Correlation of Oral Glucose Tolerance Test–Derived Estimates of Insulin Sensitivity With Insulin Clamp Measurements in an African-American Cohort

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The purpose of this study was to determine which measures obtained from an oral glucose tolerance test (OGTT) are the best estimates of insulin sensitivity measured directly using the euglycemic hyperinsulinemic clamp procedure. Data were examined from a study conducted on 307 young adult African-American men and women. An OGTT with insulin measurements was conducted after a 12-hour overnight fast. The euglycemic hyperinsulinemic clamp was used to measure insulin-stimulated glucose uptake (M) directly. Pearson's correlation analyses were performed to examine the relationship of OGTT-derived parameters with insulin sensitivity measured using the clamp. There were consistent statistically significant correlations between calculated estimates of insulin sensitivity (fasting insulin/fasting glucose, summed insulin/summed glucose, homeostasis model assessment [HOMA], Quantitative Insulin Sensitivity Check Index [QUICKI]) with insulin sensitivity measured by the insulin clamp ($P < .001$). The calculated estimates that correlated most strongly with clamp measured insulin sensitivity were QUICKI and the logarithm of summed insulin during the OGTT. These data indicate that fasting and OGTT-derived plasma insulin and glucose concentrations can be used to estimate insulin sensitivity in young adult African-Americans when it is not feasible to conduct the insulin clamp procedure. Calculated indices that include log transformation of plasma insulin concentration improve the estimation of insulin sensitivity.

INSULIN RESISTANCE, or impaired insulin sensitivity, is defined as a suboptimal response to insulin-mediated glucose uptake in tissue.[1] Consequently, greater amounts of insulin are required to achieve glucose control, resulting in relative hyperinsulinemia. Insulin resistance is an established predictor of subsequent type 2 diabetes.[2,3] Insulin resistance, even in individuals without diabetes, is associated with increased risk for cardiovascular disease.[4]

Clinical investigations on insulin resistance in young adult African-Americans demonstrate a significant correlation of insulin resistance with higher blood pressure (BP) and an atherogenic lipid pattern.[5,6] African-Americans are also at greater risk for type 2 diabetes.[7] We previously described a decrease in insulin sensitivity that concurred with deterioration in glucose tolerance in young adult African-Americans. In that study, which excluded subjects with clinical diabetes, 26% of the sample had impaired glucose tolerance or occult diabetes.[8] Therefore, measures of insulin sensitivity can be highly informative regarding health status and risk for cardiovascular disease, particularly in high-risk minority populations such as African-Americans.[9]

Insulin sensitivity is measured directly using the euglycemic hyperinsulinemic clamp procedure. In this procedure, tissue sensitivity to insulin action on glucose uptake is assessed by creating steady-state hyperinsulinemia with an insulin infusion.[10] A simultaneous glucose infusion is used to quantitate the amount of glucose required to maintain euglycemia. The rate of glucose uptake (glucose infusion rate) is then a measure of insulin sensitivity, having the standard notation of M. Higher glucose infusion rates are indicative of greater insulin sensitivity, and lower glucose infusion rates are indicative of lower insulin sensitivity or insulin resistance. The insulin clamp technique is regarded as the reference standard because it directly measures metabolic actions of insulin under steady-state conditions.[11] The procedure requires simultaneous infusions of insulin and glucose over 2 to 4 hours and multiple blood samples for analysis of glucose and insulin. Therefore, the complexity of the insulin clamp procedure limits its application in large epidemiologic investigations. Efforts to derive simpler, surrogate estimates of insulin sensitivity have examined fasting insulin, the fasting glucose to insulin ratio, the homeostasis model assessment (HOMA), and the logarithmic transformation of the homeostasis model assessment (logHOMA). Among these, the HOMA, developed from mathematical modeling of the normal physiologic balance between insulin and glucose,[12] has been used frequently in epidemiologic studies.[13] The purpose of this study was to determine which measure or combination of measures of plasma glucose and insulin concentration obtained during an oral glucose tolerance test (OGTT) are the strongest correlates of insulin sensitivity measured directly using the hyperinsulinemic euglycemic clamp procedure. Data for this study were obtained from a sample of young adult African-Americans, representative of a population at greater risk for development of type 2 diabetes and cardiovascular disease.[7]

