Comparative Evaluation of Simple Indices of Insulin Resistance

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Various surrogate methods for the quantification of insulin sensitivity have been proposed. A comparative evaluation is lacking and is relevant for the standardization of investigative methods and comparability of results. The aims of the study were to perform a comparative validation of fasting insulin, homeostasis model assessment (HOMA), Quantitative Insulin Sensitivity Check Index (QUICKI), and revised-QUICKI (R-QUICKI) against minimal model derived estimates of insulin sensitivity (SI_{MM}) in nondiabetic people and to carry out a comparative evaluation of the ability of these indices as means for the identification of individuals with the metabolic syndrome (MS) on a population basis. We used 2 data sets defined as "validation sample" and "prevalence sample". Validation sample: a total of 162 healthy men and women aged 30 to 65 years were studied by frequently sampled intravenous glucose tolerance test (FSIVGTT). SI_{MM} was calculated with the Minmod program. Prevalence sample: a total of 2,731 nondiabetic men and women aged 35 to 65 years were studied. In both samples, anthropometry, blood pressure, fasting glucose, insulin, triglycerides, high-density lipoprotein (HDL) cholesterol, and free fatty acid (FFA) were measured. HOMA, QUICKI, and R-QUICKI were calculated. The MS was defined according to the Adult Treatment Panel III. Validation sample: insulin, HOMA, QUICKI, and R-QUICKI significantly correlated with SI_{MM} ($r = -0,53$, -0.52, 0.41, 0.33; all $P < .001$). The finding was confirmed in obese (body mass index [BMI] $\geq$25 kg/m^2), but in the normal weight, the correlation coefficient for QUICKI was significantly smaller than for the other indices. Receiver operator characteristic (ROC) curve analysis performed with SI_{MM} below or above the lowest 25th percentile (ie, insulin resistance yes, no) as the outcome variable and each of the 4 indices as the test variable showed no significant differences in the areas under the curve. Prevalence sample: prevalence of the MS progressively increased across quartiles of insulin resistance as evaluated by any of the 4 indices, with no significant differences between them. The novel indices QUICKI and R-QUICKI do not perform better than HOMA and fasting insulin as surrogate measures of insulin resistance or means for the identification of people with MS in the general population.

INSULIN RESISTANCE plays a central role in the pathogenesis of a number of conditions, such as hyperglycemia, dyslipidemia, hypertension, and possibly, hypercoagulability and inflammation, which cluster in the metabolic syndrome (MS), a state associated with excess risk of diabetes and cardiovascular disease (CVD).[1-3] There is strong evidence that insulin resistance is substantially reduced by lifestyle modification and by drugs: these means have proved effective for the prevention of diabetes[4,5] and partially overlap with measures recommended for CVD prevention. Measuring insulin resistance in the general population may, therefore, be relevant for optimal targeting of preventive strategies.

The 2 well-established methods for the quantification of insulin sensitivity, the euglycemic-hyperinsulinemic clamp[6] and the minimal model (MM) analysis of the frequently sampled intravenous glucose tolerance test (FSIVGTT),[7] are not easily applied in large populations because of their complexity, cost, and invasiveness. Consequently, there is great interest in developing simple measures of insulin resistance suitable for clinical practice and epidemiologic purposes. Fasting insulin, validated against clamp, has proved a reasonably sensitive and specific measure of insulin resistance in nondiabetic people, especially if the log-transformed value is used[8] and has long been used as a surrogate measure of insulin resistance in population studies. Subsequently the homeostasis model assessment (HOMA) validated in various populations[9-12] has become the most widely used surrogate measure of insulin resistance in epidemiologic studies. More recently the Quantitative Insulin Sensitivity Check Index (QUICKI)[13] and its revised versions (R-QUICKI), which includes fasting plasma free fatty acids (FFA) in the calculations as a means for improving validity of QUICKI in lean people[14] and QUICKI-glycerol,[15] have been emphasized as simple and accurate measures of insulin resistance. However, the new indices have been validated in small groups with elevated insulin resistance, ie, in those studies the proportion of persons with diabetes/blood glucose abnormalities or obesity is largely exceeding that observed in the general population.[13-15] This may lead to overestimation of the validity of a diagnostic test and could be misleading in regard to its application in less selected groups.[16]

Therefore the advantage of using the newly proposed indices in comparison to the most widely used HOMA and fasting insulin is so far unclear, whereas it would be important to standardize the investigation methods to make results comparable.

