

## Evaluation of Insulin Sensitivity in Clinical Practice and in Research Settings

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*Insulin resistance is the core metabolic abnormality in type 2 diabetes. Its high prevalence and its association with dyslipidemia, hypertension, hyperinsulinemia, and high coronary and cerebrovascular mortality put it in the forefront as the plausible target for aggressive intervention. Measurements of insulin sensitivity provide clinicians and clinical researchers with invaluable instruments to objectively evaluate the efficiency of both current and potentially useful interventional tools. Although several methods had been developed and validated to evaluate insulin sensitivity, none of these methods can be universally used in all patients. Nonetheless, a method suitable for use in clinical or basic research may not necessarily be a practical method for use in clinical practice or for epidemiologic research. We reviewed the currently used methods for assessment of insulin sensitivity. For each method, we summarized its procedure, normal value, cut-off value for defining insulin resistance, advantages and limitations, validity, accuracy for each patient population, and suitability for use in clinical practice and in research settings. The methods reviewed include fasting plasma insulin, homeostatic model assessment, quantitative insulin sensitivity check index, glucose-to-insulin ratio, continuous infusion of glucose with model assessment, indices based on oral glucose tolerance test, insulin tolerance test, and the so called “gold standard” methods, the hyperinsulinemic euglycemic clamp and the frequently sampled–intravenous glucose tolerance test.*

**Key words:** insulin resistance, insulin sensitivity, clinical practice

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### Introduction

Insulin resistance is a state in which physiologic concentrations of insulin produce a subnormal biologic response.<sup>1</sup> It underlies abnormalities of glucose, lipid, and blood pressure homeostasis.<sup>2</sup> This cluster of metabolic abnormalities is referred to as the insulin resistance syndrome, syndrome X, or the metabolic syndrome, and is related to type 2 diabetes, obesity, hypertension, and dyslipidemia.<sup>3–5</sup> In fact, insulin resistance is present long before the clinical manifestations of the individual components of the syndrome.<sup>6–8</sup> Epidemiologic evidence indicates that insulin resistance is directly related to the risk of developing atherosclerosis and cardiovascular disease.<sup>9–11</sup>

To clinically identify patients with the metabolic syndrome, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, ATP III) suggested that individuals having three or more of the following criteria are defined as having the metabolic syndrome:<sup>12</sup>

1. Abdominal obesity: waist circumference >40 inches in men and >35 inches in women;
2. Hypertriglyceridemia: >150 mg/dL (1.69 mmol/L);
3. Low high-density lipoprotein (HDL) cholesterol: <40mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women;
4. High blood pressure:  $\geq 130/85$  mmHg;
5. High fasting plasma glucose:  $\geq 110$ mg/dL ( $\geq 6.1$  mmol/L).

A recent epidemiologic study among adults above age 20 showed that the age-adjusted prevalence of the metabolic syndrome in the United States is 23.7%, with a higher prevalence among minority populations.<sup>13</sup>

Several clinical trials have shown that lifestyle modification delays the progression to type 2 diabetes among individuals with impaired glucose tolerance,<sup>14–17</sup> however, none of these studies included quantitative evaluation of insulin sensitivity as an integral component of the study design. It is possible that an improvement in insulin sensitivity can be achieved either through lifestyle modification<sup>18–21</sup> or pharmacologically with met-

formin<sup>22,23</sup> or thiazolidinediones.<sup>24–26</sup> The Food and Drug Association (FDA) has not approved either of these pharmacologic compounds for treatment of insulin resistance in nondiabetic individuals; however, the diagnosis of type 2 diabetes, hypertension, and dyslipidemia mandates aggressive appropriate treatment with antidiabetic, blood pressure–lowering, and lipid-lowering agents aimed at reducing cardiovascular morbidity and mortality.

The rapidly growing epidemic of obesity and consequent insulin resistance has increased the interest in finding quantitative, accurate, and easy methods to evaluate insulin sensitivity in both clinical research and clinical practice. Such a tool is not only useful for early identification of insulin resistance but also to assess the degree of success in treating this syndrome and its consequences. This review will summarize our current knowledge of the available methods used to evaluate insulin sensitivity in humans. The components of each method, its indications, and its limitations are discussed.

Fasting Plasma Insulin Concentration

One of the most practical ways to estimate insulin resistance from the clinical perspective is to measure plasma insulin concentration after an overnight fast. As it is inexpensive and easy to do, it has been used in several population-based studies.<sup>27–30</sup> Very high plasma insulin values reflect the presence of insulin resistance. Despite the relatively good correlation between fasting plasma insulin and insulin sensitivity derived from the hyperinsulinemic euglycemic clamp, measures of fasting plasma insulin explain no more than 5 to 50% of the variability in insulin action seen in nondiabetic subjects.<sup>31,32</sup> This is because plasma insulin levels depend not only on insulin sensitivity, but also on insulin secretion, distribution, and degradation.<sup>33</sup>

Moreover, with the development of diabetes, fasting plasma insulin levels tend to decrease owing to beta cell dysfunction. Therefore, plasma insulin levels in diabetic patients are valid reflection of both target tissue insulin resistance and diminishing insulin production.<sup>34</sup> This explains why fasting plasma insulin levels may accurately predict insulin sensitivity among normoglycemic patients than among those with impaired glucose toler-

ance (IGT) or type 2 diabetes.<sup>32,35,36</sup> Another limitation to using fasting plasma insulin to predict insulin resistance is cross-reactivity between insulin and proinsulin. Proinsulin levels are high among insulin-resistant subjects with type 2 diabetes and IGT,<sup>37,38</sup> but not in people who are insulin resistant and normoglycemic.<sup>39</sup>

The commonly used radioimmunoassay (RIA) method has a lower specificity and sensitivity, and a higher interassay coefficient of variation, when compared with the two-site monoclonal antibody-based insulin assay methods (immuno-radiometric [IRMA], immuno-enzymometric [IEMA], and immuno-fluorimetric [IFMA]) methods.<sup>40,41</sup> The presence of anti-insulin antibodies in type 1 and type 2 diabetic patients, who are treated with human or animal insulin, can interfere with both the RIA and two-site monoclonal assay, unless removal of anti-insulin antibodies and antibody-bound insulin is performed.<sup>41,42</sup>

