



# Assessment of insulin sensitivity from plasma insulin and glucose in the fasting or post oral glucose-load state

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**OBJECTIVE:** To compare insulin sensitivity indexes derived from plasma insulin (I) and glucose (G) in the basal state (*Sib*) and at the second hour (I2h and G2h) of an oral glucose tolerance test (OGTT, *Si2h*) (i) with measurements of insulin sensitivity using the insulin modified frequently sampled intravenous glucose tolerance test (FSIVGTT) [*Si*<sub>(IVGTT)</sub>] and (ii) with modelling of fasting glucose and insulin by the homeostasis model assessment (HOMA).

**SUBJECTS:** 47 subjects entered the study. 31 subjects were classified as having normal glucose tolerance (NGT), 10 as having impaired tolerance to glucose (IGT) and six as type 2 diabetes mellitus according to the World Health Organisation (WHO) criteria.

**MEASUREMENTS:** *Sib* and *Si2h* were calculated as follows.  $Sib = 10^8 / (I \times G \times VD)$ ,  $Si2h = 10^8 / (I2h \times G2h \times VD)$  where VD is an estimate of the apparent glucose distribution volume. A third insulin sensitivity index (*SiM*) was calculated by averaging *Sib* and *Si2h*. HOMA was calculated as follows:  $I / (22.5 \times e^{-\ln G})$

**RESULTS:** *Si*<sub>(IVGTT)</sub>, *Sib*, *Si2h* and *SiM* were all significantly higher in subjects with NGT than in those with IGT or type 2 diabetes. *Si*<sub>(IVGTT)</sub> was highly correlated ( $P \leq 0.0001$ ) with the three insulin sensitivity indexes found in the total population, in subjects with NGT and in those with IGT. In type 2 diabetic patients, a significant correlation was only noted when *SiM* was tested against *Si*<sub>(IVGTT)</sub> ( $P \leq 0.05$ ). In most circumstances, the associations of *Si*<sub>(IVGTT)</sub> with *Sib*, *Si2h* and *SiM* were stronger than the corresponding associations with *Ib*, *I2h* or HOMA. *SiM* was the index that correlated best with *Si*<sub>(IVGTT)</sub> in the whole group ( $r = 0.92$ ,  $P < 0.0001$ ) as well as in NGT ( $r = 0.86$ ,  $P < 0.0001$ ), IGT ( $r = 0.96$ ;  $P < 0.0001$ ) and type 2 diabetes ( $r = 0.83$ ,  $P \leq 0.05$ ) subgroups.

**CONCLUSIONS:** Calculations of sensitivity indexes from G and I concentrations in the basal state and during a conventional 2 h OGTT appear to be useful for coupling in the same simple and single test both a determination of glucose tolerance and an estimate of insulin sensitivity.

**Keywords:** insulin resistance; plasma glucose; plasma insulin; oral glucose tolerance test; obesity

## Introduction

Obesity is an insulin resistance-state per excellence and is among the first pathologies in which resistance to insulin-mediated glucose uptake has been demonstrated.<sup>1</sup> Insulin resistance is increasingly being recognized as an important factor in the pathogenesis of a number of common diseases, including type 2 diabetes mellitus,<sup>2</sup> ischaemic heart disease<sup>3</sup> and hypertension.<sup>4</sup> It is at the core of the so-called metabolic syndrome,<sup>5</sup> and thus could be responsible for the increased cardiovascular morbidity and mortality of the obese.<sup>6</sup> Many techniques with varying degrees of complexity have been used for estimating the insulin sensitivity of peripheral tissues, but the glucose clamp as described by DeFronzo *et al*<sup>7</sup> remains the 'gold standard'. The glucose clamp uses the rate of glucose infused to maintain plasma glucose at a given level

