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CLINICAL STUDY

Insulin sensitivity in women: a comparison among values derived from intravenous glucose tolerance tests with different sampling frequency, oral glucose tolerance test or fasting

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Abstract

Objective: To determine the correlation between insulin sensitivity (S_I) obtained by the minimal model method applied to a frequently sampled ($n = 33$) intravenous glucose tolerance test ($FSIGT_{33}$), and values obtained by reduced FSIGTs, oral glucose tolerance test (OGTT), or fasting.
Design: Retrospective analysis on tests performed in prospective studies.
Methods: A total of 78 $FSIGT_{33}$, and 59 OGTT were performed in non-diabetic women of which 10 were young cyclic females in the early follicular menstrual phase, 10 were young non-obese subjects with polycystic ovary syndrome (PCOS) and 30 were in post-menopause. Some of these individuals were investigated both prior to and during specified treatments. $FSIGT_{33}$ was transformed into $FSIGT_{22}$ and $FSIGT_{12}$ by removing samples from the analysis. Values of S_I derived from reduced FSIGTs or calculations performed on glucose and insulin values observed in fasting conditions and/or during OGTT were related to those of $FSIGT_{33}$.
Results: S_I values derived from $FSIGT_{33}$ were highly correlated with those derived from $FSIGT_{22}$ ($r = 0.965$) or $FSIGT_{12}$ ($r = 0.955$), but were only weakly correlated with those derived from fasting or OGTT calculations (r below 0.5). Between-group (PCOS vs normal) or within-group (prior to and during treatment) comparisons showed that reduced FSIGTs were only slightly less powerful than $FSIGT_{33}$ in detecting differences in S_I.
Conclusions: In non-diabetic women, reduced FSIGTs but not calculations based on fasting or OGTT values may be used in place of $FSIGT_{33}$ to document S_I and its variation.

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Introduction

Determination of insulin resistance is becoming critical in clinical practice. Insulin resistance represents a pathogenic mechanism for the polycystic ovary syndrome (PCOS) (1), and an important risk factor for cardiovascular diseases (2, 3). In 1997, the Consensus Development Conference on Insulin Resistance of the American Diabetes Association (4) established that only two methods can accurately estimate peripheral resistance to insulin, i.e. the euglycemic insulin clamp and the minimal model method applied to a frequently sampled intravenous glucose tolerance test (FSIGT). Both methods are cumbersome and not applicable either to large clinical trials or to the daily clinical investigation. Accordingly, several authors have proposed analyses of insulin sensitivity (S_I) based on reduced FSIGT procedures (5–7), or on mathematical calculations applied to fasting glucose and insulin values including the fasting glucose/insulin ratio (8–10), the fasting insulin resistance index (FIRI) (11–13), the homeostasis model assessment of insulin resistance (HOMA-IR) (14–16), the sensitivity index (Sib) (17) and the quantitative insulin sensitivity check index (QUICKI) (18). Other indices based on oral glucose tolerance test (OGTT) values have also been proposed, i.e. the sensitivity index at 2 h of OGTT (Si2h) (17), the Sim (Sib+Si2h/2) (17), the ratio of the areas under the curves of glucose/insulin during the OGTT (19), or the product of the two areas (19). Furthermore, Cederholm and Wibell (20), Belfiore *et al.* (21) and Matsuda and DeFronzo (22) have recently proposed more complex calculations on fasting and OGTT-derived insulin and glucose values. The aim of the present study was twofold: (i) to evaluate the relationship among values of S_I obtained with the original FSIGT procedure, modified with the i.v. administration of insulin (23, 24) and those obtained either with

reduced FSIGTs or with calculations performed on fasting and/or OGTT values; (ii) in the case of strict relationship, to compare both in cross-sectional and longitudinal studies the capability of the alternative method vs the original FSIGT in detecting differences in S_I.