The aims of this study were to perform a comparative validation of fasting insulin, HOMA, QUICKI, and R-QUICKI against MM-derived insulin sensitivity index in a large group of nondiabetic people fairly representative of the general population and to carry out a comparative evaluation of the ability of these indices for the identification of individuals with the MS in the general population.

MATERIALS AND METHODS

Two data sets referred to as "validation sample" and "prevalence sample" were used.

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Validation Sample

A total of 162 Caucasian nondiabetic (fasting glucose <126 mg/dL and no use of hypoglycemic drugs) men (n = 86) and women (n = 76), aged 30 to 65 years, and body mass index (BMI) 22 to 32 kg/m^2 were included. None were taking drugs known to affect insulin resistance. All participants underwent FSIVGTT according to a standard protocol.[17] Briefly, 300 mg/kg body weight of glucose was given intravenously followed by a bolus of 0.03 U/kg insulin 20 minutes after the glucose. Blood samples were collected before glucose infusion and 11 times after the glucose dose up to 180 minutes using a cannula in the controlateral arm. To arterialize venous blood, the arm was kept in a 50°C electric pad during the test. The insulin sensitivity index was calculated with the Minmod program (SI_{MM}).[18] In premenopausal women, tests were all performed during the same period of the menstrual cycle. Fasting glucose was measured at the participating centers, plasma insulin was measured centrally by enzyme-linked immunosorbent assay (ELISA); details on analytical methods and study protocol have been published elsewhere.[19] FFA were measured centrally in Naples as detailed below.

Prevalence Sample

A total of 2,731 Caucasian nondiabetic men and women, in the same age and BMI range as the validation sample (ie, age 35 to 65 years and BMI 22 to 32 kg/m^2), employees of the Italian telephone company, participating in a company sponsored health screening were examined. Informed consent was obtained from all participants; the study protocol was approved by the local ethics committee. Standard protocols were used for all measurements. Blood pressure was measured in the right arm in the supine position after a 5-minute rest; the average of 3 readings was used in the analysis. Fasting glucose, triglycerides, and high-density lipoprotein (HDL) cholesterol were measured on plasma by dry chemistry methods using an Ektakem DT-60 analyzer (Eastman Kodak, Rochester, NY). The use of dry chemistry methods for large-scale screenings has been validated by us as well as by other investigators.[20,21] Accuracy and reproducibility were monitored by daily determinations of all the above parameters on each of 2 reference sera (normal and high concentration). The accuracy was 1.2% for HDL cholesterol, 3.6% for triglycerides, and 3.0% for glucose. Reproducibility as assessed by the calculation of the between-day coefficient of variation (CV) was 6.3% for HDL cholesterol, 5.9% for triglycerides, and 3.6% for plasma glucose.[20] The MS was defined according to the Adult Treatment Panel III criteria[22] (ie, presence of 3 or more of the following: waist circumference >102 cm in men and >88 cm in women; triglycerides ≥1.695 mmol/L; HDL cholesterol <1.036 mmol/L in men and 1.295 mmol/L in women; blood pressure ≥130/85 mm Hg; fasting glucose ≥6.1 mmol/L). Radioimmunoassay with double antibody was used for plasma insulin[23]; the detection limit was less than 1 mU/L; the intra-assay and interassay CVs were 3.0% and 5.8%, respectively, at the level of 25 mU/L.

For both samples, height (m) and weight (kg) were measured in light underclothes without shoes according to a standard protocol and the BMI was calculated. Waist circumference was measured with a steel tape at the natural indentation between the 10th rib and the iliac crest at end expiration. Plasma FFA was measured on frozen samples by an enzymatic colorimetric method using a commercially available kit (WAKO NEFA C test, Wako Chemicals, Richmond, VA) with a between-day CV of 2.2%. HOMA, QUICKI, and R-QUICKI were calculated as follows: HOMA = [insulin (μU/mL) × glucose (mmol/L)/22,5];[9] QUICKI = [1/(log glucose (mg/dL) + log Insulin(μU/mL)];[13] R-QUICKI = 1/(log glucose (mg/dL) + logInsulin (μU/mL) + logFFA).[14]

Statistical Analysis

Data are given as mean and standard deviations or percentages. To reduce skewness, insulin was used as log-transformed value in all analyses. Data given in text and tables represent the original values.

