Relationship Between Several Surrogate Estimates of Insulin Resistance and Quantification of Insulin-Mediated Glucose Disposal in 490 Healthy Nondiabetic Volunteers

HELEN YENI-KOMSHIAN, MD
MARCELLO CARANTONI, MD
FAHIM ABBASI, MD
GERALD M. REAVEN, MD

OBJECTIVE — The goal of this study was to define the relationship between a quantitative measure of the ability of physiological hyperinsulinemia to stimulate glucose disposal and several surrogate measures of insulin resistance.

RESEARCH DESIGN AND METHODS — Insulin-mediated glucose disposal was quantified in 490 healthy nondiabetic volunteers by determining the steady-state plasma glucose (SSPG) concentration in response to a continuous infusion of somatostatin, insulin, and glucose. Because the steady-state plasma insulin concentration was similar in all subjects during the infusion (~60 μU/ml), the SSPG concentration provided a direct estimate of insulin-mediated glucose disposal. Relationships between this specific measure of insulin resistance and several surrogate estimates of insulin resistance based on plasma glucose and insulin concentrations were then defined.

RESULTS — The surrogate measure of insulin resistance most closely related to the direct determination of insulin action was the total integrated insulin response to a 75-g oral glucose challenge with correlation coefficients (r) varying from 0.67 to 0.79. Fasting plasma insulin concentration was significantly correlated ($r = 0.61$, $P < 0.001$) to the specific estimate of insulin action. Two other surrogate estimates of insulin action, the ratio of fasting glucose-to-fasting insulin concentration and the homeostasis model assessment for insulin resistance, were no more closely related to SSPG than the fasting plasma insulin concentration.

CONCLUSIONS — The total integrated insulin response to oral glucose is the best surrogate measure of insulin resistance, accounting for approximately two-thirds of the variability in insulin-mediated glucose disposal. Fasting insulin concentration accounted for approximately one-third of the variability in insulin-mediated glucose disposal, and the use of fasting plasma glucose and insulin concentrations to calculate more sophisticated estimates of insulin resistance appears to offer little advantage over the fasting plasma insulin concentration. Given the large number of nondiabetic individuals in this study, the results should have general application in population-based studies, providing evidence for both the utility and limitation of the use of these surrogate measures.

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From the Stanford University School of Medicine, Stanford, California.

Address correspondence and reprint requests to G.M. Reaven, MD, 213 E. Grand Ave., South San Francisco, CA 94080. E-mail: greaven@shaman.com.

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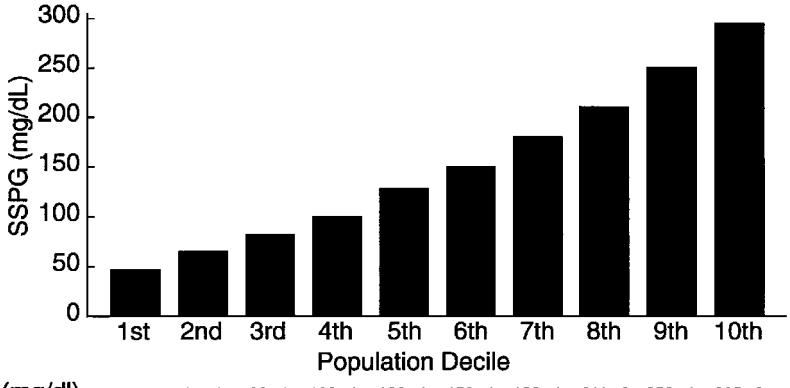
Abbreviations: CHD, coronary heart disease; FSIGT, frequently sampled intravenous glucose tolerance; HOMA-IR, homeostasis model assessment for insulin resistance; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; S_I, the estimate of insulin sensitivity with the FSIGT; SSPG, steady-state plasma glucose; SSPI, steady-state plasma insulin.

