Do We Know What Homeostasis Model Assessment Measures?

If not, does it matter?

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The point-counterpoint articles in the September issue of *Diabetes Care* (1,2) raise several interesting issues on our understanding of insulin resistance, homeostasis model assessment (HOMA), and the future of measurement shortcuts for insulin resistance and secretion. McAuley et al. (1) provide an overview of methods to assess insulin sensitivity and secretion. The conditional nature of the title of their article implies that there is room for improvement and that something better will come along to assess insulin resistance and secretion with the convenience of HOMA but with better accuracy. For the time being, however, they support its use.

Hockaday et al. (2) bring up many points that undermine confidence in HOMA as a measure of insulin resistance. Input into HOMA consists of fasting insulin and glucose concentration and thus will reflect conditions present in the basal state, with the liver as the main target for insulin action as manifested by the suppression of gluconeogenesis. A shortcoming of HOMA is the lack of complete capture of brain glucose uptake, of which 50% is non–insulin mediated. Although HOMA has been compared against the euglycemic hyperinsulinemic clamp, the current gold standard for assessment of insulin sensitivity, the latter method assesses insulin resistance in the stimulated state, which is a function to a large extent of muscle glucose disposal. Thus, an implicit assumption of HOMA is that steady-state and stimulated insulin resistance are highly correlated. Other concerns include test variability over time and the assumption that insulin resistance, if present, is common to major sites of insulin action (liver, muscle, and adipose tissue).

Similarly, a number of concerns are raised about the use of HOMA to assess insulin secretion. Of particular concern is whether β-cell glycemic sensitivity can be assumed constant. In addition, other factors bear on insulin secretion that are not directly related to β-cell mass, glycemia, or glycemic sensitivity, for example, some amino acids, nonesterified fatty acids, cortisol, and growth hormone.

Despite these concerns, Hockaday et al. accept some of the conclusions from research using HOMA and therefore at least indirectly seem to be supportive of its use for certain applications. Both articles appear accepting of HOMA use in epidemiologic research. Though Hockaday et al. do not state this directly, we nevertheless infer it from their acceptance of its use in research on "discovering the pathogenesis of type 2 diabetes."

An important issue to consider is whether it matters if we have a comprehensive understanding of what HOMA measures. Research shows that HOMA and other shortcut measures of insulin resistance and secretion can provide useful information on risk of developing diabetes and related conditions. A recent report from the Womens' Health Initiative (WHI) observational cohort—a nested, case-control study conducted within the larger cohort of 82,069 WHI women without diabetes at baseline, followed for an average of 5 years—found that the relative risks per increment SD increase in HOMA of insulin resistance (HOMA-IR) and HOMA of insulin secretion (HOMA-%B) were 3.40 and 0.57, respectively (3). Assuming for the moment that HOMA-IR and HOMA-%B really do measure insulin resistance and insulin secretion, this finding confirms that greater insulin resistance predisposes to type 2 diabetes, while better insulin secretion is protective for the development of this condition among WHI women aged 50–79 years at baseline. Similar results were reported by another study that used HOMA to predict diabetes risk (4). These same findings were also reported in a prospective study among Pima Indians that used gold standard measurements of insulin resistance (the euglycemic hyperinsulinemic clamp) and insulin secretion (acute insulin response to glucose) (5). In fact, simple measures of insulin sensitivity and secretion were later shown to be highly predictive of diabetes occurrence in the Pima population (6). HOMA has also been used effectively in nonepidemiologic studies. For example, Meyer et al. (7) used HOMA to identify differences in the mechanisms for the development of impaired fasting glucose and impaired glucose tolerance, while the UK Prospective Diabetes Study reported changes over time in HOMA measures of insulin sensitivity and secretion with different treatments (8).

