Review Article

Measurement of insulin action: a tribute to Sir Harold Himsworth

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Accepted 6 August 2011

Abstract

Sir Harold Himsworth was a renowned clinician and researcher. Among his myriad of accomplishments, he was the first to differentiate diabetes mellitus into ‘insulin-sensitive’ and ‘insulin-insensitive’ forms. To help distinguish these two types, he developed the first test to measure insulin sensitivity, the insulin–glucose test. This article reviews Himsworth’s pioneer methods and subsequent advances in the measurement of insulin action. The advantages and limitations of commonly used methods to assess insulin sensitivity are also examined.


Keywords Himsworth, insulin action, insulin resistance, insulin sensitivity

Introduction

When Himsworth began his career in 1930, diabetes mellitus was considered to be a uniform disease of hormone deficiency. This assumption was not unreasonable given the fact that replacing the hormone insulin improved the clinical syndrome of diabetes. In addition, no assay for plasma insulin was available at the time to confirm or refute the hypothesis of hormone deficiency.

Himsworth, however, was not convinced that a primary deficiency of insulin was the only or major cause of diabetes. He recognized that patients had variable responses to insulin and observed that some were ‘readily responsive to insulin’ while others were ‘surprisingly insusceptible’ [1]. He believed that ‘the question of variation in insulin activity required deeper analysis’ [1]. Thus, Himsworth devised the first measurement of insulin action.

Himsworth and the measurement of insulin action

Himsworth wanted to develop a test to quantify the efficiency of insulin to depress plasma glucose concentration. Although one could have injected a standard dose of insulin and measured the decrement in plasma glucose, he reasoned that this method would be inadequate to differentiate insulin sensitivity, as the change in glucose would also depend on the baseline glucose concentration [2,3]. Thus, he devised the ‘insulin–glucose test’, where oral glucose and intravenous insulin were given simultaneously. Because of a greater magnitude of change in glucose concentration after glucose ingestion, he found inter-individual differences in baseline glucose concentration to be less problematic. Using the insulin–glucose test, he recognized two patterns in patients with diabetes (Fig. 1): one with immediate suppression of hyperglycaemia after insulin (II) and another with attenuated suppression (I). He described the former response pattern as ‘insulin-sensitive’ and the latter response as ‘insulin-insensitive’.

The glucose response to insulin in insulin-sensitive patients with diabetes approximated that of normal individuals. Therefore, Himsworth felt assured that insulin action was normal in these patients. However, in insulin-insensitive patients with diabetes, he reasoned that several possibilities could explain their inability to respond normally to insulin: (1) the liver may be pouring so much sugar into the blood that the effect of the injected insulin is swamped; (2) the liver may be incapable of storing the ingested sugar; (3) the characteristic action of insulin in promoting storage of blood–sugar in the peripheral tissues may be unable to manifest itself [3]. To distinguish among these possibilities, he compared the difference in glucose concentration between ‘arterialized’ capillary blood (to obtain a value that approximates that of arterial blood) and venous blood following administration of either oral glucose or the combination of oral glucose and intravenous insulin. To obtain ‘arterialized’ blood, he drew blood samples from the warm ear. Figure 2 illustrates the characteristic glucose curves in representative patients classified as having either insulin-insensitive (top panel) or insulin-sensitive (bottom panel).
diabetes. By obtaining simultaneous samples of capillary and venous blood (an estimate of arterial–venous difference), he could estimate the amount of peripheral tissue glucose uptake in response to insulin. As can be seen in Fig. 2, the capillary–venous difference in glucose concentration was greatly magnified when insulin was given to an insulin-sensitive individual (bottom panel) compared with an insulin-insensitive individual (top panel). Therefore, Himsworth was able to show that, in individuals with insulin-insensitive diabetes, ‘the insulin is unable to exert its characteristic action of effecting the transference of sugar from the blood to the peripheral tissues’ [3].

In addition to the qualitative description of the two types of diabetes, Himsworth also tried to quantify differences in insulin sensitivity among individuals with diabetes by comparing glucose response curves with and without the administration of insulin. Thus, he was able to calculate the insulin area (I) to glucose tolerance area (G) ratio (I/G ratio). More specifically, the insulin area represented the area between curves after glucose alone and after glucose and insulin combination (Fig. 3). The glucose tolerance area represented the incremental glucose above baseline after the ingestion of glucose alone.

