Evaluation of the Quantitative Insulin Sensitivity Check Index as an Estimate of Insulin Sensitivity in Humans

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The goal of this study was to compare estimates of insulin resistance generated by the quantitative insulin sensitivity check index (QUICKI) with a direct measure of insulin-mediated glucose disposal in healthy, nondiabetic volunteers. For this purpose, the results of measurements of plasma glucose and insulin concentrations in 490 nondiabetic, healthy subjects were used to compute several surrogate estimates of insulin resistance, and these values were compared with a direct measure of insulin-mediated glucose disposal. The results of this analysis showed that estimates of insulin resistance derived from use of QUICKI were significantly correlated ($r = -.60$, $P < .001$) with direct measures of insulin-mediated glucose in the 490 subjects studied. It was also noted that QUICKI estimates of insulin resistance were highly correlated with fasting insulin concentrations ($r = -.98$) and the homeostasis model assessment for insulin resistance (HOMA-IR, $r = -.99$). On the other hand, the correlation between all 3 of the surrogate methods for estimating insulin resistance and the direct assessment of insulin-mediated glucose disposal was relatively weak, ie, $r = .61$, $r = .64$, and $r = -.60$) for fasting insulin concentration, HOMA-IR, and QUICKI, respectively. The results of these comparisons do not provide support for the superiority of QUICKI over other commonly used surrogate measures of insulin resistance based upon use of fasting insulin concentration or equations utilizing fasting insulin and glucose concentration. Furthermore, none of the 3 surrogate estimates can account for more than approximately 40% of the variability of the difference in insulin-mediated glucose disposal measured directly in 490 healthy, nondiabetic volunteers.

INSULIN RESISTANCE AND its consequent metabolic abnormalities play an important role in the pathophysiology of type 2 diabetes mellitus, coronary heart disease (CHD), and hypertension.[1,2] As most direct measures of insulin resistance are performed in research settings, considerable interest has been generated in quantifying insulin resistance using surrogate measures of insulin resistance that are based on values of fasting plasma insulin and glucose concentrations. In this regard, our research group[3] has recently published a report comparing a direct measure of insulin-mediated glucose disposal using the insulin suppression test (IST)[4,5] with several different surrogate estimates of insulin sensitivity based on values of fasting plasma glucose and insulin concentrations. The results of this comparison showed that although the various surrogate estimates of insulin resistance were significantly correlated with the direct measure of insulin-mediated glucose disposal, they could only account for approximately 35% to 60% of the variability in insulin action as measured directly. More recently, a report by Katz et al[6] described a novel quantitative insulin sensitivity check index (QUICKI) that was shown to be strongly correlated with insulin resistance as measured by the hyperinsulinemic, euglycemic clamp method. As there is a high degree of correlation ($r > .9$) between measurements of insulin resistance made with the clamp technique and the IST,[4] we thought it would be interesting to further evaluate the potential utility of QUICKI by comparing that estimate of insulin resistance to the results of the IST obtained in our study population of 490 volunteers. By so doing, we would expand the number of comparisons of indirect and direct estimates of insulin resistance made with this measurement by approximately 10-fold. The results to be presented suggest that estimates of insulin resistance using QUICKI in a large population of nondiabetic individuals were not obviously superior to other indirect estimates of insulin-mediated glucose disposal.

MATERIALS AND METHODS

The study population consisted of 230 men and 260 women who had participated in our research studies between 1990 to 1998. Most participants were of European ancestry (77%) with a small percentage of individuals of Asian (10%), Hispanic (12%), and African (1%) background. All participants were determined to be nondiabetic by the criteria of the American Diabetes Association.[7] The participants had a mean (± SD) age of 48 ± 13 years (range, 19 to 79), and body mass index (BMI) of 26.3 ± 4.4 kg/m^2 (range, 18.0 to 42.2). Individuals with BMI less than 30 kg/m^2 were classified as nonobese.