If HOMA represented random noise, it would not be consistently associated with disease states in a manner that to some extent can be predicted with other biologic information. Although admittedly noisy (having some degree of error), the signal (insulin sensitivity or secretion) is still detectable in some research studies. Holding HOMA to an extremely high standard of accuracy would not be consistent with other widely used surrogate measures in diabetes research and clinical care, such as BMI for overall adiposity, waist circumference as a measure of visceral fat, or race/ethnicity as a marker for

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Abbreviations: HOMA, homeostasis model assessment; HOMA-%B, HOMA of insulin secretion; HOMA-IR, HOMA of insulin resistance; QUICKI, quantitative insulin sensitivity check index; WHI, Women's Health Initiative.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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genetic and/or environmental exposures. Less than perfect accuracy is no stranger to medical diagnostic tests either. For example, hemoccult screening for early detection of colorectal cancer is insensitive and detects <50% of neoplasms (9,10). Yet its use has been shown to reduce the occurrence of advanced disease and death due to this cancer, demonstrating that an imperfect test can have clinical value.

If inaccurate measurements are still useful in clinical and epidemiologic research, why do we worry about accuracy? The first and most obvious reason is to avoid use of a measurement that provides a result no different from random chance. In this case, the measurement is of no value, whether it be of insulin resistance or anything else.

Second, an inaccurate measurement that has some information about the underlying condition of interest will require a greater sample size to detect associations, as would be the case if the surrogate measurement and the underlying condition were continuous measures that correlated with, for example, $r = 0.60$. The consequence of such measurement error is a decrease in the statistical power of detecting an association between the surrogate measure and an outcome compared with a perfectly accurate test, thereby reducing the chances of finding an important association and falsely concluding that no effect is present (11).

Third, inaccurate measurements will impair ability to adjust for important potential confounding factors. For example, differences in overall adiposity may be considered important in explaining the effects of different ethnicities on diabetes risk. In what is referred to as residual confounding, adjustment for BMI as an imperfect surrogate for adiposity will not be complete, and even if differences in percentage of body fat in fact explained all of the disparity in diabetes risk between, for example, Caucasian and Hispanic subjects, a difference in risk would remain after adjustment for BMI (12). For these reasons, of two surrogate measurements that take the same amount of effort to perform, the more accurate measure will be preferred. For example, waist circumference is at present preferred to subscapular skinfold thickness as a measure of central adiposity, as the former captures visceral and subcutaneous fat, while the latter assesses subcutaneous fat only. We should aim to use the most accurate surrogate measurement that we have available and recognize the limitations of inaccuracy, which in some circumstances can be overcome.

Hockaday et al. imply that current gold standard methods to measure insulin sensitivity do not capture the complete range and types of this phenomenon. This might lead to the conclusion that there is no point in developing a surrogate measure if we do not have a gold standard. This approach, however, would be unnecessarily nihilistic, as a current gold standard such as the euglycemic hyperinsulinemic clamp has been shown to be associated with important diabetes outcomes (5). Therefore it appears reasonable and potentially useful to develop surrogate measures for what are considered current gold standards, imperfect though they may be.

Much research has been conducted to develop simple measures of insulin resistance and secretion using physiologic reasoning that focus mainly on the use of fasting glucose and insulin concentrations. Examples include HOMA and the quantitative insulin sensitivity check index (QUICKI) (13–15). Surrogate measures for insulin sensitivity and secretion have also been used based on glucose and insulin values obtained from an oral glucose tolerance test (16–19). Measures utilizing postprandial glucose and insulin measurements generally are more strongly correlated with gold standard measures of insulin sensitivity and secretion (16,20,21).

When compared with one another, measures based on fasting glucose and insulin values in general yield the same degree of accuracy, particularly in individuals who have diabetes and are overweight or obese (22). Similar mathematical formulations of these measures may account for their similar performance. For example, HOMA-IR = (glucose × insulin)/22.5, which can be rewritten after taking log-(HOMA-IR) as log(glucose) + log(insulin) − 1.35, since multiplication of numbers can be performed by adding the logarithms of the numbers. Another fasting glucose– and insulin-based measure called QUICKI is calculated as 1/[log(glucose) + log(insulin)] (13). Since 1/QUICKI = log(glucose) + log(insulin), log(HOMA) = 1/QUICKI − 1.35. One would expect a strong correlation between HOMA and QUICKI given that log-(HOMA) equals the inverse of QUICKI − 1.35. We believe that it will be difficult to develop further variations on the fasting glucose and insulin two-note theme.

