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Insulin Sensitivity and Its Measurement: Structural Commonalities among the Methods*

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ABSTRACT

Insulin is the principal hormone of metabolic regulation. Reduced responses to insulin constitute an underlying feature of type 2 diabetes. It is, therefore, incumbent on those who work in this area (as well as many others) to characterize this response, in as simple and consistent a way as possible, so that this measure can be used both in the investigational and clinical setting. This type of approach, although eminently useful, is necessarily an oversimplification. Not only does insulin sensitivity change in pathological situations, but also in normal physiology. Tissue-specific, metabolite-specific, as well as process-specific responses may be expected to occur. Variations also occur in time—depending on the physiological state of the individual (*e.g.* pregnancy, aging) or following diurnal rhythms. It is perhaps remarkable that any consistent assessment of overall insulin sensitivity can be made. The observation that this can often be achieved has led to hypotheses suggesting that sensitivity to insulin is primarily determined at a single site (tissue, metabolite). At the same time, there are many discussions about the inconsistencies inherent in different approaches to the measurement of this parameter, suggesting that some of these variants, metabolic or otherwise, could lead to the low correlation between methods sometimes seen. Nevertheless, most methods used in the assessment of insulin sensitivity examine the response to insulin of a single metabolite, glucose, primarily in the muscle and liver, and under fasting conditions and should, therefore, demonstrate insulin sensitivity that is comparable among methods. (*J Clin Endocrinol Metab* **85:** 4426–4433, 2000)

IT IS THE contention of this short review that most methods for measuring insulin sensitivity yield values that are correlated not just because they are addressing the same question, but also because they are based on metabolic models that share certain structural features. The review was prompted by the recent article by Katz *et al.* (1), entitled "Quantitative Insulin-sensitivity Check Index (QUICKI): a simple and accurate method for assessing insulin sensitivity in humans." which exemplifies one approach to the assessment of insulin sensitivity. It is based on the steady-state (or quasi-steady-state) glucose and insulin concentrations that are achieved after an overnight fast. It defines insulin sensitivity as proportional to the inverse of the log of the product of fasting insulin and glucose concentrations. It demonstrates good correlation with the "gold standard" method, or the hyperinsulinemic euglycemic clamp. In this regard, it seems to compare favorably with the minimal model approach. It is, therefore, added to the list of approaches that are used to gain some insight on sensitivity and resistance to insulin. With the ever-increasing armamentarium of methods for the measurement of insulin sensitivity/resistance, the choice may seem bewildering. It does not have to be. It depends much more on the problem in hand, its goals, and the experimental limitations. These issues and an understanding of what is being determined using the different methodologies are the most important criteria in the decision process. It may be useful, therefore, in the context of this review to try to step back and, at least semiquantitatively, explore the evolution and conceptual underpinnings of some of the different methods.

Glucose tolerance is an expression of the efficiency with which homeostatic mechanisms restore glycemia to basal levels after a perturbation. Clinically, the most common assessment is following an oral glucose load, a surrogate for a more physiological meal. The homeostatic response includes an increase in the insulin levels and, therefore, also the insulin-dependent processes that lower glycemia. Theoretically, the oral glucose tolerance test should yield an estimate of insulin sensitivity, if insulin concentrations are measured. Indeed, a number of formulae have been developed both in the past (*e.g.* Ref. 2) as well as more recently (*e.g.* Refs. 3–5). After oral glucose or meals, the increments in insulin do not depend entirely on glucose, but also on such factors as gut hormones and neural stimulation, the insulin response deviates from the purely glucose-dependent pattern. Glucose concentrations also change in a manner that is partly dependent on insulin, but also partly on gastric emptying and absorption. In general, therefore, attempts have been made to isolate the glucose-insulin relationship, as much as possible, from other factors.

