Insulin Sensitivity of Blood Glucose Versus Insulin Sensitivity of Blood Free Fatty Acids in Normal, Obese, and Obese-Diabetic Subjects

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We calculated insulin sensitivity indices (ISI) concerning the insulin effect on both glycemia and blood free fatty acids (FFA), named ISI(gly) and ISI(ffa), respectively, in 34 normal, 27 obese, and 11 obese-diabetic subjects by using the following formulas: ISI(gly)= 2/[(INSp × GLYp) +1], and ISI(ffa)= 2/[(INSp × FFAp)+1], in which INSp, GLYp, and FFAp = insulinemic, glycemic, and FFA areas during oral glucose tolerance test (OGTT) (75 g glucose, suggested sampling time: 0, 1, and 2 hours) of the person studied. A slight modification of these formulas allows the calculation of insulin resistance indices (IRI), ie, IRI(gly) and IRI(ffa). ISI and IRI are complementary, as their sum is always equal to 2, so that IRI can be deduced from ISI and vice versa. By using basal levels instead of areas, insulin sensitivity (or resistance) in the basal state can also be measured. Basal levels and areas are expressed by taking the mean normal value as 1, so that in normal subjects ISI(gly) and ISI(ffa), as well as IRI(gly) and IRI(ffa), are always around 1, with maximal variations comprised between 0 and 2. ISI(ffa) was markedly reduced in both the obese (mean, 0.47 ± 0.04) and the obese-diabetic (mean, 0.41 ± 0.06) subjects, whereas ISI(gly) was less reduced in the obese (mean, 0.57 ± 0.04) than in the obese-diabetic (mean, 0.40 ± 0.03) subjects. ISI(gly)-basal was less affected than ISI(ffa)-basal in both groups. Multiple regression showed that ISI(gly) and ISI(ffa) were significantly inversely correlated with age, body mass index (BMI), and diastolic (but not systolic) blood pressure. Meta-analysis of data from the literature showed that ISI(gly) was significantly correlated with the hyperinsulinemic-euglycemic clamp data. However, the "clamp" is performed under artificial, persistent hyperinsulinemia (which entails FFA suppression) as never occurs in the life of patients, whereas our indices are performed under physiologic conditions, and represent simple tools suitable for clinical or epidemiologic studies, allowing assessment of whole-body insulin sensitivity with regard to both glycemia and blood FFA.

REDUCED INSULIN sensitivity is now recognized to play a role in an increasing number of disease states including the metabolic syndrome and its components (obesity, type 2 diabetes, hyperuricemia, hypertension, etc), as well as less common disorders such as insulin receptor alterations and still others.[1-5] Therefore, there is the widespread need to find a simple method for measuring insulin sensitivity suitable for the clinical setting. In searching for the most appropriate method, the following considerations should be taken into account. (1) The whole-body insulin action consists of the lowering of blood glucose and free fatty acids (FFA). It follows that the measurement of insulin sensitivity should include both these facets of insulin action, ie, the insulin sensitivity of both the blood glucose and the blood FFA should be measured. (2) The effectiveness of insulin may be different in the basal, or fasting, state compared with the highly dynamic absorption period. Hence, a method is needed that allows the measurement of insulin sensitivity both in the fasting state and during the absorption period. (3) Insulin sensitivity should be measured under physiologic conditions, ie, during glucose assumption per os, avoiding the intravenous infusion of insulin and/or glucose, which may alter insulin effectiveness. For instance, the persistent hyperinsulinemia produced during the euglycemic-hyperinsulinemic clamp suppresses FFA, which are recognized contributors to insulin resistance. (4) Finally, methods to measure insulin sensitivity should be simple enough to be suitable for clinical and epidemiologic studies.

Presently, most methods available for the evaluation of insulin sensitivity entail intravenous glucose and/or insulin administration. These intravenous tests include the insulin suppression test,[6-8] the euglycemic-hyperinsulinemic clamp procedure,[9] the intravenous glucose tolerance test (IVGTT) with minimal model,[10,11] the continuous infusion of glucose with model assessment (CIGMA) test,[12] and the insulin tolerance test.[13] None of these methods, however, fulfills the above-listed criteria. In fact, these methods are rather complex and/or are performed under nonphysiologic conditions, primarily because glucose and/or insulin are administered by intravenous route, thus bypassing the important splanchnic steps. Moreover, they are unable to measure the effectiveness of insulin towards blood FFA. More physiologic test, using data recorded in the fasting state or during the oral glucose tolerance test (OGTT) (fasting/OGTT-data tests) have also been proposed. These are the tests deduced from the basal insulin,[14,15] or the basal insulin and glucose (homeostasis model assessment [HOMA] test[16]), as well as those using the insulin area[17,18] or the insulin and glucose areas[19,20] during OGTT. Although these tests are simpler and performed under more physiologic conditions, they suffer from several limitations, as will be discussed later on.

On these grounds, we set up a simple method capable of measuring whole body insulin sensitivity under physiologic conditions (ie, basal condition and postglucose load), with regard to both blood glucose and FFA.[21,22] This is done by using formulas, allowing the calculation of indices of insulin sensitivity, which measure the insulin effect on the blood levels of both glucose and FFA. These indices are easily derived from blood glucose, FFA, and insulin levels measured during a 2-hour OGTT or in the basal state. In the present study, we used this new method to assess insulin sensitivity in normal, obese,

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Table 1. Characteristics of the Subjects Studied

Parameters	Normal	Obese	Obese-Diabetic
No.	34	27	11
Sex	26 M/8 F	13 M/14 F	3 M/8 F
Age	28.35 ± 1.45	36.7 ± 2.56	47.45 ± 3.08
		$P < .01$	$P < .001$
BMI	24.61 ± 0.61	35.24 ± 1.57	37.87 ± 1.74
		$P < .001$	$P < .001$
W/H	0.87 ± 0.01	0.92 ± 0.02	0.96 ± 0.02
		$P < .05$	$P < .001$
SBP	121.44 ± 1.44	136.11 ± 3.75	142.73 ± 7.90
		$P < .001$	$P < .001$
DBP	78.82 ± 1.22	87.81 ± 2.14	92.00 ± 4.67
		$P < .001$	$P < .001$

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

or obese-diabetic patients and to correlate insulin sensitivity to several parameters known to be associated with increased insulin resistance.

