QUICKI is a useful index of insulin sensitivity in subjects with hypertension

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Quick Check Insulin Index

QUICKI is a useful index of insulin sensitivity in subjects with hypertension. Am J Physiol Endocrinol Metab 284: E804–E812, 2003. First published January 7, 2003; 10.1152/ajpendo.00330.2002.—Insulin resistance may link disorders of metabolic homeostasis such as diabetes and obesity with disorders of hemodynamic homeostasis such as hypertension. Thus it is of interest to validate simple methods for quantifying insulin sensitivity in hypertensive patients. The quantitative insulin-sensitivity check index (QUICKI) is a novel mathematical transformation of fasting blood glucose and insulin levels. In obese and diabetic subjects, QUICKI has a significantly better linear correlation with glucose clamp determinations of insulin sensitivity than minimal-model estimates. To determine whether QUICKI is also useful in hypertensive subjects, we performed glucose clamps and frequently sampled intravenous glucose tolerance tests (FSIVGTT) on 27 hypertensive subjects taken off antihypertensive medication. Indexes of insulin sensitivity derived from glucose clamp studies (SI Clamp) were compared with QUICKI, minimal-model analysis of FSIVGTTs (SI MM), and homeostasis model assessment (HOMA). The correlation between QUICKI and SI Clamp (r = 0.84) was significantly better than that between SI MM and SI Clamp (r = 0.65; P < 0.028). The correlation between QUICKI and SI Clamp was comparable to that between 1/HOMA and SI Clamp (r = 0.82). When studies were repeated in 14 subjects who had resumed antihypertensive medications, the percent changes in SI Clamp for each of these patients were significantly correlated with percent changes in QUICKI (r = 0.61) and HOMA (r = −0.54) but not SI MM (r = −0.18). We conclude that QUICKI is a simple, robust index of insulin sensitivity that is useful for evaluating and following the insulin resistance of hypertensive subjects in both research studies and clinical practice.

insulin resistance; diabetes; glucose clamp

Insulin resistance is a prominent feature of essential hypertension and other cardiovascular diseases (8, 15, 16, 36). Insulin-signaling mechanisms in vascular endothelium-mediating increased production of nitric oxide with subsequent vasodilation and increased blood flow (30, 43, 44) share many features in common with insulin-signaling pathways in skeletal muscle and adipose tissue that promote increased glucose disposal (31, 32). Thus hemodynamic and metabolic homeostasis may be coupled with insulin action in the vasculature. Moreover, insulin resistance may provide a pathophysiological link among hypertension, diabetes, and obesity (22, 31). Recent evidence suggests that there is a shared genetic component underlying both hypertension and insulin resistance that is independent of obesity (42). In addition, hypertension greatly increases the risk of developing other vascular complications of diabetes (40). Given the importance of hypertension as a public health problem and the potential contribution of insulin resistance to the pathophysiology of hypertension, it is of great interest to establish a simple, reliable method for evaluating insulin sensitivity in hypertensive subjects. Such a method will be valuable not only for large epidemiological and clinical investigations but also for following the clinical course of individual hypertensive patients in response to various therapies.

Recently, we developed the quantitative insulin sensitivity check index (QUICKI), which can be determined from a mathematical transformation of fasting blood glucose and plasma insulin levels (24). In our initial validation study for obese, nonobese, and diabetic subjects, the overall linear correlation between QUICKI and the reference glucose clamp index of insulin sensitivity (SI Clamp) was significantly better than that between minimal-model estimates of insulin sensitivity (SI MM) and SI Clamp or between homeostasis model assessment (HOMA (29)) and SI Clamp (24). Importantly, test characteristics of QUICKI (including the coefficient of variation and the discriminant ratio) are comparable to those of the glucose clamp and superior to other simple indexes of insulin sensitivity such as HOMA and 1/(fasting insulin) (20, 28). Since our initial reports, several additional independent studies have confirmed the excellent correlation between QUICKI and SI Clamp in similar populations (3, 38).
23, 28, 35) as well as in subjects with polycystic ovarian syndrome (PCOS) (28) and pregnancy with or without gestational diabetes (25). QUICKI is also a useful index of insulin sensitivity in obese adolescents (17, 20), subjects with hyperandrogenism (14), young girls with premature adrenarche (38, 39), and patients with non-alcoholic steatohepatitis (9). Furthermore, QUICKI is useful for following improvements in insulin sensitivity in subjects with type 2 diabetes treated with diet and exercise (23) and in subjects with PCOS or obesity treated with insulin sensitizers (17, 28). However, QUICKI has not yet been validated as a useful index of insulin sensitivity in hypertensive populations. In the present study, we compared QUICKI and HOMA with $S_{\text{IClamp}}$ and $S_{\text{IMM}}$ in subjects with essential hypertension both on and off antihypertensive medication. Our results strongly suggest that QUICKI is a robust and simple index of insulin sensitivity that will be a useful tool for studying the role of insulin resistance in hypertension.