Materials and methods

Subjects

Seventy-eight FSIGTs were performed in 50 non-diabetic women aged between 17 and 63 years (mean age 43.9±2.7 years), with a body mass index (BMI) between 20 and 29 (23.3±0.7) (Table 1). Most of these FSIGTs were performed during specific protocols and part of these results have already been published (25–27). All procedures were previously approved by the local ethical committee on human experimentation and performed in accordance with the Helsinki declaration as revised in 1983. A written informed consent was obtained from each woman at enrolment. Ten women were young normal cyclic individuals, 10 were non-obese women suffering from polycystic ovary syndrome (PCOS), and 30 were postmenopausal women. PCOS was defined as persistent amenorrhea or oligomenorrhea of perimenarchal onset, with three or more of these features: the ratio of luteinizing hormone/follicle stimulating hormone >1.5, ovarian hyperandrogenism as defined by high levels of total testosterone, free testosterone or androstenedione, Ferriman Gallwey hirsutism score >10, ultrasound evidence of PCOS (25). None of the subjects was suffering from non insulin-dependent diabetes mellitus (NIDDM) or IDDM, nor was on medications known to influence glucose metabolism. As part of ongoing clinical trials in our laboratory, in most of the subjects FSIGTs were repeated twice, prior to and during a particular treatment. Gonadotropin-releasing hormone (GnRH) analogs (3.6 mg Zoladex; Zeneca, Milan, Italy) were administered for 3 months to young individuals with ($n = 8$) and without ($n = 7$) PCOS, while tibolone (Organon Italia, SpA, Rome, Italy; 2.5 mg/day; $n = 13$) was administered for 3 months to women in post-menopause. Results of these trials and their rationale have already been published (25, 26). In 59 cases, an OGTT had also been performed in the 7 days preceding FSIGT.

Table 1 Subjects characteristics.

	Young	PCOS	Menopause
Age (years)	23.5±1.5	22.8±1.3	52.9±0.9*
BMI (kg/m^2)	20.1±0.6	20.5±0.8	23.4±0.4*
Fasting glucose (mmol/l)	3.9±0.2	3.7±0.1	4.8±0.1*
Fasting insulin (pmol/l)	66.7±13.0	108.6±20.1†	62.7±4.4

*$P < 0.01$ vs. Young and PCOS; †$P < 0.01$ vs Young and Menopause.

Methods

Frequently sampled intravenous glucose tolerance test Two polyethylene catheters placed in two antecubital veins were kept patent by a slow infusion of saline solution. One catheter was used for intravenous glucose or insulin administration and the other for blood collection. Glucose (0.3 g/kg) was injected over 1 min intravenously and was followed 20 min later by an i.v. insulin bolus (0.03 U/kg). As reported by Welch *et al.* (24), arterialized blood was collected at time −15, −10, −5, −1, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 160 and 180 min after glucose load ($FSIGT_{33}$).

Oral glucose tolerance test A polyethylene catether was inserted in an antecubital vein, and was kept patent by a slow infusion of saline solution. Samples of arterialized blood, obtained by forearm warming, were collected at −15, 0, 15, 30, 60, 90, 120 and 180 min following an oral glucose load of 75 g over 5 min.

Processing of samples Blood samples were collected into heparinized glass tubes, placed on ice, and immediately centrifuged in a refrigerated centrifuge.

Glucose and insulin were measured in all samples. Serum glucose was immediately assayed by an auto-analyzer using the glucose oxidase method. Another aliquot of serum was immediately frozen at −25 °C until assayed. Insulin levels were assayed in duplicate by a radioimmunometric method using a commercially available kit (Biodata, Guidonia Montecelio, Rome, Italy) (25), with intra- and interassay coefficients of variation of 6.2% and 7% respectively, and a sensitivity of 14.35 pmol/l.

All the results are expressed as the mean±standard error.

Calculations

Comparisons of different FSIGT tests Glucose and insulin values obtained during the FSIGTs were used to calculate S_I, which is inversely related to insulin resistance, and fractional glucose utilization independent on insulin (S_G) (23, 24). Analyses were performed by the minimal model method, using a computerized algorithm (MINMOD) (23, 24). S_I was expressed in units$\times 10^{-4}$/min$\times$mU/ml, and S_G in units$\times 10^{-4}$/min. Furthermore, AIRg (incremental insulin above baseline at the different time points between 2 and 10 min of FSIGT/number of time points considered), the disposition index (AIRg × S_I), basal insulin effectiveness (BIE; $S_I\times$fasting insulin), and glucose effectiveness at zero insulin (GEZI; S_G-BIE) were also calculated (28).