when an hyperinsulinaemic state is created by a sustained insulin infusion at a constant rate. This procedure is time consuming and requires considerable expertise and equipment. The use of computer modelling for glucose and insulin kinetics during a frequently sampled intravenous glucose tolerance test (FSIVGTT) is relatively easier to implement<sup>8</sup> and has been well validated against clamp measures over a wide range of glucose tolerance.<sup>9–12</sup> Although it has been proven that this technique is feasible on such large sample studies as the Insulin Resistance Atherosclerosis Study (IRAS),<sup>13</sup> there remains that a simplified method is required for estimating the insulin sensitivity of the increasing number of obese,<sup>14</sup> especially in large scale epidemiological studies. On the other hand, such simple methods as measurements of the insulin concentrations<sup>15</sup> or of the ratio of insulin-to-glucose concentrations (I/G) at fasting, have been widely proposed, for several years, to estimate the magnitude of both insulin secretion and tissue sensitivity to insulin.<sup>16</sup> However, the interpretation of such an index, based on the measurement of two variables, is quite difficult, because neither variable can be held constant. In healthy subjects, it has been established that insulin sensitivity times  $\beta$ -cell function is a

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Received 3 March 1998; revised 2 July 1998; accepted 28 December 1998

constant for a given tolerance to glucose.<sup>17</sup> Therefore, in this group of individuals, any change in insulin sensitivity normally results in an inverse variation of the I/G ratio. This relationship disappears<sup>16,18</sup> and a diminution in the I/G ratio cannot be interpreted as an improvement in insulin sensitivity as soon as the patients suffer from a certain degree of  $\beta$ -cell deficiency.<sup>19</sup> It has been demonstrated that increasing hyperglycaemia in type 2 diabetic patients results simultaneously or sequentially from both a progressive reduction in insulin sensitivity and a worsening in insulin secretion.<sup>19,20</sup> A computer-solved model of insulin:glucose interactions has also been proposed to estimate  $\beta$ -cells deficiency and insulin resistance (homeostasis model assessment, HOMA),<sup>21</sup> but up to now, the use of the HOMA remains relatively restricted.

Since any decrease in insulin secretion should be compensated, or even 'overcompensated', by an increase in plasma glucose concentrations,<sup>20</sup> it is reasonable to postulate that plasma insulin levels times plasma glucose concentration (I $\times$ G) might correlate better than the I/G ratio, and more likely in a negative manner, with the tissue sensitivity to insulin. In order to gain further insight into this problem and considering that the minimal model is known as a well-recognized method for estimating insulin sensitivity,<sup>9–12</sup> we were led to investigate whether measurements of insulin sensitivity (using the insulin-modified FSIVGTT) correlate or not with the inverse of the I $\times$ G product in subjects with normal tolerance to glucose and in patients suffering from impaired glucose tolerance or type 2 diabetes.

## Research design and methods

Forty seven subjects consulting at our center for being overweight or for weight gain entered the study. All participants were submitted to an insulin-modified FSIVGTT preceded by an oral glucose tolerance test (OGTT) at a one week-interval during which they were maintained on their usual diet. Thirty one subjects were classified as having normal glucose tolerance (NGT), 10 as impaired tolerance to glucose (IGT) and six as overt type 2 diabetes mellitus (Type 2) according to the World Health Organization (WHO) criteria.<sup>22</sup> The main clinical characteristics and basic laboratory data of the subjects are given in Table 1. None of these 47 subjects were taking medications known to interfere with glucose metabolism.

On each test day (OGTT, FSIVGTT), all subjects were admitted to the Metabolic Disease Department at 08.00 h after an overnight (12 h) fast and remained at bed rest for the entire period of the tests. All subjects were studied after giving their informed consent to participate in the study.

**Table 1** Characteristics of the study subjects

	NGT	IGT	Type 2
<i>n</i>	31	10	6
Gender ratio (M/F)	4/27	3/7	2/4
Age (y)	38 $\pm$ 2 [19–64]	49 $\pm$ 3 [37–62]	50 $\pm$ 5* [33–67]
BMI (kg/m <sup>2</sup> )	33.4 $\pm$ 1.2 [23.7–53.6]	36.3 $\pm$ 2.0 [27.9–50.0]	35.3 $\pm$ 1.3 [31.6–41.7]
Fasting plasma glucose (mg/dl)	95 $\pm$ 2 [75–118]	109 $\pm$ 3* [90–128]	133 $\pm$ 14*** [94–190]
2 h Post-load plasma glucose (mg/dl)	109 $\pm$ 4 [65–139]	161 $\pm$ 5* [140–185]	243 $\pm$ 20*** [207–341]
Fasting plasma insulin ( $\mu$ U/ml)	9.9 $\pm$ 1.0 [3.2–28.0]	20.6 $\pm$ 5.9* [3.0–68.0]	13.9 $\pm$ 1.7 [8.3–21.2]
2 h Post-load plasma insulin ( $\mu$ U/ml)	81.3 $\pm$ 9.8 [26.0–251.0]	164.5 $\pm$ 31.7* [47–357]	88.3 $\pm$ 17.5** [22–150]