METHODS

This study was approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute, and the procedures followed were in accordance with institutional guidelines. Informed consent and routine laboratory tests were obtained for each subject. Each subject received a standard physical examination. A glucose clamp study and an insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT) were performed on each subject ≥1 wk apart, and the order of the studies was randomized. Each subject had antihypertensive medications withdrawn for 1 wk before each study. Thus, for some patients, several weeks elapsed between clamp and FSIVGTT studies. Studies were repeated in 14 subjects after they were put back on their antihypertensive medications for ≥1 mo.

Subjects. This study included 27 hypertensive subjects whose blood pressure was well controlled on medication and who could safely be taken off antihypertensive medication for a period of 1–2 wk (blood pressure between 140/95 and 170/109 mmHg off medication). The ages of the subjects ranged between 21 and 54 yr old. Clinical characteristics of the study subjects are listed in Table 1. Among these subjects were 14 Caucasians, 10 African Americans, 2 Asians, and 1 Hispanic. Patients with diabetes and thyroid, liver, kidney, or pulmonary disease as well as end-organ damage such as renal insufficiency, coronary artery disease, heart failure, or peripheral vascular disease were excluded from our study. Patients with a positive pregnancy test or whose blood pressure exceeded 170/109 mmHg off antihypertensive medication were also excluded.

Hyperinsulinemic isoglycemic glucose clamp. At ~8:00 AM, after an overnight fast of ≥10 h, subjects were admitted as outpatients to the Clinical Center at the National Institutes of Health and placed in a recumbent position in an adjustable bed. An intravenous catheter was placed in an antecubital vein for infusion of insulin, glucose, and potassium phosphate. Another catheter was placed in the contralateral hand for blood sampling. The hand used for sampling was warmed with a heating pad to arterialize the blood. An insulin solution (regular Humulin, Eli Lilly, Indianapolis, IN) was prepared with normal saline at a concentration in the range of 0.8–1.2 U/ml. The insulin solution was allowed to dwell in the intravenous lines for ≥15 min, and the lines were then flushed before the beginning of the insulin infusion. Insulin was infused at 120 mU·m⁻²·min⁻¹ for 4 h using a calibrated syringe pump (model A-99, Razel Industries, Stamford, CT). A solution of potassium phosphate was also infused at the same time (0.23 meq·kg⁻¹·h⁻¹) to prevent hypokalemia. Blood glucose concentrations were measured at the bedside every 5–10 min with a glucose analyzer (YSI 2700 Select, YSI, Yellow Springs, OH), and an infusion of 20% dextrose was adjusted to maintain the blood glucose concentration at the fasting level. Blood samples were also collected every 20–30 min for determination of plasma insulin concentrations (DPC Immulite 2000, Diagnostic Products, Los Angeles, CA). The steady-state period of the clamp was defined as a ≥60-min period (2 h after the beginning of the insulin infusion) when the coefficient of variation for blood glucose, plasma insulin, and glucose infusion rate was <5%. Mean values during the steady-state period were used to calculate $S_{\text{IClamp}}$. As previously described (24), the $S_{\text{IClamp}}$ was defined as $M/(G \times \Delta I)$ corrected for body weight (where $M$ is steady-state glucose infusion rate [mg/min], $G$ is steady-state blood glucose concentrations [mg/dl], and $\Delta I$ is difference between basal and steady-state plasma insulin concentration [µU/ml]). Comparable results were obtained if data from the last 30 or 60 min of the clamp were used. We did not correct $S_{\text{IClamp}}$ for urinary loss in glucose or change in glucose space, because we clamped all subjects at their fasting glucose level with minimal changes in plasma glucose concentration, as shown in Fig. 1. Thus these corrections would not significantly change our results.