After signing an informed consent, participants were admitted to the Stanford General Clinical Research Center for metabolic testing. A medical history, physical examination, and routine clinical laboratory tests were performed. A 75-g oral glucose test was performed after a 12-hour overnight fast. On a separate day, insulin-mediated glucose disposal was assessed by determining the steady state plasma glucose (SSPG) concentration at the end of a 180-minute continuous infusion of octreotide, insulin, and glucose.[3-5] During this test, the steady-state plasma insulin (SSPI) concentrations are similar in all individuals, and the SSPG concentrations provide a direct estimate of insulin-mediated glucose disposal; the higher the SSPG concentration, the more resistant the individual. Plasma glucose and insulin concentrations were measured as described previously.[3-5]

QUICKI was calculated[6] using the formula: 1/[log(Fasting Insulin) + (log(Fasting Glucose)]. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using formula the described by Matthews et al;[8] (Fasting Insulin [μU/mL] × Fasting Glucose [mMol/L]/22.5).

Data are described as mean ± SEM. Fasting insulin, the total integrated insulin area under the curve following oral glucose (insulin-AUC), and HOMA-IR were log transformed to improve kurtosis and

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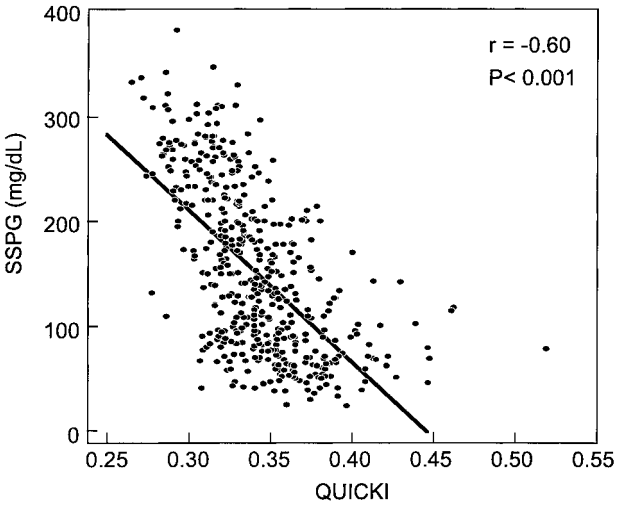

Fig 1. Relationships between the SSPG concentration and the QUICKI estimate of insulin resistance.

skewness. Pearson's correlation coefficients were calculated between SSPG and fasting insulin, insulin-AUC, HOMA-IR, and QUICKI.

RESULTS

The relationship between QUICKI and SSPG is depicted in Fig 1. It is apparent that both SSPG and QUICKI varied approximately 4- to 5-fold and were significantly correlated ($-.60$, $P < .001$). The range of QUICKI (.265 to .518) in our study population was comparable to that described by Katz et al.[6]

Table 1 shows the correlation coefficients between SSPG and, fasting insulin concentration, insulin-AUC, HOMA-IR, and QUICKI. These results clearly indicate that the relationship between QUICKI and SSPG was essentially identical to that between SSPG and the fasting insulin concentration. As a corollary, and not surprisingly, the correlation between fasting insulin concentration and QUICKI was almost perfect ($r = -.98$), as was the correlation between HOMA-IR and QUICKI ($r = -.99$).

To further explore the relationship between QUICKI and SSPG, we divided our 490 subjects into obese (BMI > 30 kg/m^2, n = 114) and nonobese (BMI < 30 kg/m^2, n = 376) groups as had Katz et al[6] for their analysis. We then compared the degree of relationship between QUICKI and the values of

Table 1. Correlation Coefficients (Pearson) Between Insulin Resistance as Measured by the IST (SSPG) and Several Surrogate Estimates of Insulin Resistance

Variable	Fasting $Insulin_{LOG}$	$Insulin\text{-}AUC_{LOG}$	$HOMA\text{-}IR_{LOG}$	QUICKI	SSPG
Fasting $insulin_{LOG}$	1				
$Insulin\text{-}AUC_{LOG}$	.72	1			
$HOMA\text{-}IR_{LOG}$	.98	.72	1		
QUICKI	−.98	−.69	−.99	1	
SSPG	.61	.77	.64	−.60	1

NOTE. All P values were $< .001$.