The normal range for insulin levels using RIA is 3 to 32 mU/L.<sup>43,44</sup> However, there is no defined cut-off value indicating insulin resistance. This lack of consensus stems partly from the various means used to define abnormal. In a population-based study examining the association between insulin levels and cardiovascular risk, Lindahl et al.<sup>8</sup> defined insulin resistance as a plasma insulin level >7.2 mU/L. Using the hyperinsulinemic euglycemic clamp as the reference standard, McAuley et al.<sup>45</sup> found that a fasting insulin >12.2 mU/L predicted insulin resistance among normoglycemic adults. Laakso,<sup>32</sup> also using the hyperinsulinemic clamp in normoglycemic adults, arrived at a cut-off of 18 mU/L. Finally, defining the abnormal range as the upper 10% percentile, Ascaso et al.<sup>46</sup> defined insulin resistance in nondiabetic individuals when plasma insulin levels were equal or greater than 16.7 mU/l (Table 1). While these variations illustrate how study designs influences what insulin level is determined to represent insulin resistance, the lack of established standards for insulin assay procedures further complicates the issue.<sup>47</sup>

Another limitation for measurement of fasting plasma insulin is the pulsatile mode of insulin secretion (pulses with a periodicity of 10–15 minutes, and ultradian oscillations periods of 1 to 3 hours). The periodicity, amplitude, and ultradian oscillations of insulin pulses

Table 1. Comparison of Fasting Plasma Insulin Values and Insulin Assays Used to Assess Insulin Sensitivity in Different Studies

Study	Year	Population	Insulin Assay	Insulin Resist Value
Lindahl et al. <sup>8</sup>	1993	General population	RIA	>7.2 mU/L
McAuley et al. <sup>45</sup>	2001	General population	RIA	>12.2 mU/L
Laakso et al. <sup>32</sup>	1992	Normoglycemic	RIA	>18 mU/L
Ascaso et al. <sup>46</sup>	2001	Normoglycemic	RIA	≥16.7 mU/L

RIA = radioimmunoassay.

vary in the fasting state, and are altered in IGT and in type 2 diabetes.<sup>41</sup> Because of these limitations, fasting plasma insulin levels are of limited value for clinical purposes, but have some utility as a research tool in population-based studies.

### The Homeostasis Model Assessment (HOMA)

Because fasting insulin per se does not provide an accurate measure of insulin sensitivity in diabetic patients, efforts have been made to incorporate fasting plasma glucose in a formula to arrive at a better estimate of insulin-sensitivity. HOMA was developed by Matthews et al.<sup>48</sup> as a method for estimating insulin sensitivity from fasting serum insulin (FI) and fasting plasma glucose (FG) using the following mathematic formula:

$$\text{HOMA Insulin Resistance (HOMA}_{\text{IR}}) = \text{FI} \times \text{FG} / 22.5$$

FI is measured in  $\mu\text{U/mL}$  and FG is measured in  $\text{mmol/L}$ . Low HOMA<sub>IR</sub> indicates high insulin sensitivity, whereas high HOMA<sub>IR</sub> indicates low insulin sensitivity. In their original report, Matthews et al. found HOMA<sub>IR</sub> ranges between 1.21 and 1.45 in normal subjects and between 2.61 and 2.89 in insulin-resistant diabetic subjects.<sup>48</sup> However, further epidemiologic studies performed in the general population reported higher HOMA<sub>IR</sub> values of 2.1,<sup>44</sup> 2.7,<sup>31</sup> and 3.8.<sup>46</sup>

Because fasting insulin is a major component of the HOMA<sub>IR</sub> calculation, all previously mentioned limitations should apply to this formula. Three samples for fasting plasma insulin should be drawn 5 minutes apart to avoid errors that may arise owing to the pulsatile nature of insulin secretion. However, most studies use only one basal insulin measurement to calculate HOMA<sub>IR</sub>.

HOMA<sub>IR</sub> correlates well with the glucose disposal rate derived from the hyperinsulinemic euglycemic clamp.<sup>49–53</sup> In addition, two authors found a good correlation between the HOMA<sub>IR</sub> and the insulin sensitivity index ( $S_i$ ) derived from the frequently sampled intravenous glucose tolerance test (FSIVGT).<sup>54,55</sup> By contrast, Anderson et al.<sup>35</sup> failed to demonstrate a good correlation between the two. Furthermore, some of the studies that initially demonstrated significant correlation between the HOMA<sub>IR</sub> and the clamp-derived insulin sensitivity used a low insulin infusion rate of  $20 \text{ mU} \cdot \text{m}^{-2} \cdot \text{minute}^{-1}$  during the clamp, which might not have completely suppressed the hepatic glucose production and may have created an error in calculating the glucose uptake by peripheral tissues.<sup>51,52</sup>

One of the limitations of HOMA<sub>IR</sub> is the model assumption that insulin sensitivity in the liver and peripheral tissues are equivalent, whereas it is known that they can differ considerably in the same individual.<sup>50</sup> Furthermore, some data suggest that the accuracy of

HOMA<sub>IR</sub> is limited by hyperglycemia. Those studies that demonstrated good correlations between HOMA<sub>IR</sub> and the clamp-derived insulin sensitivity in diabetic patients tended to enroll patients without significant hyperglycemia.<sup>48–50,52,53</sup> Mari et al.<sup>56</sup> failed to show a significant correlation between HOMA<sub>IR</sub> and clamp in type 2 diabetic patients with higher glucose levels (mean basal plasma glucose of 205 mg/dL). In addition, Anderson et al.<sup>35</sup> and Brun et al.<sup>57</sup> found that the correlation between HOMA<sub>IR</sub> and  $S_i$  derived from the FSIVGT weakened as glycemia increased. These results suggest a non-linear relationship between  $S_i$  and HOMA<sub>IR</sub>.

The coefficient of variation (CV) for HOMA<sub>IR</sub> is as high as 31%,<sup>48</sup> which limits its use in clinical practice and clinical research.<sup>47</sup> Optimizing sample size and insulin assay method reduce HOMA<sub>IR</sub> CV to 8 to 12%.<sup>49,51</sup>

In conclusion, HOMA<sub>IR</sub> is mostly useful for the evaluation of insulin sensitivity in euglycemic individuals and in persons with mild diabetes; however, this index appears to offer little or no advantage over the fasting insulin concentration alone.<sup>31,45,58</sup> In patients with severe hyperglycemia or in lean diabetic patients with beta cell dysfunction, the HOMA<sub>IR</sub> may not be accurate. Its usefulness should therefore be restricted to large population-based studies that require a simple method to assess insulin sensitivity.