FSIVGTT and minimal-model analysis. At ~8:00 AM, after an overnight fast of ≥10 h, subjects were admitted as outpatients to the Clinical Center at NIH and placed in a recumbent position in an adjustable bed. Intravenous catheters were placed in the antecubital vein of each arm. An insulin-modified FSIVGTT was performed as described previously (24). Briefly, a bolus of glucose (0.3 g/kg) was infused intravenously over 2 min. Twenty minutes after initiation of the glucose bolus, an intravenous infusion of insulin (4 mU·kg⁻¹·min⁻¹ of regular Humulin) was given for 5 min. Typically used insulin doses in the literature range between 0.02 and 0.05 U/kg. Blood samples were collected for blood glucose and plasma insulin determinations at ~10, ~1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 160, and 180 min, as described (34).

Table 1. Clinical characteristics of study subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>BP, mmHg</th>
<th>Duration of HTN, yr</th>
<th>Duration of Meds, yr</th>
<th>Fasting Glucose, mg/dl</th>
<th>Fasting Insulin, µU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off meds</td>
<td>M</td>
<td>11</td>
<td>45 ± 2</td>
<td>31.2 ± 1.1</td>
<td>152 ± 2/88 ± 2</td>
<td>7.3 ± 1.4</td>
<td>4.9 ± 1.3</td>
<td>83 ± 2</td>
</tr>
<tr>
<td>On meds</td>
<td>F</td>
<td>16</td>
<td>45 ± 2</td>
<td>31.6 ± 1.7</td>
<td>128 ± 3/75 ± 3</td>
<td>6.9 ± 1.9</td>
<td>4.4 ± 1.4</td>
<td>83 ± 2</td>
</tr>
</tbody>
</table>

Data shown are means ± SE from the glucose clamp study. BMI, body mass index; BP, blood pressure; HTN, hypertension; Meds, antihypertensive medications.
using units of millimoles per liter for glucose and microunits for insulin (29). Thus QUICKI is directly proportional to \(1/\log\text{HOMA}\).

**Statistical analysis.** Student’s \(t\) tests were used to compare differences between various parameters when appropriate. Pearson correlation coefficient values \((r)\) were calculated for comparisons between different indexes of insulin sensitivity. To evaluate the significance of differences in \(r\) values for various comparisons, a percentile method bootstrap technique was used to calculate \(P\) values (13). The bootstrap method was required because \(r\) values indicating correlations between the various indexes were derived from the same group of subjects, and thus pairs of \(r\) values are not statistically independent. Values of \(P < 0.05\) were considered to indicate statistical significance.

**RESULTS**

**Study subjects.** The clinical characteristics of our study subjects are shown in Table 1. As expected, mean blood pressure was elevated in the 27 subjects when they were taken off their antihypertensive medications. These subjects were also overweight on average, with a mean body mass index (BMI) of \(\sim 31\ \text{kg/m}^2\). In the 14 subjects who were restudied on their antihypertensive medications, the mean blood pressure was substantially reduced (128 \(\pm\) 3/75 \(\pm\) 3 vs. 152 \(\pm\) 2/88 \(\pm\) 2 mmHg, \(P < 0.001\)). There were no significant differences found in mean BMI, fasting glucose, or fasting insulin values when subjects on and off antihypertensive medication were compared. When the 27 subjects were categorized into nonobese (BMI < 30 kg/m\(^2\); \(n = 12\)) and obese (BMI \(\geq\) 30 kg/m\(^2\); \(n = 15\)) subgroups, the mean BMI for the nonobese group was significantly less than that of the obese group (27 \(\pm\) 0.7 vs. 35 \(\pm\) 1.1 kg/m\(^2\), \(P < 3 \times 10^{-6}\)), but there were no other significant differences found in age, blood pressure, fasting blood glucose, or fasting plasma insulin levels between the subgroups (Table 2).

**Glucose clamp and insulin-modified FSIVGTT studies.** At least 1 wk after antihypertensive medications were discontinued, each subject underwent a hyperinsulinemic isoglycemic glucose clamp using an insulin infusion rate of 120 mU \(\cdot\text{m}^2\) \(\cdot\text{min}^{-1}\) (Fig. 1A). Steady-state conditions were achieved \(\sim 2\) h after initiation of each study and were maintained for \(\geq 60\) min. At steady state, the mean blood glucose level was 83.3 mg/dl, the mean plasma insulin level was 302 \(\mu\text{U/ml}\), and the mean glucose infusion rate was 800 mg/min. The glucose clamp studies were repeated in 14 subjects after they had resumed taking their antihypertensive medications for \(\geq 1\) mo (data not shown). Under these conditions, the mean steady-state blood glucose level