Data are given as means  $\pm$  s.e.m. \*  $P \leq 0.05$  vs NGT, \*\*  $P \leq 0.05$  vs IGT.

Ranges are indicated between brackets.

NGT = normal glucose tolerance; IGT = impaired glucose tolerance; Type 2 = Type 2 diabetes; BMI = body mass index.

### OGTTs

A 75 g glucose load in 200 ml of water was administered orally over a period < 5 min. Blood samples were collected through an indwelling catheter implanted in the cubital vein before ingestion of glucose and at 30 min intervals after the glucose load over a 2 h period. Plasma glucose was measured using the glucose oxidase technique on an automated analyzer (Kodak, Paris, France). Plasma insulin concentrations (I) were measured using a radioimmunoassay (RIA; Cis Bio International, Gil-pun-Yvette, France).

### Insulin-modified FSIVGTTs

Antecubital veins were cannulated in both arms, one for sampling and the other for administration of glucose and insulin. After basal sampling for glucose and insulin, glucose (300 mg/kg) was administered at a constant rate for 2 min from  $t = 0$  min. At 20 min, 0.05 U/kg Actrapid (Novo Nordisk, Copenhagen, Denmark) was given as a bolus injection. Blood samples for glucose and insulin were taken at  $t = -15$  min,  $-10$  min,  $-5$  min, 0 min, 2 min, 3 min, 4 min, 5 min, 8 min, 10 min, 18 min, 20 min, 28 min, 32 min, 40 min, 60 min, 70 min and 240 min.<sup>23</sup> The insulin and glucose kinetics were modelled using the minimol model,<sup>8</sup> which provides an estimate of insulin sensitivity ( $Si_{(IVGTT)}$ ) expressed as  $10^4 \cdot \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ .

### Insulin sensitivity estimates derived from plasma insulin and glucose

Two insulin sensitivity indexes were derived from plasma insulin and plasma glucose concentrations in the basal state ( $Sib$ ) and at the second hour of an OGTT ( $Si2h$ ):  $Sib = 10^8 / (I \times G \times VD)$  and  $Si2h = 10^8 / (I2h \times G2h \times VD)$ . G and I were fasting plasma glucose (mg/dl) and insulin ( $\mu$ U/ml) concentrations, respectively, while G2h and I2h were plasma glucose

(mg/dl) and insulin ( $\mu\text{U}/\text{ml}$ ), respectively, at the second hour of the OGTT. VD was an estimate of the apparent glucose distribution volume and its value was derived from calculations using a monocompartmental model:  $\text{VD} = 150 \text{ ml}/\text{kg}$  of body weight.<sup>24</sup>

An additional insulin sensitivity index (*SiM*) was calculated by averaging *Sib* and *Si2h* after balancing *Sib* by a coefficient of 0.137 in order to give the same importance to both indexes. The value of the weighing-coefficient was obtained by calculating the ratio of the mean *Si2h* to the mean *Sib*. *SiM* was finally calculated by the following formula:

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

### HOMA

Insulin sensitivity was calculated, according to the HOMA, as described by Matthews *et al.*:<sup>21</sup>

$$\text{HOMA} = I/(22.5 \times e^{-\ln G})$$

where I and G were obtained before the oral glucose load.