In the broadest sense, there seems to be two approaches to the measurement of insulin sensitivity: the dynamic intervention (glucose, insulin, and tolbutamide injection or infusion) and the steady-state (usually fasting) assessment. Needless to say, the steady-state situation (when it truly exists) is the culmination of the evolution of processes that

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bring the glucose system back to a set point, more or less quickly, after a perturbation. The two situations are, therefore, related. One can also characterize the approaches by whether they are "open loop" or "closed loop," that is, whether they evaluate the action of insulin (often exogenous) on a specific parameter, or invoke a more self-contained metabolic model that incorporates a description of the feedback relationships between insulin and glucose. In the first category, we include: the hyperinsulinemic glucose clamp (6), the iv glucose tolerance test (IVGTT; Refs. 7 and 8) approaches, and the insulin tolerance (9) or suppression tests (10). In the second category we have continuous infusion of glucose with model assessment (11), homeostasis model assessment (HOMA; Ref. 12), and now QUICKI (1). It may be of note that the first category also includes dynamic interventions, and the second, perhaps because the closed loop formulation is better equipped to describe the evolution of processes to a steady-state, is often based on fasting measurements.

The correlations between measures of insulin sensitivity (S_I) by apparently disparate methods have often been shown to be quite good. As already stated, a reasonable hypothesis might be that this arises, at least partly, from the fact that the methods are built on a common description of the glucose-insulin system. Without elaborating the complete mathematical solutions, we shall attempt to show the basis for this conclusion. Although it likely applies to most of the methods currently in use, we shall focus primarily on the methods discussed in (1).

Insulin and its effect compartment

The glucose-insulin system is composed of a complex set of metabolic interactions and regulatory components. Even if all these were included in the description of the system, it would be a significant oversimplification because the system is embedded within the entire complex, which is made up of energy metabolism and its hormonal and neural regulation. Many mathematical formulations for the glucose system have been made, from the comprehensive to the relatively simple. Only the latter are applicable to situations such as the clinical assessment of insulin sensitivity because of limitations on the interventions that can be made and on sampling. Overly simple descriptions are, in turn, limited because the glucose-insulin system is nonlinear. This means essentially that, because of considerations such as the actions of insulin and saturability, if the glucose input (production/infusion) is doubled, the concentration will not necessarily be doubled. In the context of the methods being presently discussed, the best expression of this nonlinearity has been through the concept of an "effect compartment" for insulin. This can be summarized by the following equations:

$$\frac{dg}{dt} = -kg + \frac{R_a}{V} \quad \text{(I)}$$

$$\frac{dk}{dt} = -a_1 k + a_2 i \quad \text{(II)}$$

where g is the plasma concentration of glucose and i, that of insulin. R_a is the glucose input rate, and k is the fractional disappearance rate of glucose. V is the volume of distribution of glucose, and a_1 and a_2 are constant parameters. In this illustrative development, we have, for simplicity, neglected the insulin-independent component of k. Eq I describes simple one-compartment kinetics for glucose. It states that the changes in glucose concentration are determined by the balance between the influx of glucose into the system (liver, kidney, exogenous administration) and its efflux from the system. k (which is equivalent to the metabolic clearance of glucose divided by V) is the parameter that determines how efficiently glucose is removed from the circulation. It depends on all the factors that may alter glucose disposal, particularly insulin, but also glucose. Eq II is an expression of the effect compartment for insulin: insulin exerts its effect on k. k, however, is not proportional to i but rather to insulin in a compartment, remote from circulating insulin. Effect compartments such as this one have frequently been used in the pharmacodynamic description of drug actions (*e.g.* Ref. 13), mediated, for example, by active metabolites or at sites distal to the circulation. Initially, they were applied to insulin in the context of euglycemia (14, 15), which is important in the interpretation of clamp data. It has been suggested, moreover, that for insulin the remote or effect compartment might be insulin that has penetrated the endothelial barrier and is present in the interstituum and, therefore, available for binding to cell-surface receptors (16).

The hyperinsulinemic euglycemic clamp (6)

This is frequently (*e.g.* Ref. 1) referred to as the gold standard in the measurement of insulin sensitivity. It is a conceptually simple test, although technically, somewhat more complex. It is performed by infusing insulin at a constant rate to achieve physiological suprabasal levels. Glucose is monitored frequently and infused at variable rates (often according to an algorithm; Ref. 6) to maintain near-constant glycemia, which is equivalent to normal fasting glucose levels (or in the isoglycemic case, the patient's own fasting glycemia). When the glucose infusion rate (*Ginf*) has stabilized (2–3 h), this rate, divided by the insulin level (possibly subtracting basal insulin), is defined as S_I. Because glycemia is constant, the only variable is glucose requirement, which is then directly proportional to k in the above equations. From Eq II, since k is constant,

$$S_I = k/i = a_2/a_1 \sim Ginf/i \quad \text{(III)}$$

and, as shown by the equivalence in Eq III, is proportional to the usual definition of clamp-derived S_I, *Ginf*/*i*. Under the steady-state conditions, reestablished during the clamp, therefore, Eqs I and II reduce to the simple expression given by Eq III.