### Quantitative Insulin Sensitivity Check Index (QUICKI)

QUICKI is another mathematic model available to estimate insulin sensitivity.<sup>59</sup>

$$\text{QUICKI} = 1 / [\log(I0) + \log(G0)],$$

where I0 is the fasting plasma insulin level in  $\mu\text{U/mL}$ , and G0 is the fasting plasma glucose level in mg/dL. The mean QUICKI for lean, obese, and obese-diabetic subjects are 0.382, 0.331, and 0.304, respectively.<sup>59</sup> Although other studies have found a similar range for a normal healthy population of 0.372 and 0.366,<sup>60,61</sup> one study showed a wider range between 0.265 and 0.518.<sup>62</sup>

The mathematic difference between the QUICKI and the HOMA<sub>IR</sub> is that the former uses the reciprocal of the logarithm of both glucose and insulin to account for the skewed distribution of fasting insulin values. As expected, there is very good correlation between QUICKI and HOMA<sub>IR</sub>,<sup>63</sup> especially when the HOMA<sub>IR</sub> is log-transformed.<sup>59,62,64,65</sup>

Although two studies failed to demonstrate any real advantage of QUICKI when compared with log HOMA<sub>IR</sub>,<sup>62,65</sup> other studies argue that QUICKI has the advantage of being applied to wider ranges of insulin sensitivity.<sup>61,63,64</sup> QUICKI was also shown to correlate well with the FSIVGT<sup>66</sup> and the hyperinsulinemic euglycemic clamp.<sup>58</sup> However, the correlation is weaker

when insulin levels were low, as seen in non-obese insulin-sensitive subjects and diabetic patients with diminished insulin production,<sup>59,60,62,65,67,68</sup> this is because low insulin levels lead to variability in determined insulin concentrations and because of the oscillatory pattern of insulin secretion in healthy individuals. Other limitations to this mathematic method include its limited applicability for type 1 diabetic patients owing to lack of endogenous insulin secretion,<sup>59</sup> and its inaccuracy if conducted following exercise training.<sup>67</sup>

In conclusion, the QUICKI may be a useful and simple tool for assessing insulin sensitivity in epidemiologic settings; it may offer some advantage over the HOMA<sub>IR</sub>, especially in obese and diabetic individuals with relatively preserved beta cell function. However, the model needs validation in a wider range of subjects with different glucose tolerance patterns in order to confirm its reliability for use in clinical practice and in research settings.

### Fasting Plasma Glucose-to-Insulin Ratio (G/I)

G/I is another mathematic method that uses fasting plasma insulin and fasting plasma glucose to estimate insulin sensitivity. The higher the ratio, the more insulin-resistant an individual is.

The index generally correlates well with other indices of insulin sensitivity.<sup>1,45,69–75</sup> It correlated with insulin sensitivity indices derived from the oral glucose tolerance test (OGTT,  $r = 0.82$ ,  $P < 0.05$ ),<sup>1,71</sup> and FSIVGT ( $r = 0.76$ ,  $P < 0.001$ ).<sup>1,69,72</sup> Vuguin et al.<sup>72</sup> found that a fasting G/I ratio  $< 7$  provided 87% sensitivity and 89% specificity for identifying low insulin sensitivity in young girls with premature adrenarche. In another study of white nondiabetic women with polycystic ovarian syndrome (PCOS), Legro et al.<sup>69</sup> found the G/I ratio to be the best screening test for insulin resistance. The authors showed that a cut-off  $< 4.5$  provided an 87% positive predictive value and 94% negative predictive value in screening for insulin resistance in PCOS. G/I ratio was found to correlate well with HOMA<sub>IR</sub> ( $r = 0.83$ ,  $P < 0.01$ ), fasting insulin ( $r = 0.95$ ,  $P < 0.001$ ),<sup>73</sup> and QUICKI ( $r = 0.91$ ,  $P < 0.0001$ )<sup>74</sup> in healthy individuals. Data on the correlation between G/I ratio and insulin sensitivity derived from the euglycemic clamp procedure are inconsistent; whereas two studies found a significant correlation,<sup>1,45</sup> another did not.<sup>50</sup> Adding to the previously mentioned problems that include precision of insulin assay, pulsatile pattern of insulin secretion, and cross reactivity with proinsulin, the major problem with using the G/I ratio is its inaccuracy in diabetic patients owing to defects in insulin secretion and high plasma fasting glucose.<sup>1,50,70,76</sup> In subjects with normoglycemia, G/I ratio offered little advantage over the 1/insulin measure<sup>76</sup> or fasting insulin.<sup>45</sup> Moreover, it

provides indirect information on whole-body sensitivity but not on the effect of insulin in peripheral tissues.<sup>1</sup> In conclusion, this index, like the previously described indices, should be limited to the nondiabetic population. For research purposes, its superiority over the fasting insulin is questionable.

### Continuous Infusion of Glucose with Model Assessment (CIGMA)

Because of the inaccuracy that may result from low basal insulin concentrations, an alternative mathematic method was proposed. This method assesses insulin sensitivity through the evaluation of the near-steady state glucose and insulin concentrations after a continuous infusion of glucose with model assessment.<sup>77</sup> This procedure mimics postprandial glucose and insulin concentrations. CIGMA not only provides information about glucose tolerance and insulin sensitivity, but also about beta cell function. Using a mathematic model of glucose homeostasis, glucose and insulin values are compared with known physiologic data of glucose and insulin kinetics in response to glucose infusion that are derived from healthy lean subjects with no family history of diabetes.