### Statistical analysis

Data were analyzed using Statview (version F4.-5) for Apple Macintosh. Results are expressed as means  $\pm$  s.e.m. Comparisons between groups were made by analysis of variance (ANOVA). Within-group comparisons were performed with the paired two-way Student *t*-test. Correlation coefficients were used to study the strength of association between measurements of insulin sensitivity. Linear regression was used to evaluate the agreement between determinations of insulin sensitivity derived from the above-defined indexes and those derived from the minimal model. Slopes were compared by analysis of covariance as described in Zar.<sup>25</sup> Comparisons between two correlation coefficients were tested by the use of  $Z = z_1 - z_2 / \sigma z_1 - z_2$  as described in Zar.<sup>25</sup> *P* values  $\leq 0.05$  were considered as statistically significant.

## Results

Clinical and laboratory characteristics are given in Table 1. As expected, IGT and type 2 diabetic patients were older and more obese than individuals with normal tolerance to glucose, even though the difference did not reach the threshold of statistical significance for body mass index (BMI). No major differences were observed between IGT and diabetic patients.

### *Sib*, *Si2h* and *SiM* vs minimal model

*Si*<sub>(IVGTT)</sub>, *Sib*, *Si2h* and *SiM* were all significantly higher in subjects with NGT than in those with IGT or type 2 diabetes (Table 2). However, none of the

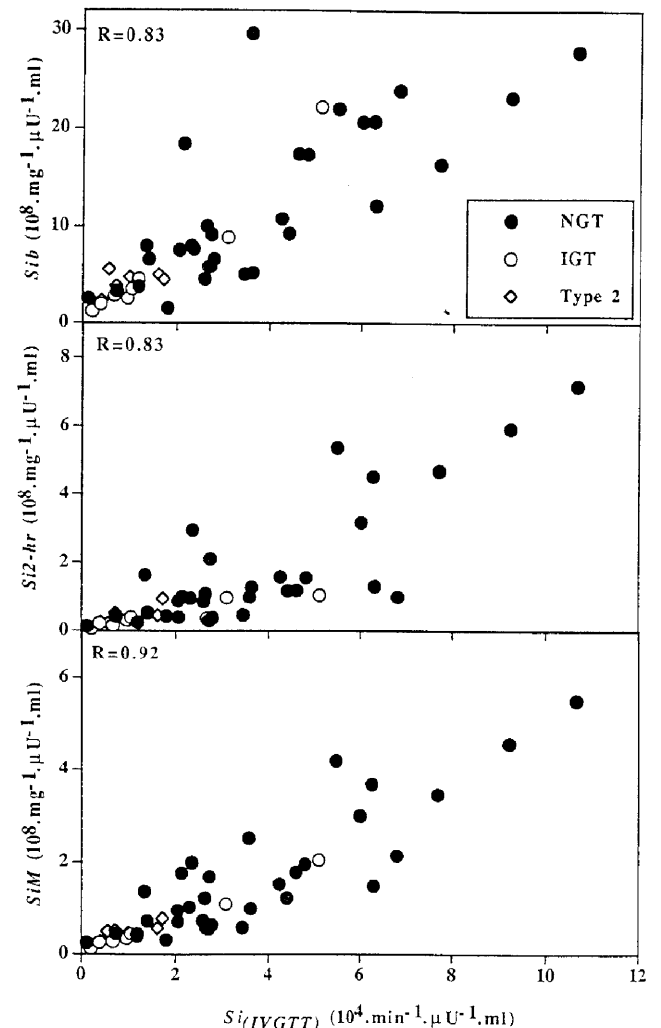
**Table 2** Estimates of insulin sensitivity according to the glucose tolerance status

	NGT	IGT	Type 2
<i>n</i>	31	10	6
<i>Si</i> <sub>(IVGTT)</sub> ( $10^4 \cdot \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ )	$3.80 \pm 0.45$ [0.11–10.65]	$1.63 \pm 0.49^*$ [0.2–5.1]	$0.98 \pm 0.23^*$ [0.39–1.70]
<i>Sib</i> ( $10^8 \cdot \text{mg}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ )	$11.99 \pm 1.43$ [1.49–29.58]	$5.78 \pm 1.94^*$ [1.23–22.15]	$4.33 \pm 0.46^*$ [2.34–5.57]
<i>Si2h</i> ( $10^8 \cdot \text{mg}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ )	$1.79 \pm 0.33$ [0.14–7.19]	$0.41 \pm 0.10^*$ [0.06–1.04]	$0.45 \pm 0.11^*$ [0.23–0.94]
<i>SiM</i> ( $10^8 \cdot \text{mg}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ )	$1.71 \pm 0.24$ [0.24–5.50]	$0.60 \pm 0.18^*$ [0.12–2.04]	$0.52 \pm 0.06^*$ [0.29–0.78]

Data are given as means  $\pm$  s.e.m., \**P*  $\leq 0.0001$  vs NGT.