SUBJECTS AND METHODS

Subjects

The characteristics of the subjects studied are shown in the Table 1. All subjects gave their informed consent. Glucose tolerance and the diabetic state were assessed by OGTT according to the National Diabetes Data Group (NDDG) criteria.[23]

Normal subjects were studied while on their usual diet (2,000 to 2,400 kcal/d), obese and obese-diabetic patients were studied while on a balanced, moderately hypocaloric diet (1,800 kcal/d). In all instances, percent kcal were about 55% to 60% from carbohydrate (CHO), 15% from proteins, and 25% to 30% from fat. None of the diabetic subjects was on oral or insulin therapy. Women were never tested during menses. All subjects were submitted to a 120-minute OGTT (75 g glucose) with measurement of blood insulin, glucose, and FFA at 30-minute intervals.

Measurement of Insulin Sensitivity

We used the formulas recently proposed by us[21] to calculate the insulin sensitivity index for glycemia, or ISI(gly), and the insulin sensitivity index for blood FFA, or ISI(ffa). These formulas are as follows: $ISI(gly) = 2/[(INSp \times GLYp) + 1]$ and $ISI(ffa) = 2/[(INSp \times FFAp) + 1]$, where INSp, GLYp, and FFAp indicate insulinemic, glycemic, and blood FFA areas, respectively, of the person under study recorded during OGTT. It should be pointed out that INSp, GLYp, and FFAP are expressed by taking the mean normal value as 1, ie, by dividing the value observed in the person under study by the mean normal value so that, if INSp (or GLYp or FFAp) is 1.5-fold the mean normal values, it will be considered as equal to 1.5, if INSp (or GLYp or FFAp) is 2-fold the mean normal values, it will be considered as equal to 2, and so on. It is critical to use appropriate "mean normal values", which should be derived from data obtained in each laboratory that uses the indices.

Using basal (fasting) values (mean of 3 measurements at 5-minute intervals) instead of areas, insulin sensitivity in the basal state can be measured. As noted for the areas, the basal values also must be expressed by considering the mean normal value as equal to 1.

As published recently by us,[22] a slight modification can be introduced in the above formulas, consisting of the substitution of $(INSp \times GLYp)$ with $1/(INSp \times GLYp)$ in the formula to calculate ISI(gly), and of $(INSp \times FFAp)$ with $1/(INSp \times FFAp)$ in the formula for the calculation of ISI(ffa). This make it possible to calculate the insulin resistance indices, ie, the IRI(gly) and IRI(ffa). Figure 1 shows the 4 formulas concerning insulin sensitivity or resistance of glycemia and blood FFA. A computer program, running under Windows, has been developed by the authors, which allows the instant calculation of these indices by entering insulin, glucose, and FFA values recorded at 0, 1, and 2 hours during OGTT (this program can be freely obtained from the authors).

Using the "mean normal value" as the unit in our formulas entails that, in subjects with normal insulin sensitivity, both ISI(gly) and ISI(ffa), as well as IRI(gly) and IRI(ffa), give a value close to 1, regardless of the units in which insulinemia, glycemia, and FFA are expressed, whereas among patients with altered insulin sensitivity, the values range from a maximum of 2 to a minimum of 0, following a slightly curvilinear (hyperbolic) course (Fig 2). Of course, in the case of ISI(gly) and ISI(ffa), the value of 2 indicates extremely high insulin sensitivity, whereas the value of 0 indicates extremely low insulin sensitivity. In the case of IRI(gly) and IRI(ffa), the value of 2 indicates extremely high insulin resistance and the value of 0 extremely low insulin resistance.

The values of IRI(gly) and IRI(ffa) change in a complementary manner with respect to those of ISI(gly) and ISI(ffa), inasmuch as the sum of ISI(gly) and IRI(gly), as well as the sum of ISI(ffa) and IRI(ffa), is always equal to 2. This is apparent from Fig 2, which shows the curves of the ISI(gly) and IRI(gly) of 6 hypothetical patients with increasing insulin and glycemia levels within a wide range of values (from two thirds to 3-fold the mean normal value). It is evident that the behavior of ISI(gly) values is symmetrical to that of IRI(gly) values. The maximum, theoretical range of values for both tests is between 2 and 0. In the panel at the bottom, we report the ISI(gly) and IRI(gly) values for each point of the 2 curves. It is noteworthy that the sum of the values of the 2 indices is always equal to 2, which allows 1 index to be derived from the other. It is possible, therefore, to choose whether to express insulin effectiveness in a given subject as insulin sensitivity or insulin resistance, ie, as ISI(gly) or IRI(gly) with regard to the insulin effect on glycemia, and as ISI(ffa) or IRI(ffa) with regard to the insulin effect on blood FFA.

It should be pointed out that, although among normal subjects the value of our indices is close to 1, the average value of both the sensitivity and the resistance indices is not exactly 1, being slightly higher (around 1.05) or lower (around 0.95) for the sensitivity and resistance indices, respectively. This is due to the slightly curvilinear behavior of these indices (see Fig 2), which entails that, among the normal group, the values of insulin, glucose, and FFA that are higher

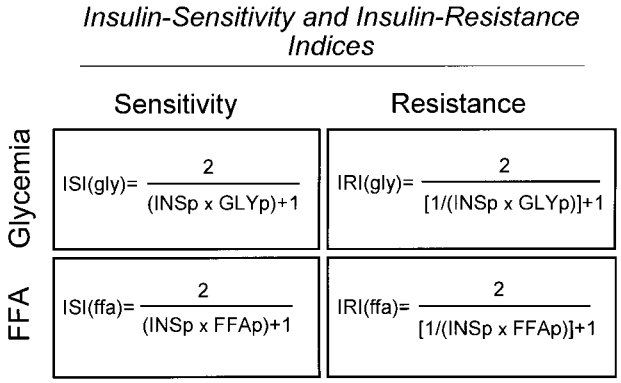
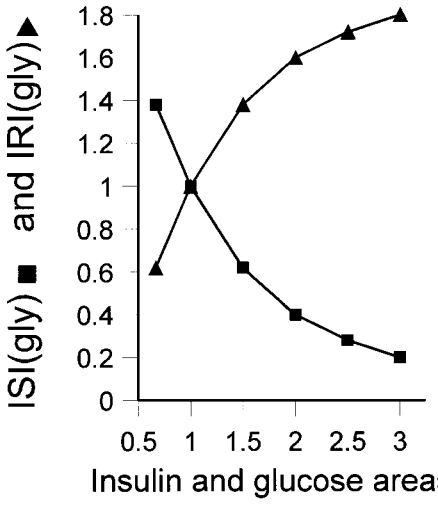


Fig 1. Formulas to calculate insulin sensitivity indices for glycemia and FFA, ie, ISI(gly) and ISI(ffa) or the corresponding insulin resistance indices, ie, IRI(gly) and IRI(ffa).