**Table 2. Clinical characteristics of 27 study subjects off antihypertensive medication subdivided into nonobese and obese groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>Age, yr</th>
<th>BMI, kg/m(^2)</th>
<th>BP, mmHg</th>
<th>Fasting Glucose, mg/dl</th>
<th>Fasting Insulin, (\mu\text{U/ml})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonobese</td>
<td>M = 4</td>
<td>42 (\pm) 3</td>
<td>27 (\pm) 0.7</td>
<td>153 (\pm) 5/88 (\pm) 4</td>
<td>82 (\pm) 3</td>
<td>9.2 (\pm) 1.2</td>
</tr>
<tr>
<td>Obese</td>
<td>M = 7</td>
<td>46 (\pm) 1</td>
<td>35 (\pm) 1.1</td>
<td>152 (\pm) 2/88 (\pm) 2</td>
<td>84 (\pm) 3</td>
<td>12.0 (\pm) 1.5</td>
</tr>
</tbody>
</table>

Data shown are means \(\pm\) SE from the glucose clamp study.
was 81 mg/dl, mean plasma insulin level was 315 μU/ml, and the mean glucose infusion rate was 817 mg/min.

In addition to the glucose clamp studies described, each subject also underwent an insulin-modified FSIVGTT with minimal-model analysis after discontinuing antihypertensive medications for ≥1 wk (Fig. 1B). For 3 of 27 subjects, a negative value for SI\textsubscript{MM} was obtained after minimal-model analysis. Because negative values for SI\textsubscript{MM} are nonsensical from a physiological point of view, we excluded these data from further analyses. The mean fractional standard deviation (FSD) for SI\textsubscript{MM} for the 24 nonnegative values of SI\textsubscript{MM} in our study was 4.4 ± 1.3%, with a range between 0.71 and 32.2%. There were only three subjects with FSD >6% (9, 11, and 32%). Exclusion or inclusion of these subjects (i.e., setting a cutoff of 6%) did not substantially alter subsequent analyses. As expected, the minimal-model simulations of glucose disappearance fit well with the actual blood glucose disappearance curves during the FSIVGTT (Fig. 1B). This implies that the precision of the blood glucose measurements was sufficient for adequate minimal-model analysis. These studies were also repeated in 14 subjects after they had resumed taking their antihypertensive medications for ≥1 mo (data not shown).

Comparison between SIClamp and alternative indexes of insulin sensitivity. Mean values for SIClamp, QUICKI, HOMA, and SI\textsubscript{MM} were determined in the cohort of 27 subjects taken off antihypertensive medication (24 subjects for SI\textsubscript{MM}; Table 3). As expected, the mean values for all of these indexes of insulin sensitivity and resistance in our group of hypertensive subjects reflected decreased insulin sensitivity compared with values obtained previously with a healthy control group (24). When our subjects were divided into obese and nonobese subgroups, there was a tendency for the mean indexes to have slightly lower insulin sensitivity in the obese subgroup, but these small differences did not achieve statistical significance (Table 3). The SIClamp in 27 subjects was first compared with alternative QUICKI and HOMA indexes that were derived from fasting glucose and insulin values obtained from the clamp studies (Fig. 2, A and B). The linear correlation of QUICKI with SIClamp in these hypertensive subjects was excellent (r = 0.84). Comparable linear correlations were found when obese and nonobese subgroups were analyzed separately (r = 0.82 and 0.88, respectively), suggesting that the contribution of obesity to insulin resistance in these subjects was not required for the excellent correlation between SIClamp and QUICKI. When 1/HOMA was compared with SIClamp, the correlation was also good (r = 0.82 overall). Because of the mathematical relation between QUICKI and HOMA, the correlations between QUICKI and 1/HOMA (r = 0.97) and QUICKI and logHOMA (r = −0.99) were excellent.

Table 3. Insulin sensitivity indexes for 27 hypertensive subjects off antihypertensive medication (overall) as well as nonobese and obese subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>SIClamp</th>
<th>QUICKI</th>
<th>HOMA</th>
<th>SI\textsubscript{MM}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.70 ± 0.19</td>
<td>0.349 ± 0.007</td>
<td>2.26 ± 0.25</td>
<td>3.14 ± 0.34</td>
</tr>
<tr>
<td>Non-obese</td>
<td>4.09 ± 0.27</td>
<td>0.356 ± 0.010</td>
<td>1.91 ± 0.29</td>
<td>3.71 ± 0.44</td>
</tr>
<tr>
<td>Obese</td>
<td>3.39 ± 0.25</td>
<td>0.342 ± 0.009</td>
<td>2.54 ± 0.40</td>
<td>2.57 ± 0.48</td>
</tr>
</tbody>
</table>