The glucose and insulin values used for CIGMA are obtained during the last 15 minutes of the 60-minute continuous glucose infusion (5 mg glucose  $\cdot$  kg ideal body weight<sup>-1</sup>  $\cdot$  minute<sup>-1</sup>). Samples are collected at five-minute intervals, to avoid the oscillatory variation in insulin concentration. The average is then compared with predicted values from the computer model. The median value for normal subjects is 1.35 and for diabetic patients with mild hyperglycemia is 4.0.<sup>77</sup>

Although CIGMA has been used in several studies to evaluate insulin resistance,<sup>78–83</sup> few studies have compared CIGMA with other insulin sensitivity indices. In elderly normoglycemic patients, CIGMA significantly correlated with mean fasting plasma insulin concentrations.<sup>84</sup> Hermans et al.<sup>55</sup> compared CIGMA, HOMA<sub>IR</sub>, FSIVGT, and the insulin tolerance test (ITT), in subjects with glucose tolerance ranging from normal to frank diabetes. They found that CIGMA and HOMA<sub>IR</sub> were able to discriminate differences in insulin sensitivity among subjects as well as the FSIVGT and better than the ITT. Among the four methods, CIGMA was the best discriminatory test in precision analysis. It is worth mentioning that CIGMA in this study derived from a 2-hour test (compared with the original 1-hour CIGMA). Other studies have also reported data from 2-hour CIGMA.<sup>85,86</sup>

Data aiming to validate CIGMA against the clamp-derived insulin sensitivity index are scarce. In the original article, CIGMA was shown to correlate well with the euglycemic hyperinsulinemic clamp ( $r = 0.87$ ,  $P < 0.0001$ )<sup>77</sup> in normal subjects and in diabetic patients

with mild hyperglycemia. However, the relationship between CIGMA and the clamp was nonlinear for diabetic patients with severe insulin resistance. Nijpels et al.<sup>70</sup> studied 90 subjects, most of them with normal or impaired glucose tolerance, and found a modest correlation between CIGMA and the clamp-derived insulin sensitivity ( $r = 0.66$ ;  $P < 0.05$ ). The CV of CIGMA ranges between 17%<sup>84</sup> and 20%.<sup>77</sup>

There are two main advantages of CIGMA over HOMA<sub>IR</sub>. First, the insulin values that are measured in CIGMA are much higher than those in HOMA<sub>IR</sub> owing to the glucose stimulus; therefore, the high insulin inter-assay CV (10–15%)<sup>41,47</sup> that is problematic at low insulin concentration is avoided.<sup>55</sup> Second, higher insulin concentration in CIGMA stimulates peripheral glucose uptake producing a steady-state glucose concentration, which is a better reflection of the peripheral insulin sensitivity.

Although CIGMA is more physiologic, practical, cheaper, and less invasive than the FSIVGT and clamp procedure, the model incorrectly assumes that levels of insulin resistance at the liver and peripheral tissues are equal. Furthermore, in insulin-deficient subjects, where the insulin response is insufficient to stimulate glucose uptake, the interpretation of CIGMA is difficult.<sup>33</sup> As CIGMA is a procedure and not a simple test such as fasting insulin or the HOMA<sub>IR</sub>, its use in clinical practice is limited. Moreover, due to insufficient data comparing CIGMA against the “gold standard” euglycemic hyperinsulinemic clamp, its use in research settings should also be viewed with caution.

## The Oral Glucose Tolerance Test (OGTT)

Because oral glucose tolerance is in part determined by sensitivity of peripheral tissues to insulin, the OGTT has been used to evaluate insulin release and the sensitivity of the peripheral tissue to the insulin action. Being a less costly and less labor-intensive procedure compared with the FSIVGT and the euglycemic clamp, the OGTT has been considered a practical method for epidemiologic studies,<sup>58</sup> for population screening, and for large-scale intervention trials.<sup>50,63,87</sup> Several indices to estimate insulin sensitivity have been derived from the four samples of insulin and glucose (0, 30, 60, and 120 minutes) taken after ingestion of 75 grams of glucose (Table 2).

## Insulin Sensitivity Indices Based on the OGTT

Levine et al.<sup>88</sup> was one of the first authors to use the product of the area under the curve for glucose (AUC G) and the area under the curve for insulin (AUC I) during the OGTT to derive an estimate of insulin sensitivity. Later, AUC I was used alone as an estimate.<sup>31,36,89</sup>

## Cederholm and Wibell Index<sup>90</sup>

$$SI = M/G \cdot \log I,$$

where M = glucose load / 120 + (0-h plasma glucose concentration – 2-h plasma glucose concentration)  $\times$  1.15  $\times$  180  $\times$  0.19  $\times$  body weight/120; where G = mean plasma glucose concentration, and I = mean serum insulin. A normal reference value is  $79 \pm 14$ .

## Gutt et al. Index<sup>91</sup>

ISI 0,120 = MCR/log MSI (mean serum insulin), uses the fasting (0 min) and 120 min post-load insulin and glucose concentrations, where MCR (metabolic clearance rate) is m/MPG (mean plasma glucose), where m = (75000 mg + [0 min glucose – 120 min glucose]  $\times$  0.19  $\times$  body weight)/120 min. The reference range for lean controls was  $89 \pm 39$ , for obese  $58 \pm 23$ , for IGT  $46 \pm 12$ , and for diabetic patients  $23 \pm 19$ .

## Avignon et al. Index<sup>92</sup>

$$Sib = 10^8 / (I \times G \times VD) \cdot$$

$$(\text{normal range} = 11.99 \pm 1.43)$$

$$Si2h = 10^8 / (I2h \times G2h \times VD) \cdot$$

$$(\text{normal range} = 1.79 \pm 0.33),$$

where I = fasting insulin, G = fasting plasma glucose, G2h and I2h = plasma glucose and insulin at the second hour of the OGTT, and VD = volume distribution (150 mL/kg of body weight). An additional insulin sensitivity index ( $S_iM$ ) was derived by the average of the 2, after multiplying  $S_{ib}$  by a correcting factor:

$$SiM = [(0.137 \times Sib) + Si2h] / 2$$

$$(\text{normal range} = 1.71 \pm 0.24).$$

## Matsuda et al. Index<sup>50</sup>

$$ISI (\text{composite}) = 10,000 / \sqrt{(FPG \times FPI) \times (G \times I)},$$

where FPG = fasting plasma glucose, FPI = fasting plasma insulin, and G = mean plasma glucose, and I = mean plasma insulin concentration.