ISI(gly)=1.38 - 1.00 - 0.62 - 0.40 - 0.28 - 0.20
IRI(gly)=0.62 - 1.00 - 1.38 - 1.60 - 1.72 - 1.80

Fig 2. Curves of insulin sensitivity index for glycemia or ISI(gly) and of insulin resistance index for glycemia or IRI(gly) in hypothetical patients with increasing insulin and glycemia levels, from 2/3 to 3-fold the mean normal value (taken as 1).

than the mean value have a major weight than the values that are lower than the mean value.

The procedure can be made simpler if instead of the full areas (measurements at 30-minute intervals, according to NDDG[23]), we use the 0-1-2h areas (measurements at 0, 1, and 2 hours only) or even the 0-2h areas (measurements at 0 and 2 hours only). The use of 0-1-2h areas or 0-2h areas bears the practical advantage of making the calculation of the area values very easy. In fact, when area values are expressed as unit/volume $\cdot h^{-1}$ (as done in this report), the 0-1-2h area is equal to the sum of ½ value at 0 min + the value at 1 h + ½ value at 2 h, while the 0-2h area is equal to the sum of values at 0 and at 2 h.

As mentioned above, the "mean normal value" for insulin, glucose, and FFA areas and basal values should be fixed to use our indices. This is a critical point for our procedure. Every laboratory in which insulin, glucose, and FFA are measured and OGTT performed should have its normal reference values. It is mandatory that each laboratory relies on its own data. This is because although mean normal values for basal and OGTT-induced insulin, glucose, and FFA, obtained from large study populations and with comparable methods, can be found in the literature (see review Belfiore et al[21]), there may be significant interlaboratory variability.

To compare our ISI(gly) with the data obtained with the hyperinsulinemic-euglycemic clamp procedure, we performed meta-analysis of published data. To this end, we calculated the correlation between ISI(gly) and the clamp data referring either to mean values obtained in 12 groups (from Hollenbeck and Reaven,[24] Golay et al,[25] and Reaven et al[26]) or to 21 individuals values (from Andrews et al[27]). Most of these data were retrieved from scanned figures by using the computer program "Grab It" (Datatrend Software, Raleigh, NC).

Assays and Calculations

Blood samples taken during the OGTT test were used for the measurement of insulin (by the largely used radioimmunoassay method: polyethylene glycol precipitation radioimmunoassay (RIA) assay, using the kit by ARES-SERONO, Milan, Italy), glycemia (glucose-oxidase method, Glucinet kit, by Sclavo, Siena, Italy), and FFA (NEFA-Quick kit by Boehringer-Mannheim-Yamanouchi, Tokyo, Japan).

Areas under the curves were calculated geometrically by using a specifically made computer program (which can be freely obtained from the authors). We calculated both the total area (deduced from measurements made every 30 minutes from the time 0 to the time 2 hours), as well as the 0-1-2h area (deduced from values at 0, 1, and 2 hours), and the 0-2h area (from values at 0 and 2 hours).

Data are given as mean ± SEM. Statistical analysis included the Student's *t* test for unpaired data and multiple regression analysis, which were performed using the SPSS for Windows, release 6.1.3 (SPSS, Chicago, IL). A P value $< .05$ was considered statistically significant.

RESULTS

The insulin, glucose, and FFA curves obtained with data recorded at 0, 30, 60, 90, and 120 minutes during OGTT in the 3 groups of subjects studied are shown in Fig 3. The corresponding mean values of the basal levels and of the areas under the curve are reported in Table 2.

It is apparent that both the insulinemic and glycemic areas and basal values are higher in the 2 groups of patients compared with normal subjects. In addition, as expected, glycemic areas and basal values were also higher in obese-diabetic patients compared with obese nondiabetic subjects (Table 2).

FFA areas and basal values, compared with normal, were increased both in obese and in obese-diabetic subjects, whereas no difference occurred between these 2 groups of patients (Table 2).

In the study group as a whole, ISI(gly) and ISI(ffa) obtained with "total areas" of insulin, glucose, and FFA (ie, areas resulting from measurements at 0, 0.5, 1, 1.5, and 2 hours) were highly correlated with the corresponding values obtained with "simplified areas", ie, with areas resulting from measurements at 0-1-2h, as well as with those obtained with areas deduced from just 2 measurements, at 0 and 2 hours (Table 3). Therefore, in discussing our data, we will refer to the indices obtained with 0-1-2h measurements. The correlation was lower, yet still highly significant, with the ISI(gly) and ISI(ffa) obtained with basal level of insulin, glucose, and FFA (Table 3).

Both ISI(gly) and ISI(ffa) were markedly decreased in obese and even more in obese-diabetic patients (Fig 4), with $P < .001$ in all instances. This was true for both the indices calculated from the 0-1-2h areas (Fig 4, left panel) and the indices calculated from the basal levels (Fig 4, right panel) of insulin, glucose, and FFA. Values for ISI(gly) and ISI(ffa) based on 0-1-2h areas were: 0.57 ± 0.04 and 0.47 ± 0.04 in the obese and 0.40 ± 0.03 and 0.41 ± 0.06 in the obese-diabetic patients, respectively. Values for ISI(gly)-basal and ISI(ffa)-basal were 0.64 ± 0.05 and 0.46 ± 0.05 in the obese and 0.56 ± 0.06 and 0.40 ± 0.06 in the obese-diabetic subjects, respectively.

The indices calculated from 0-2h areas showed a very similar behavior. This was expected, considering the high correlation between the indices calculated from the 0-1-2h areas and those obtained from the 0-2h areas (Table 3).