Ranges are indicated between brackets.

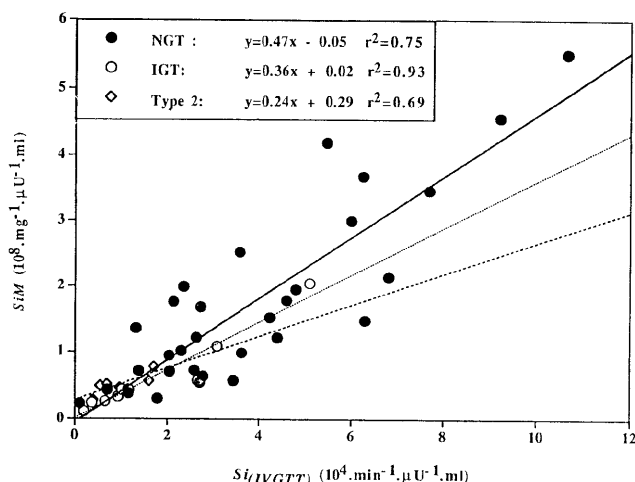
NGT=normal glucose tolerance; IGT=impaired glucose tolerance; Type 2=type 2 diabetes; *Si*=; IVGTT=intravenous glucose tolerance test; *Sib* =  $10^8 / (I \times G \times \text{VD})$ ; *Si2h* =  $10^8 / (I_2 \times G_1 \times \text{VD})$ ; *SiM* =  $[(0.137 \times \text{Sib}) + \text{Si2h}]/2$ .



**Figure 1** Relationship between *Sib*, *Si2-hr*, *SiM* and *Si*<sub>(IVGTT)</sub>.

determinations differed significantly in these two latter groups.

In the 47 patients considered as a whole, *Sib*, *Si2h* and *SiM* were highly correlated with *Si*<sub>(IVGTT)</sub> (*P*  $< 0.0001$ ) (Figure 1). When the insulin sensitivity was analyzed separately in the different subsets of



**Figure 2** Correlation lines of *SiM* against *Si<sub>IVGTT</sub>* according to glucose tolerance status: normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and type 2 diabetes (Type 2).

**Table 3** Correlations of *Si<sub>IVGTT</sub>* with *Sib*, *Si2h*, *SiM*, *Ib*, *I2h* and homeostasis model assessment (*HOMA*)

	All subjects	NGT	IGT	Type 2
<i>n</i>	47	31	10	6
<i>Sib</i>	0.83*	0.77*	0.95*	NS
<i>Si2h</i>	0.83*	0.81*	0.91*	NS
<i>SiM</i>	0.90*	0.89*	0.96*	0.83****
<i>Ib</i>	-0.68*	-0.63*	-0.83***	NS
<i>I2h</i>	-0.59*	-0.60**	-0.73****	NS
<i>HOMA</i>	-0.68*	-0.64*	-0.83***	NS

\* $P \leq 0.0001$ , \*\* $P \leq 0.001$ , \*\*\* $P \leq 0.01$ , \*\*\*\* $P \leq 0.05$ .

NS = not significant.

NGT = normal glucose tolerance; IGT = impaired glucose tolerance.

patients, *Si<sub>IVGTT</sub>* was found highly correlated with *Sib*, *Si2h* and *SiM* both in subjects with NGT ( $r = 0.77$ ,  $r = 0.81$  and  $r = 0.86$ , respectively;  $P < 0.0001$ ) and in those with IGT ( $r = 0.95$ ,  $r = 0.91$  and  $r = 0.96$ , respectively;  $P < 0.0001$ ).