Reliance on physiologic understanding to develop surrogate measures may limit their development. Using physiologic information to develop surrogate measures may depend on an accurate and complete understanding of the phenomenon. As described by Hockaday et al., both insulin resistance and secretion are complex processes not completely captured by available measurement methods. If the physiology is incompletely understood or incorrect, the ability to develop useful surrogate measures will be impaired.

Prediction is possible without a complete understanding of physiologic processes using statistical methods, and surrogate measures of insulin sensitivity have been developed recently that provide an increase in accuracy over measures based on fasting glucose and insulin alone. These models use not only fasting glucose and insulin concentrations but also other factors that are associated with insulin resistance, such as BMI, ethnicity, HDL cholesterol, and triglyceride concentrations (23–27). Model development is driven by the goal of developing the best fit to the data, so statistical considerations have an important role, such as the inclusion of statistically significant predictors and the identification of nonlinearity. This strategy has not to our knowledge been utilized in the development of similar types of models to predict insulin secretion most likely because less is known about correlates of insulin secretion.

The statistical modeling approach has the potential to improve our ability to estimate insulin resistance with readily available data. For example, McAuley et al. reported that a model using fasting insulin and triglyceride concentrations had greater accuracy in predicting insulin resistance as measured with the clamp than HOMA or several other proposed surrogate measures (28). We believe that there is additional progress to be made through use of this strategy. We are not suggesting that physiologic data has a minor role in developing surrogate measures or prediction models. On the contrary, it has the very important role of describing mechanisms on which a surrogate measure could be based. But in addition to this information, other known correlates of insulin resistance should be considered.

Using statistical methods to identify surrogate measures for insulin resistance and secretion may lead to inclusion of factors that have no physiologic role but are simply correlates of causes. Given the commentary of Hockaday et al., the same can probably be said of HOMA modeling.

Identifying a correlate of a true cause may lead to progress in understanding the disorder and may provide clues for further investigation.

McCauley et al. describe a simpler procedure for assessing insulin sensitivity when compared with clamp or minimal model approaches. The data that they present show that it is more accurate than HOMA in predicting insulin sensitivity. We feel that it is unlikely that this method will replace HOMA because it requires an indwelling catheter, infusion of both glucose and insulin solutions, and 30–45 min to perform. The beauty of HOMA is the ease of obtaining the input for the calculation. If further testing proves it to be as accurate as the initial evaluations, this method may be considered a substitute method for the clamp or minimal model to achieve a gold standard level of accuracy.

The original developers of HOMA now offer an updated version called HOMA2 that includes several enhancements requiring use of a computer program, which they provide online (15). To our knowledge, the changes that have been incorporated have never been described in the peer-reviewed literature (other than an overview of the enhancements and an initial description in a letter to the editor) (15,29). It is our opinion that the new method should receive the sanction of peer review and be reported in greater detail in the literature before the original formulation is replaced.

In summary, neither the commentary by McCauley et al. nor that by Hockaday et al. implies that HOMA is the end of the road for simple assessment of insulin resistance and secretion. Additional work is needed to develop better ways to measure insulin sensitivity and secretion. Prediction models should ideally be based on a comprehensive understanding of physiology, but good predictions can be made without a complete understanding of these mechanisms using well-established statistical methods and available knowledge on correlates of the phenomenon of interest. Although it may not be completely clear what HOMA measures, this can be forgiven if it succeeds in describing important phenomena and accurately predicts outcomes of interest. Improved measures of insulin sensitivity and secretion that incorporate not just fasting insulin and glucose will likely improve our ability to conduct clinical and epidemiologic research that furthers our understanding of the development of diabetes and its complications.

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