In the validation sample, Pearson correlation was used to explore the strength of the association of the 4 simple indices (insulin, HOMA, QUICKI, and R-QUICKI) with SI_{MM}. Concordance of each of the indices and SI_{MM}, was tested by κ statistics. The receiver operator characteristic (ROC) curve was used to comparatively evaluate the ability of the calculated indices as means for the identification of insulin resistance as defined by SI_{MM}.

In the prevalence sample, correlation analyses were used to explore the relationship of the 4 indices with each of the variables described in the MS. The prevalence of the MS was analyzed across quartiles of insulin, HOMA, QUICKI, and R-QUICKI; the odds ratio and 95% confidence interval (CI) were calculated for those most insulin resistant versus those less insulin resistant. The ROC analysis was used to comparatively evaluate the ability of the 4 indices as means for the identification of the MS in the general population.

The statistical analysis was conducted by the SPSS package for Windows (SPSS, Chicago, IL).[24]

RESULTS

Validation Study

The study population is composed of 162 nondiabetic men (53%) and women; average age and BMI were 49 ± 8 years and 26.4 ±2.9 kg/m^2. All the calculated indices (insulin, HOMA, QUICKI, and R-QUICKI) showed a statistically significant (all $P < .001$), but relatively low order, correlation with SI_{MM} (Table 1). The correlation was stronger for HOMA ($r = 0.53$) and weaker for R-QUICKI ($r = 0.32$); analysis by gender showed a similar pattern for men and women, although coefficients were generally slightly higher for men (range, 0.63 to 0.41) than for women (range, 0.51 to 0.32). The analysis by BMI showed that unlike insulin and HOMA, which performed similarly in normal weight and overweight people, for QUICKI the correlation with SI_{MM} was much lower, and not statistically significant, in the normal weight than in the overweight group. The incorporation of FFA in the calculation and the use of R-QUICKI did improve QUICKI performance in normal weight people, but the revised index did not perform better than HOMA or fasting insulin.

We also explored the ability of the various indices as means for the identification of individuals with insulin resistance in the population. For this purpose, insulin resistance was arbitrarily defined as a SI_{MM} value in the lowest quartile of the distribution (ie, $SI_{MM} < 1.53$) and the ROC analysis was performed with insulin resistance yes/no as the outcome vari-

Table 1. Correlation Coefficients Between Simple Indices of Insulin Resistance and Insulin Sensitivity as Assessed by FSIVGTT (SI_{MM})

	All (n = 162)	Men (n = 86)	Women (n = 76)	BMI < 25 (n = 55)	BMI ≥ 25 (n = 107)
Insulin	−0.52*	−0.63*	−0.49*	−0.39*	−0.50*
HOMA	−0.53*	−0.61*	−0.51*	−0.48*	−0.49*
QUICKI	0.41*	0.46*	0.41*	0.20	0.48*
R-QUICKI	0.33*	0.41*	0.32*	0.38*	0.32*

NOTE. SI_{MM} is calculated by the minimal model.
*$P < .001$.

Table 2. ROC Analysis of the Ability of Simple Measures of Insulin Resistance as Means for the Identification of Insulin Resistance Defined According to SI_{MM} and Concordance Across Quartiles Between Each of the Indices and SI_{MM} Estimates

	ROC Analysis (area under the curve (95% CI))	Concordance Between Quartiles (kappa)
Males		
Insulin	0.87 (0.82-0.93)	0.31
HOMA	0.88 (0.82-0.94)	0.35
QUICKI	0.88 (0.82-0.94)	0.35
R-QUICKI	0.86 (0.80-0.92)	0.28
Females		
Insulin	0.75 (0.65-0.86)	0.16
HOMA	0.76 (0.65-0.86)	0.19
QUICKI	0.76 (0.65-0.86)	0.19
R-QUICKI	0.80 (0.71-0.90)	0.28

NOTE. n = 162.

able and insulin, HOMA, QUICKI, and R-QUICKI as the test variables. The areas under the curve and their 95% CI are given in Table 2 for men and women. Somewhat lower values were observed in females than in males; however for both groups, the areas under the curve for insulin, HOMA, QUICKI, and R-QUICKI showed a substantial overlapping, thus indicating that none of the simple calculated measures offers advantages over the others in the identification of people with insulin resistance as measured by SI_{MM}. Concordance between each of the indices and SI_{MM} estimates of insulin sensitivity was also explored by κ statistics across quartiles. K values were generally lower in females; however for either males and females, κ values were substantially similar for the 4 indices (Table 2).