MATERIALS AND METHODS

Experimental Subjects

Data for this analysis were obtained from a cohort of young adult African-American men and women enrolled in investigations of BP, insulin sensitivity, and cardiovascular risk. The total cohort size is approximately 500 subjects, all volunteers. Data on 307 cases that included both insulin clamp and OGTT values were analyzed. For this study, cases with known diabetes were excluded. We also excluded women who were pregnant, lactating, or 6 months postpartum. Written informed consent was obtained from each participant at the time of

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enrollment on an institutionally approved protocol and consent form. Female participants were evaluated during the follicular phase of the menstrual cycle to reduce hormone-induced variability.

Experimental Protocol

Information on health status and current health behaviors was obtained by interview. Anthropometric measurements of height, weight, and skinfold thickness were obtained. Body mass index (BMI) was calculated as weight (kilogram) divided by height squared (m^2). An OGTT was conducted after a 12-hour overnight fast. A fasting blood sample for serum insulin and glucose was obtained, and then 75 g glucose solution (Glucola; Ames Diagnostics, Elkhart, IN) was ingested. Blood samples were obtained at 30, 60, and 120 minutes after ingestion and were assayed for glucose and insulin concentrations. Glucose tolerance was defined according to the criteria of the American Diabetes Association (ADA).[14] Subjects were classified according to the results of the OGTT as normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetic (DM).[14]

The euglycemic hyperinsulinemic clamp was used to measure insulin-stimulated glucose uptake.[10,15] Approximately 2 to 4 weeks after the OGTT, each subject returned to the clinical research unit following a 12-hour overnight fast, at which time the euglycemic clamp procedure was conducted according to methods described previously.[16] In brief, venous catheters were placed for infusion and sample withdrawal. After determination of fasting plasma glucose concentration, hyperinsulinemia was established with a primed constant infusion of insulin using the method of Rizza et al[15] to compute the priming dose and infusion rate (1 mU/kg-min). This insulin infusion rate achieved steady-state hyperinsulinemia of 80 to 120 μU/mL above fasting, a level that suppresses hepatic glucose production. Clamp studies using radioactive tracer to demonstrate suppression of endogenous glucose production have previously been performed on the cohort.[17] Insulin (Eli Lilly, Indianapolis, IN) was administered as 1,000 mU/mL in normal saline. Hyperinsulinemia was maintained for 120 minutes, during which time the euglycemia was achieved using a variable infusion of 20% dextrose in water (Abbott Labs, Abbott Park, IL). Euglycemia was defined as the fasting glucose level in each subject. For any subject with a fasting glucose concentration above 100 mg/dL, the euglycemia target during the procedure was set at 100 mg/dL. The glucose infusion rate was adjusted using the negative feedback equation of DeFronzo et al,[10] according to plasma glucose sampled every 10 minutes. The coefficient of variation for the plasma glucose concentration during the final 60 minutes of the procedure was 2.44%. The coefficient of variation for the steady-state plasma insulin concentration was 4.20%. Insulin-stimulated glucose uptake (M) was computed as the mean glucose infusion rate during the final 60 minutes of the procedure and was expressed as milligrams per kilogram per minute. Because the level of steady-state hyperinsulinemia achieved during the clamp procedure varied somewhat among the cases, an index of insulin sensitivity (M/I_c) was computed by dividing the glucose infusion rate (M) by the mean insulin level (I_c) achieved during the final 60 minutes of steady-state hyperinsulinemia. Muscle tissue is more insulin sensitive relative to adipose tissue. For this reason, we then adjusted the measured insulin-mediated glucose uptake for adiposity. Anthropometric measurements were used to estimate fat-free mass,[18,19] and the insulin-stimulated glucose uptake was computed in milligrams per kilogram of fat-free mass per minute (M'). The index of insulin sensitivity was also adjusted for adiposity and expressed as M'/I_c.

Plasma glucose concentration was analyzed with the glucose oxidase technique (YS Model 27; Glucostat, Yellow Springs, OH). Plasma insulin concentration was determined with a solid phase radioimmunoassay (Coat-a-Count; Diagnostic Products, Los Angeles, CA). The coefficients of variation for the glucose and insulin assays were 0.57% and 4.5%, respectively.