Multiple correlations of both ISI(gly) and ISI(ffa) with several parameters, including age, body mass index (BMI), waist-to-hip ratio (W/H), systolic blood pressure, and diastolic blood

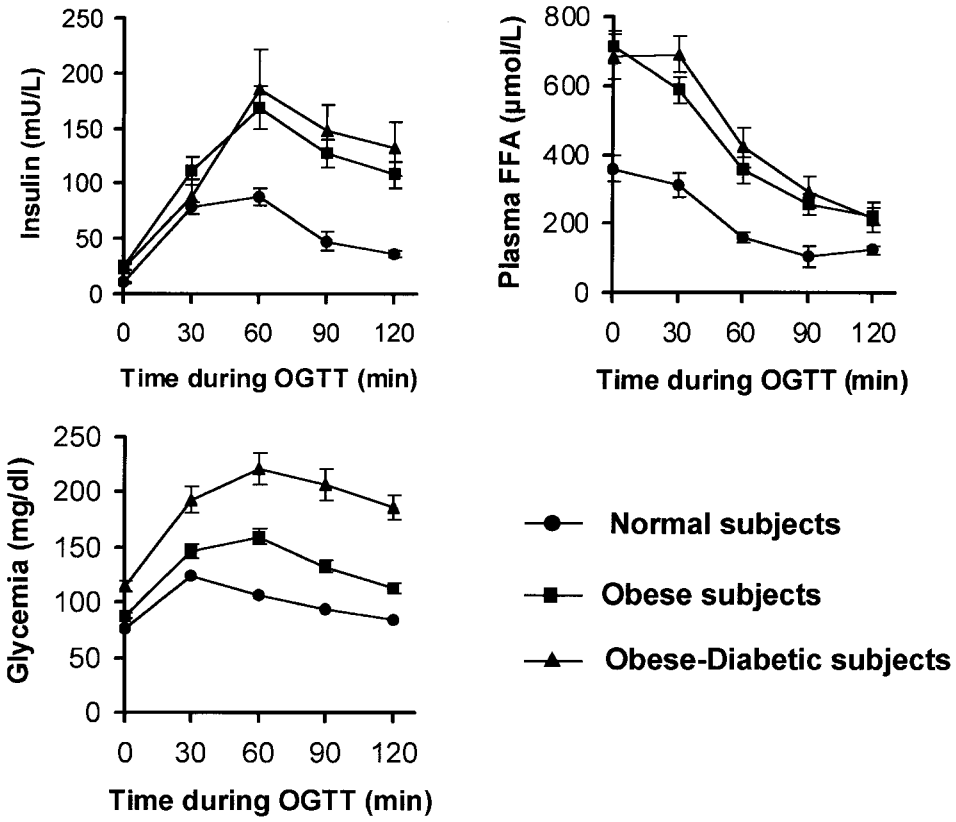


Fig 3. Curves of plasma insulin, glucose, and FFA recorded during a 2-hour OGTT in 34 lean normal subjects, 27 obese, and 11 obese-diabetic patients. Data are means ± SEM.

pressure, calculated in the study population as a whole, are reported in Table 4.

Comparison between ISI(gly) and ISI(ffa) showed the following. In the basal state, ISI(ffa) is more reduced that ISI(gly), both in the obese and in the obese-diabetic patients (Fig 4, right panel). On the other hand, the indices obtained with the areas during OGTT showed that in the obese-diabetic patients, both indices were markedly reduced to the same extent, whereas in the obese nondiabetic subjects, the ISI(gly) was less reduced than ISI(ffa) (Fig 4, left panel). The different behavior of ISI(gly) compared with ISI(ffa) is more evident if we consider the ratio of these 2 indices shown in Fig 5. Figure 6 shows the plotting of ISI(gly) and ISI(ffa) against the BMI in obese and obese-diabetic subjects.

The correlation between ISI(gly) and glucose utilization during the hyperinsulinemic-euglycemic clamp, based on meta-analysis of published data,[24-27] is shown in Figs 7 and 8, which refer to the correlation studied among 12 subject groups or among individual values, respectively.

DISCUSSION

Methodologic Aspects

Characteristics of our formulas. In the organism as a whole, the main effect of insulin is to decrease blood glucose, as well as to lower the blood FFA level (primarily through the suppression of lipolysis[28]). It follows that the degree of insulin sensitivity concerning blood glucose is indicated by the levels of both plasma insulin and/or glucose. Therefore, an index that expresses the degree of insulin sensitivity can be constructed by combining the change in plasma insulin and that in plasma glucose into 1 value. Of course, the same is true for an index that should express the insulin sensitivity of blood FFA, in which instance, the 2 factors to be combined are blood insulin and FFA. This is what is done with our index, in which changes in plasma insulin and glucose (or in plasma insulin and FFA) are combined by multiplying these 2 factors by each other. The product of this multiplication is put in the denominator of a fraction in such a way to obtain the hyperbolic function of it. Indeed, as pointed out recently by us,[29] the combination of 2 or more factors contributing to a disease state (or protecting from it) can be accomplished by multiplication, as well as by addition, the better solution being to use both addition and multiplication. On these grounds, we recently proposed a formula[29] allowing us to combine any number of factors into 1 value. The formulas presented in this report are a simplification of more general formulas allowing the calculation of indices combining any number of factors.[29] Even slightly simpler formulas have been proposed consisting of the product of insulin by glucose concentrations (expressed by considering the mean normal value = 1),[30] ie, (INSp × GLYp), or by the average value of these 2 factors,[31] ie, (INSp + GLYp)/2, which, however, offer no advantages over the formulas presented in the present work and are suitable only to express altered insulin effectiveness as increased insulin resistance, but not as decreased insulin sensitivity.

Our formulas have the advantage of measuring insulin sen-

Table 2. Insulin, Glucose, and FFA Basal Levels and Area Values

	Normal	Obese		Obese-Diabetic		
	Values ± SE	Values ± SE	% Change (*P*) (*v* normal)	Values ± SE	% Change (*P*) (*v* normal)	% Change (*P*) (*v* obese)
Insulin, basal (mU/L)	10.93 ± 0.81	24.85 ± 3.00	+127.45 ($P < .01$)	22.82 ± 4.20	+108.83 ($P < .001$)	−8.18 (NS)
Glycemia, basal (mg/dL)	76.03 ± 2.08	88.37 ± 2.40	+16.23 ($P < .001$)	113.64 ± 5.05	+49.46 ($P < .001$)	+28.59 ($P < .001$)
FFA, basal (μmoles/L)	359.24 ± 37.07	712.93 ± 46.69	+98.46 ($P < .001$)	684.64 ± 65.22	+90.58 ($P < .001$)	−3.97 (NS)
Insulin area (total) (mU/L/h)	126.11 ± 7.87	242.37 ± 20.36	+92.19 ($P < .001$)	254.84 ± 31.68	+102.08 ($P < .001$)	+5.15 (NS)
Insulin area (0-1-2h)*	111.88 ± 8.74	237.20 ± 21.28	+112.02 ($P < .01$)	262.55 ± 39.05	+134.67 ($P < .01$)	+10.68 (NS)
Insulin area (0-2h)*	47.33 ± 3.50	132.59 ± 13.42	+180.13 ($P < .01$)	154.18 ± 25.81	+225.74 ($P < .01$)	+16.28 (NS)
Glycemia area (total)* (mg/dL/h)	203.12 ± 6.13	271.91 ± 9.90	+33.87 ($P < .001$)	374.16 ± 19.60	+84.21 ($P < .001$)	+37.61 ($P < .001$)
Glycemia area (0-1-2h)*	186.29 ± 5.86	260.63 ± 9.50	+39.90 ($P < .01$)	363.09 ± 19.46	+94.90 ($P < .001$)	+39.31 ($P < .001$)
Glycemia area (0-2h)*	160.65 ± 4.13	201.70 ± 5.67	+25.56 (NS)	294.00 ± 15.65	+83.01 ($P < .001$)	+45.76 ($P < .001$)
FFA area (total)* (μmol/L/h)	429.19 ± 36.12	849.12 ± 60.85	+97.84 ($P < .001$)	941.32 ± 92.12	+119.32 ($P < .001$)	+10.86 (NS)
FFA area (0-1-2h)*	403.38 ± 31.98	823.06 ± 58.12	+104.04 ($P < .001$)	872.55 ± 101.43	+116.31 ($P < .01$)	+6.01 (NS)
FFA area (0-2h)*	483.47 ± 40.86	935.15 ± 55.84	+93.42 ($P < .001$)	903.45 ± 89.53	+86.87 ($P < .01$)	−3.39 (NS)

