

Impact of Degree of Obesity on Surrogate Estimates of Insulin Resistance

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OBJECTIVE— To evaluate the role of adiposity in the relationship between specific and surrogate estimates of insulin-mediated glucose uptake (IMGU) in a large nondiabetic population.

RESEARCH DESIGN AND METHODS— Healthy volunteers were classified by BMI into normal weight ($<25.0 \text{ kg/m}^2$, $n = 208$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$, $n = 168$), and obese ($\geq 30.0 \text{ kg/m}^2$, $n = 109$) groups. We then assessed how differences in BMI affect the correlation between steady-state plasma glucose (SSPG) concentration at the end of a 180-min infusion of octreotide, glucose, and insulin (a specific measure of IMGU) and five surrogate estimates: fasting plasma glucose, fasting plasma insulin, homeostasis model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), and area under the curve for insulin in response to oral glucose (I-AUC).

RESULTS— Correlation coefficients (r values) between SSPG and surrogate measures of IMGU were all significant ($P < 0.05$), but the magnitude varied between BMI groups: normal weight: fasting plasma glucose 0.20, fasting plasma insulin 0.33, HOMA-IR 0.36, QUICKI -0.33 , and I-AUC 0.69; overweight: fasting plasma glucose 0.19, fasting plasma insulin 0.55, HOMA-IR 0.55, QUICKI -0.54 , and I-AUC 0.72; and obese: fasting plasma glucose 0.40, fasting plasma insulin 0.56, HOMA-IR 0.60, QUICKI -0.61 , and I-AUC 0.69.

CONCLUSIONS— The relationship between direct and surrogate estimates of IMGU varies with BMI, with the weakest correlations seen in the normal-weight group and the strongest in the obese group. In general, I-AUC is the most useful surrogate estimate of IMGU in all weight groups. Fasting plasma insulin, HOMA-IR, and QUICKI provide comparable information about IMGU. Surrogate estimates of IMGU based on fasting insulin and glucose account for no more than 13% of the variability in insulin action in the normal-weight group, 30% in the overweight group, and 37% in the obese group.

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Individuals with insulin resistance are at increased risk to develop a series of adverse clinical outcomes, including diabetes, cardiovascular disease, essential hypertension, polycystic ovary syndrome, and nonalcoholic fatty liver disease (1–5).

Because of the number and severity of

the clinical syndromes associated with insulin resistance, there is considerable interest in ways to identify the presence of this defect in insulin action in apparently healthy individuals. Although established techniques to quantify insulin-mediated glucose uptake (IMGU) are available (6,7), they are often viewed as being too

time- and labor-intensive for routine use in studies of insulin resistance. In an attempt to overcome this perceived problem and enhance investigation of the role of insulin resistance in human disease, a variety of surrogate estimates of IMGU have been proposed (8–10). These approaches all have the advantage of being derived from measurements of fasting plasma glucose and insulin concentrations and thus provide the simple way to measure IMGU that is desired. On the other hand, they are likely to account for no more than 40% of the variability in IMGU in the nondiabetic population at large (11,12). In addition, the reliability of these surrogate estimates may vary with degree of obesity because adiposity is known to modify the relationship between insulin resistance, plasma glucose, and plasma insulin concentrations (13–15). This may explain some of the conflicting reports in the literature about the performance of these tests, such that a skewed BMI distribution in the study population may overstate (10,16–18) or seem to understate (19) the relationship between direct and indirect tests of IMGU. Few studies have addressed the role of adiposity on the efficacy of surrogate measures of IMGU; even then, these studies have been limited by small sample sizes (10,16–18,20), loose BMI-group categories (18,20,21), and inclusion of both nondiabetic and diabetic individuals in the analysis (18,21). Information concerning this issue would be particularly useful in understanding the utility of these surrogate measures, particularly in the midst of the current obesity epidemic (22–24). In order to address this issue we have evaluated the relationship between IMGU as quantified by the insulin suppression test (IST) and five surrogate estimates in 485 nondiabetic individuals, subdivided into three groups on the basis of their BMI: normal weight ($n = 208$), overweight ($n = 168$), and obese ($n = 109$).