Data Analysis

Data analysis was conducted to determine the relationship of measurements from the OGTT with measurements of insulin sensitivity derived from the clamp. Pearson's correlation analyses were performed on each of the OGTT measures of glucose and insulin against each of the insulin clamp variables. Other estimates of insulin resistance calculated from the OGTT were also analyzed. These included the ratio of insulin to glucose (I/G) at fasting and each time point of the OGTT, the area under the curve (AUC) of glucose measurements, AUC of insulin measurements, numerical sum of glucose measures at time 0, 30, 60, and 120, and numerical sum of insulin measures at time 0, 30, 60, and 120. The AUC was calculated using the trapezoidal rule, which is the formula $0.5 \cdot \text{time } 0 + \text{time } 30 + 1.5 \cdot \text{time } 60 + \text{time } 120$. Therefore, the difference between the numerical sum and the AUC is equivalent to changes in weights for time 0 and time 60. Because plasma insulin values are not normally distributed, the logarithmic values for plasma insulin were computed. Additionally, the percent change in glucose was calculated using the formula: (glucose at 120' − fasting glucose)/fasting glucose.

We also calculated the HOMA[12] and Quantitative Insulin Sensitivity Check Index (QUICKI)[20] from the values of fasting insulin and glucose obtained at the start of the 2-hour OGTT (HOMA-1 and QUICKI-1) and again from the fasting samples obtained prior to performing the insulin clamp (HOMA-2 and QUICKI-2). HOMA was calculated according to the method of Matthews et al[12] from the equation: HOMA = [fasting glucose (mmol/L) × fasting insulin (μU/mL)]/22.5. To convert glucose in mg/dL to mmol/L, the value of glucose in mg/dL was multiplied by a factor of 0.05551 before insertion into the HOMA equation. The QUICKI was calculated based upon the method of Katz et al[20] using the equation: QUICKI = 1/[log fasting glucose (mg/dL) + log fasting insulin (μU/mL): in measured units without SI conversion]. Therefore the QUICKI is the reciprocal of log of insulin × glucose. While higher HOMA values correspond to decreased insulin sensitivity, higher QUICKI values correspond to increased insulin sensitivity.

Comparisons between the results of the clamp procedure and each of the estimates of insulin resistance were performed on the 307 subjects with complete data from both the OGTT and clamp by using the Pearson correlation coefficient (r). To compare the correlation coefficients of the different calculated indices of insulin sensitivity with each of the 4 parameters of insulin sensitivity measured directly by the insulin clamp (M, M', M/I_c, and M'/I_c), we ran the jackknife version of the bootstrap method for testing the equality of correlation coefficients, which was performed as follows.[21] We randomly selected 50% of the N = 307 cases and calculated the absolute value of the Pearson r ($|r|$) for each index versus each measure of insulin sensitivity. We then repeated this sampling procedure 100 times. We computed the mean $|r|$ among indices and compared mean $|r|$ among indices using a 1-way analysis of variance.

RESULTS

Complete metabolic data were analyzed on 108 men and 199 women. Age at time of examination ranged from 20 to 43 years (mean, 32 years). A description of the study sample is provided in Table 1. Mean BMI values were 27.8 ± 6.0 for men and 31.9 ± 8.7 for women. The study sample included 31 obese men and 106 obese women defined by BMI greater than 30 kg/m^2, corresponding with obesity in 28.7% of men and 53.3% of women. Overall, the study subjects were representative of young adult African-Americans nationally. Using the ADA-defined criteria for type 2 diabetes mellitus (DM) and prediabetes,[9] the OGTT identified 19 subjects with previously undetected DM and 62 subjects with previously undetected

Table 1. Characteristics of Study Sample

Demographic	
N	307
35.2% males, 64.8% females	
Age (yr)	32.0 ± 4.1
BMI (kg/m^2)	30.4 ± 8.1
Obese (%)	44.6
Undiagnosed IGT (%)	20.2
Undiagnosed diabetes (%)	6.2

NOTE. Values shown are mean ± SD.
Abbreviations: IGT, impaired glucose tolerance.

prediabetes. Overall, 26.3% of the subjects in our study sample were found to have abnormal glucose tolerance.