During a clamp, insulin is administered as a constant infusion and, therefore, does not reflect the variations inherent in endogenous secretion. Moreover, also unlike the physiological case, insulin is given peripherally, which reverses the normal gradient between portal and peripheral insulin. Finally, the peripheral and the hepatic responses to insulin are assumed to occur in parallel, which, based on the known dose responses, is not likely to occur (17). Nevertheless, because glycemia is kept constant, *Ginf* and, therefore, k depend

only on i, and the ratio is considered as the most reliable measure of S_I. It has been widely applied and provides good discrimination between normal subjects and those with insulin resistance (18).

Methods based on the IVGTT

It was recognized by Bergman, Cobelli, and colleagues (7, 16) that the physiological response to iv glucose injection (or rapid infusion) is a very dynamic situation and, therefore, rich in information. Initially, rapid sampling for plasma insulin and glucose was used to yield data that was used to identify the parameters of a model intrinsically similar to that described by Eqs I and II. This model also included an insulin-independent component and was termed the "minimal model," because it was the mathematical model with the fewest parameters that was found to provide a good fit to the data—and the fits to data are remarkably good (*e.g.* Ref. 7). It should be noted that the fits are obtained using, for example, nonlinear least squares techniques: parameters are varied according to a defined strategy and are assigned a final value that minimizes the sum of squares of differences between the data and the glucose and insulin values predicted by the model (which is nonlinear) for any parameter set. The goodness of fit and, therefore, the reliability of the parameters can then be evaluated statistically (7, 16).

The S_I is calculated from the ratio of a_2 and a_1 (Eq III), parameters that are determined from the model fit. It can be seen that the expression for S_I is identical to that which is derived from the clamp technique. It is not surprising, therefore, that good correlations between the methods have been found.

The dynamic and physiological nature of this test and the relative simplicity of its performance, count among its attractive features. Differences and potential problems arise from the same source: the rapid dynamics may confound transients based on the distribution of glucose throughout the system and those due to glucose removal. This and the wide range over which rapid changes in glucose concentration occur, may induce nonlinearities in the system that are not accounted for by the model, such as renal glucose removal. These may, in turn, obscure changes in slope, from which k is obtained, particularly in the context of highly resistant states such as advanced type 2 diabetes, where both the signal (insulin) and the response may be small. To counter this problem, the signal was enhanced using iv administration either of tolbutamide (19) or of insulin (20), 20 min after the glucose injection. This allowed identification of the insulin-independent part of the process from data obtained before tolbutamide or insulin administration, and provided a stronger signal for the insulin-dependent processes afterward. The expression for S_I, however, remains the same with the change of protocol. As indicated (1), as well as in other work (21), some discrimination may be lost within the diabetic population because a proportion of the S_I becomes less than or equal to zero. Two-pool or higher order descriptions of glucose dynamics and the use of tracers were suggested (22, 23) as possible solutions to such difficulties.

It can be seen that potential changes made to accommodate the widest range of sensitivities possible may render the protocol and the analysis somewhat more complex. This was partially alleviated by reducing the number of samples necessary (24), at least in the context of population studies. It should be pointed out that the methodology remains consistent since the undetectable S_I do correspond to very low responses to the insulin signal and, therefore, severe insulin resistance. However, in going from the situation where glycemia is maintained constant with a glucose clamp to that where it is variable, additional assumptions must be made: that the glucose concentrations themselves do not contribute to the dynamics in a nonlinear fashion and that the insulin acts in a uniform manner on all relevant tissues at all concentrations. It is possible that one of these assumptions may not apply at the limits of the range of sensitivities considered. It may, therefore, be difficult to describe this system in an identifiable way, over the entire range of S_I, given a limited data set. The sources of these problems, however, also embody the potential of this model: much more development can be done, using this model, in exploring the detailed dynamics of glucose and insulin and the causes of insulin resistance.