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

In 1988, Reaven (1) introduced the notion that there was a cluster of abnormalities associated with insulin resistance and compensatory hyperinsulinemia in nondiabetic individuals that greatly increased the risk of coronary heart disease (CHD). The abnormalities initially associated with insulin resistance in nondiabetic individuals included hyperinsulinemia, borderline glucose tolerance, an increase in plasma triglycerides, a decrease in plasma HDL cholesterol concentration, and hypertension. The list of the abnormalities associated with insulin resistance has continued to grow and now includes enhanced postprandial lipemia (2), decreased LDL-particle diameter (3), higher plasma uric acid concentrations (4), enhanced renal sodium retention and decreased urinary uric acid clearance (4–6), higher resting heart rate (7), dysfibrinolysis (8), and polycystic ovary syndrome (9). Thus, in a little more than a decade, the importance of insulin resistance has evolved as a health-related issue that far transcends the initial descriptions from almost 30 years ago of its role in the pathogenesis of type 2 diabetes (10,11).

In parallel with the awareness of the importance of insulin resistance in a variety of clinical syndromes, there have been increased efforts to define the pathophysiological role of insulin resistance. To avoid the need to directly quantify insulin-mediated glucose disposal, many studies have been and continue to be performed with insulin concentration serving as a surrogate measure of insulin resistance. This approach has almost universally been used in large population-based epidemiological studies in which direct measures of insulin action have been deemed impractical. In most instances in which insulin action is not experimentally determined, fasting plasma and/or postglucose load plasma insulin concentrations have been used as the surrogate measure of insulin resistance. More recently, efforts have been made to use both the fasting plasma glucose and insulin concentration to arrive



	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
SSPG (mg/dl)	47±1	65±1	82±1	100±1	126±1	150±1	180±1	211±2	250±1	295±3
SSPI (μU/ml)	46±2	46±2	51±2	48±2	51±2	52±2	56±3	54±3	55±4	54±3
F Insulin (μU/ml)	7±0.4	7±1	9±1	10±1	10±1	10±1	12±1	13±1	18±1	22±1

Figure 1—*SSPG concentrations of the 490 volunteers divided into deciles. The mean (± SEM) SSPG, SSPI, and fasting (F) insulin concentration of each decile are shown below each bar.*

at a more precise estimate of insulin-mediated glucose disposal, and several such indices have been proposed (12–14). Obviously, the utility of the surrogate estimates of insulin action depends on the degree to which they correlate with direct measures of this variable. To the best of our knowledge, results of five such studies have been published, based on comparison of 22, 55, 50, 62, 78, and 15 nondiabetic volunteers, respectively (12,13,15–18). Given the importance of this issue, we have recently defined the degree of correlation between a quantitative assessment of insulin resistance and various surrogate estimates in 490 nondiabetic individuals.

RESEARCH DESIGN AND METHODS

The study population of 490 subjects, which includes 230 men and 260 women, was selected from our database of individuals who have participated in various research studies over the past 7 years. To be included in the study, subjects must have had a normal medical history, a physical examination, and routine clinical laboratory tests, completed a 75-g oral glucose tolerance test (OGTT) and an insulin suppression test, and been determined to be nondiabetic by the criteria of both the American Diabetes Association (19) and the World Health Organization (20). The participants had a mean (± SD) age of 48 ± 13 years (range 19–79) and BMI of 26.3 ± 4.4 kg/m^2 (18.0–42.2). The majority of the volunteers were Caucasian (77%) with smaller percentages of individuals of Asian (12%), Hispanic (10%), and African (1%) ancestries. The OGTT was normal in 86% of the population with 14% classified (19) as having impaired glucose tolerance (IGT).

All subjects were tested at the Stanford General Clinical Research Center. Fasting plasma glucose (21) and insulin (22) concentrations were measured before and 30, 60, 120, and 180 min after the ingestion of a 75-g oral glucose challenge. The total integrated insulin response was quantified by calculating the insulin area under the curve by use of the trapezoidal method. The analytical methods used for determining plasma glucose and insulin concentrations were identical over the duration of the study.