## Belfiore et al. Index<sup>93</sup>

$$ISI = 2 / (INSp \times GLYp) + 1,$$

where INSp and GLYp are the insulinemic and glycemic areas of the person under study recorded during OGTT. Reference value in normal controls was around 1, but

**Table 2.** OGTT-derived Indices to Estimate Insulin Sensitivity and their Correlation with the Euglycemic Hyperinsulinemic Clamp or Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGT) in Various Populations

	Formulae	Subjects	Correlation with
1.	AUC I	NGT	Euglycemic clamp <sup>89</sup> $r = 0.61, P = 0.001$ IST <sup>31</sup> $r = 0.79, P < 0.001$ ITT <sup>36</sup>
	AUC I	NGT, IGT	$r = -0.51, P < 0.001$
	I 30 min		$r = -0.43, P < 0.001$
	I 2 hr		$r = -0.39, P < 0.001$
	G 30 min		$r = -0.28, P = 0.01$
	G 2 hr		$r = -0.38, P < 0.001$
2.	$SI = \frac{M}{G \times \log I}$	NGT, IGT, DM	Euglycemic clamp <sup>90</sup> $r = 0.62, P < 0.0001$
3.	ISI 0, 120 = MCR/log MSI	NGT, IGT, DM	Euglycemic clamp <sup>91</sup> $r = 0.63, P < 0.001$
4.	Sib = $10^8/(fI \times fG \times VD)$ Si2h = $10^8 (I2h \times G2h \times VD)$ SiM = $[(0.137 \times Sib) + Si2h]/2$	NGT, IGT, DM	FSIVGT <sup>92</sup> $r = 0.90, P < 0.0001$
5.	$ISI(Comp) = \frac{10,000}{\sqrt{(FPG \times FPI) \times (G \times I)}}$	NGT, IGT, DM	Euglycemic clamp <sup>50</sup> $r = 0.73, P < 0.0001$
6.	$ISI = \frac{2}{(INSp \times GLYp) + 1}$	NGT, O, ODM	Euglycemic clamp <sup>93</sup> $r = 0.96, P < 0.001$
7.	$MCR_{est} = 18.8 - 0.271 \text{ BMI} - 0.0052 \times I_{120} - 0.27 \times G_{90}$	NGT, IGT	Euglycemic clamp <sup>94</sup> $r = 0.80; P < 0.00005$
8.	$OGIS_{180} = [637 \cdot 10^6 (G_{120} - 90) + 1] \cdot Cl_{ogtt}$	L, O, IGT, DM	Euglycemic clamp <sup>56</sup> $r = 0.73; P < 0.0001$

AUC I = area under the insulin curve, NGT = normal glucose tolerance, IGT = impaired glucose tolerance, I 30 min = 30 minutes post-load insulin, I 2 hr = 2 hours post-load insulin, G 30 min = 30 minutes post-load glucose, G 2 hr = 2 hour post-load glucose, ITT = insulin tolerance test, SI = insulin sensitivity, M = glucose uptake rate in  $\text{mg} \cdot \text{min}^{-1}$ , G = mean glucose concentration, I = mean insulin concentration, DM = type 2 diabetes, ISI 0, 120 = index of insulin sensitivity from fasting and 120 minutes post OGTT insulin and glucose concentrations, MCR = metabolic clearance rate, MSI = mean serum insulin, Sib = insulin sensitivity in the basal state, Si2h = insulin sensitivity at the second hour,  $fI$  = fasting insulin concentration,  $fG$  = fasting glucose concentration,  $VD = 150 \text{ mL/kg}$  of body weight, SiM = insulin sensitivity index, ISI (Comp) = composite whole-body insulin sensitivity index, FPG = fasting plasma glucose, FPI = fasting plasma insulin, G = glucose, I = insulin, ISI = insulin sensitivity index, INSp = insulinemic area, GLYp = glycemic area,  $MCR_{est}$  = metabolic clearance rate estimate, OGIS = oral glucose insulin sensitivity, Do = oral dose glucose,  $Cl_{ogtt}$  = glucose clearance.

markedly reduced in the obese and obese-diabetic subgroups.

**Stumvoll et al. Index<sup>94</sup>**

$$MCR_{est} (OGTT) = 18.8 - 0.271 \text{ BMI} - 0.0052 \times I_{120} - 0.27 \times G_{90},$$

where  $MCR_{est}$  stands for metabolic clearance rate estimate derived from the OGTT, BMI = body mass index,  $I_{120}$  = plasma insulin at 120 minutes OGTT, and  $G_{90}$  = plasma glucose at 90 minutes OGTT.

**Mari et al. Index<sup>56</sup>**

$$OGIS_{180} = [637 \cdot 10^6 (G(120) - 90) + 1] \cdot Cl_{ogtt},$$
  
where OGIS 180 = oral glucose insulin sensitivity,  $G_{120}$  = plasma glucose at 2h OGTT, and

$$Cl_{ogtt} = \frac{289 \text{ Do} - 104[G(180) - G(120)/60]}{G(120)} + \frac{14.0}{G(0)} \frac{103}{I(120) - I(0) + 270},$$

where  $Cl$  = glucose clearance in  $\text{mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ , Do = oral glucose dose in  $\text{g/m}^2$ ,  $G(120)$  = plasma

glucose at 120 minutes OGTT,  $G(180)$  = plasma glucose at 180 minutes OGTT,  $G(0)$  = fasting plasma glucose,  $I(120)$  = insulin levels at 120 minutes, and  $I(0)$  = fasting insulin. Reference values in lean controls ranged 300–600  $\text{mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ .

As shown in Table 2, the insulin sensitivity measures derived from these formulas correlate well with insulin sensitivity determined by the euglycemic clamp<sup>50,89,90,93</sup> and FSIVGT.<sup>93</sup> However, the correlation was weaker in type 2 diabetic patients<sup>50,92,94</sup> and in the IGT group.<sup>36,58</sup> Belfiore et al.<sup>93</sup> advocate that their formula should not be used in type 2 diabetic patients with significant insulin deficiency. On the other hand, Mari et al. formula (OGIS),<sup>56</sup> showed a positive correlation with the clamp data in type 2 diabetic patients ( $r = 0.49$ ,  $P < 0.002$ ).

In addition to the inadequacy of this method in insulin deficient states, other problems should be considered. First, during the oral glucose tolerance test suppression of hepatic glucose production is minimal, confounding interpretation of the plasma glucose level. Thus, it is impossible to differentiate among whole-body, peripheral, or hepatic insulin sensitivity separately using data from the OGTT.<sup>49</sup> Second, the insulin level achieved in response to an oral glucose load involves gut hormones, neural stimulation, and of course the integrity of the pancreatic beta cells.<sup>68</sup> For example it has been shown that after 75 grams of glucose, obese subjects exhibit insulin hypersecretion,<sup>95</sup> while type 2 diabetes patients show a blunted response.<sup>96</sup> Third, glucose homeostasis in the postprandial state depends partly on the suppression of glucagon secretion and partly on the rate of entry of ingested glucose into the circulation. This rate is determined by the rate of gastric emptying and splanchnic glucose uptake.<sup>60,61</sup> Fourth, the OGTT is poorly reproducible. Several studies show only about 50 to 65% reproducibility of the results of an OGTT.<sup>63,97,98</sup>

Despite these limitations, the OGTT may be used in clinical settings to assess insulin action and in large-scale clinical and epidemiologic studies. However, the glucose and insulin excursions in the OGTT should be interpreted with caution in populations with varying glucose tolerance.