HOMA (12)

To avoid complex procedures or widely changing glucose levels, the homeostatic model assessment focuses on basal fasting glucose and insulin levels. HOMA yields a formula for insulin resistance, R_{HOMA}, defined by:

$$R_{HOMA} = g \cdot i/22.5 \quad \text{(IV)}$$

It was demonstrated in a number of publications (11, 12, 25, 26) that the correlations between derivatives of this formula and clamp-derived S_I are surprisingly good considering the simplicity of the formula. Let us examine the possible reasons why.

The starting point of this method was the development of a comprehensive mathematical model of glucose-insulin homeostasis (11, 12). This was based either on a series of functional forms (27) or equations (11) that depicted the nonlinearities inherent in the system. If values based on literature data were assumed for most of the parameters, then glucose and insulin data during a constant glucose infusion over 60 min could be fitted in individual studies by adjusting "insulin resistance" and "β-cell function" parameters as a fraction of the preset ideal normal case. Because of its comprehensive and closed-loop nature the model could not only predict the evolution of glucose and insulin levels in response to the glucose infusion, but could predict their final steady-state, fasting concentrations (12). Simulations were then used to generate an array of fasting glucose and insulin levels that would be expected for different degrees of β-cell deficiency and insulin resistance. Conversely, given fasting glucose and insulin concentrations, unique values of relative β-cell function and insulin resistance can be read from the grid. The approximate formula (Eq IV) is also derived from this graphic representation (12). This approximation has been widely used, although the authors do recommend using the full equations (28).

Interestingly, there is another perspective from which Eq IV may be derived, based only on the assumptions made in

the development of the homeostatic approach and Eqs I–III. The basic rationale for the model is stated (12) as: "The basal hyperglycemia of diabetes may be considered as a compensatory response with a major role in maintaining sufficient insulin secretion, from a reduced β-cell capacity, to control hepatic glucose efflux." Interestingly, precisely the same principle was used (29) to explain the well known increase in insulin concentrations following pancreas transplantation with peripheral venous drainage or the diversion of pancreatic venous drainage from the portal vein to the systemic circulation either by surgical intervention or possibly due to porto-systemic shunting in cirrhosis (30, 31): peripheral insulin concentrations needed to be maintained at levels sufficiently high to generate portal concentrations which can maintain normal basal glucose production. It has also been stated that hyperglycemia and hyperinsulinemia are necessary in the insulin resistant state, to maintain near-normal peripheral glucose uptake when metabolic glucose clearance at a specific inuslin concentration is decreased because of insulin resistance (32). This was supported by muscle biopsies in insulin-resistant humans, showing normalization of glycogen synthesis and synthase activity in the presence of hyperinsulinemia and hyperglycemia (23). Under steady-state conditions then, the feedback loop will both compensate for insulin resistance with higher insulin levels and ensure high enough glycemia to stimulate the higher insulin. Let us see how this can be expressed more quantitatively using Eqs I–III.

In steady state, from Eq I,

$$\frac{dg}{dt} = 0; \therefore R_a = Vkg \tag{V}$$

Similarly, from Eq II:

$$k = \frac{a_2}{a_1} \cdot i; \therefore R_a = \frac{Va_2 \cdot i \cdot g}{a_1} = V \cdot S_I \cdot i \cdot g \tag{VI}$$

The homeostatic principle quoted asserts that the goal of the system is to maintain the same rates of basal glucose production (and utilization) in a test subject; for example, one with diabetes (no subscript) as in a defined normal ($_n$). This implies:

$$R_a = R_{an} \Rightarrow V \cdot S_{In} \cdot i_n \cdot g_n = V \cdot S_I \cdot i \cdot g \Rightarrow \frac{S_I}{S_{In}} = \frac{i_n \cdot g_n}{i \cdot g} \tag{VII}$$

$$\therefore S_{IHOMA} = 22.5/(i \cdot g)$$

where $i_n \cdot g_n$ equals 22.5 (*e.g.* glucose concentration of 4.5 mM and insulin of 5 μU/mL). We then have a formula for the insulin sensitivity index in a given subject relative to a defined normal S_{IHOMA}. This is exactly the inverse of the formula for resistance shown in Eq IV—as it should be.