RESEARCH DESIGN AND METHODS

The study population consisted of 485 nondiabetic (25) volunteers who had participated in our research

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Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; I-AUC, area under the curve for insulin in response to oral glucose; IMGU, insulin-mediated glucose uptake; IST, insulin suppression test; QUICKI, quantitative insulin sensitivity check index; SSPG, steady-state plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Clinical characteristics of the study population

	Normal weight (BMI <25 kg/m ²)	Overweight (BMI 25–29.9 kg/m ²)	Obese (BMI ≥30 kg/m ²)	P*
n	208	168	109	—
Age (years)	46.0 ± 13.6	51 ± 12.6†	49.2 ± 12.1	0.001
Sex (M/F)	89/119	88/80	48/61	NS
BMI (kg/m ²)	22.4 ± 1.8	27.1 ± 1.4	32.8 ± 2.5	<0.001‡
SSPG (mmol/l)	5.9 ± 2.9	9.0 ± 4.2	11.8 ± 4.1	<0.001‡
Fasting glucose (mmol/l)	4.8 ± 0.6	5.1 ± 0.6	5.4 ± 0.6	<0.001‡
Fasting insulin (pmol/l)	58.3 ± 26.6	80.2 ± 37.4	125.5 ± 66.6	<0.001‡
HOMA-IR	1.82 ± 0.90	2.66 ± 1.39	4.42 ± 2.57	<0.001‡
QUICKI	0.36 ± 0.03	0.34 ± 0.03	0.32 ± 0.02	<0.001‡
I-AUC (pmol · l ⁻¹ · 3 h ⁻¹)	864.6 ± 464.4	1,254.3 ± 838.9	1,853.9 ± 1,278.2	<0.001‡

Data are means ± SD. *P values reflect differences between the three groups and are assessed by one-way ANOVA; †P value = 0.001 for comparison between normal-weight versus overweight groups; ‡P value <0.001 for comparison between normal weight versus overweight, normal weight versus obese, and overweight versus obese.

studies from 1990 to 1998. The mean age (±SD) was 48 ± 13 years (range 19–79). Most participants were of European ancestry (77%), with the remainder being of Hispanic (12%), Asian (10%), and African (1%) background. Individuals were classified by BMI as normal weight (<25 kg/m², n = 208), overweight (25–29.9 kg/m², n = 168), or obese (≥30 kg/m², n = 109).

After signing an informed consent, participants were admitted to Stanford's General Clinical Research Center for metabolic testing. We quantified IMGU by a modification of the IST (26) as originally introduced and validated by our research group (6,27). After an overnight fast, an intravenous catheter was placed in each of the subjects' arms. One arm was used for the administration of a 180-min infusion of octreotide (0.27 μg · m⁻² · min⁻¹), insulin (32 mU · m⁻² · min⁻¹), and glucose (267 mg · m⁻² · min⁻¹); the other arm was used for collecting blood samples. Blood was drawn every 30 min initially and then at 10-min intervals from 150 to 180 min of the infusion in order to determine the steady-state plasma glucose (SSPG) and steady-state plasma insulin concentrations. Because steady-state plasma insulin concentrations are similar in all subjects, the SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; therefore, the higher the SSPG concentration, the more insulin resistant the individual.

On a separate admission, fasting plasma glucose and insulin concentrations were measured before and 30, 60, 120, and 180 min after oral ingestion of

75 g of glucose (11,12). From these measurements, we evaluated five surrogate measures of insulin-mediated glucose disposal: 1) fasting plasma glucose, 2) fasting plasma insulin, 3) homeostasis model assessment of insulin resistance (HOMA-IR), 4) quantitative insulin sensitivity check index (QUICKI), and 5) total integrated area under the curve for insulin in response to oral glucose (I-AUC). I-AUC was quantified by calculating the insulin area under the curve by use of the trapezoidal method. We used the following formulas (9,10) for HOMA-IR (fasting insulin [in microunits per milliliter] × fasting glucose [in millimoles per liter]/22.5) and QUICKI (1/log fasting insulin [in microunits per milliliter] + log fasting glucose [in milligrams per deciliter]).

Data are expressed as means ± SD. All analyses were performed using Systat version 10 for Windows (Systat Software, Point Richmond, CA). Statistical differences in baseline characteristics between normal-weight, overweight, and obese groups were assessed by one-way ANOVA followed by the Bonferroni post hoc pairwise comparison for continuous variables and χ^2 tests for dichotomous variables. Pearson correlation coefficients were calculated between SSPG and fasting glucose, fasting insulin, HOMA-IR, QUICKI, and I-AUC. To account for skewness and kurtosis, fasting insulin, HOMA-IR, and I-AUC were log transformed. The strongest correlation coefficient between SSPG and a surrogate test of IMGU was compared with the other correlations to assess significant differences between the associations by a two-tailed t test (28).