Using these methodologies, Himsworth made some surprisingly modern observations. In addition to differentiating two categories of diabetes, which are commonly referred to as Type 1 (insulin sensitive) and Type 2 (insulin insensitive) diabetes today, he also recognized that insulin sensitivity of individuals without diabetes varied. He noted that ‘intermediate degrees (of insulin sensitivity) occur in the apparently healthy and are found with increasing frequency in the older age groups’ [1]. Although he did not report on change in insulin sensitivity with weight loss, he observed that, in obese individuals with insulin-insensitive diabetes, ‘reducing the patient’s weight by any dietary means not only removes the symptoms and signs of diabetes but also restores the sugar-tolerance curve to normal’ [1].

**Measures of insulin action after Himsworth**

Unfortunately, Himsworth’s novel concepts were largely ignored for a few decades, but the notion that ‘insulin insensitivity’ existed became the focus of new investigators, primarily as the result of the development of the insulin radioimmunoassay by Yalow and Berson in 1960 [4]. Once plasma insulin concentrations could be quantified, it was noted that patients with maturity-onset diabetes (or insulin-insensitive diabetes) did not have a deficiency in insulin, but actually had insulin concentrations that were higher than individuals without diabetes following an oral glucose challenge. Although these results supported Himsworth’s views on the existence of
Provided a quantitative measure of insulin-mediated glucose uptake, the steady-state plasma glucose concentration was comparable among individuals, the steady-state insulin concentrations were comparable among insulin-reached steady-state plasma concentrations. As the rate of glucose was also infused. After 180 min, both glucose and insulin concentration to levels seen during the postprandial state. A fixed rate of exogenous insulin was also infused to raise plasma insulin concentration. Insulin secretion was therefore suppressed by infusing epinephrine and propranolol. A fixed plasma glucose concentration. Insulin secretion was therefore hypothesized to explain the results. For example, these patients 'suppressed' by infusing epinephrine and propranolol. A fixed plasma glucose concentration. Insulin secretion was therefore suppressed by infusing epinephrine and propranolol. As insulin and glucose remain infused at a constant rate, no rate adjustments are required during the test. Blood samples are drawn at baseline, 30, 60, 90, 120, 150, 160, 170 and 180 min for glucose and insulin concentrations. The last four values are used to calculate steady-state plasma insulin and steady-state plasma glucose concentrations.

For safety, if an individual's glucose concentration decreases below 2.8 mmol/l, the test is halted. Therefore, one potential limitation of the insulin suppression test is that it may underestimate insulin sensitivity in very insulin-sensitive individuals. The insulin suppression test may also underestimate degree of insulin resistance in very insulin-resistant individuals, as glycosuria may occur when glucose exceeds the renal threshold and endogenous insulin secretion may break through the octreotide suppression.

**Hyperinsulinaemic euglycaemic clamp**

Described in 1979 [7], the hyperinsulinaemic euglycaemic clamp, is often referred to as the 'gold' or reference standard measure of insulin sensitivity. Like the insulin suppression test, the clamp measures peripheral glucose uptake in response to a fixed infusion of exogenous insulin. Instead of giving octreotide, endogenous insulin secretion is prevented by 'clamping' the glucose concentration at a normal value (usually 5 mmol/l). In order to maintain euglycaemia, the glucose infusion rate is continually adjusted during the test. Therefore, the higher the glucose infusion rate needed to maintain euglycaemia, the more insulin sensitive is the individual.

One of the assumptions of the clamp is that the glucose infusion rate is equal to the glucose being metabolized ('M') under steady-state conditions, provided that endogenous glucose production is also completely suppressed. 'M' is the metric used to summarize insulin sensitivity during the clamp. Insulin sensitivity can be adjusted for urinary loss of glucose and fluctuations in plasma glucose during the clamp. It is generally recommended that insulin sensitivity be normalized to fat-free mass, as glucose uptake occurs primarily in lean tissue. In practice, insulin sensitivity measured by the clamp is also frequently divided by the steady-state plasma insulin concentration.