Prevalence Study

The study population consisted of 2,731 nondiabetic men and women, employees of the telephone company participating in a health screening. Average age and BMI were comparable with that of the validation sample (age, 45 ± 6 years and BMI, 26.3 ± 3.2 kg/m^2).

Insulin, HOMA, QUICKI, and R-QUICKI were significantly correlated with each of the components of the MS (Table 3): coefficients were of low order and generally lower for blood pressure than for other variables. Some specificity was observed: insulin and HOMA showed the strongest correlation with waist circumference ($r = 0.37$ and 0.33, respectively, $P <$ .001), whereas QUICKI correlated better with plasma glucose levels ($r = -0.45$, $P < .001$) and R-QUICKI with triglycerides ($r = -0.32$, $P < .001$). When the analysis was performed by BMI ($<$ or $\geq$25 kg/m$^{2)}$, correlations were generally stronger for insulin and HOMA in overweight people and for R-QUICKI in the normal weight group (data not shown).

For all the calculated indices, the prevalence of the MS increased with increasing insulin resistance, both in men and in women, with a significant linear trend. Odds ratio and 95% CI for the prevalence of the syndrome calculated for the most insulin-resistant versus less insulin-resistant people (ie, quartile 4 *v* quartiles 1 to 3 for insulin and HOMA; quartile 1 *v* quartile 2 to 4 for QUICKI and R-QUICKI) were not significantly different for the 4 indices (Table 4).

This issue was explored further by performing the ROC analysis with the MS yes/no as the outcome variable and insulin, HOMA, QUICKI, and R-QUICKI as the test variable. The areas under the curve and their 95% CI were 0.70 (0.67 to 0.72), 0.73 (0.71 to 0.75), 0.73 (0.71 to 0.75), 0.73 (0.71 to 0.76) in men and 0.70 (0.63 to 0.74), 0.74 (0.67 to 0.80), 0.74 (0.67 to 0.80), 0.74 (0.67 to 0.81) in women, respectively, for fasting insulin, HOMA, QUICKI, and R-QUICKI, thus indicating substantial equivalence between them.

DISCUSSION

Findings of this study conducted in large groups of people fairly representative of the general population indicate that all the surrogate measures of insulin resistance evaluated are relatively crude methods for the quantification of insulin resistance in comparison to the MM analysis of the FSIVGTT; correlation coefficients with SI_{MM} range from 0.53 for HOMA to 0.33 for R-QUICKI. The low order correlation coefficients are somewhat expected as FSIVGTT is a dynamic test, whereas fasting insulin–derived indices are static measures of insulin resistance. What is more important in the context of this study, however, is the comparative validation of the various fasting insulin–derived indices.

In agreement with recently published data of an elegant study,[14] the incorporation of FFA in the calculation of QUICKI improves the performance of QUICKI as an estimate of insulin sensitivity in normal weight individuals, however, neither QUICKI nor R-QUICKI in our study proved significantly better than fasting insulin alone or HOMA in both men and women, obese or non-obese.

Some expected relationships were confirmed in this study, ie, all 4 indices were significantly correlated with each of the components of the MS, thus conferring internal consistency to the findings; but we were not able to provide evidence of any superiority of the recently proposed QUICKI or R-QUICKI over the more widely used fasting insulin and HOMA as means for the quantification of insulin sensitivity or for the identification of people with the MS on a population basis. When compared with SI_{MM}, no differences were observed between the 4 indices in their ability to rank people according to insulin resistance status. Furthermore, no significant differences were observed in the ability of the 4 indices in the identification of individuals with the MS. The prevalence of the syndrome was nearly 3 times higher in those most insulin resistant irrespective

Table 3. Correlation Coefficients of Simple Measures of Insulin Resistance With Each of the Components of the Metabolic Syndrome

	Insulin	HOMA	QUICKI	R-QUICKI
Waist circumference	0.37†	0.33†	−0.36†	−0.31*
Systolic BP	0.10†	0.09†	−0.10†	−0.15*
Diastolic BP	0.12†	0.12†	−0.11†	−0.15*
HDL cholesterol	0.13†	0.11†	0.12†	0.07*
Tryglicerides	0.23†	0.20†	−0.23†	−0.32*
Glucose	0.25†	0.34†	−0.45†	−0.37*

NOTE. n = 2,731.
Abbreviation: BP, blood pressure.
*$P < .01$; †$P < .001$.