Abbreviation: NS, not significant.

*Total, area deduced from measurements at 0, 0.5, 1, 1.5, and 2 hours during OGTT; (0-1-2h), area deduced from measurements at 0, 1, and 2 hours during OGTT; (0-2h), area deduced from measurements made at 0 and 2 hours during OGTT.

sitivity under rather physiologic conditions (fasting state or postoral glucose load), with regard to the insulin effect on both blood glucose and FFA. This is in contrast to other methods proposed for measuring insulin sensitivity in vivo, all of which are unable to measure insulin sensitivity with regard to blood FFA. Moreover, several methods (the intravenous tests)[6-13] are performed under artificial conditions, entailing intravenous glucose and/or insulin administration. Other procedures (the "fasting/OGTT-data tests"), are performed under more physiologic conditions, ie, in the basal state or in the postglucose load period. Of these, some[14-16] are limited to measurement only in the basal (fasting) state and yield results linked to the units in which insulin and glucose are expressed. With regard to those tests based on the measurement of the basal insulin[14,15] or the insulin area during OGTT,[17,18] it should be noted that, although these parameters are certainly correlated with other estimates of insulin sensitivity, they express only 1 of the 2 factors (insulinemia and glycemia) that define the insulin sensitivity status from the clinical standpoint, and therefore they cannot detect the difference in insulin sensitivity that undeniably exists between 2 patients with equally elevated insulin (basal level or area), but 1 of whom has a higher glycemic level than the other. Two methods remain to be considered,[19,20] which take into account both the insulin and the glucose response during OGTT. Of these, 1[19] introduces in the calculation formula the factor "VD", the estimate of the apparent glucose distribution volume, which makes the formula less simple compared with that proposed by us. Moreover, the results are linked to the units in which insulin and glucose are expressed. The latter criticism also applies to the index of insulin sensitivity proposed by Matsuda and DeFronzo,[20] which is calculated by dividing 10,000 by the square root of the product of "fasting insulin" by "fasting glycemia" by "mean insulin during OGTT" by "mean glycemia during OGTT" (in this formula, insulin and glucose are expressed as mg/dL and μU/mL, respectively). However, it should be pointed out that these 2 methods,[19,20] compared with our formulas, have the following disadvantages: (1) they are more complex; (2) they do not allow measurement

Table 3. Correlations of ISI(gly) and ISI(ffa) Based on Total Areas and the ISI(gly) and ISI(ffa) Based on "Simplified" Areas or Basal Levels of Insulin, Glucose, and FFA

	ISI(gly) Total		ISI(ffa) Total
ISI(gly)-0-1-2h	$r = .97$ ($P < .001$)	ISI(ffa)-0-1-2h	$r = .98$ ($P < .001$)
ISI(gly)-0-2h	$r = .87$ ($P < .001$)	ISI(ffa)-0-2h	$r = .92$ ($P < .001$)
ISI(gly)-Basal	$r = .68$ ($P < .001$)	ISI(ffa)-Basal	$r = .83$ ($P < .001$)

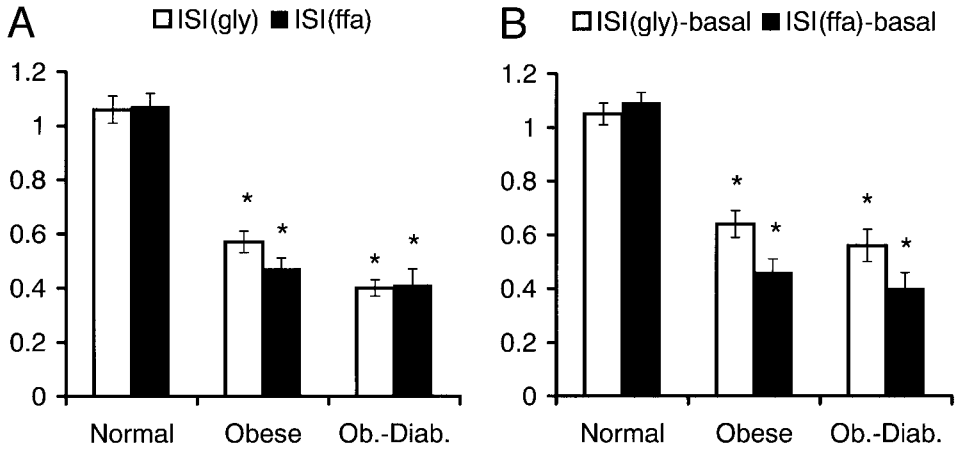


Fig 4. ISI of glycemia [ISI(gly)] and blood FFA [ISI(ffa)] in normal, obese, and obese-diabetic subjects. (A) Indices calculated with the 0-1-2h areas of insulin, glucose, and FFA during OGTT. (B) Indices calculated with the basal levels of insulin, glucose, and FFA. * indicates a *P* value < .001 (comparison with the normal).

of insulin sensitivity with only 3 or 2 sampling during OGTT; (3) their results are linked to the units in which insulin and glucose are expressed (the mean value of the index in the normal group from Matsuda and DeFronzo,[20] as deduced from Fig 1 of that report, would change from approximately 3.75 to approximately 67.42, if glucose is expressed as mmol/L instead of mg/dL); (4) they are unable to measure insulin sensitivity of blood FFA; (5) they do not allow expression of altered insulin sensitivity either as reduced insulin sensitivity or increased insulin resistance; (6) 1 of these 2 methods,[20] being based on the multiplication of the fasting value by the OGTT-induced insulin and glucose levels, is unable to distinguish insulin sensitivity in the basal state and during the postglucose load period.