The same calculations performed on the $FSIGT_{33}$ were repeated by progressively removing some time points, and thus obtaining the $FSIGT_{22}$ (−15, −10, −5, −1, 2, 3, 4, 5, 6, 8, 10, 14, 20, 22, 25, 30, 40, 50,

70, 100, 160 and 180), and the $FSIGT_{12}$ (−5, 2, 4, 8, 20, 22, 30, 40, 50, 70, 100 and 180), the latter two were similar to those used by Saad *et al.* (5). Values of the different indices calculated with $FSIGT_{22}$ and $FSIGT_{12}$ were regressed on the corresponding values of $FSIGT_{33}$ by linear regression analysis.

Furthermore, the capability of $FSIGT_{22}$ and $FSIGT_{12}$ to detect differences in S_I and S_G among different groups of subjects (by Student's *t*-test) or in the same group of subjects prior to and during a treatment (by *t*-test for paired data) was also tested. Analysis of variance (ANOVA) was also used as specified, and when significant was followed by the post-hoc test of Scheffé.

Comparison of FSIGT with fasting calculations Calculations of S_I obtained by considering fasting levels of glucose and insulin, as obtained during the $FSIGT_{33}$ procedure, were regressed on S_I values obtained with $FSIGT_{33}$. The following calculations were tested: fasting glucose/fasting insulin (G/I) (8–10); FIRI: fasting values of glucose×insulin/25 (11–13); HOMA-IR: fasting values of glucose×insulin/22.5 (14–16); Sib: 10^8/fasting glucose×fasting insulin×150×kg (17); QUICKI: 1/(log fasting glucose+log fasting insulin) (18).

Comparison of FSIGT with OGTT-derived calculations Calculations of S_I obtained by considering calculations on levels of glucose and insulin during OGTT were regressed on S_I values obtained with $FSIGT_{33}$. The following calculations were tested: area under the curve of glucose/area under the curve of insulin during OGTT (G/I OGTT) (8); area under the curve of glucose×area under the curve of insulin during OGTT (G×I OGTT) (19); Si2h: 10^8/glucose at 2 h of OGTT×insulin at 2 h of OGTT×150×kg (17); Sim: Sib+Si2h/2 (17); Cederholm equation: M/MPG/log MSI; where M is oral glucose load in mg/120 + (0 h − 2 h glucose levels in mmol/l) × 180 × 0.19 × body weight/120; MPG is mean glucose at 0 h and 2 h of OGTT and MSI is mean insulin at 0 h and 2 h of OGTT (20, 29); Belfiore equation: 2/mean OGTT glucose×mean OGTT insulin/constant+1 (21); Composite evaluation: 10 000/square root of (mean glucose of OGTT×mean insulin of OGTT)×(fasting glucose×fasting insulin) (22).

Results

The clinical data of the three subsets of subjects in which investigations were performed are shown in Table 1.

$FSIGT_{33}$ vs $FSIGT_{22}$ and $FSIGT_{12}$

Modeling of the results was not possible with both $FSIGT_{22}$ and $FSIGT_{12}$ in 3 out of the 78 investigations (3.8%) in which modeling was possible with $FSIGT_{33}$. Linear regression analysis furnished a strong relationship between S_I obtained from $FSIGT_{33}$ and that from $FSIGT_{22}$ ($r = 0.965$; $P = 0.0001$) or $FSIGT_{12}$ ($r = 0.955$; $P = 0.0001$) (Fig. 1). A lower relationship was observed for S_G values obtained from $FSIGT_{33}$ and those from $FSIGT_{22}$ ($r = 0.754$; $P = 0.0001$) or $FSIGT_{12}$ ($r = 0.726$; $P = 0.0001$) (Fig. 1). Strong relationships, all close to unity and with *r* values higher than 0.94, were observed for AIRg, glucose disposition index and BIE from $FSIGT_{33}$ and the respective indices from $FSIGT_{22}$ and $FSIGT_{12}$. GEZI from $FSIGT_{33}$ showed a lower relationship than the other indices to GEZI from $FSIGT_{22}$ ($r = 0.815$; $P = 0.0001$) or $FSIGT_{12}$ ($r = 0.811$; $P = 0.0001$).