## The Insulin Tolerance Test (ITT)

ITT was one of the first methods developed to assess insulin sensitivity *in vivo*.<sup>99</sup> In this method, a fixed bolus of regular insulin (0.1 U/kg body weight) is given intravenously after an 8- to 10-hour fast. The plasma glucose decrement over 60 minutes is then measured. The faster the decline in glucose concentration, the more insulin sensitive the subject is. The slope of the linear decline in plasma glucose ( $K_{\text{ITT}}$ ) can be calculated by dividing

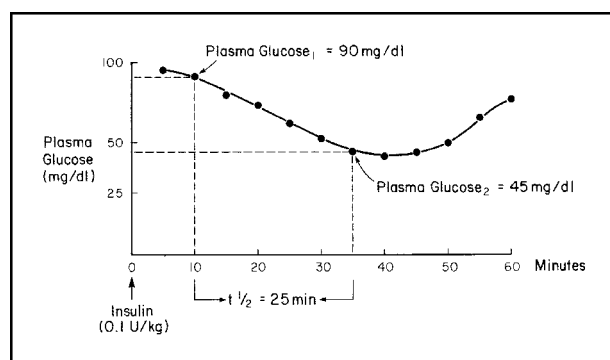
0.693 by the plasma glucose half-time (50% from baseline, Figure 1).<sup>100</sup>

$$K_{\text{ITT}} = 0.693/t^{1/2} \times 100,$$

where  $t^{1/2}$  represents the half-life of plasma glucose decrease. Normal  $K_{\text{ITT}}$  is  $>2.0\%$ /minute and values  $<1.5$  are considered abnormal. This method gives an indirect estimate of overall insulin sensitivity. It has been shown to correlate with the euglycemic clamp ( $r = 0.811$ ,  $P < 0.001$ )<sup>101</sup> in several studies.<sup>101–104</sup> Some of the drawbacks of this method include the supraphysiologic insulin dose used,<sup>102</sup> and also the fact that the test does not differentiate peripheral versus hepatic insulin resistance.

A major limitation of this test is the risk of hypoglycemia, particularly in normoglycemic subjects and in elderly diabetic patients. Moreover, hypoglycemia triggers counterregulatory hormonal responses, which may interfere with insulin sensitivity. A lower insulin dose method of 0.05 units/kg, or shortening the test to 15 minutes was suggested as an attempt to decrease the risk of hypoglycemia.<sup>105–107</sup> The lower dose ITT has also been shown to correlate well with the clamp.<sup>105</sup> However, some studies failed to demonstrate reduction of the risk of hypoglycemia in insulin sensitive subjects.<sup>55,108,109</sup> They also showed a higher CV (16 and 31%) in comparison to the conventional dose ITT (6–9% CV).<sup>101,103,104,110</sup> The shorter version<sup>101,103</sup> evolved from the notion that the counterregulatory hormone response occurs only after 20 minutes of the insulin infusion.<sup>111–113</sup> The short ITT yielded a good correlation with the euglycemic clamp<sup>101,103,105</sup> and has been used in most of the recent studies.<sup>114–117</sup>

In conclusion, the ITT should be used with great caution in insulin sensitive individuals because of the increased risk of hypoglycemia, even when the smaller



**Figure 1.** Calculation of the  $K_{\text{ITT}}$  (percentage decline in plasma glucose concentration per minute) in nondiabetic subjects.<sup>100</sup> The time ( $t_{1/2}$ ) required for the plasma glucose concentration to decline by 50% (i.e., from 90 to 45 mg/dL) was 25 minutes. From the equation,  $K_{\text{ITT}} = 0.693/t^{1/2} \times 100$ , the  $K$  rate was determined to be 2.77%.

dose version of the test is used. The shorter ITT is a valid test in large-scale studies, especially when the site of resistance is not of importance.

## The Gold Standard Methods

According to the American Diabetes Association Consensus Development Conference on insulin resistance, the euglycemic insulin clamp and the minimal model method applied to a FSIVGT are the only two methods that satisfactorily assess peripheral insulin resistance.<sup>34</sup>

### Hyperinsulinemic Euglycemic Clamp

It is regarded as being the gold standard to quantify insulin sensitivity *in vivo*.<sup>118,119</sup> It measures the steady-state amount of glucose metabolized per unit of body weight during a whole-body exposure to a predetermined amount of insulin, while maintaining the plasma glucose within the euglycemic range. The word “clamp” is used in analogy to the voltage clamp method, in which the potential difference across a cell membrane is clamped at its basal level.<sup>68</sup> Similarly, in the clamp procedure, the variables of interest such as glucose and insulin are “clamped” and therefore can be manipulated independently.

This technique involves a primed continuous infusion of insulin while maintaining euglycemia (e.g., around 90 mg/dL) by infusing a variable amount of glucose. The glucose infusion is adjusted according to the plasma glucose collected from an arterialized venous blood sample. For a valid result, the hyperinsulinemic euglycemic clamp assumes that, as a result of insulin and glucose infusion, endogenous hepatic glucose production (HGP) is completely inhibited, and that the plasma glucose is maintained with minimal variability within the euglycemic range. The quantity of exogenous glucose infused to maintain euglycemia is a reflection of the amount of glucose metabolized in peripheral tissues (M value), and therefore reflects the sensitivity of target tissues to insulin.<sup>1</sup> The more glucose infused per unit of time, the more sensitive the individual is to insulin. M values in normal, nonobese, and non-elderly volunteers range between 4.7 and 8.7 mg · kg<sup>-1</sup> · minute<sup>-1</sup>.<sup>119,120</sup> Other values that are calculated include metabolic clearance rate for insulin (MCR), MCR of plasma glucose, and M/I:

MCR = insulin infusion rate/increase

in plasma [insulin] above basal

MCR of plasma glucose

= glucose uptake/steady-state plasma [glucose]

M/I, where M is the rate of glucose metabolism = rate of glucose infusion if HGP is totally suppressed and I is the

mean insulin level during the test, typically from 15 (or 20) to 120 minutes.