On a separate admission, insulin-mediated glucose disposal was estimated by a modification (23) of the insulin suppression test as introduced and validated by our research group (10,25). After an overnight fast, an intravenous catheter was placed in each of the patients' arms. One arm was used for the administration of a 180-min infusion of somatostatin (250 μg/h), insulin (25 mU · m^{-2} · min^{-1}), and glucose (240 mg · m^{-2} · min^{-1}), and the other arm was used for collecting blood samples. Blood was sampled every 30 min initially and then at 10-min intervals from 150 to 180-min of the infusion to determine the steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations for each individual. Because SSPI concentrations are similar for all subjects, the SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; the higher the SSPG, the more insulin resistant the individual.

All calculations of fasting insulin and glucose were performed with values obtained on the day of the OGTT. Different units are used in the calculations to match the units used by the group that proposed the surrogate measure. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the formula, as described by Matthews et al. (12): (fasting insulin [μU/ml] × fasting glucose [mmol/l])/22.5.

All data are expressed as means ± SEM or means ± SD, and all analyses were performed using the Systat 7.0.1 package for Windows (SPSS, Chicago). All of the surrogate measures of insulin resistance were correlated to SSPG initially and then fasting insulin, insulin at 120 min in the OGTT, insulin area under the curve during the OGTT, the ratio of fasting glucose to fasting insulin concentration and HOMA-IR were log-transformed to improve skewness and kurtosis for another calculation of correlation. SSPG had a normal distribution. Spearman's rank correlation coefficients were also calculated on the unadjusted data.

RESULTS

Although all 490 subjects were nondiabetic, their values for SSPG varied widely. Figure 1 shows the distribution of SSPG concentrations across the study population divided into deciles. In addition, mean (± SEM) values for SSPG, SSPI, and fasting insulin concentrations of each decile are given below each SSPG bar. It can be seen that the mean SSPG of the upper 10% of this nondiabetic population was more than sixfold the value of the 10% with the lowest SSPG concentrations. The SSPI concentrations were similar in each decile, indicating that the dramatic variation in SSPG concentration was independent of differences in SSPI concentration. The fasting plasma insulin concentrations increased progressively in parallel with the SSPG concentrations, but, in contrast to the sixfold variation in SSPG concentration, they increased only threefold. It should also be noted that 35 of the 69 individuals with IGT were in the upper two SSPG deciles.

Values of various surrogate measures of insulin resistance for the 490 participants are shown in Table 1. Several variations of a formula that involves multiplying the fasting insulin by the fasting glucose concentrations have been suggested as a useful surrogate measure (12,13), but because correlations did not change with these variations, we chose to present only the most

Table 1—*Values of surrogate measures of insulin resistance in 490 individuals*

Fasting insulin (μU/ml)	12 ± 0.3 (1–58)
Insulin at 120 min of OGTT (μU/ml)	66 ± 3 (3–533)
Insulin area under the curve ($\mu U \cdot ml^{-1} \cdot 180\ min^{-1}$)	178 ± 6 (20–1,227)
Fasting glucose/fasting insulin ($mg/10^{-4}$ U)	10.7 ± 0.34 (1.8–85.0)
HOMA-IR ($\mu U \cdot mol^{-1} \cdot l^{-3}$)	2.7 ± 0.1 (0.2–14.6)

Data are means ± SEM (range).

commonly used measure, HOMA-IR (12).

The correlation coefficients and confidence limits between SSPG concentration and the various surrogate measures of insulin resistance are shown in Table 2. These results demonstrated that simple Pearson's correlation coefficients between SSPG and all five of the surrogate measures of insulin resistance were statistically significant ($P < 0.001$). The integrated insulin response during the OGTT was most closely correlated with SSPG concentration, accounting for 45% of the variability of SSPG. At the other extreme, the ratio of fasting glucose to fasting insulin accounted for only 17% of the variability in SSPG.