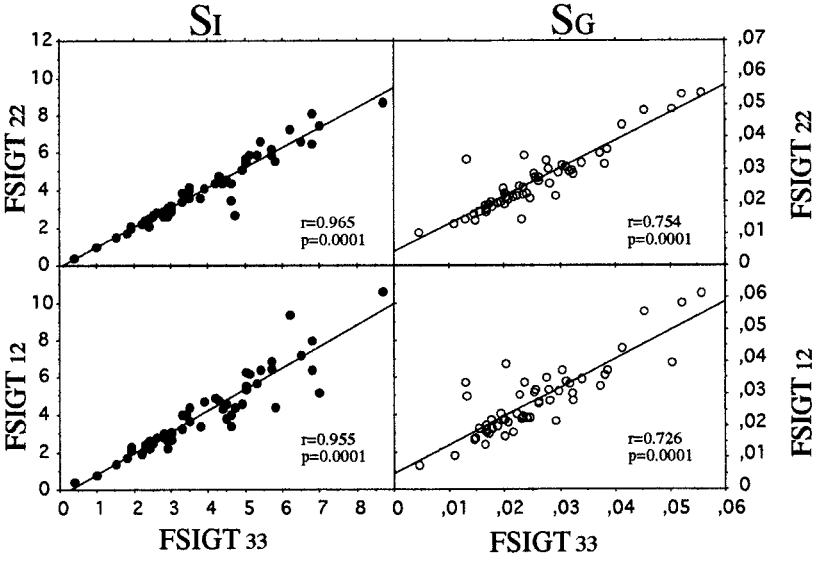

Figure 1 Regression analysis between insulin sensitivity (S_I; on the left) or glucose utilization independent of insulin (S_G; on the right) obtained with $FSIGT_{33}$ and those obtained with $FSIGT_{22}$ (top) and $FSIGT_{12}$ (bottom).