Table 4. Prevalence (%) of the Metabolic Syndrome by Insulin Resistance Status Defined According to Simple Measures of Insulin Resistance

Quartile	1 (n = 569)	2 (n = 603)	3 (n = 630)	4 (n = 631)	OR (95% CI)*
Males					
Insulin	8.6	14.9	20.5	37.2	3.0 (2.4-3.7)
HOMA	7.9	13.7	19.5	37.2	3.7 (3.0-4.5)
QUICKI	39.7	20.0	15.1	7.9	3.8 (3.1-4.8)
R-QUICKI	39.7	21.3	12.7	8.2	4.0 (3.2-4.9)
Quartile	1 (n = 98)	2 (n = 69)	3 (n = 70)	4 (n = 61)	OR (95% CI)*
Females					
Insulin	7.1	13.0	24.3	41.0	4.3 (2.3-8.0)
HOMA	7.4	14.1	30.9	38.6	3.6 (1.9-6.8)
QUICKI	45.0	28.4	14.8	7.3	4.4 (2.2-9.0)
R-QUICKI	40.0	32.0	10.4	6.3	3.7 (1.9-7.1)

*High *v* low insulin resistance (ie, quartile 4 *v* quartiles 1 to 3 for insulin and HOMA; quartile 1 *v* quartile 2 to 4 for QUICKI and R-QUICKI).

of whether fasting insulin, HOMA, QUICKI, or R-QUICKI was used for the quantification of insulin resistance.

Widely accepted methods for the evaluation of insulin sensitivity in vivo, such as the euglycemic clamp and the minimal model analysis of the FSIVGTT, are not easily applicable in epidemiologic studies due to their cost, complexity, and relative invasiveness. Consequently, over the past few years, many indices based on various weighted combinations of glucose and insulin at fasting or during oral glucose tolerance test (OGTT) have been proposed (reviewed in Hanley et al[25]). We focus on indices relying upon single fasting samples, as this is the most feasible procedure in population studies. QUICKI and R-QUICKI have been recently emphasized as reliable and accurate surrogate measures of insulin resistance.[13,14,26-31] Studies reporting a comparative validation of the newly proposed indices and the most widely used fasting insulin and HOMA against clamp or FSIVGTT are few and have yielded apparently inconsistent results.[13,14,32-34] To some extent, this may relate to the fact that these indices have been mainly validated in small groups in which insulin-resistant people, ie, obese, diabetic, or glucose intolerant, were largely overrepresented as compared with the general population. It is well established that the performance of a diagnostic test heavily depends on the prevalence of the condition of interest and improves exponentially with increasing prevalence, ie, the predictive value of a test with 90% specificity and sensitivity increases from 1.8%, with a prevalence rate of 0.2% for the condition of interest, to 32.0%, with a prevalence rate of 5%.[16] The use, in previous studies, of samples with high prevalence of conditions associated with insulin resistance may have led to various degrees of overestimation of the validity of the novel indices QUICKI and R-QUICKI.

This study expands current knowledge in which a comparative validation of insulin, HOMA, QUICKI, and R-QUICKI was performed using the same data set, a large sample of nondiabetic people with a wide range of age and BMI. Furthermore, for the first time to our knowledge, the 4 indices were comparatively evaluated as means for the identification of individuals with the MS on a population basis. Study limitations include the use of single measurements, which did not permit assessment of reproducibility.

In conclusion, this study shows that the fasting insulin–derived measures of insulin resistance so far proposed are relatively crude methods for the quantification of insulin resistance in comparison to the MM analysis of the FSIVGTT and are, therefore, of limited value for the assessment of the metabolic status of an individual patient. When used in epidemiologic studies, fasting insulin alone, or the widely used HOMA, perform at least as well as QUICKI and R-QUICKI as surrogate measures of insulin resistance or means for the identification of individuals with the MS in the general population.

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