Concerning the known variability of the OGTT,[32,33] which obviously affects the results of our indices, it should be noted that the variability of the OGTT data is due to changing factors, which are physiologically present and active in the organism and therefore cannot be ignored in the clinical study of patients by creating an artificial steady-state condition, as it is made with the clamp technique. Variability of the factors contributing to our indices should induce us to make more than 1 measurement in the same subject.

It may be of interest to note that ISI(gly) primarily reflects insulin sensitivity of liver and muscle, these 2 tissues being the main sites of the alterations leading to sensitivity to insulin action.[34] On the other hand, ISI(ffa) may reflect insulin sensitivity of adipose tissue (ie, the sensitivity of lipolysis to the inhibition by insulin), as well as of the tissues which take up and utilize FFA.

Measurement of insulin sensitivity of blood FFA level. With regard to ISI(ffa), it should be mentioned that no other satisfactory method is available to measure the insulin sensitivity of plasma FFA, because the simple degree of FFA suppression during OGTT[35,36] may not be fully indicative of the insulin sensitivity of FFA, as it does not take into account the insulin levels, ie, it does not combine into 1 value both the FFA and the insulin values and therefore is unable to detect the difference in insulin sensitivity of blood FFA that undeniably exists between 2 patients with the same degree of FFA suppression, 1 of whom has an insulin curve much higher than the other. Measurement of FFA suppres-

Table 4. Multiple Regression Analysis of Variables Modifying ISI(gly) and ISI(ffa)

	ISI(gly)	ISI(ffa)	ISI(gly)	ISI(ffa)	ISI(gly)	ISI(ffa)
	Areas (0-1-2h)		Areas (0-2h)		Basal Levels	
Age	B = −0.0089	B = −0.0057	B = −0.0085	B = −0.0068	B = −0.0039	B = −0.0040
	β = −0.3147	β = −0.1783	β = −0.2935	β = −0.2035	β = −0.1545	β = −0.1269
	$P < .0011$	$P < .0525$	$P < .0019$	$P < .0325$	$P < .1175$	$P < .2065$
BMI	B = −0.0197	B = −0.0265	B = −0.0288	B = −0.0320	B = −0.0195	B = −0.0288
	β = −0.4547	β = −0.5393	β = −0.5831	β = −0.6260	β = −0.5080	β = −0.5965
	$P < .0001$	$P < .0001$	$P < .0001$	$P < .0001$	$P < .0001$	$P < .0001$
W/H	B = 0.7735	B = 1.1143	B = 0.9076	B = 1.4713	B = −0.1008	B = 0.7758
	β = 0.1802	β = 0.2296	β = 0.2070	β = 0.2908	β = −0.0265	β = 0.1623
	$P = .0787$	$P < .0292$	$P < .0404$	$P < .0058$	$P = .8044$	$P = .1406$
SBP	B = 0.0018	B = −6.5680	B = 0.0027	B = 7.2422	B = −2.2429	B = −0.0014
	β = 0.0938	β = −0.0299	β = 0.1364	β = 0.031	β = −0.0130	β = −0.0638
	$P = .4468$	$P = .8118$	$P = .2611$	$P = .7992$	$P = .9201$	$P = .6311$
DBP	B = −0.0131	B = −0.0113	B = −0.0105	B = −0.0099	B = −0.0052	B = −0.0052
	β = −0.4165	β = −0.3171	β = −0.3271	β = −0.2694	β = −0.1886	β = −0.1480
	$P < .0022$	$P < .0201$	$P < .0129$	$P < .0449$	$P = .1756$	$P = .2965$

Note. Results of the analysis are expressed as regression coefficient (B), standardized coefficient (β), and *P* values.

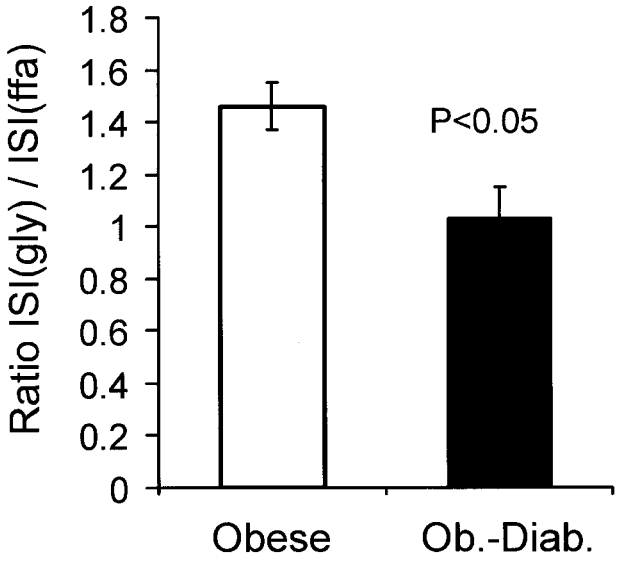


Fig 5. ISI(gly) to ISI(ffa) ratio in obese and obese-diabetic patients.

sion during hyperinsulinemic clamp,[28,37,38] apart from the complexity of the procedure, suffers from the fact that the induced insulin levels are arbitrary and artificial with regard to both their height and duration.

Comparison with other tests. It is generally expected that any newly proposed method is "validated" through comparison with other well-standardized methods. However, it should be pointed out that ISI(gly) and ISI(ffa) do not need to be validated, because they are based on the direct measurement of the clinical parameters of insulin action (insulin and glucose or insulin and FFA levels) under unmodified condition. The same can be said for the clamp technique, which has not been validated, being based on the direct measurement of the physiologic parameters of insulin action (glucose utilization by tissues), even if measured under artificial steady-state conditions, which never occur spontaneously in the life of the patients. It should also be underlined that our indices and the "clamp" technique measure insulin sensitivity under so different conditions that any comparison between the 2 tests is not very meaningful, as the 2 tests are expected to behave somewhat differently. Indeed, the euglycemic clamp test,[9] generally considered as the "gold standard" method for the measurement of in vivo insulin sensitivity in man, is performed under nonphysiologic steady-state metabolic conditions because: (1) glucose is given intravenously, thus bypassing the gastrointestinal tract and therefore preventing the effects of intestinal motility and absorption, the enterohormone response, the hepatic glucose afflux, the physiologic kinetics of glucose absorption, and insulin secretion, etc; (2) there is persistent, fixed exogenous hyperinsulinemia with consequent suppression of FFA level, which is a known determinant of insulin sensitivity. In this regard, it should be pointed out that FFA (and their products of activation, long-chain Acyl-CoA) exert both short-term (minutes) and long-term (several hours) effects on glucose utilization.[39,40] Therefore, the FFA suppression during the hyperinsulinemic-euglycemic clamp entails that the short-term effects on insulin sensitivity exerted by the pretest FFA level are lost. These and other considerations account for the reported observation that in obese patients, the "clamp" technique may show normal insulin sensitivity, whereas the OGTT indicates insulin resistance (elevated insulin curve).[41] Finally, it should be underlined that the "clamp" technique is unable to measure insulin sensitivity with regard to the insulin effect on FFA.