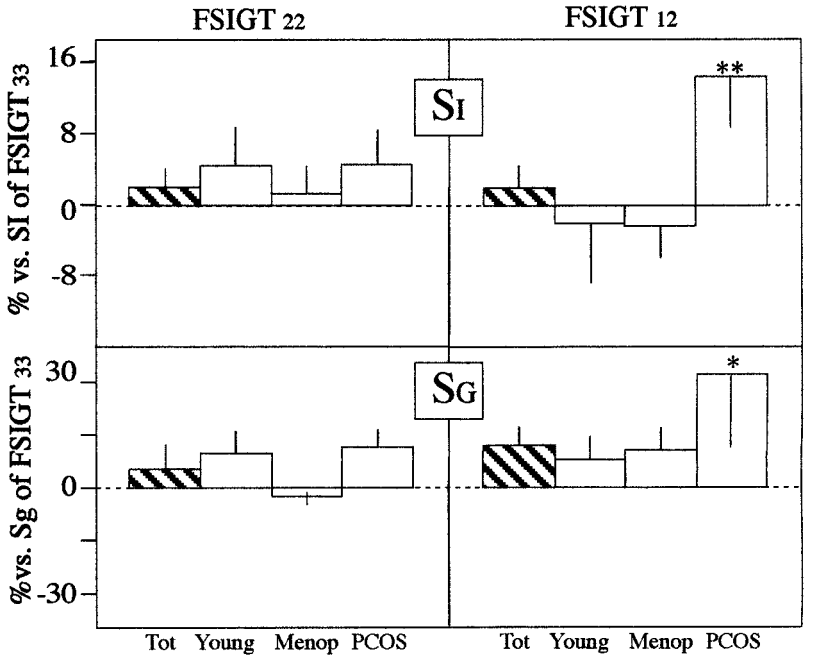

Figure 2 Mean (±S.E.) percentage difference between insulin sensitivity (S_I; top) and glucose utilization independent of insulin (S_G; bottom) obtained with $FSIGT_{22}$ (left) and $FSIGT_{12}$ (right) vs $FSIGT_{33}$. Calculations were performed considering all the women together (Tot) or the different subsets of young regularly cyclic women (young), postmenopausal women (Menop), and young lean women with polycystic ovary syndrome (PCOS). $^*P < 0.05$, $^{**}P < 0.025$ vs the other two subsets (by ANOVA).

Application to cross-sectional studies Overall S_I and S_G values obtained from $FSIGT_{33}$ were similar to those obtained from $FSIGT_{22}$ or $FSIGT_{12}$ (Fig. 2).

When S_I or S_G values obtained with the three different procedures were compared in the different subgroups of subjects, $FSIGT_{12}$ tended to furnish similar S_I values in young (6.029±2.06 vs 5.27±1.24; −2.3%) and postmenopausal (4.25±0.39 vs 4.16±0.44; −2.6%) women, and higher S_I values in young non-obese women with PCOS (2.9±0.32 vs 3.34±0.43; +13.8%; $P = 0.025$) (Fig. 2). The difference in S_I between young non-obese women with and without PCOS detected with $FSIGT_{33}$ ($P = 0.026$) was reduced but still significant when the same data were analyzed with $FSIGT_{22}$ ($P = 0.039$) and $FSIGT_{12}$ ($P = 0.048$).

S_G obtained with $FSIGT_{12}$ was similar to that obtained with $FSIGT_{33}$ in both young normal (0.26±0.004 vs 0.03±0.003; +7.9%) and postmenopausal (0.031±0.004 vs 0.03±0.003; +9.2%) women, but was significantly higher in women with PCOS (0.026±0.003 vs 0.029±0.004; +32.3%; $P < 0.05$) (Fig. 2).

Application to prospective studies By using $FSIGT_{33}$, we documented, as previously reported (26), that in postmenopausal women ($n = 13$) the administration of tibolone for 2 months enhances S_I (5.34±0.485 vs 8.44±1.4; $P = 0.04$). This conclusion was confirmed also with $FSIGT_{22}$ (5.64±0.45 vs 7.35±0.9; $P = 0.046$) and $FSIGT_{12}$ (5.84±0.6 vs 8.64±1.1; $P = 0.039$). The same was true for non-obese women with PCOS, in which the administration for 3 months of a GnRH analog ($n = 8$) increased S_I, as evaluated by $FSIGT_{33}$ (3.1±0.38 vs 4.0±0.20; $P = 0.004$). The statistical significance remained although reduced with $FSIGT_{22}$ (3.46±0.43 vs 4.23±0.17; $P = 0.036$) and $FSIGT_{12}$ (3.57±0.44 vs 4.5±0.16; $P = 0.040$). In young non-PCOS women the administration for 3 months of the GnRH analog did not modify S_I as evaluated by $FSIGT_{33}$ (4.1±0.4 vs 4.6±1.5). Similarly, no difference was observed with $FSIGT_{22}$ (4.2±0.5 vs 4.5±1.1) or $FSIGT_{12}$ (4.2±0.5 vs 5.0±1.3).

Comparison of FSIGT with fasting calculations

S_I values obtained with $FSIGT_{33}$ were weakly related to S_I values obtained by fasting values of glucose or insulin and the derived calculations. Among all, the best correlation was found with Sib. However, the coefficient of correlation between Sib and S_I derived from $FSIGT_{33}$ was only 0.324 (Table 2).

Table 2 Coefficients of correlation among insulin sensitivity derived from FSIGTs (F33, F22, F12) and insulin sensitivity derived from calculations performed on glucose and insulin values observed in fasting conditions.

