounts of intravenous glucose (10 g) and insulin (1 unit), has no special techniques and tracers, and is performed by a registered nurse under medical supervision in an outpatient setting. Blood samples for glucose, insulin, and C-peptide enable a glucose and insulin profile and an estimate of endogenous insulin secretion to be generated for each individual. With significant advances in the modeling of glucose and insulin kinetics and in the model parameter identification methods used, this method has generated insulin sensitivity values that correlate very highly with euglycemic insulin clamp results ($r = 0.97$, $n = 60$) (28). In addition to providing a quantitative measure of insulin sensitivity, the test also provides a profile of glucose and insulin metabolism, including blood glucose concentration in response to a small glucose and insulin challenge, basal insulin levels, first-phase insulin response, and the endogenous insulin secretion peak and decay. This comprehensive profile adds considerably over and above the usual known risk factors for type 2 diabetes and would allow a more detailed classification of a heterogeneous group of individuals. Examples of individual glucose, insulin, and insulin secretion profiles generated by this method are shown in Fig. 1.

This method now needs to be tested and validated in a new population, but it already shows promise for generating useful, reliable, and accurate data from a relatively easy to perform safe test. This would likely convince those who have previously given up assessing insulin sensitivity that there is a useful and practical method that provides a glucose and insulin profile rather than just a metric for insulin sensitivity.

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