RESULTS— The clinical characteristics of the three BMI groups are provided in Table 1 as well as the various measures of insulin action. The groups are comparable in terms of age and sex distribution, with the only difference being that the overweight individuals are slightly older than their normal-weight counterparts. The results also indicate that the degree of insulin resistance, as estimated by either SSPG concentration or the five surrogate estimates of IMGU, increases progressively as the magnitude of adiposity increases.

Looking at Table 1 more closely, it appears that the degree of variability (±SD) for SSPG and the five surrogate measures appear quite different. In fact, in the whole study population, fasting plasma glucose concentrations vary by as little as 1.8-fold (3.66–6.66 mmol/l) and by as much as 24-fold for fasting insulin concentrations (6.95–167 pmol/l) when outliers are excluded (defined as >1.5 times the interquartile range). The distribution of these surrogate measures also varies by degree of obesity and insulin resistance. For example, Fig. 1 illustrates the increase in the range of fasting insulin concentrations in obese insulin-resistant individuals.

In the whole study population, the relationship (Pearson correlation coefficient) between SSPG and each indirect measure of IMGU with 95% CIs are as follows: fasting plasma glucose 0.38 (0.3–0.45, R² = 0.14), fasting plasma insulin 0.61 (0.55–0.66, R² = 0.37), HOMA-IR_{log} 0.64 (0.58–0.69, R² = 0.41), QUICKI -0.60 (-0.65 to -0.54, R² = 0.36), and I-AUC_{log} 0.77 (0.73–0.80, R²

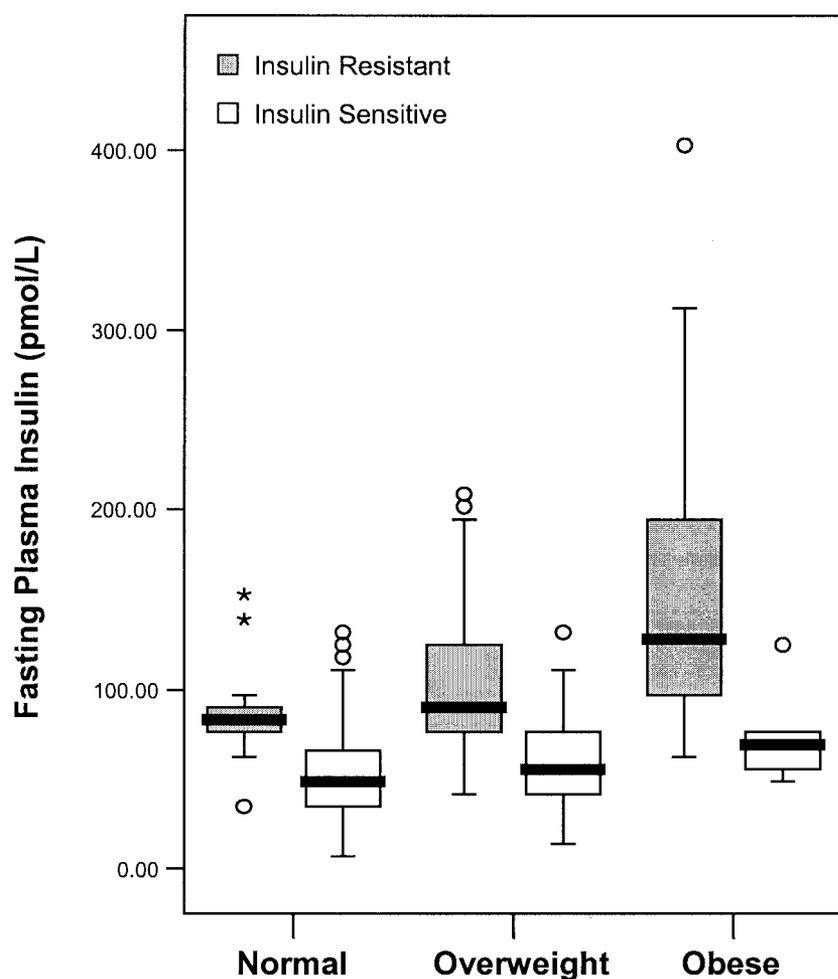


Figure 1—Box plots illustrating the median and range of fasting plasma insulin concentrations in insulin-resistant (highest tertile of SSPG) and insulin-sensitive (lowest tertile of SSPG) individuals according to degree of obesity. Boundaries of the box signify the lower and upper quartiles. ○, outliers with values between 1.5 and 3 box lengths from the boundaries of the box. *Extreme values representing >3 box lengths.