In type 2 diabetic patients, a significant correlation was only noted when *SiM* was tested against *Si<sub>IVGTT</sub>*:  $r = 0.83$ ,  $P \leq 0.05$ . The lack of correlation with the other indexes was probably due to the fact that the number of patients in this group was limited to six. The slopes of correlation lines of *SiM* against *Si<sub>IVGTT</sub>* were compared between the three subgroups of subjects: NGT, IGT and overt type 2 diabetes, but no differences were observed (Figure 2). Therefore it seems that the relationship between *Si<sub>IVGTT</sub>* and *SiM* remains valid over a wide range of glucose tolerance from normal to type 2 diabetes.

#### Basal insulin (*Ib*), second hour post oral glucose load insulin (*I2h*) and *HOMA* vs minimal model

*Ib*, *I2h* and *HOMA* were correlated with *Si<sub>IVGTT</sub>* in the whole group ( $r = -0.68$ ,  $r = -0.59$  and  $r = -0.68$ , respectively;  $P \leq 0.0001$ ) as well as in the NGT and IGT subgroups (Table 3). No significant

correlations were observed in the type 2 diabetes subgroup.

Even though the differences did not always reach the level of statistical significance, the correlations of *Si<sub>IVGTT</sub>* with *Ib*, *I2h* or *HOMA* tended to be weaker than the corresponding correlations with *Sib*, *Si2h* or *SiM* (Table 3).

Considering the group as a whole, the association of *Si<sub>IVGTT</sub>* with *Ib*, *I2h* or *HOMA* ( $r = -0.68$ ,  $r = -0.59$ ,  $r = -0.68$ , respectively) was weaker than the association of *Si<sub>IVGTT</sub>* with *SiM* ( $r = 0.90$ ;  $P \leq 0.01$ ). The association of *Si<sub>IVGTT</sub>* with *I2h* ( $r = -0.59$ ) was also weaker than the association of *Si<sub>IVGTT</sub>* with either *Sib* or *Si2h* ( $r = 0.83$ ,  $r = 0.83$ , respectively;  $P \leq 0.02$ ).

In the subset of patients with NGT, the association of *Si<sub>IVGTT</sub>* with *Ib*, *I2h* or *HOMA* ( $r = -0.63$ ,  $r = -0.60$ ,  $r = -0.64$ , respectively) was weaker than the association of *Si<sub>IVGTT</sub>* with *SiM* ( $r = 0.89$ ;  $P \leq 0.05$ ).

In the subset of patients with IGT, correlations of *Si<sub>IVGTT</sub>* with *Ib*, *I2h* or *HOMA* tended to be weaker than the corresponding associations with *SiM*, but the comparison of the correlations two by two, did not reach statistical significance. As we have already mentioned, in the type 2 diabetes subgroup, *Si<sub>IVGTT</sub>* did not correlate with *Ib*, *I2h* or *HOMA*, whereas *Si<sub>IVGTT</sub>* correlated with *SiM* ( $r = 0.83$ ;  $P \leq 0.05$ ).

## Discussion

The data of the present work indicate that determinations of the insulin sensitivity by using the minimal model analysis of an insulin-modified FSIVGTT correlate strongly with indexes of insulin sensitivity, as determined by the mathematical product of such simple parameters as plasma glucose and insulin concentrations at fasting and/or at the second hour of an oral glucose loading. As expected, the insulin sensitivity measured either by the indexes, as proposed in the present work, or by the minimal model analysis, was significantly higher in subjects with NGT than in patients with IGT or type 2 diabetes. The differences between the two latter groups were less significant, this finding being in agreement with the results of previous studies.<sup>10,26,27</sup> The correlation of *SiM*, with the minimal model determinations of insulin sensitivity was strong both in the group considered as a whole and in each subgroup defined from levels of glucose tolerance. In type 2 diabetic patients, the correlation was weaker than in the two other groups when the calculation was made between the minimal model and the index of insulin sensitivity based on measurements of fasting plasma glucose and insulin concentrations (*Sib*). This might be simply due to the fact that the levels, and therefore the ranges of insulin sensitivity, are markedly reduced in diabetic

patients, leading thus to a diminished correlation. This drawback was mostly overcome by using plasma glucose and insulin concentrations at the second hour of an OGTT and by averaging these two parameters with the values obtained at fasting (*SiM*). Hence, *SiM* appears as the most reliable index of insulin sensitivity through the range of glucose tolerance, ranging from normal to type 2 diabetes.