However, through meta-analysis of published data,[24-27] despite the differences just mentioned, we found significant correlation between ISI(gly) and hyperinsulinemic-euglycemic clamp data. As shown in Fig 7, among 12 subject groups, we found a $r = .96$ ($P < .001$), while among individual measurements, the correlation coefficient found was .51 ($P < .05$) when the hyperinsulinemic clamp was performed at approximately 250 mU/L insulin and .67 ($P < .05$) when the "clamp" was performed at approximately 100 mU/L insulin (Fig 8). Recently, Matsuda and DeFronzo[20] studied the correlation between data obtained with the euglycemic-hyperinsulinemic clamp with those obtained with our ISI(gly) or with their own formula, and they found "*r*" values of .65 and .73, respectively, among nondiabetic subjects.[20] However, as already pointed out by us recently,[42] due to a mistake made by these investigators in calculating our ISI(gly) (primarily because they divided the insulin and glucose during OGTT by an arbitrary "constant" instead of by the respective "mean normal values"), the re-

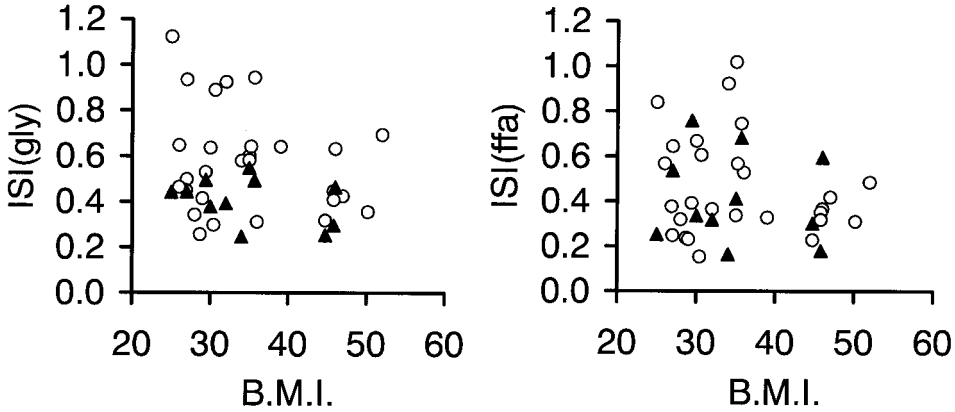


Fig 6. Plot of ISI(gly) and ISI(ffa) against BMI in obese and obese-diabetic subjects. ○ indicates obese subjects. ▲ indicates obese-diabetic patients.

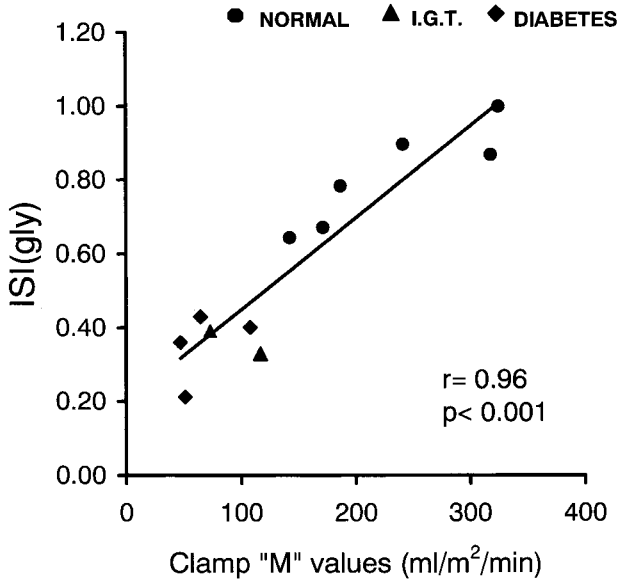


Fig 7. Meta-analysis of published data[24-26] showing the correlation of ISI(gly) with the "M" value obtained during hyperinsulinemic-euglycemic clamp studied among groups of subjects. Data were retrieved from scanned figures by using the computer program "Grab It." Groups shown include: (1) 100 nondiabetic individuals with BMI less than 30, divided into 4 quartiles with different insulin sensitivity, whose data were taken from Figs 1, 2, and 3 of Hollenbeck and Reaven[24]; (2) 3 groups comprising control, IGT, and type 2 diabetic subjects, whose data were taken from Figs 1 and 4 of Golay et al[25]; and (3) 5 groups including normal and IGT subjects as well as 3 groups of type 2 diabetic patients with increasing fasting glucose (<8 mmol/L, 8 to 15 mmol/L, and >15 mmol/L), whose data were taken from Figs 1, 2, and 3 of Reaven et al.[26] In calculating ISI(gly), the insulin and glucose values of the quartile with the highest insulin sensitivity among those reported in Hollenbeck and Reaven[24] was taken as the "mean normal value."

ported difference between their index and our ISI(gly) cannot be evaluated. It may be of interest to mention that in our study population, the correlation between our ISI(gly) and the Matsuda and DeFronzo formula was high ($r = .88$, $P < .0001$).

Conclusions about ISI(gly) and ISI(ffa). To sum up, the advantage of our indices are as follows: (1) they are easy to perform, being based on simple formulas; (2) they make possible measurement of insulin sensitivity (or resistance) with only 3, or even 2, sampling during OGTT; (3) they are performed under rather physiologic conditions, with all of the metabolic and hormonal variables unmodified; (4) they give always a value close to 1 in subjects with "normal" insulin sensitivity, with extreme variations among patients between 0 and 2, regardless of the units in which insulin, glucose, and FFA are expressed; (5) they allow altered insulin sensitivity to be expressed as reduction of the ISI or as increase of the insulin resistance index (IRI), 1 index being easily deduced from the other as their sum is always equal to 2; (6) they are able to measure insulin sensitivity (or resistance) both in the basal state or during the postglucose load period; (7) they make possible the measurement of insulin sensitivity with regard to the insulin effect on both glycemia and blood FFA. Because of these characteristics, the indices obtained with our formulas are suitable for use in the clinical setting and in epidemiologic studies.