Data shown are means ± SE. SIClamp, insulin sensitivity derived from glucose clamp studies; QUICKI, quantitative insulin sensitivity check index; HOMA, homeostasis model assessment; SI\textsubscript{MM}, minimal-model analysis of frequently sampled intravenous glucose tolerance tests. Note that the values for SI\textsubscript{MM} reflect an overall group of 24, with 12 nonobese subjects and 12 obese subjects, since negative values of SI\textsubscript{MM} were excluded from analysis. Units for SIClamp are 10\textsuperscript{-4} dl·kg\textsuperscript{-1}·min\textsuperscript{-1}/(μU·ml); units for SI\textsubscript{MM} are 10\textsuperscript{-4} min/(μU·ml).
As previously demonstrated for obese and diabetic subjects (24), the linear correlation between the reference SI_{Clamp} and the minimal-model-derived SI_{MM} for 24 hypertensive subjects with nonnegative SI_{MM} (r = 0.65 overall, r = 0.68 for obese subjects, r = 0.54 for nonobese subjects) was substantially worse than that between SI_{Clamp} and QUICKI (P < 0.028; Fig. 2C). If the three subjects with FSD >6% were excluded, the overall correlation coefficient for SI_{Clamp} and SI_{MM} was r = 0.60. When SI_{MM} and HOMA were compared with QUICKI, the correlation coefficients were r = 0.70 and −0.89, respectively. Comparable correlation results were obtained when QUICKI and HOMA were calculated from fasting glucose and insulin levels obtained from the FSIVGTT studies. For example, the correlation coefficient for comparison of SI_{MM} and QUICKI when QUICKI was calculated from the FSIVGTT data was r = 0.72 (similar to r = 0.70 when QUICKI was calculated from clamp data and compared with SI_{MM}). This suggests that the improved performance of QUICKI relative to SI_{MM} when compared with SI_{Clamp} is not due simply to the fact that clamp and FSIVGTT studies were performed on different days.

Assessing changes in insulin sensitivity associated with antihypertensive therapy. To evaluate the utility of QUICKI for following changes in insulin sensitivity with antihypertensive therapy, we restudied 14 subjects after they had resumed their medication for 1 mo. Reinstitution of antihypertensive therapy was clearly effective in lowering the mean blood pressure of these subjects into the normal range (Table 1). Drugs such as diuretics, β-blockers, and calcium channel blockers are associated with worsening insulin resistance, whereas angiotensin I-converting enzyme (ACE) inhibitors have been implicated in improving insulin sensitivity (18). Because each of our subjects was taking different drugs from among these various classes of antihypertensive agents, it is not that surprising that the mean insulin sensitivity determined by glucose clamp did not change significantly when subjects on and off medication were compared (SI_{Clamp} = 3.54 ± 0.38 and 3.56 ± 0.20, respectively). However, there were significant increases or decreases in insulin sensitivity for some of the individual subjects. The change in SI_{Clamp} between subjects off and on medication is shown for each of the 14 patients in Fig. 3A. The mean insulin sensitivity determined by QUICKI also did not change significantly when subjects on and off medication were compared (QUICKI = 0.338 ± 0.008 and 0.343 ± 0.006, respectively). The change in QUICKI for each of the 14 patients off and on medication is shown in Fig. 3B. When the percent change in SI_{Clamp} was compared with the percent change in QUICKI for each subject, we observed a significant positive correlation (r = 0.61), suggesting that both positive and negative changes in SI_{Clamp} are reflected by similar changes in QUICKI (Fig. 3C). Indeed, the direction of change in SI_{Clamp} was accurately reflected by QUICKI in 11 of 14 subjects. Analysis of percent change in HOMA on and off medication gave a similar correlation to percent change in QUICKI.

Fig. 3. SI_{Clamp} (A) and QUICKI (B) for each of 14 hypertensive subjects off and on their antihypertensive medications are shown. Percent change in SI_{Clamp} is plotted against percent change in QUICKI (C) or percent change in SI_{MM} (D). Note that the values for SI_{MM} reflect an overall group of 11, since negative values of SI_{MM} were excluded from analysis.
change in $S_{\text{Clamp}}$ ($r = -0.54$). In sharp contrast, the percent change in $S_{\text{MM}}$ off and on medication was unrelated to changes in $S_{\text{Clamp}}$ ($r = -0.18$) and significantly worse than the correlation between percent change in $S_{\text{Clamp}}$ and percent change in QUICKI ($P < 0.02$; Fig. 3D). When percent changes in $S_{\text{MM}}$ and HOMA were compared with percent changes in QUICKI, the correlation coefficients were $r = -0.05$ and $-0.98$, respectively.