It has sometimes been concluded that the HOMA index does not correlate well with other measures of insulin sensitivity as can be seen in Fig. 6 of Ref. 1 [the fact that it is (−HOMA) does not change matters]. It is critical to note, however, that HOMA is an index of insulin resistance (identical to R_{HOMA}), and, as demonstrated above, an index of resistance will be the inverse of the corresponding index of sensitivity. It is not surprising, therefore, that when the HOMA index is plotted against, for example, S_{Iclamp}, the curve is hyperbolic (26, 27). On the other hand, when ln(HOMA) is plotted against ln(S_{Iclamp}) (or glucose disposal at euglycemia), the correlation improves dramatically (26). This is because of the following set of relationships:

$$S_{IHOMA} = 1/R_{HOMA} \text{ and } S_{Iclamp} = A \cdot S_{IHOMA} \tag{VIII}$$
$$\Rightarrow \ln(S_{Iclamp}) = \ln(A) + \ln(S_{IHOMA}) \Rightarrow \ln(S_{Iclamp}) = \ln(A) - \ln(R_{HOMA})$$

where A is a constant factor between two S_I indices, usually based on the different units used. Clearly, the correlation coefficient improves because the nonlinear hyperbolic relationship is transformed into a linear one. Because ln(S_{Iclamp}) is related to S_{Iclamp}, even the correlation between S_{Iclamp} and ln(R_{HOMA}) will improve, although the correlation coefficient is likely to be intermediate.

The common background of all three models used for comparison in Ref. 1 is the most likely explanation for the good correlations between these methods frequently seen, when the comparison is performed appropriately. Divergence likely arises because of the different additional assumptions made when moving away from the clamp technique. This has already been discussed for the IVGTT/minimal model approaches. For HOMA, the differences lie in the basal nature of the assessment, which is consequently focused somewhat more on the liver than the other methods. It is also dependent on a homeostatic principle that asserts that the maintenance of a fixed basal glucose turnover rate is the primary goal of the system. Because only a basal measurement is used, it is critical and, as indicated by the authors (12), should entail an average of sufficient samples to take into account noise and the pulsatile nature of insulin secretion and concentrations. Although not always found, the reported parallelism between the estimates, at least under steady-state conditions, is nevertheless striking.

QUICKI

The expression used as an index of insulin sensitivity is (1):

$$QUICKI = 1/[\log(I_0) + \log(G_0)] \tag{IX}$$

where I_0 and G_0 are the fasting insulin and glucose (and the same as i and g used previously). This was obtained by examining a variety of transformations of these fasting data and choosing the one that correlates best to S_{Iclamp}. From Eq IV it is clear that:

$$\log(R_{HOMA}) = \log(22.5) - \log(i \cdot g) = \log(22.5) - 1/QUICKI \tag{X}$$

$$\text{or } QUICKI = 1/[\log(HOMA) + \log(22.5)]$$

The authors point out that the correlation coefficient between the log(R_{HOMA}) and QUICKI is 0.98. Based on the discussion above, the correlation might more likely be between 1/QUICKI and log(R_{HOMA}) or log (*HOMA*), where *HOMA* is identical to R_{HOMA}. It is nevertheless interesting

and important that QUICKI, which although more empirically derived, correlates well with S_{Iclamp} since it, indeed, corresponds to a measure of sensitivity.

Because the HOMA index may not always have been optimally compared with other indices, as discussed, and because the same may be true in Ref. 1, it remains to be seen whether QUICKI offers real advantages compared with HOMA. It is suggested by Katz *et al.* (1) that the logarithmic transformations are used to normalize a skewed distribution of insulin values. Again, this might be because insulin levels, in themselves, are indicators of insulin resistance (*e.g.* Ref. 34) rather than sensitivity and, therefore, should be inversely related. The fact that HOMA and QUICKI might well be nearly equivalent is shown in Fig. 1, based on individual data from Hosker *et al.* (11), where both resistance and sensitivity measures (HOMA) and QUICKI are compared with S_{Iclamp}. Although the statistical analysis is not done since this is for discussion only, it is clear that when sensitivity is compared with sensitivity, the correlations will not likely vary to a great degree between the two measures compared. The work of Katz *et al.* (1) is, however, important because it clearly demonstrates that the comparisons were not always done appropriately and emphasizes that fasting measures are likely useful in examining insulin sensitivity among populations. Certainly, investigators will have ample opportunity to compare the two indices because the same data are used for both.