When the glucose and insulin values were logarithmically transformed, the level of the correlation with SSPG increased somewhat and reached the highest level when Spearman's rank correlation coefficients were calculated. When this was done, the insulin response during the OGTT accounted for 62% of the variability in SSPG with the ratio of fasting glucose to insulin predicting only 30% of the variability in SSPG.

CONCLUSIONS — In 1973, we published the first article defining the relationship between a specific method for measuring insulin resistance and insulin concentration (15). The study was performed in 50 individuals with normal fasting glucose concentrations (<110 mg/dl) by using the insulin suppression test to quantify insulin resistance. The results demonstrated a highly significant correlation ($r = 0.69$, $P < 0.001$) between SSPG and fasting insulin concentration. We next addressed this question in 1984 (16), and on this occasion demonstrated that insulin resistance (as measured with the euglycemic-hyperinsulinemic clamp) and the integrated insulin response during an OGTT were highly correlated ($r = 0.61$, $P < 0.001$) in 62 subjects with normal oral glucose tolerance. The fact that the results of these two earlier studies were so comparable, despite the use of two different methods for assessing insulin resistance, was not surprising, given the evidence (24) that the two methods themselves are highly correlated ($r > 0.9$).

Based on the results of these two studies, we concluded that measures of plasma insulin can account for no more than 50% of the total variance in insulin action seen in nondiabetic subjects. As such, we suggested that determination of plasma insulin concentration can only provide a qualitative estimate of insulin resistance. The results of the present study of 490 subjects provide overwhelming support for our earlier conclusions. This is particularly true if fasting insulin concentrations are to be used as surrogate measures of insulin action. The situation is somewhat better when plasma insulin concentrations in response to an oral glucose challenge are used as a surrogate measure of insulin resistance. However, even in this instance, the insulin response accounts only for ~50% of the variability in insulin action. It should also be noted that the only other publication reporting results of a similar study in which a substantial number of nondiabetic subjects ($n = 78$) were studied resulted in very similar relationships (17).

Efforts to use both fasting glucose and insulin concentrations to create indices that would improve the relationship to specific measures of insulin resistance did not seem to be particularly useful. Specifically, the data in Table 2 suggest that neither HOMA-IR nor the ratio of fasting glucose-to-insulin concentration resulted in a greater correlation with the specific measure of insulin resistance in the 490 volunteers we studied than did the simple measurement of insulin concentration. This result was somewhat surprising, until we discovered that the correlation between fasting plasma insulin concentration and HOMA-IR was almost equal ($r = 0.98$) with almost no scatter. The relatively poor correlation between these two indices and insulin resistance observed in our study is somewhat disparate from the published results achieved through these methods. Thus, Matthews et al. (12) reported that estimates of insulin resistance using HOMA were highly correlated with results of either the euglycemic ($r = 0.83$) or hyperglycemic ($r = 0.55$) clamp technique. On the other hand, these comparisons were made in only 12 and 10 nondiabetic subjects, respectively. Furthermore, those data were normalized to take into account differences in body weight. In light of the above, we think it is reasonable to conclude that our results in 490 subjects are likely to be more representative of the nature of the relationship among HOMA estimates of insulin resistance, using values for fasting glucose and insulin concentrations, and specific estimates of insulin action.