Table 2. Pearson Correlation Coefficients Between QUICKI and Estimates of Insulin Resistance With Euglycemic Clamp and the IST

Group	Institution	No.	Estimate of Insulin Resistance			
			IST		Clamp	
			r	P	r	P
Nonobese	Stanford	376	−.49	<.001	–	–
	NIH	28	–	–	.49	<.001
	Indiana	14	–	–	.91	<.001
Obese	Stanford	114	−.61	<.001	–	–
	NIH	13	–	–	.89	<.001
	Indiana	21	–	–	.74	<.001

direct measurements of insulin resistance obtained with either the euglycemic, hyperinsulinemic clamp (studied at the National Institutes of Health [NIH]) or the IST (performed at Stanford). In addition, we included a third group in this comparison, using the values of individuals whose clamp studies were performed at the University of Indiana, and included in the report by Katz et al.[6]

These results are shown in Table 2. The correlation between QUICKI and insulin resistance as measured by either the clamp or IST techniques was identical in nonobese individuals studied at either the NIH or Stanford ($r = .49$). In contrast, the correlation coefficient between the clamp and QUICKI was almost perfect in subjects studied at Indiana. However, it should be noted that only 14 nonobese individuals were evaluated.

It is also apparent from Table 2 that the correlation between insulin resistance as measured by the clamp and the QUICKI estimate tended to be greater in the obese individuals ($r = .89$ and .74 in the NIH and Indiana studies, respectively). This was not true of the correlation between QUICKI and the IST, and in this case, the correlation between the direct and surrogate estimate was similar in the nonobese ($r = -.49$) and obese ($r = -.61$) groups. It should also be noted that the correlation between QUICKI and the clamp results in patients studied at the NIH was much greater in obese ($r = .89$) than in nonobese ($r = .49$) subjects, whereas it was the opposite in individuals studied at Indiana ($r = .74$ in the obese v $r = .91$ in the nonobese). At each institution, the highest r values were seen when the population was smallest, ie, 13 obese subjects in the NIH group, and 14 nonobese individuals were studied at Indiana.

DISCUSSION

It is apparent from the results presented that the QUICKI approach to assessing insulin resistance was no more closely related to direct measurements of insulin resistance using the IST than were either the fasting insulin concentration or the HOMA-IR. Indeed, there was almost a perfect correlation ($r = -.99$) between estimates of insulin resistance obtained with QUICKI and HOMA-IR; not surprising, given the fact that both approaches involve mathematical manipulations of the fasting glucose and insulin concentrations.

Perhaps the best evidence that caution should be expressed when evaluating the utility of surrogate measures of insulin

resistance, particularly when based upon relatively small numbers, is seen in Table 2. The closest correlation between insulin resistance measured with the clamp and estimated by QUICKI was in the obese individuals, with correlation coefficients of 0.89 and 0.74 for subjects studied at the NIH and University of Indiana, respectively. Similar calculations in nonobese individuals yielded correlation coefficients of 0.49 and 0.91 for the same 2 groups. Obviously, QUICKI worked reasonably well when applied to both obese (n = 21) and nonobese (n = 14) subjects studied at Indiana University, but not nearly as well when applied to obese (n = 13) and nonobese (n = 28) subjects evaluated at the NIH. In contrast, the correlation coefficient between QUICKI estimates of insulin resistance and measurement of insulin-mediated glucose disposal with the insulin suppression test were much similar, ie, $r = -.49$ and $r = -.61$ when applied to much greater numbers of nonobese (n = 376) and obese (n = 114) subjects.

In conclusion, we were not able to demonstrate any superiority of using QUICKI as a surrogate measure of insulin resistance as compared with other approaches relying primarily upon determination of fasting plasma glucose and insulin concentrations.

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