When the glucose infusion rate is stabilized, this steady-state rate divided by the insulin level is defined as insulin sensitivity. For accuracy of the results, a correction is built in the equation to adjust for small changes in steady-state glucose concentration when plasma glucose levels are not perfectly stable (space correction [SC]).<sup>119</sup>

The euglycemic hyperinsulinemic clamp can be employed in combination with other techniques (isotopes, regional tissue sampling, indirect calorimetry, and nuclear magnetic resonance scans) in order to enhance the information on an enormous variety of physiologic aspects of glucose homeostasis. Of particular interest is the use of radioisotopes (e.g., <sup>3</sup>H-3-glucose), enabling the quantification of residual endogenous glucose production, and consequent differentiation of hepatic versus peripheral sensitivity to insulin.<sup>119,121</sup> By the same token, tracers of glycerol and amino acids assess the insulin influence on lipolysis and protein metabolism.<sup>122</sup>

Furthermore, insertion of catheters into the hepatic and femoral veins allows for the assessment of splanchnic and peripheral glucose uptake.<sup>123</sup> Glucose oxidation and nonoxidative glucose metabolism can be calculated using indirect calorimetry that measures oxygen consumption, carbon dioxide production and urinary protein excretion.<sup>124</sup> Positron emission tomography (PET) has also been used to measure regional insulin-mediated glucose uptake.<sup>125</sup> Lastly, muscle biopsies before and after the clamp have been used to determine the effect of insulin on muscle glycogen repletion, while less invasive methods such as nuclear magnetic resonance are used for the quantification of not only muscle, but also hepatic glycogen repletion.<sup>126</sup>

The glucose clamp itself can be implemented in a number of ways. The insulin infusion rates can be individualized according to the population studied and the research question asked. Insulin resistant states such as type 2 diabetes and obesity may require higher insulin infusion rates (120 mU/m<sup>2</sup> minute) in order to appropriately assess glucose disposal. It is of extreme importance in these circumstances to rule out incomplete hepatic glucose production through the use of labeled glucose, so that M does not underestimate glucose metabolism. On the other hand, lower insulin infusion rates of 40 mU/m<sup>2</sup> minute, which raises the plasma insulin concentration by 100 μU/mL above baseline, may be appropriate in non-obese individuals. Studies using this insulin infusion rate and <sup>3</sup>H-3-glucose in normal subjects have been able to show a decrease in hepatic glucose production to less than 10 to 15% of basal levels.<sup>121</sup>

The euglycemic hyperinsulinemic clamp is presently the most widely used method in the research setting and it is highly reproducible, with CV as low as 6.3 ±



0.9%.<sup>102,119</sup> Some of its advantages include (1) assessment of a quantitative measure of insulin-mediated glucose disposal, (2) the ability to define the exact site of insulin resistance (liver versus peripheral tissues), (3) assessment of the contribution of hyperglycemia on hepatic glucose production and glucose uptake, (4) the possibility to establish the time course of change in tissue sensitivity to insulin since the rate of glucose metabolism is determined at 5-minute intervals, and (5) hypoglycemia and its consequent counter regulatory hormone response are avoided by the use of a continuous glucose infusion, providing a more physiologic estimate of body's insulin sensitivity.<sup>102</sup>

There are still many drawbacks of this method. First, it is a costly and an invasive procedure that requires highly trained personnel, limiting its use to research settings. Secondly, the sustained hyperinsulinemia obtained in the procedure does not reproduce normal physiology.<sup>68</sup>

Furthermore, high plasma insulin levels prevent the assessment of adipocyte lipolysis, which is maximally regulated at low physiologic plasma insulin concentrations.<sup>127</sup> In addition to the complex nature of this methodology, it has been recognized that the results may be difficult to interpret if comparisons are to be made at different plasma glucose<sup>128</sup> and/or insulin levels,<sup>129</sup> important particularly when comparing individuals with fasting hyperglycemia.<sup>130</sup> Furthermore, data derived from the clamp does not distinguish insulin-dependent and insulin-independent glucose disposal.<sup>131,120</sup> This distinction is of value particularly in hyperglycemic and insulin resistant states, where the proportion of noninsulin-mediated glucose uptake is greater.<sup>128</sup>

### **Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGT) and Minimal Model**

The second gold standard for estimating insulin sensitivity involves data analysis of the FSIVGT.<sup>132</sup> This method avoids the problems of glucose absorption and gastrointestinal hormone stimulation because the glucose is given intravenously. The FSIVGT glucose and insulin dynamics fit into two independent mathematic models (minimal model approach-MINMOD) that accounts for the effect of glucose to enhance its own disappearance independent of an insulin increase (glucose effectiveness-S<sub>g</sub>), and the insulin-enhanced glucose disappearance from extracellular fluid (insulin sensitivity index-S<sub>i</sub>). The FSIVGT consists of a glucose bolus of 0.3 g/kg body weight at time zero and measurement of plasma glucose and insulin at -15, -10, -5, -1, 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180. The glucose and insulin data are then mathematically interpreted, allowing the calculation of S<sub>i</sub> for each individual through the MINMOD computation developed by Bergman and his

group.<sup>133</sup> S<sub>i</sub> represents the glucose clearance rate per change in plasma insulin concentration, and it ranges from 5 to 7 min<sup>-1</sup>/μU per mL in nonobese and from 2 to 3.5 min<sup>-1</sup>/μU per mL in obese subjects.<sup>59,134,135</sup>