= 0.59). All of the correlation coefficients are statistically significant ($P < 0.001$), but the magnitude of the relationship clearly differs. I-AUC is the most closely related with SSPG, and this correlation is significantly different from the other r values ($t > 6$ for all comparisons, degrees of

freedom 482, $P < 0.001$). Therefore, I-AUC is the best surrogate estimate of IMGU, accounting for 59% of the variability in SSPG concentration. In contrast, fasting glucose is the least useful and accounts for only 14% of the variability. The correlation coefficients between SSPG and fasting insulin,

HOMA-IR, and QUICKI are quite similar, with differences in each of these values explaining <41% of the variability in SSPG concentration.

The results in Table 2 display the relationship between SSPG and the five surrogate estimates of IMGU when the population is subdivided on the basis of adiposity into normal-weight, overweight, and obese groups. These data are similar to values obtained in the whole study population in that the strongest relationship is between SSPG and I-AUC, the weakest between SSPG and fasting glucose, and intermediate between SSPG and fasting insulin, HOMA-IR, and QUICKI. However, the results in Table 2 provide two additional important points. First, I-AUC is the only surrogate estimate that yields a consistent relationship with SSPG across weight groups. In contrast, the relationship between SSPG and fasting glucose, fasting insulin, HOMA-IR, and QUICKI change substantially as a function of BMI. Thus, in the obese group none of these surrogate estimates based on fasting glucose and insulin can account for >37% of the variability in IMGU as measured by SSPG and only ~13% of the variability of IMGU in normal-weight individuals. Secondly, it is once more apparent from Table 2 that essentially identical estimates of IMGU are obtained with use of fasting insulin concentration, HOMA-IR, or QUICKI. This is not surprising given the near-perfect correlation between fasting insulin, HOMA-IR, and QUICKI (correlation between fasting insulin_{log} and HOMA-IR_{log}, 0.98; fasting insulin_{log} and QUICKI_{log}, -0.98; and HOMA-IR_{log} and QUICKI_{log}, -0.99; all $P < 0.001$). It should also be noted that the data in Table 2 do not meaningfully change when these relationships are adjusted for age (data not shown).

Table 2—Pearson correlation coefficients between SSPG and surrogate measures of insulin resistance by degree of obesity

	Normal weight		Overweight		Obese	
	r (95% CI)	R^2	r (95% CI)	R^2	r (95% CI)	R^2
Fasting glucose	0.20 (0.07–0.33)*	0.04	0.19 (0.04–0.33)†	0.04	0.40 (0.23–0.55)	0.16
Fasting insulin _{log}	0.33 (0.20–0.45)	0.11	0.55 (0.43–0.65)	0.30	0.56 (0.42–0.68)	0.31
HOMA-IR _{log}	0.36 (0.24–0.47)	0.13	0.55 (0.43–0.65)	0.30	0.60 (0.46–0.71)	0.36
QUICKI	-0.33 (-0.45 to -0.20)	0.11	-0.54 (-0.64 to -0.42)	0.29	-0.61 (-0.72 to -0.48)	0.37
I-AUC _{log}	0.69 (0.61–0.76)	0.48	0.72 (0.64–0.79)	0.52	0.69 (0.58–0.78)	0.48

* $P < 0.01$; † $P < 0.05$; all other P values are <0.001.

CONCLUSIONS— Before discussing the significance of the study results, we should first address whether the IST provides a specific measure of IMGU. The IST, initially described and validated in 1970 (6), is conceptually very similar to the glucose clamp (7) method for measuring IMGU. Both techniques are based on measuring glucose disposal rates during a steady-state period of physiological hyperinsulinemia, but they differ in the variable that is used to quantify IMGU. The IST is based on infusing a fixed glucose load and allowing the plasma glucose concentration to seek its own level. In contrast, the glucose clamp method relies on maintaining the plasma glucose concentration constant by varying the amount of glucose infused. Thus, differences in IMGU with the IST are a direct function of the height of the plasma glucose concentration achieved during the infusion (SSPG concentration), whereas the difference in the amount of glucose infused provides the measure of IMGU with the glucose clamp. Not only are the two methods conceptually quite similar, they are highly correlated ($r > 0.9$) when both techniques are used to quantify IMGU in individuals over a wide range of insulin sensitivity (27). Based on the above considerations, we believe that the IST provides a specific measurement of IMGU that can be used as a standard to evaluate the adequacy of surrogate estimates of this variable.