	F33	F22	F12	G/I	HOMA/FIRI	Sib	QUICKI
F33	1	0.965	0.955	0.151	0.224	0.324	0.196
F22		1	0.957	0.147	0.189	0.438	0.172
F12			1	0.064	0.193	0.280	0.179
G/I				1	0.555	0.913	0.853
HOMA/FIRI					1	0.724	0.813
Sib						1	0.979
QUICKI							1

Table 3 Coefficients of correlation among insulin sensitivity derived from $FSIGT_{33}$ (F33) and insulin sensitivity derived from calculations performed on glucose and insulin values observed during OGTT ($n = 59$).

	F33	G/I OGTT	G×I OGTT	Si2h	Sim	Cederholm	Belfiore	Composite
F33	1	0.199	0.194	0.079	0.449	0.411	0.208	0.192
G/I OGTT		1	0.155	0.434	0.500	0.261	0.743	0.292
G×I OGTT			1	0.311	0.652	0.687	0.405	0.405
Si2h				1	0.169	0.317	0.698	0.0168
Sim					1	0.612	0.619	0.941
Cederholm						1	0.639	0.682
Belfiore							1	0.832
Composite								1

Comparison of FSIGT with OGTT-derived calculations

Among the indices derived from OGTT calculations, two were more related than others to S_I as derived from $FSIGT_{33}$: i.e. Sim and the S_I from the Cederholm calculation. Values of S_I derived from the Belfiore calculation or the Composite evaluation were only weakly related to S_I values derived from $FSIGT_{33}$ (Table 3).

Comparisons of FSIGT with fasting or OGTT-derived calculations in more insulin resistant subjects Correlations of S_I derived from $FSIGT_{33}$ with those derived from $FSIGT_{22}$ or $FSIGT_{12}$ were virtually unchanged in individuals whose S_I was below 4 ($n = 42$). On the other hand, a better but still low correlation was observed with S_I derived from HOMA/FIRI ($r = 0.363$), Sib ($r = 0.367$) or QUICKI ($r = 0.34$). In this subset of more insulin resistant individuals, S_I derived from $FSIGT_{33}$ was also better correlated with calculations performed on OGTT as G/I OGTT ($r = 0.41$), Si2h ($r = 0.25$), Sim ($r = 0.59$), the Cederholm's index ($r = 0.59$), the Belfiore's index ($r = 0.43$), or the Composite evaluation ($r = 0.25$). Also, in this subset Sim and the Cederholm's calculations were the two which were more closely related to values of S_I derived from $FSIGT_{33}$.

Discussion

In this study, we considered S_I obtained by the minimal model method associated with $FSIGT_{33}$ as the reference value towards which to compare S_I obtained by other methods or calculations. All the methods used to evaluate S_I are based on assumptions that may reduce their accuracy. Some clinicians consider that the 'gold standard' to evaluate S_I is the clamp. This method is highly reproducible and capable of furnishing accurate data on glucose metabolism by the liver when associated with isotopes. On the other hand, it is very cumbersome, and requires multiple investigations at different insulin levels in order to assess the full spectrum of S_I (4). In spite of its reputation, the clamp does not distinguish between insulin-dependent and -independent glucose utilization, and investigates the effect of insulin in a steady state, which is reached very slowly. This is different from the physiological dynamic of insulin which is secreted in acute bursts, followed by quick declines dependent upon insulin clearance. How well the steady state insulin predicts the effect of insulin in a dynamic situation is presently unknown. The minimal model method evaluates the effect of insulin in a dynamic situation. It is easier to perform and, in contrast to the clamp, allows the separate determination of insulin-dependent and insulin-independent glucose utilization (30). The drawbacks of this method are that it does not distinguish between hepatic and peripheral glucose utilization, and that it is based on the assumption that liver extraction of insulin is constant throughout the test. Furthermore, it has been suggested that physiological oversimplification by the model leads to errors in estimation of S_G (31, 32), although very likely not of S_I (33, 34). In spite of the differences between the minimal model method and the clamp, values of S_I obtained by the two methods are strongly related (correlation coefficient of $r = 0.89$) (23), and are likely predictive of true S_I (4).