Table 2 provides the data on insulin sensitivity parameters. Mean values for insulin sensitivity measured directly by insulin clamp (M) are provided along with estimated insulin sensitivity parameters calculated from the OGTT.

Table 3 provides the correlation coefficients of calculated estimates of insulin sensitivity from the OGTT with insulin clamp measures of insulin sensitivity. Among the 13 indices listed in Table 3 compared with M (the first parameter of insulin sensitivity measured by the clamp), we found that the strongest correlate was the logarithm of summed insulin during the OGTT ($r = -0.62$, $P < .001$). Using the jackknife method to compare $|r|$ among the 13 indices versus M, we found that the logarithm of the sum of insulin during the OGTT was significantly better than any of the others ($P < .001$). In Table 3, all indices are ranked in order of the jackknife results versus M. The jackknife rankings for M are in the same order as the raw correlation coefficients. Using this method to compare $|r|$ among the 13 indices versus M' (the second parameter of insulin sensitivity measured by the clamp), we again found that the logarithm of summed insulin during the OGTT was significantly higher than any of the others ($P < .001$).

Using the jackknife method to compare $|r|$ among the 13 indices versus M/I_c, we found that $|r|$ was significantly higher for the logarithm of summed insulin during the OGTT than for any of the other indices ($P < .001$) except for QUICKI-2 ($P = .74$ is the significance value for the difference in r between M/I_c versus QUICKI-2 and M/I_c versus logarithm of summed insulin). Using this method to compare $|r|$ among the 13 indices versus M'/I_c, we found that QUICKI-2 was significantly higher than any of the others ($P < .001$). The logarithm of summed insulin during the OGTT was the second best measure. Figure 1A demonstrates the relationship of log summed insulin with clamp measured insulin sensitivity, and Fig 1B shows the relationship of QUICKI with the clamp for all subjects.

Overall, there are statistically significant correlations between all the estimates of insulin sensitivity and insulin sensitivity measured by the insulin clamp (all $P < .001$). Notable is the higher correlation coefficients obtained by log transformation of insulin, analogous to the log transformation of insulin found in the QUICKI formula. These correlation coefficients are greater than the correlation obtained with HOMA. All parameters derived from the fasting sample result in stronger correlation coefficients with insulin clamp measures when the insulin values are log transformed. The strongest correlate of OGTT measurements with insulin sensitivity measured by insulin clamp is the log of summed insulin.

Table 4 shows the correlation coefficients of calculated estimates of insulin sensitivity from the OGTT with insulin clamp

Table 2. Insulin Sensitivity: Measured and Calculated Indices in Young Adult African-Americans

Insulin sensitivity measured by insulin clamp	
M (mg/kg/min)	5.5 ± 2.8
M′ (mg/kg FFM/min)	7.7 ± 3.6
M/I_c	7.5 ± 5.5
M'/I_c	10.7 ± 7.8
Insulin sensitivity indices calculated from OGTT-derived values	
Fasting glucose (mg/dL)	95.6 ± 18.2
Summed glucose (mg/dL)	532.4 ± 117.9
Fasting insulin (mU/mL)	13.3 ± 11.1
Summed insulin (mU/mL)	358.2 ± 231.8
Fasting insulin/fasting glucose	0.13 ± 0.10
Summed insulin/summed glucose	0.58 ± 0.35
HOMA-1	3.36 ± 3.93
HOMA-2	2.84 ± 2.50
QUICKI-1	0.15 ± 0.018
QUICKI-2	0.15 ± 0.016
Change in glucose (%)	29.6% ± 33.1
Log fasting insulin	2.32 ± 0.72
Log summed insulin	5.54 ± 0.65

NOTE. Values shown are mean ± SD of the calculated indices. HOMA-1 AND QUICKI-1 are calculated from the fasting glucose and insulin values obtained from the OGTT; HOMA-2 AND QUICKI-2 are calculated from the fasting glucose and insulin values obtained from the clamp. To convert mg/dL to mmol/L (of glucose), multiply by 0.055 or divide by 18. To convert μIU/mL to pmol/L (of insulin), multiply by 6.945 or divide by 0.144.