A computer-solved model of insulin: glucose interactions has been developed to estimate  $\beta$ -cell deficiency and insulin resistance.<sup>21</sup> However, up to now, this technique called the HOMA analysis has been used only in a few laboratories and the validation remains questionable since wide coefficients of variation are usually observed. Our results demonstrate that the association of the insulin resistance measured by the minimal model with the HOMA or with a simple measure of plasma insulin either in the basal state or after oral glucose loading is weaker than its association with the indexes used in the present study. Other authors have proposed a fasting insulin resistance index (FIRI) based on basal plasma glucose and insulin.<sup>28</sup> However, this index has never been validated through a wide range of insulin resistance and the value of the results remains questionable, even in NGT subjects.<sup>29</sup>

From this, we suggest that the indexes of insulin sensitivity used in the present study (*Sib* and *SiM*) and based on the inverse of plasma insulin times plasma glucose levels in the basal state or after an oral glucose load might be a reflection of insulin sensitivity *per se* and as such be used for its evaluation. Therefore the determination could be used routinely by almost every medical center, since the only requirement is a reliable dosage of plasma glucose and insulin. For that reason, it seems reasonable to suggest that in subjects with fasting plasma glucose < 110 mg/dl (that is, in patients who are expected to be at very low risk of having a two-hour post OGTT glucose concentration > 200 mg/dl)<sup>30</sup> *Sib* could be considered a good index of insulin sensitivity. Only subjects with fasting plasma glucose > 110 mg/dl might require an oral glucose load to calculate *SiM* as an estimate of insulin sensitivity, thus reducing drastically the clinical indication of OGTTs.

Hence, it seems reasonable to postulate from the above considerations that the methods for estimating insulin sensitivity based on plasma glucose and insulin concentrations would be of interest since measurements of insulin sensitivity by either the minimal model or the glucose clamp is not routinely available for every physician. Since it has been reported that in simple obesity, insulin resistance might not be as prevalent as previously thought and is less frequent than insulin hypersecretion,<sup>31</sup> a simple index of insulin sensitivity could be useful in helping the general practitioner to recognize those obese individuals who are insulin resistant and thus at risk for developing type 2 diabetes and/or cardiovascular disease (CVD).

## Conclusion

In summary, calculations of sensitivity indexes from plasma glucose and insulin concentrations in the basal state and during a conventional two-hour OGTT provide estimates of insulin sensitivity that correlate significantly with those obtained with the minimal model and the euglycemic hyperinsulinemic clamp. Furthermore, such markers appear to be useful for coupling in the same simple and single test both a determination of glucose tolerance according to the WHO criteria and an estimate of insulin sensitivity. They might prove to be a valuable tool to study insulin resistance and related metabolic complications in such common conditions as obesity.