In order to reduce complexity (blood sampling at 1-min intervals) and costs, minimal modeling of intravenous glucose tolerance tests with less frequent sampling have been proposed and used (5–7, 30, 32, 35). In terms of S_I, reduction in sampling frequency has already proved satisfactory for the original and the tolbutamide-modified FSIGTs (36, 37). Herein, we show that the same is true for the insulin-modified FSIGT. S_I values derived from insulin-modified reduced FSIGTs are not only related among each other, as previously reported (5), but are also strongly related to $FSIGT_{33}$. The strict correlation is reflected in the capability of reduced FSIGTs to document S_I differences in cross-sectional and prospective clinical trials. Indeed, in both between and within groups' comparisons, reduced FSIGTs were only slightly less powerful than $FSIGT_{33}$ in detecting S_I differences. Accordingly, it can be suggested that reduced FSIGTs, in particular $FSIGT_{12}$, may replace $FSIGT_{33}$ in most clinical settings. $FSIGT_{12}$ is easier to perform because it eliminates samplings at 1-min intervals, requires fewer tubes to handle, and its cost is almost one third that of $FSIGT_{33}$.

It still requires a time expenditure of 3 h, but this represents the same time required for an OGTT with only 5 more blood samples.

In clinical practice, evaluation of S_I obtained by fasting samples would be preferable. Unfortunately, the present data show that all the indices calculated on fasting values correlate poorly with S_I values obtained by $FSIGT_{33}$. The best correlation with $FSIGT_{33}$ was obtained by Sib, but the correlation coefficient of 0.325 seems too weak to suggest Sib as a valid alternative to $FSIGT_{33}$.

Oral glucose tolerance test is commonly used to evaluate glucose tolerance, and the possibility to obtain a contemporaneous estimate of S_I is appealing. In the present study, S_I estimations derived from mathematical calculations applied to values of OGTT were poorly correlated with those obtained from $FSIGT_{33}$. S_I values derived from Sim (17) or Cederholm (20, 29) calculations were the most related, but the correlation coefficients remained below 0.5 for both of them.

In comparison to the correlation performed among different FSIGTs and fasting, the correlations performed among $FSIGT_{33}$ and OGTT-derived S_I values were performed in a smaller but still significant number of tests ($n = 59$), sufficient to document clear correlations among different S_I values in previously published studies (5, 6, 10–12, 14, 17, 23, 24). In addition, because they necessarily include between-tests and between-days variations, a lower correlation has to be expected. Nevertheless, the very low coefficients of correlation detected may have several additional explanations. All S_I indices derived from OGTT are based on assumptions that although correct bring a mathematical approximation capable of substantially influencing S_I results. Among these assumptions are that in the post-absorptive state, glucose uptake occurs only in insulin-dependent tissues (22), that endogenous glucose production is equal to hepatic glucose production (22), and that hepatic insulin sensitivity is equivalent to peripheral tissue insulin sensitivity (14–16). Most importantly, the route of glucose administration is likely to play a major role. In contrast to the intravenous, the oral administration of glucose activates gastrointestinal factors that may induce marked modifications in insulin secretion and peripheral glucose utilisation (25, 27, 38). Accordingly, OGTT-derived S_I values are frequently not interchangeable with those obtained by intravenous glucose administration, and unfortunately cannot be used in their place to document S_I. Reported correlation among S_I values from OGTT or fasting and the clamp are not confirmed by the present data with the minimal model method. Unless it is ascertained that the minimal model method estimation of S_I is completely wrong, we feel that present results do not substantiate the clinical use of OGTT or fasting calculations to assess S_I.

In the subset of more insulin resistant individuals, a greater correlation ($r = 0.59$) was observed between values of S_I derived from $FSIGT_{33}$ and those derived from OGTT, particularly for Sim and the Cederholm's calculation. An alternative index should be related to the method of reference across a wide range of S_I values. However, it is possible that in states of severe insulin resistance a better correlation can be defined between S_I derived from calculations on fasting or OGTT values and those derived from the minimal model method. Indeed, diabetic and frankly obese women were not included in the present study, and our results cannot be applied to this subset of individuals.

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