Additional consideration: insulin-independent component of glucose removal

The formulas used in the above descriptions were in the simplest form possible to illustrate the relationships that exist among the different methods of measuring insulin sensitivity. One of the major assumptions made was that the insulin-independent component of glucose removal could be neglected. This may be reasonable when insulin concentrations are increased and insulin resistance is not severe. It becomes a problem when the insulin-independent and insulin-dependent components become quantitatively equivalent. For example, inspection of Eq III reveals that if an important part of k was insulin-independent, than Eq III would yield an overestimate of S_I. In this section, we will briefly examine the implications on the different methods discussed of including this component in the formulas. As might be expected, in the methods that are based on steady-state measurements, decoupling of the two components can be achieved more easily, whereas out of steady state, this becomes a more difficult issue.

The steady-state methods. Of the methods discussed here, these include clamp-based techniques, HOMA, and QUICKI. In Eq I, let us first define

$$k = k_g + k_i \qquad \text{(XI)}$$

where k_g is the insulin-independent and constant part of k and k_i changes with insulin level, so that:

$$(k_g + k_i)g = \frac{R_a}{V};\ (k_g + k_i(0))g(0) = \frac{R_a(0)}{V} \qquad \text{(XII)}$$

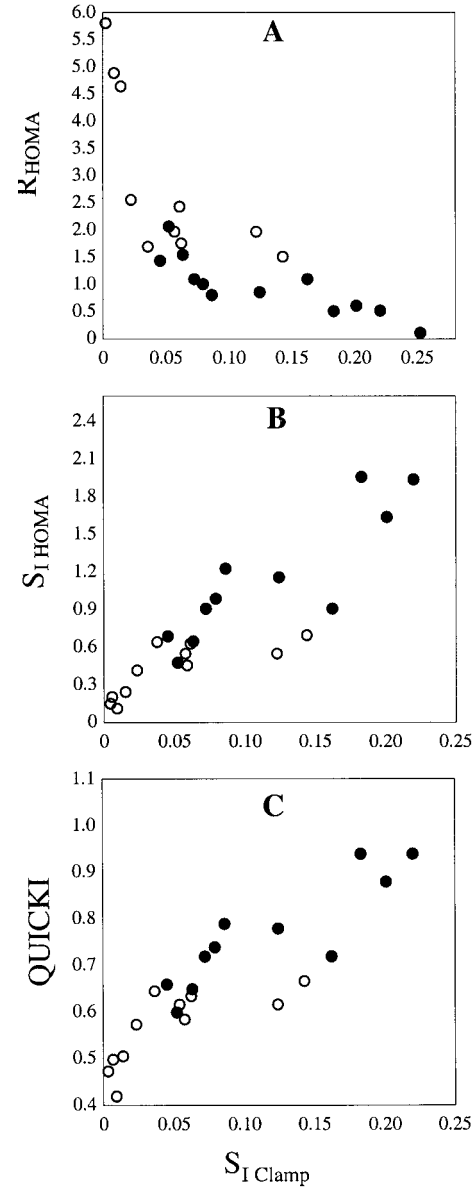

FIG. 1. A, The HOMA index (of insulin resistance) plotted against S_{Iclamp}. The distribution of the data are manifestly hyperbolic demonstrating the inverse relationship between insulin resistance and sensitivity. ●, Normal subjects; ○, subjects with diabetes. Data from Ref. 7 was used in this illustration. B, The inverse of the HOMA resistance index, equivalent to a HOMA-determined sensitivity, is plotted against S_{Iclamp}, for the same subjects as above. A linear relationship is demonstrated. C, QUICKI is also plotted against S_{Iclamp} for the same data set, also demonstrating a linear relationship, although with a positive y-intercept.

where $k_i(0)$, g(0) and $R_a(0)$ are the quantities at time zero or under basal conditions.

From Eq III, the appropriate relationship between k and i becomes

$$a_1 k_i = a_2 i \qquad \text{(XIII)}$$

Under basal conditions, the same equality holds:

$$a_1 k_i(0) = a_2 i(0) \qquad \text{(XIV)}$$

where $k_i(0)$ and $i(0)$ are the basal values of the fractional disappearance rate and insulin concentration.