Clinical Data

In consideration of the well-known variability of data obtained with the OGTT,[32,33] in performing our test, maximum effort has been made to improve reproducibility. To this end, we standardized some factors (period of fasting, carbohydrate intake before fasting, time of day of the test, concentration of the glucose solution drunk and rate of ingestion, exercise before and during the test, ambient temperature, timing of blood sampling, phase of menstrual cycle) and excluded others (smoking, acute illnesses, or psychological stresses), which may cause variability of OGTT results.[32,33] However, there may be an "intrinsic" variability, which persists even if the procedure is strictly standardized, because it is linked to the peculiar biological characteristics of a given subject. We think it could be an advantage that our test reflects this variability, without bypassing it (as it happens with other "intravenous" tests).

In calculating the indices in our study population, we used the mean normal value calculated with data obtained in our normal group. Our mean normal values for insulin, glucose, and FFA, both as basal level and areas during OGTT (Table 2), are comparable with those reported in the literature.[24,25,35,36]

ISI(gly) and ISI(ffa) obtained with the "total areas" (measurements at 0, 30, 60, 90, and 120 minutes) were highly correlated with the corresponding indices obtained with the 0-1-2h areas or the 0-2h areas (Table 3). This suggests that the easier to perform ISI(gly) based on the 0-1-2h areas can be used instead of the more demanding 1 based on the "total areas". For this reason, the present discussion is referred to the indices based on the 0-1-2h areas. Indeed, high correlation was also shown by the indices based on the 0-2h areas, which indicates that even this very simple procedure can be used, especially for the meta-analysis of the several published articles reporting

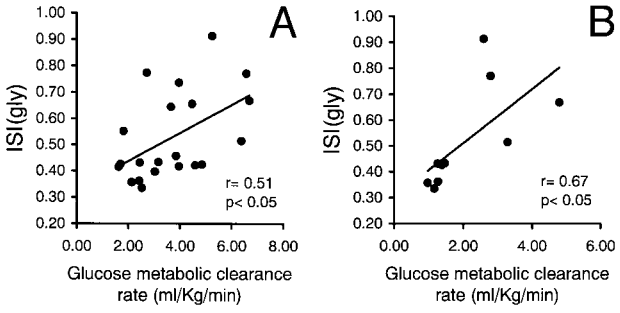


Fig 8. Meta-analysis of published data[27] showing the correlation of ISI(gly) with the glucose metabolic clearance rate during hyperinsulinemic-euglycemic clamp performed at approximately 250 mU/L insulin (A) or at approximately 100 mU/L insulin (B), studied among individuals with diabetes. These subjects were studied before insulin treatment when they were hyperglycemic and 2 times after treatment, when their glycemia was very close to normal. Data shown in this Fig (21 measurements in A and 10 in B) refer only to data obtained after treatment to avoid possible influence of basal hyperglycemia. Data were retrieved from scanned figures (Figs 2, 4, and 5 of Andrews et al[27]) by using the computer program "Grab It".

data recorded only at 0 and 2 hours during OGTT. As expected by the above considerations, the reduction of ISI(gly) and ISI(ffa) observed in our obese or obese-diabetic patients was almost the same whether the tests were obtained with the "total areas" or the 0-1-2h or the 0-2h areas. Both ISI(gly) and ISI(ffa) were remarkably lower in obese and obese-diabetic patients than in normal subjects (Fig 4).

Data in Fig 4 indicate significant differences between the behavior of ISI(gly) and that of ISI(ffa). The indices calculated with the basal levels (Fig 4B) show hat ISI(ffa)-basal is more reduced than ISI(gly)-basal, both in the obese and in the obese-diabetic patients. The indices obtained with the 0-1-2h areas (Fig 4A) indicate that ISI(gly) is less reduced than ISI(ffa) in the obese group, whereas both ISI(gly) and ISI(ffa) are severely reduced in the obese-diabetic patients. The different behavior of ISI(gly) compared with ISI(ffa) is more evident if we consider the ratio of these 2 indices, ie, the ISI(gly)/ISI(ffa) ratio, which is higher in obese than in obese-diabetic patients (Fig 5). Accordingly, by plotting the ISI(gly) and the ISI(ffa) against the BMI, it appears that all ISI(gly) values in the group of obese-diabetic patients were less than .60, whereas in the obese group, several subjects showed ISI(gly) higher than .60 (Fig 6). This might suggest that progression of obesity to diabetes is linked (in addition to the secretory exhaustion) to a decrease in the ISI(gly) value, ie, in the index reflecting the insulin sensitivity of the carbohydrate metabolism. This assumption, however, should be confirmed by longitudinal studies. Because reduction in the ISI(ffa) should entail increased blood FFA, these data are in keeping with the well-known role of FFA as inhibitors of insulin-mediated glucose utilization.[39,40]

It should be pointed out that, although our data were obtained in patients (obese or obese-diabetic) with elevated insulin response to glucose, our indices also applies to patients with blunted insulin response. This is because in a given patient, if the insulin response is reduced, the glucose and FFA levels will be (roughly proportionally) increased, so that the product "insulin $\times$ glucose" and "insulin $\times$ FFA" (which are the core of our formulas) will not change appreciably. However, our formulas should not be used in diabetic patients with severe insulin deficiency, in whom 1 of the factors of our formulas, (insulin) is practically absent.

Multiple regression analysis (Table 4) showed a different behavior of the indices deduced from OGTT areas from those deduced from basal values. Concerning the indices deduced from areas, both ISI(gly) and ISI(ffa), were negatively correlated with several parameters, including age, BMI, and diastolic blood pressure, but not with the systolic blood pressure (Table 4). Of interest and unexpected was the lack of significant negative correlation with the W/H ratio, whereas the correlation of ISI(gly) with the BMI is in keeping with the known role of the degree of obesity in the phenomenon of insulin resistance.[43] On the other hand, both indices deduced from basal values showed significant negative correlation only with the BMI.

The above-reported data and discussion suggest that our formulas, making it possible to measure in a simple way the whole-body insulin sensitivity of glycemia and blood FFA under physiologic conditions, appear as suitable tools to assess the insulin sensitivity of a given patient from the clinical standpoint as well as to perform epidemiologic investigations.

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