## References

- 1 Rabinowitz D, Zierler KL. Forearm metabolism in obesity and its response to intraarterial insulin. Characterization of insulin resistance and evidence for adaptive hyperinsulinism. *J Clin Invest* 1962; **12**: 2173–2181.
- 2 Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospective studies of Pima Indians. *N Engl J Med* 1993; **329**: 1988–1991.
- 3 Shinozaki K, Suzuki M, Ikebuchi M, Hara Y, Harano Y. Demonstration of insulin resistance in coronary artery disease documented with angiography. *Diabetes Care* 1996; **19**: 1–7.
- 4 Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S. Insulin resistance in essential hypertension. *N Engl J Med* 1987; **317**: 350–357.
- 5 Reaven GM. Banting Lecture. Role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595–1607.
- 6 Manson J, Colditz G, Stampfer MJ, Willett WC, Rosner B, Monson RR, Speizer FE, Hennekens. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med* 1990; **322**: 882–889.
- 7 DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; **237**: E214–E223.
- 8 Bergman RN, Ider YZ, Bowdler CR, Cobelli C. Quantitative estimation of insulin sensitivity. *Am J Physiol* 1979; **236**: E667–E677.
- 9 Bergman RN, Prager R, Volund A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J Clin Invest* 1987; **79**: 790–800.
- 10 Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YD, Sands RE, Pei D, Savage PJ, Bergman RN; for the Insulin Resistance Atherosclerosis Study. A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. *Diabetes* 1994; **43**: 1114–1121.
- 11 Coates PA, Luzio SD, Brunel P, Owens DR. Comparison of estimates of insulin sensitivity from minimal model analysis of the insulin-modified frequently sampled intravenous glucose tolerance test and the isoglycemic hyperinsulinemic clamp in subjects with NIDDM. *Diabetes* 1995; **44**: 631–635.
- 12 Anderson RL, Hammann RF, Savage PJ for the Insulin Resistance Atherosclerosis Study. Exploration of Simple Insulin Sensitivity measures derived from frequently sampled intravenous glucose tolerance (FSIGT) tests. *Am J Epidemiol* 1995; **142**: 724–732.

- 13 Anderson RL, Burke GL, Rewers M, Saad MF; for the Insulin Resistance Atherosclerosis study group. Assessment of insulin sensitivity in populations via intravenous glucose tolerance test: Insulin Resistance and Atherosclerosis Study (IRAS). *Diabetes* 1994; **43**: 27A.
- 14 Kuczmarski R, Flegal K, Campbell S, Johnson C. Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA* 1994; **272**: 205–211.
- 15 Laakso M. How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 1993; **137**: 959–965.
- 16 DeFronzo RA. The triumvirate:  $\beta$ -cell, muscle, liver, a collusion responsible for NIDDM. *Diabetes* 1988; **37**: 667–687.
- 17 Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP. Quantification of the relationship between insulin sensitivity and  $\beta$ -cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 1993; **42**: 1663–1672.
- 18 Golay A, Felber JP. Evolution from obesity to diabetes. *Diab Metab* 1994; **20**: 3–14.
- 19 Yki-Järvinen H. Role of insulin resistance in the pathogenesis of NIDDM. *Diabetologia* 1995; **38**: 1378–1388.
- 20 Ward WK, Beard JC, Halter JB, Pfeifer MA, Porte D Jr. Pathophysiology of insulin secretion in non-insulin dependent diabetes mellitus. *Diabetes Care* 1984; **7**: 491–502.
- 21 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and  $\beta$ -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.
- 22 WHO Study Group on Diabetes Mellitus. *Diabetes Mellitus: Report of a WHO Study Group*. World Health Organization: Geneva, (WHO Tech. Rep. series no. 727) 1985.
- 23 Coates PA, Ollerton RI, Luzio SD, Ismail IS, Owens DR. Reduced sampling protocols in estimation of insulin sensibility and glucose effectiveness using the minimal model in NIDDM. *Diabetes* 1995; **42**: 1635–1641.
- 24 Cobelli C, Mari A, Ferrannini E. Non-steady state: error analysis of Steele's model and developments for glucose kinetics. *Am J Physiol* 1987; **252**: E679–E689.
- 25 Zar JH. *Biostatistical analysis* (2nd edn) Prentice-Hall Inc: Englewood Cliffs, 1984.
- 26 Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, Groop L. Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 1989; **321**: 337–343.
- 27 Reaven GM, Hollenbeck CB, Chen Y-DI. Relationship between glucose tolerance, insulin secretion and insulin action in non-obese individuals with varying degrees of glucose tolerance. *Diabetologia* 1989; **32**: 52–55.
- 28 Duncan MH, Singh BM, Wise PH, Carter G. A simple measure of insulin resistance. *Lancet* 1995; **346**: 120–121.
- 29 Del Prato S, Pozzilli P. FIRI: fasting or false insulin resistance index. *Lancet* 1996; **347**: 132.
- 30 The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1997; **20**: 1183–1197.
- 31 Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G, on behalf of the European Group for the Study of Insulin Resistance (EGIR). Insulin resistance and hypersecretion in obesity. *J Clin Invest* 1997; **100**: 1166–1173.