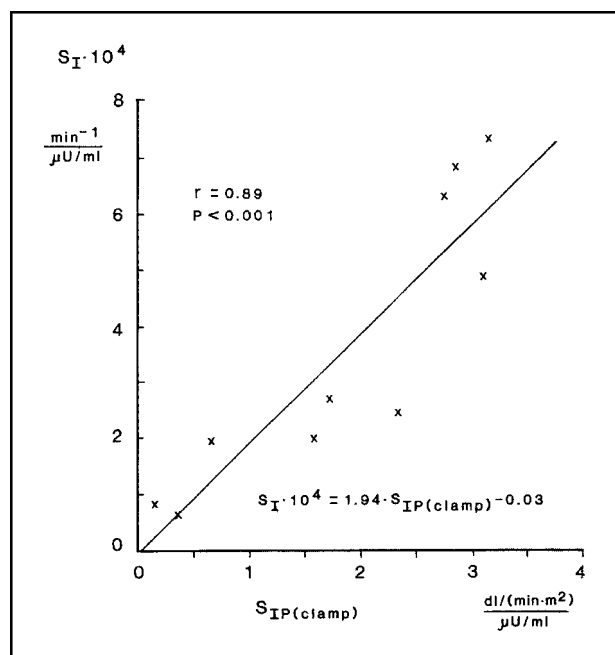
A modified protocol including tolbutamide infusion 20 minutes after the glucose infusion begins was suggested Beard et al.<sup>136</sup> to assure adequate endogenous plasma insulin response and was found to enhance the correlation between S<sub>i</sub> and the euglycemic clamp. Because this modification can only be applied to subjects with preserved beta cell response to secretagogues, the identification of S<sub>i</sub> in subjects with impaired insulin secretion such as type 1 and insulin-deficient type 2 diabetes patients has often forced several authors to replace tolbutamide by insulin.<sup>137-141</sup> Studies comparing the insulin sensitivity estimates derived from the insulin-modified FSIVGT with the tolbutamide-modified FSIVGT found good correlation between the two ( $r > 0.85$ ,  $P < 0.001$ ), although S<sub>i</sub> (insulin) appears to be persistently lower than S<sub>i</sub> (tolbutamide) and M values from clamp studies,<sup>141-143</sup> pointing to an underestimation of insulin sensitivity by the model.<sup>35,139,144</sup> This is thought to be due to a combination of oversimplification of the physiology in the model,<sup>145-148</sup> and because of shorter exposure of tissues to hyperinsulinemia in the FSIVGT when compared with the glucose clamp.<sup>139</sup>

The near physiologic nature of this test and its easier performance with only one intravenous catheterization make it attractive to researchers. It has been used in multicenter epidemiologic studies, such as the HERITAGE study<sup>149</sup> and the Insulin Resistance and Atherosclerosis Study,<sup>150-153</sup> which showed a statistically significant association between S<sub>i</sub> and cardiovascular risk factors.

The initial studies that compared S<sub>i</sub> derived from FSIVGT with that from hyperinsulinemic euglycemic clamp found weak correlations between the two.<sup>154,155</sup> As previously mentioned, the sequential injection of glucose and tolbutamide,<sup>136,156</sup> or insulin,<sup>139</sup> greatly improved the performance of this method ( $r = 0.83$ ,  $P < 0.001$ ,  $r = 0.89$ ,  $P < 0.001$ , and  $r = 0.55$ ,  $P < 0.001$ , respectively, Figure 2)

The magnitude of the correlation was still weaker in markedly obese subjects, IGT, and diabetic patients<sup>35,55,59,139</sup> possibly due to diminished insulin secretory capacity and questions regarding optimal amount of exogenous insulin in the insulin modified FSIVGT.<sup>35</sup> Extending the period of the sampling and/or giving a larger insulin dose is likely to make the test more suitable in IGT and diabetic subjects, at the expense of an increased risk for hypoglycemia.<sup>55</sup> However, the optimal insulin dose for performing the modified FSIVGT in patients with type 2 diabetes has not been determined.

The CV of the FSIVGT ranges between 14 and



**Figure 2.** Linear relationship between sensitivity indices obtained from fitting the minimal model to the FSIVGT (ordinate) or from the euglycemic glucose clamp data (abscissa).<sup>156</sup> Note that  $S_I$  and  $S_{IP(clamp)}$  are expressed in different units.

30%.<sup>55,143,157–159</sup> A reduced version of the protocol with only 12 samples was suggested.<sup>159</sup> The correlation between  $S_I$  obtained from 30 samples and 12 samples FSIVGT were shown to be strong ( $r = 0.9$ ,  $P = 0.0001$ ).<sup>131</sup> Data on the CV of  $S_I$  calculated from the reduced version are somewhat controversial. In obese and lean nondiabetic subjects, Duysinx et al. were able to maintain a moderate intrasubject variability of  $S_I$  of  $19 \pm 4\%$  (mean  $\pm$  SD) using the reduced version without tolbutamide injection,<sup>160</sup> while Steil et al. found that the reduction in the number of samples, maintaining tolbutamide injection, increased variability from  $20$  to  $28 \pm 5.4\%$ .<sup>159</sup> These authors therefore suggest that the reduced protocol with insulin or tolbutamide be only used in epidemiologic studies with large numbers of subjects or when a large treatment effect on  $S_I$  is expected. The FSIVGT, in contrast to the clamp, measures not only insulin-dependent glucose uptake but also tissue sensitivity to glucose uptake independent of insulin.<sup>131,154</sup> However, the minimal model technique does not permit determination of the individual contributions of hepatic and peripheral tissues to overall tissue sensitivity to insulin.<sup>131</sup>

The test results are more variable than the results from the clamp, and the correlation coefficient between insulin sensitivity measures achieved by the FSIVGT/minimal model and the clamp may vary quite widely from 0.30 to 0.89, depending on the protocol used.<sup>136,139,154</sup> As already mentioned, the test requires a

large insulin response to obtain a precise  $S_I$ , limiting its use in insulin deficient subjects.<sup>35,55,59,139</sup> Furthermore, the model determinations comprise data in a nonsteady-state format and the calculations are based on many assumptions about insulin and glucose kinetics, which may lead to systematic errors.<sup>145–148</sup>

In summary, it remains a lengthy and invasive test that requires approximately 30 timed samples over a 3-hour period and sophisticated data analysis, and therefore is not applicable to clinical practice. Its utility is limited to research settings that cautiously address the pros and cons of this method.

## Conclusion

Groop<sup>161</sup> suggested that the ideal method for measuring insulin sensitivity should satisfy five requirements: (1) to achieve insulin concentrations high enough to stimulate glucose metabolism and detect small differences in sensitivity of glucose uptake to insulin; (2) to distinguish between peripheral and hepatic insulin sensitivity; (3) to measure steady-state conditions; (4) to rest on physiologic sound assumptions about body glucose system; and (5) to achieve a degree of hyperglycemia not overtly non-physiologic. In addition, the ideal test should also score high in analysis of performance to allow comparison between individuals with minimal risk, be simple, and cheap.

Unfortunately, no available test meets all of these criteria. The clamp procedure is the best method available for clinical research, and the technique should be individualized according to the population studied. The choice of method for assessing insulin sensitivity will invariably depend on the questions to be answered in a particular study, the type and size of population being examined, and the information required. Moreover, further research is needed in order to develop inexpensive, simple, physiologic, and noninvasive tools to assess insulin sensitivity.

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