Our data were also somewhat disparate from those of Legro et al. (13), who defined the relationship between the ratio of fasting glucose to insulin concentrations to values of insulin resistance using the frequently sampled intravenous glucose tolerance test (FSIGT) in 55 women, 40 of whom had polycystic ovary syndrome. They described a correlation coefficient ($r = 0.73$) between the glucose-to-insulin ratio and the estimate of insulin sensitivity with the FSIGT (S_I). This degree of relationship between the surrogate and specific measures of

Table 2—*Correlation of SSPG to surrogate measures of insulin resistance*

	Pearson's correlation (*r*)	Pearson's correlation log transformation (*r*)	Spearman's correlation (rho)
Fasting insulin	0.61 (0.55 to 0.66)	0.61 (0.56 to 0.66)	0.61 (0.56 to 0.67)
Insulin at 120 min of OGTT	0.62 (0.53 to 0.70)	0.71 (0.66 to 0.75)	0.73 (0.68 to 0.77)
Insulin area under the curve	0.67 (0.57 to 0.75)	0.77 (0.73 to 0.80)	0.79 (0.75 to 0.81)
Fasting glucose/ fasting insulin	−0.42 (−0.48 to −0.36)	−0.56 (−0.61 to −0.50)	−0.55 (−0.61 to −0.48)
HOMA-IR	0.62 (0.56 to 0.67)	0.64 (0.58 to 0.68)	0.64 (0.58 to 0.69)

Confidence intervals are given in parentheses. All correlations were statistically significant ($P < 0.001$).

insulin resistance is obviously closer than the one we observed (Table 2). However, the results of Legro et al. (13) are based on a study of only 40 women, all of whom have a syndrome associated with insulin resistance. Indeed, the mean S_I of the 40 women was 1.81×10^{-4} min · μU · ml^{-1}. Furthermore, 5 of the 40 women in the study group had an S_I value $>3.0 \times 10^{-4}$ min · μU^{-1} · ml^{-1}, and the values in these women seem to have a disproportionate impact on the relationship between S_I and the ratio of fasting glucose-to-fasting insulin.

Although not the central point of this article, the data shown in Fig. 1 are worthy of comment concerning the relationship between degree of insulin resistance and glucose tolerance status. As indicated previously, 69 individuals (14% of the total study population) had IGT, and 60 of those patients with this diagnosis (87%) were in the last four SSPG deciles. These results further emphasize earlier observations that the vast majority of individuals with IGT are insulin resistant (26). However, it should also be noted that 70% of individuals in the last four SSPG deciles were still normal glucose tolerant. Thus, although the majority of patients with IGT are insulin resistant, insulin resistance is also quite common; in those with normal glucose tolerance, this finding is also consistent with results of earlier studies (1,27,28).

The results of this study, as obtained in 490 nondiabetic volunteers by using two different techniques, have validated our previous findings as to the relationship between specific estimates of insulin resistance and plasma insulin concentrations. Both of the infusion techniques used previously provide estimates of glucose disposal by muscle. The clamp technique provides a measure of the amount of glucose disposed in the basal state plus the amount disposed because of the hyperinsulinemia. The insulin suppression test provides an estimate of both insulin- and glucose-mediated glucose disposal. Although the two techniques differ somewhat as described above, their measures of insulin-mediated glucose disposal they provide are almost identical ($r > 0.9$) (24). Furthermore, it should be emphasized that it was not the goal of our earlier studies (15,16) or of this one to evaluate the effect of lifestyle variables (i.e., degree of obesity, level of physical activity, etc.) on degree of insulin resistance. Rather, the purpose of this communication was to provide only a quantitative estimate of the degree to which the simple measures of insulin action used in epidemiological studies to evaluate insulin resistance reflect the physiological variable in question. With this goal in mind, we can conclude that the total insulin response during an OGTT provides the best surrogate measure of insulin resistance. Simply measuring the fasting insulin concentrations provides an estimate that accounts for approximately one-third of the variance in insulin action in 490 nondiabetic volunteers. Finally, the use of the fasting glucose and insulin concentrations to calculate indices of insulin resistance appear to offer little advantage over the fasting insulin concentration itself as a surrogate marker of insulin resistance. On the other hand, 77% of our population was of European ancestry, and the conclusions we have drawn may not apply to other ethnic groups.

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