Table 3. Correlation Coefficients of Insulin Sensitivity Indices Derived From the OGTT With Insulin Sensitivity Measured by Insulin Clamp

Clamp Insulin Sensitivity Measure	M	M′	M/I_c	M'/I_c
Log summed insulin	−0.623	−0.577 (1)	−0.659	−0.576 (2)
Summed insulin	−0.546	−0.516 (2)	−0.567	−0.512 (5)
Log fasting insulin	−0.538	−0.494 (3)	−0.613	−0.557 (3)
QUICKI-1	0.533	0.481 (5)	0.634	0.566 (4)
QUICKI-2	0.527	0.490 (4)	0.651	0.628 (1)
Summed insulin/ summed glucose	−0.487	−0.445 (6)	−0.519	−0.450 (6)
Fasting insulin/ fasting glucose	−0.44	−0.420 (8)	−0.46	−0.44 (8)
Summed glucose	−0.405	−0.424 (7)	−0.378	−0.377 (10)
Glucose change (%)	−0.401	−0.374 (9)	−0.315	−0.268 (12)
Fasting insulin	−0.380	−0.366 (10)	−0.436	−0.413 (9)
HOMA-2	−0.345	−0.338 (11)	−0.443	−0.443 (7)
HOMA-1	−0.272	−0.264 (12)	−0.356	−0.338 (11)
Fasting glucose	−0.194	−0.189 (13)	−0.270	−0.251 (13)

NOTE. $P < .001$ for all raw r values. Number in parentheses under r value denotes the ranking for M′ and M'/I_c. HOMA-1 AND QUICKI-1 are calculated from the fasting glucose and insulin values obtained from the OGTT; HOMA-2 AND QUICKI-2 are calculated from the fasting glucose and insulin values obtained from the clamp.

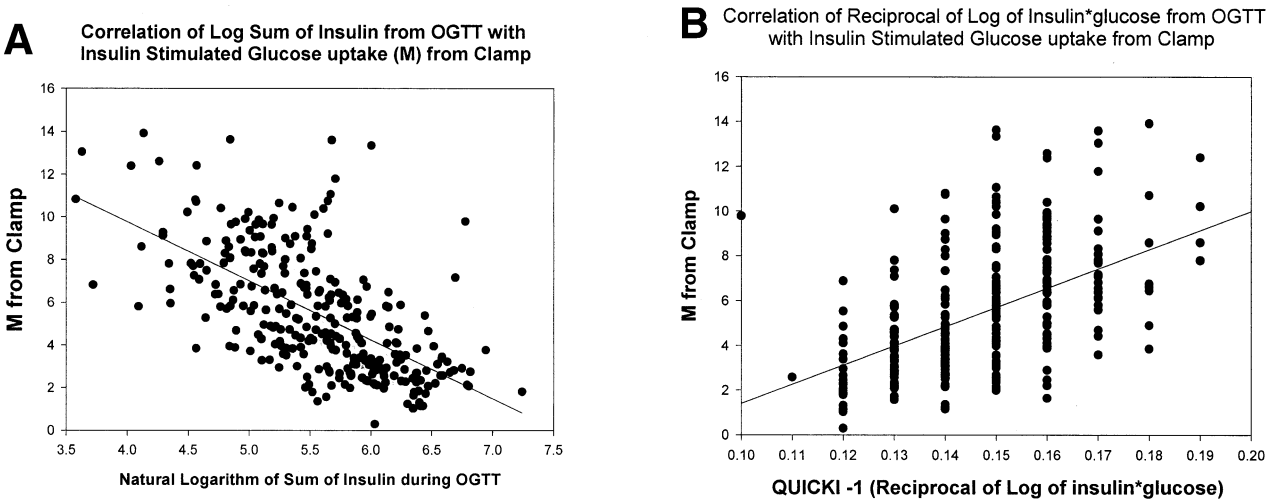

Fig 1. (A) Correlation of log summed insulin with clamp-measured insulin sensitivity (M from clamp) for all subjects: $r = -0.623$. (B) Correlation of QUICKI with clamp-measured insulin sensitivity (M from clamp) for all subjects: $r = 0.533$.

measures of insulin sensitivity analyzed by glucose tolerance status (normal or impaired/diabetic). QUICKI and log of summed insulin consistently provide the highest correlation coefficients for both normoglycemic and glucose-intolerant individuals. Of note is the substantial decrease in the correlation coefficient for HOMA with insulin sensitivity that occurs with deterioration in glucose tolerance.