Focusing on the relative utility of the five surrogate estimates of IMGU, three issues seem worthy of discussion. To begin, the results presented provide an unequivocal answer to the question posed in the introduction: the five surrogate estimates of IMGU vary dramatically with the degree of adiposity. The lowest correlations between SSPG and these surrogate tests are seen in the normal-weight group and the highest in the obese group. This may only reflect the higher prevalence of insulin resistance in the obese group. However, if this were the only factor, the association between SSPG and I-AUC would also differ as a result of BMI, but it does not. What is more likely is that the degree of obesity modifies the relationship among insulin resistance, insulin secretion, and insulin catabolism, such that plasma glucose and insulin concentrations are better able to delineate differences in IMGU in more obese individuals. The mechanism by which this occurs is

debated with evidence for increased insulin secretion (13,29–31) and decreased insulin clearance (14,32) in obesity. Regardless, hyperinsulinemia in obesity has long been appreciated, with higher insulin concentrations seen during fasting and postglucose challenge conditions in obese individuals when compared with normal-weight individuals, even when they are matched for glucose tolerance (33) or insulin sensitivity (13,15,34). The hyperinsulinemia is even more pronounced in obese insulin-resistant individuals (13,15,34). This phenomenon may better help delineate differences in insulin sensitivities in obese individuals, especially when utilizing fasting values. To illustrate this point, Fig. 1 shows box plots of fasting insulin concentrations in the different weight classes subdivided by insulin-resistant (highest tertile of SSPG) and insulin-sensitive (lowest tertile of SSPG) groups. Obese insulin-resistant individuals have higher insulin concentrations, a greater range in insulin values, and a clearer delineation from their insulin-sensitive counterparts when compared with normal-weight individuals who are insulin resistant. Therefore, how insulin is regulated may make fasting insulin a better surrogate measure of IMGU in obese individuals but not in normal-weight or overweight individuals.

Although not the primary goal of our study, the results provide additional evidence that fasting plasma glucose and insulin measurements do not provide precise estimates of IMGU. The information in Table 1 shows that the range in fasting plasma insulin concentrations in this population is greater than that for fasting plasma glucose concentrations and can vary by 24-fold versus only 1.8-fold for fasting glucose. This finding is consistent with the physiological fact that it is the compensatory hyperinsulinemia in insulin-resistant individuals that prevents the decompensation of glucose homeostasis. Thus, the observation that fasting plasma glucose accounts for ~14% of the variability in IMGU, compared with ~37% for fasting insulin, is predictable. Similarly, surrogate estimates of IMGU based on using both fasting glucose and insulin concentrations cannot be that different from those obtained with insulin levels alone; the impact of a variable that varies by 24-fold (fasting insulin) will outweigh the contribution of one that changes by only 1.8-

fold (fasting glucose) and be the major determinant of the combined effect.

It must be noted that other studies have reported higher correlations between a specific measure of IMGU and HOMA-IR or QUICKI than we have found. The highest r values are reported in the original works for HOMA-IR (9) ($r = 0.83$), which included only 12 nondiabetic subjects (90–142% of ideal body weight), and for QUICKI (10) ($r = 0.89$), which included 13 obese (BMI ≥ 30 kg/m²) subjects. In fact, most previous studies validating the use of HOMA-IR and QUICKI usually have <30 nondiabetic subjects by any specific weight class (16–18,20,35). In addition, weight classifications have not been as rigorously delineated as they have in this study, with some groups defining obesity as BMI greater than or equal to 25 (21) or 27 (18,20) kg/m². Therefore, it is not surprising that subgroup analyses by weight either have not been done or have given conflicting reports, with some noting correlation coefficients between specific and surrogate estimates of IMGU as being similar between nonobese and obese individuals (18,21), as higher in nonobese individuals (20), and as lower in nonobese individuals (10,17,35). To the best of our knowledge, this is the only work that has specifically analyzed the impact of degree of obesity in a large nondiabetic population by three different weight categories.

In conclusion, useful information may be gained by using measurements of fasting glucose and insulin concentrations to estimate insulin resistance in large population-based studies, but these values will vary with degree of obesity and explain as little as ~13% of the variability in IMGU in normal-weight individuals and no more than ~37% in obese people. In addition, more sophisticated calculations incorporating fasting glucose and insulin add little to the information gained from fasting insulin alone. Thus, use of these surrogate estimates of insulin resistance in physiological studies involving relatively few subjects has considerable potential for providing confounded experimental data.

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