The clamp technique is laborious and requires bedside measurements of glucose concentration every 5 min to maintain glucose concentration within 5% of target. In addition, as opposed to the insulin suppression test, an operator needs to monitor and adjust glucose infusion rates throughout the study, which may introduce bias. One study found that the glucose infusion rates can be knowingly varied by 16% while still conducting a good clamp [8].

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secretory function [7]. Nevertheless, insulin sensitivity can also be calculated. At the start of the test, a priming dose of glucose is necessary to raise glucose concentration (usually 6.9 mmol/l above baseline). Similar to the euglycaemic clamp, variable infusion of glucose is necessary to maintain the hyperglycaemia and is the metric used to summarize insulin sensitivity. Exogenous insulin, however, is not given. Although different approaches to calculating insulin sensitivity from the hyperglycaemic clamp have been reported [9,10], the glucose infusion rate is generally divided by the average insulin concentration during the last hour of the study. It should be noted that insulin concentrations continuously increase and the glucose infusion rate does not reach steady-state within the usual 2- to 3-h length of the test, as opposed to the steady-state values reached during the euglycaemic clamp [11].

Both the insulin suppression test and the euglycaemic clamp have been used extensively to provide a direct measure of insulin sensitivity. Although protocols are different, they both aim to measure insulin-mediated glucose uptake, a fundamental metric of insulin action, under controlled conditions. In addition, the measures of insulin sensitivity produced with both methods are essentially identical, with correlation coefficients between the two methods of $> 0.9$ [8,12]. Finally, in addition to supporting Himsworth’s classification of diabetes [5], both techniques have been used to further refine and expand the role of insulin resistance in human disease. In particular, although Himsworth’s focus was on differentiating two patterns of diabetes, insulin sensitivity has been shown to vary up to sixfold among individuals without diabetes [13,14].

Using these techniques, insulin resistance in individuals without diabetes has also been associated with a host of other diseases, including dyslipidaemia [15,16], hypertension [17], cardiovascular disease [18] and non-alcoholic steatohepatitis [19].

**Frequently sampled intravenous glucose tolerance**

The frequently sampled intravenous glucose tolerance test was initially introduced by Bergman et al. in 1979 and has become a popular method to estimate insulin sensitivity [20,21]. Although often viewed as simpler than the insulin suppression test or the clamp method, as the name implies, frequent samples are required during the 180-min test. Various protocols for blood sampling exists with one representative sequence as follows: −15, −10, −5, −1, 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, 180 [22]. Modifications of the number of blood draws have been proposed but a minimum of 12 samples are required [23].

The frequently sampled intravenous glucose tolerance test derives insulin sensitivity ($S_i$) based on ‘minimal model’ analysis [21]. In the original description of the frequently sampled intravenous glucose tolerance test, a single bolus of glucose was given and glucose and insulin concentrations were measured before and sequentially for 180 min following the bolus. Insulin sensitivity was calculated based on parameters obtained after inputting measured glucose and insulin values into a mathematical model.

Insulin sensitivity calculated from the original frequently sampled intravenous glucose tolerance test was poorly correlated with insulin sensitivity as measured by the hyperinsulinaemic euglycaemic clamp [24,25]. One potential explanation was that the minimal model, initially developed in dogs, was less applicable in humans [24,25]. For example, humans have an earlier insulin secretory response to the glucose bolus given in the frequently sampled intravenous glucose tolerance test than dogs [26]. In addition, a certain threshold of insulin secretion was necessary to obtain a valid insulin sensitivity [27]. Therefore, to improve its accuracy, the frequently sampled intravenous glucose tolerance protocol was modified to include the administration of tobutamid [27,28], which enhanced endogenous insulin secretion, or exogenous insulin [29]. The insulin-modified frequently sampled intravenous glucose tolerance test is the most commonly used form of this test today. In general, glucose is injected over 1 min and insulin is given as an intravenous bolus 20 min after the start of the glucose injection. A computer program is used to calculate parameters used to derive insulin sensitivity.