The effect of logarithmic transformation on the distribution of plasma insulin in the study sample is presented in Fig 2. Figure 2A provides the distribution of cases according to the measured fasting insulin and demonstrates a skewed distribution of fasting plasma insulin with a long tail in the upper range of values. Figure 2B provides the distribution following logarithmic transformation of the fasting plasma insulin concentrations, which normalizes the distribution of insulin values. From plasma insulin concentrations obtained during an OGTT, logarithmic transformation of the fasting plasma insulin concentration or sum of all insulin values from an OGTT results in the strongest correlations with direct measurement of insulin sensitivity by the insulin clamp procedure.

Table 4. Correlation Coefficients of Insulin Sensitivity Indices Derived From the OGTT With Insulin Sensitivity Measured by Insulin Clamp in NGT and IGT/DM

Clamp Insulin Sensitivity Measure	NGT (n = 209)		IGT/DM (n = 72)	
	M	M'/I_c	M	M'/I_c
Fasting insulin	−0.430†	−0.417†	−0.140	−0.362*
Summed insulin	−0.522†	−0.466†	−0.454†	−0.542†
HOMA-1	−0.423†	−0.412†	−0.0055	−0.288
HOMA-2	−0.400†	−0.457†	−0.152	−0.436†
QUICKI-1	0.480†	0.531†	0.409†	0.503†
QUICKI-2	0.469†	0.580†	0.497†	0.681†
Log fasting insulin	−0.504†	−0.531†	−0.384†	−0.476†
Log summed insulin	−0.593†	−0.530†	−0.569†	−0.611†

Abbreviations: NGT, normoglycemic individuals; IGT/DM, individuals with abnormal glucose tolerance.

*$P < .01$.

†$P < .001$.

DISCUSSION

Analysis of metabolic data in this study demonstrates a consistent relationship of oral glucose tolerance with insulin sensitivity measured by the hyperinsulinemic clamp in a young adult African-American cohort. The strongest correlates that can be obtained from a fasting sample are the log of fasting insulin or the QUICKI. The log of summed insulin from a complete OGTT provides a somewhat better estimate of insulin sensitivity measured by insulin clamp.

Our study appears to be the largest, to date, examining the relationship of OGTT-derived estimates of insulin sensitivity with insulin sensitivity measured by the euglycemic hyperinsulinemic clamp technique in African-Americans. A previous study of 457 subjects was conducted by Hanson et al[22] in the unique ethnic subgroup of Pima Indians. They found that in this population fasting serum insulin concentration and the insulin sensitivity index ($10^4/[I_0 \times G_0]$) had a correlation of approximately 0.60 with clamp-derived insulin sensitivity measures. Although they tested different OGTT-derived estimates of insulin sensitivity than we did, using subjects of different ethnicity, their correlation between OGTT and clamp-derived measures of insulin sensitivity was similar to ours.

In another study of 115 subjects, Bonora et al[23] reported a correlation of −0.82 ($P < .0001$) between HOMA and insulin clamp measures. The subjects in their study were older (19 to 67 years old) and drawn from an Italian population. The age and ethnicity differences between their study sample and ours could account for the disparity in results. However, the smaller age range in our sample should have resulted in less variability in the measurements.

Katz et al[20] studied a sample of 56 subjects and found that QUICKI correlated more strongly with clamp data than HOMA. Mather et al[13] compared insulin sensitivity estimates