The hyperinsulinemic euglycemic clamp

Subtracting Eq XIV from Eq XIII and taking ratios we have:

$$S_I = \frac{a_2}{a_1} = \frac{\Delta k}{\Delta i} \text{ where } \Delta k = k_i - k_i(0);\ \Delta i = i - i(0) \qquad \text{(XV)}$$

Similarly, from Eq XII:

$$\Delta k \cdot g = \frac{\Delta R_a}{V};\ \text{Therefore } S_I = \frac{G_{inf}}{Vg\Delta i} \sim \frac{G_{inf}}{\Delta i} \qquad \text{(XVI)}$$

where the last equivalence is a common expression for S_I and is proportional to insulin sensitivity since, during a euglycemic clamp, both V and g are constant. It should be noted the glucose infusion, G_{inf}, will compensate both for increases in glucose removal (due to Δk) as well as insulin-induced decreases in glucose production, which are, therefore, included in this estimate. Although an expression of insulin sensitivity, unless $V\Delta k \gg$ suppression of R_a, it does not represent a pure peripheral insulin sensitivity.

HOMA. The expression of relative insulin sensitivity is derived under steady-state conditions (Eq VII). To account for k_g, we use Eqs III, XII, and XIV to write:

$$V(S_I i + k_g)g = V(S_{IN} i_N + k_g)g_N \qquad \text{(XVII)}$$

where it is assumed that k_g remains substantially the same across the normal and patient population. From Eq XVII, and using the definition of S_{IHOMA} in Eq VII, we can then write:

$$S_{IHOMA} = \frac{i_N g_N}{ig} = \frac{S_I}{S_{IN}} + \frac{k_g(g - g_N)}{S_{IN} ig} \qquad \text{(XVIII)}$$

where S_I/S_{IN} is the actual relative insulin sensitivity. It can be seen that, if $g > g_N$, then S_{IHOMA} will overestimate the actual relative sensitivity. Clearly, the HOMA method based on Eq VII will, within the assumptions made, be accurate as long as basal glycemia remains near normal. As g increases and i falls, the second term on the right in Eq XVIII will increase, introducing a nonlinearity into the expression for S_{IHOMA}. As g increases further and the renal threshold is exceeded, further losses will take place by glycosuria, which are also insulin independent. These types of effects may contribute to the increasing nonlinearity of the simulations of insulin and glucose concentrations, at any level of insulin resistance as β-cell function falls (35), since the full model does take insulin-dependent and -independent effects into account. It may also explain why HOMA provided an effective estimate of insulin resistance and predicted the development of non-insulin-dependent diabetes mellitus (36): the subjects in these studies tended to have fasting glucose levels near normal. It was less effective, however, where a large number of subjects had well established type 2 diabetes (37).

Although the derivation of QUICKI is more empirical, similar considerations apply as for HOMA: this measure is also likely to be more accurate when glycemia is near normal and β-cell function has not deteriorated greatly.

Nonsteady-state methods. In this review, this has been represented by the minimal model analysis of the IVGTT. Under these conditions, it is more difficult to decouple the insulin-dependent and -independent terms. These are estimated as S_I and S_G, respectively (38). S_G is estimated as the effectiveness of glucose at a basal insulin concentration (38, 39), which means that it includes a component of insulin sensitivity (39). This may contribute to the explanation of why S_G was found to be a function of insulin release (40). Thus, S_G is, in general, overestimated (22), with the result that there is a compensatory underestimation of the effects of incremental insulin, or $S_{I.}$ (41), also perhaps helping to explain why estimates of S_I are lower than expected in insulin-resistant subjects (21). This was addressed by calculating glucose effectiveness at zero insulin (GEZI = S_G - $S_{I\ i}$, ref 39). This helps to resolve the problem but does not alter any changes that may have occurred in S_I. Although, it has been suggested that the effect of insulin on the periphery and the liver may occur at least partially in parallel (16); any deviation from such behavior could also confound the estimates, a problem that is largely avoided in steady state because all fluxes are then constant.