Even with the insulin-modified frequently sampled intravenous glucose tolerance test, the correlation between insulin sensitivity measured with the modified protocol and insulin sensitivity measured during the euglycaemic clamp is modest. For example, Saad et al. found a correlation coefficient of 0.62 between the two tests [22]. In addition, insulin sensitivity was unable to be calculated in half the individuals with diabetes. In the Insulin Resistance and Atherosclerosis Study, a large multicentre, epidemiologic study of insulin resistance, up to 15% of individuals had an insulin sensitivity of zero using the frequently sampled intravenous glucose tolerance test [30]. Because of these limitations, it might be reasonable to view the frequently sampled intravenous glucose tolerance test as a surrogate measure of insulin sensitivity.

**Homeostasis model assessment of insulin resistance**

Although Himsworth and subsequent researchers that followed were concerned with developing the most direct methods to quantify insulin action, recent efforts have focused on developing surrogate markers or biomarkers for insulin resistance. In general, the aim has been to simplify the measurements of insulin sensitivity in humans. The most commonly used surrogate measure is probably the homeostasis model assessment of insulin resistance (HOMA-IR), which was introduced by Matthews et al. in 1985 [31]. HOMA-IR represents a ‘computer-solved model of insulinglucone interactions’. The original cohort used to create the model included six ‘normal subjects’ and five ‘patients with maturity-onset diabetes’. To compute, HOMA-IR requires only the knowledge of fasting glucose and insulin concentrations. The simplified formula in the original description [31] is as follows:
HOMA-IR = \frac{\text{fasting glucose (mmol/l)}}{\text{fasting insulin(µIU/ml)}} \times 22.5

In 2004, the authors also made available the ‘computer model’, which is a non-linear solution calibrated in line with current insulin assays [32]. The Quantitative Insulin Sensitivity Check Index (QUICKI) is another calculation based on fasting glucose and insulin concentrations [33]. QUICKI is essentially identical to HOMA-IR. As pointed out by Wallace et al. [32], it represents the log transformation of the glucose insulin product:

\[
\text{QUICKI} = \frac{1}{\log(\text{fasting plasma glucose (mg/dl)}) + \log(\text{fasting plasma insulin(µIU/ml))}} = \frac{1}{\log(\text{fasting plasma glucose}} \times \text{fasting plasma insulin)]}
\]

While the convenience of using a measure based on fasting values is undeniable, several caveats should be kept in mind when choosing this method. First, in individuals without diabetes, the relationship between HOMA-IR and fasting plasma insulin concentration is nearly identical, with a correlation coefficient close to 1 [34]. This is attributable to the fact that, in individuals without diabetes, the glucose concentration fluctuates less than insulin concentration and essentially functions as a constant. Second, HOMA-IR explains less than 40% of the variability in insulin sensitivity as measured by the insulin suppression test [13] or euglycaemic clamp [35] in individuals without diabetes. The original study [31] reported a high degree of correlation \((r = 0.83)\) between the HOMA-IR and insulin sensitivity derived from the hyperinsulinaemic euglycaemic clamp; however, the sample size was small \((n = 12\) individuals without diabetes). In a recent study from the Ely and European Group for the Study of Insulin Resistance, the relationship between HOMA-IR and insulin sensitivity measured by the hyperinsulinaemic euglycaemic clamp was \(-0.48\) in 2097 individuals without diabetes; coincidentally, the relationship was similar \((-0.49)\) between fasting insulin concentration and insulin sensitivity, as measured by the clamp [35]. Lastly, the relationship between HOMA-IR and a direct measure of insulin sensitivity can vary with the degree of obesity [34]. In normal-weight individuals, the correlation–coefficient can be as low as 0.36 between HOMA-IR and insulin resistance quantified during the insulin suppression test compared with 0.6 in obese individuals.

**Oral glucose tolerance test**

Next to fasting samples, the oral glucose tolerance test represents the second most commonly used surrogate test for the evaluation of insulin sensitivity. There have been several formulas and models proposed to calculate insulin sensitivity based on the oral glucose tolerance test. Although not an exhaustive list, some indices named after their authors are as follows:

1. Cederholm [36]: glucose uptake/(Gmean × log Imean)

2. Belfiore [37]: \(2/(\text{IAUC}/\text{meanAUC} \times G_{\text{AUC}}/\text{meanG}_{\text{AUC}}) + 1\)

3. Matsuda [38]: \(10^{25}/(G_0 \times I_0 \times \text{Gmean} \times \text{Imean})\)

4. Strumvoll [39]: \(0.226 - 0.0032 \times \text{BMI} - 0.0000645 \times I_{120} - 0.00375 \times G_{90}\)

\((\text{glucose uptake} = \text{glucose load}/120 + (G_0 - G_{2h}) \times 1.15 \times 180 \times 0.19 \times \text{body weight}/120; G_0, \text{fasting glucose}; I_0, \text{fasting insulin}; G_{\text{AUC}}, \text{average of insulin values obtained during OGTT}; I_{\text{mean}}, \text{average of insulin values obtained during OGTT}; G_{\text{mean}}, \text{area under the curve of glucose during OGTT}; I_{\text{AUC}}, \text{area under the curve of insulin during OGTT}).\)

Although the formulas are varied, there are many commonalities among these indices derived from the oral glucose tolerance test. First, at the simplest level, they all include some measurement of glucose and insulin concentrations. Second, many represent insulin sensitivity as a product of the two concentrations. Third, insulin sensitivity calculated based on oral glucose tolerance test measurements tend to be more closely related to direct measures of insulin sensitivity than values derived from fasting measures [13,34,38,40].

Finally, as a general rule, these indirect measures derived from an oral glucose tolerance test are more accurate in individuals without diabetes than with diabetes [38,41]. This is likely attributable to the fact that, in individuals with diabetes, the insulin response to an oral glucose challenge is markedly attenuated. As the variability in insulin concentration is greater than glucose concentration and is better correlated with degree of insulin resistance, the major indicator for insulin resistance is lost in individuals with diabetes who have been assessed by an oral glucose tolerance test. For example, in one study, 446 individuals without diabetes were divided into quartiles of insulin resistance using the insulin suppression test [42]. Quartile 1 was the most insulin sensitive and quartile 4 was the most insulin resistant. The glucose area under the curve following a 75-g glucose challenge increased as follows from quartile 1 to 4: 166, 180, 193 and 225 mmol/l × 3 h. The corresponding increase in insulin response was as follows: 570, 780, 1093 and 1991 pmol/l × 3 h. Compared with individuals in the most insulin-sensitive quartile (quartile 1), those in the most insulin-resistant quartile (quartile 4) had an insulin response that was 3.5 times greater. Comparatively, the glucose response was only 1.4 times greater in individuals in quartile 4 compared with quartile 1. Therefore, when using the oral glucose tolerance test measurements as a surrogate of insulin resistance, it should be remembered that the insulin response is a major determinant of insulin resistance. For this reason, insulin response alone can be used as a surrogate measure of insulin resistance in individuals without diabetes [34]. The limitations of using the oral glucose tolerance test as a surrogate measure of insulin sensitivity also highlights the benefit of using a specific measure of insulin action; for example, the insulin suppression test or the euglycaemic clamp. Unlike the oral glucose tolerance test, neither relies on an endogenous insulin response and can reliably measure insulin-mediated glucose uptake in various populations.
Table 1 summarizes the most commonly used measures of insulin sensitivity and their relationship to the euglycaemic hyperinsulinaemic clamp. To avoid bias, the correlations reported in the original studies validating the methods are not used. The insulin suppression test has the highest correlation with the clamp with a nearly perfect r-value (0.91). The r-values between the clamp and the surrogate measures of insulin sensitivity in Table 1 are more modest and vary between 0.44 to 0.77.

Conclusion

Himsworth once began his lecture to the Royal College of Physicians with this statement, ‘The history of modern knowledge is concerned in no small degree with man’s attempt to escape from his previous concepts’ [1]. Without a doubt, Himsworth ‘modernized’ the view of diabetes from a disease purely of hormone deficiency to one that could also be distinguished by insulin sensitivity. Important to making this progress was his emphasis on the need to better characterize insulin sensitivity using the most direct methods possible in his time. It is interesting that, in our ‘modern’ era, the focus has shifted to developing more biomarkers and simpler methods for assessing insulin resistance. Although not without some benefit, simplified estimates of insulin resistance have limitations and have not yet allowed us to ‘escape’ from using direct measures in order to provide precise estimates of insulin action.

Competing interests

Nothing to declare.

References


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