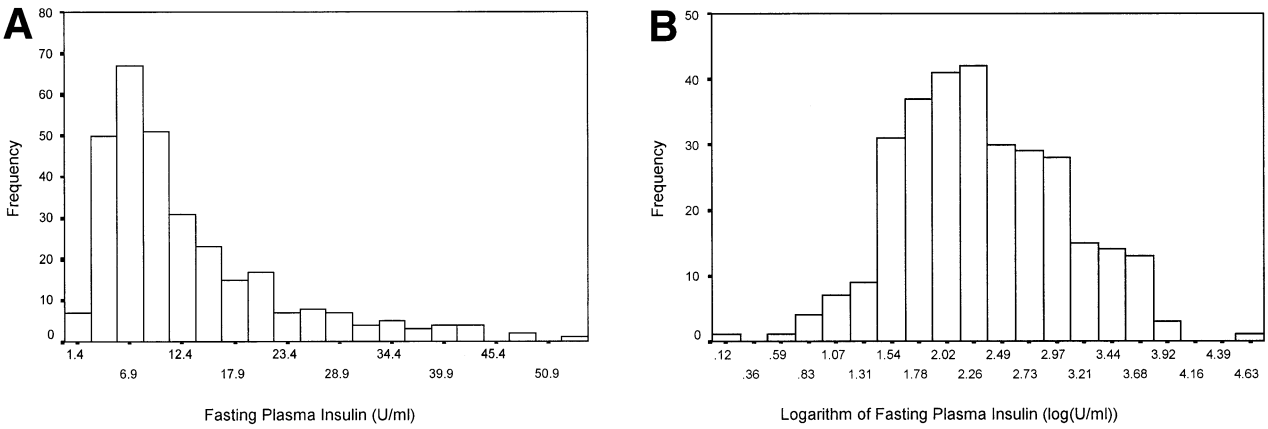

Fig 2. (A) Distribution of cases according to level of fasting plasma insulin concentration. (B) Distribution of cases according to logarithmic transformation of fasting plasma insulin concentration. Frequency = number of cases.

using fasting insulin values with insulin clamp measurements in 152 subjects. Among their correlates of insulin sensitivity, they found that logHOMA and QUICKI correlated most strongly with clamp measures and had the smallest coefficients of variation. In another study by Abbasi et al[24] on 490 obese and non-obese subjects, the correlation of various insulin sensitivity indices with steady-state plasma glucose (SSPG) derived from insulin suppression test (IST) measurements, another measure of insulin sensitivity, was examined. In that study, the correlation coefficient for the log of summed insulin (AUC) with SSPG was higher ($r = 0.77$) than HOMA ($r = 0.64$), log of fasting insulin ($r = 0.61$), or QUICKI ($r = -0.60$). These investigators did not describe using a statistical method to verify the order of the raw correlation coefficients. However, our data also demonstrate that the log of summed insulin, compared with other OGTT- derived estimates, has the highest correlation with direct measurements of insulin sensitivity. A recent study conducted by Soonthornpun et al[25] demonstrated a strong correlation (0.869) of their new index of insulin sensitivity, ISI_{OGTT} with insulin clamp measurements. Because the formula for this index requires urinary glucose measurements, which we did not collect, we were unable to include this index in our current analysis.

Because the relationship between HOMA and clamp measures of insulin sensitivity is hyperbolic, it follows that logarithmic transformation of HOMA improves the correlation and clamp measures.[26] Our data clearly demonstrate the effect of logarithmic transformation on plasma insulin concentration, with normalization of a skewed distribution. The QUICKI[20] is a reciprocal logarithmic transformation of HOMA. Data from our study demonstrate that QUICKI correlates more strongly than HOMA with clamp measures of insulin sensitivity. Subgroup analysis according to glucose tolerance status indicates that the validity of the log-transformed insulin estimates of insulin sensitivity is maintained despite deterioration in glucose tolerance.

While the BMI and percent obesity were high in our sample, they are reflective of the prevalence of obesity found in young African-Americans nationally.[27,28] To some extent, the generalizability of this study is limited in that our cohort consisted of African-Americans only. However, African-Americans are a large ethnic group at high risk for development of IGT and overt diabetes.[7]

Insulin resistance, or impaired insulin sensitivity, precedes type 2 diabetes and is also associated with increased risk for cardiovascular disease. The euglycemic hyperinsulinemic clamp procedure provides the most precise measure of insulin sensitivity (or insulin resistance). However, because the insulin clamp is a long and technical procedure, it is difficult to apply in studies with large numbers of subjects. Measures that are both feasible and reliable to estimate insulin sensitivity are needed for use in epidemiologic studies or large clinical trials. Data from this study demonstrate that the QUICKI (computed from fasting glucose and fasting insulin), or the log of summed insulin derived from a complete OGTT, provide good surrogate estimates of insulin sensitivity measured by the insulin clamp.

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