Additional consideration: assessment of peripheral and hepatic insulin resistance

In all of the above analyses, The issue of separating peripheral and hepatic insulin sensitivity clearly becomes important in the analysis of the nonsteady-state response to perturbations such as the IVGTT, because the assumption that the liver and the periphery respond to insulin in a parallel fashion may be critical. It is also useful in all the other analyses because the development of insulin resistance in the liver and in the periphery may be different in the pathogenesis of diabetes (42). With the complication of additional laboratory analyses, this is usually accomplished by the use of glucose tracers. A tracer is a substance that is chemically identical but separately detectable from the tracee, glucose, which is present in negligibly small quantities that do not in themselves perturb metabolism, and which does not recycle through metabolic pathways. Examples include: [6-^{3}H]glucose or [U-^{13}C]glucose. The administration of a tracer (usually infusion) is a procedure that is used to measure the metabolic clearance rate of glucose (43). The rate of appearance (R_a) of glucose can then be determined from this metabolic clearance and the glucose concentrations.

This approach has been routinely applied in clamp studies (18), in the context of more intensive investigations. It has also been demonstrated to provide improved estimates of S_I when the minimal model approach to the IVGTT is used (23). In the former case, a (usually primed) infusion of glucose tracer is started before the clamp and, a basal measurement of the metabolic clearance rate (MCR_g) of glucose is obtained when concentrations of tracer are constant. This is calculated as the rate of tracer infusion divided by its plasma concentration. A primed infusion of insulin is then initiated, glucose infused at rates appropriate to clamp the levels, and, once steady state of the tracer concentration and glucose infusion rate are again reached, a second measurement of MCR_g is made. The rate of endogenous glucose production (R_{ae}) is obtained by first calculating total Ra (MCR_g g, where g is

again the glucose concentration). Under basal conditions this is the R_{ae}. During the clamp R_{ae} is obtained by subtracting the (steady-state) rate of glucose infusion from the total R_a. Suppression of basal R_{ae} by insulin is obtained by comparing R_{ae} under clamp and basal conditions. Tracer is frequently added to the variable glucose infusion used for clamping to maintain near-constant plasma ratios of tracer to glucose (44, 45). This should not be necessary if true tracer steady-state is reached during the clamp, but may help in calculating changing R_{ae} more accurately (44, 45), during the transient period, particularly if model order is not optimal. The importance of reaching tracer and glucose steady-state both under basal conditions and during clamping must also be emphasized (46, 47).

Although the same tracer infusion protocol could be used with the IVGTT, adding the tracer to the injected glucose has been demonstrated to yield reasonable estimates of R_{ae} following iv glucose injection (48).

Clearly, the use of tracers enables the separate assessment of the effect of insulin on the liver and on the periphery. With more care (and samples), time courses of these changes can be separately determined. Using clamp techniques, dose-response curves to insulin were developed for both the glucose production and clearance, demonstrating the increased sensitivity of the liver to insulin relative to the periphery (17).

Discussion

In this brief review, the goal was not to emphasize the differences among methods of measuring insulin sensitivity, but rather to demonstrate the remarkable similarity of their conceptual and theoretical foundations. All three principle methods discussed (clamp, minimal model, and HOMA) arise from a common system description. This is likely the basis of the observation that, more often than not, they correlate well. They diverge primarily on the basis of additional assumptions made to analyze a particular data set. Because glycemia is fixed, the hyperinsulinemic euglycemic clamp requires the fewest structural assumptions and is, therefore, considered the most reliable. To examine the more complex physiological responses to a glucose injection or to consider only simple basal measurements, further assumptions must be made about the nature of glucose dynamics or about the homeostatic principle involved. Many methods (hyperglycemic clamp, insulin suppression tests, QUICKI) constitute variations on these basic approaches, with individual goals of emphasizing some aspect of the sensitivity measurement.

It is also worth reemphasizing that, in general, insulin sensitivity and resistance measures are related in an inverse fashion and that correlations should be examined among sensitivities or among resistance measurements. Thus, although logarithmic transformations provide reasonable comparisons, the most straightforward comparison between a different index of sensitivity and the HOMA index, which is a measure of insulin resistance, is obtained by first inverting it so that it is also expressed as a sensitivity.

To enhance the information obtained using a given method, tracers can be added, arterio-venous differences measured across organs, various tissue biopsies performed, and different metabolites determined. The choice of approach that is most appropriate in a particular experimental situation is therefore *not* made on the basis of the relative validity of the basic methods discussed, since all are valid, within the framework of their assumptions. Rather it should be made, based on the goals of a particular study, the size and kind of the population, the interventions which are feasible and precisely what metabolic relationships are to be examined. A balance must be drawn between the interpretative restrictions imposed by the assumptions inherent in a particular method and the experimental or clinical situation.

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