**DISCUSSION**

Insulin resistance is a cardinal finding in essential hypertension and other cardiovascular abnormalities that belong to the metabolic syndrome (16, 36). Developing simple, reliable methods for quantifying insulin sensitivity in vivo may be important for helping to elucidate the contribution of insulin resistance to disorders of metabolic and hemodynamic homeostasis. In the present study, we used the reference method for assessing insulin sensitivity in vivo (hyperinsulinemic isoglycemic glucose clamp) to validate QUICKI as a useful index of insulin sensitivity in subjects with essential hypertension.

**Hypertensive subjects.** In the present study, we excluded hypertensive subjects with other medical conditions such as diabetes, abnormal blood glucose levels, pregnancy, thyroid disease, liver disease, peripheral vascular disease, pulmonary disease, or other vascular end-organ damage, since the presence of these conditions may have an independent influence on insulin resistance. In addition, we initially studied patients after they were taken off their antihypertensive medications because many antihypertensive medications themselves can influence insulin sensitivity (21). The mean BMI for our hypertensive subjects was $31 \text{ kg/m}^2$. Although obesity is an independent determinant of insulin sensitivity, the presence of obesity did not affect our analyses, as subdivision of subjects into obese and nonobese groups did not result in significant differences in any parameters except for BMI (Tables 2 and 3). The mean value for $S_{\text{Clamp}}$ of 3.68 obtained in hypertensive subjects is significantly lower than the mean value of 6.19 that we obtained previously in a healthy control group (24), consistent with the presence of insulin resistance in our group of subjects with essential hypertension. Similarly, the mean values obtained for QUICKI, HOMA, and $S_{\text{MM}}$ also reflected the insulin resistance of our hypertensive group.

The overall correlation coefficient between $S_{\text{MM}}$ and $S_{\text{Clamp}}$ in the present study ($r = 0.65$) is comparable to the mean correlation coefficient of two independent comparisons between insulin-modified FSIVGTT and clamp studies in subjects with normal glucose tolerance ($r = 0.62$) (see Table 1 in Ref. 24). Thus the technical quality of our glucose clamp and FSIVGTT studies is likely to be comparable to that of other published studies from independent groups. The mean correlation coefficient of three comparisons between tolbutamide-modified FSIVGTT and clamp studies in subjects with normal glucose tolerance is $r = 0.81$ (see Table 1 in Ref. 24). Even though the hypertensive subjects in our study probably had normal glucose tolerance, they were more insulin resistant than normal subjects, and it is known that the minimal model does not perform as well in insulin-resistant populations.

**Validation of QUICKI against a reference standard.** Among the three alternative indexes of insulin sensitivity evaluated here, the best linear correlation with the reference $S_{\text{Clamp}}$ was observed for QUICKI ($r = 0.84$). Moreover, comparable correlations were observed in both nonobese and obese subgroups, suggesting that an independent contribution of obesity to insulin resistance is not required for the excellent correlation between $S_{\text{Clamp}}$ and QUICKI in subjects with essential hypertension. We used a relatively high infusion rate for insulin in our clamp studies (120 mU·m$^{-2}·\text{min}^{-1}$), which resulted in average steady-state plasma insulin levels of ~300 µU/ml. This was done for several reasons. First, we wanted to be consistent with the original study, which had defined and validated QUICKI in normal, obese, and diabetic subjects by use of clamps with a high insulin infusion rate (24). The original QUICKI study had used high insulin infusion rates because of the expectation that obese and diabetic subjects would be significantly insulin resistant (24). Similarly, as demonstrated in the present study, our hypertensive subjects were insulin resistant, suggesting that a high insulin infusion rate is also appropriate for this population. Moreover, when lower insulin infusion rates (e.g., 40 mU·m$^{-2}·\text{min}^{-1}$) are used in normal subjects, the correlation between $S_{\text{Clamp}}$ and QUICKI is comparable to correlations obtained using $S_{\text{Clamp}}$ derived from clamps with high insulin infusions (24).

$1/HOMA$ also correlated well with $S_{\text{Clamp}}$ in hypertensive subjects, with a correlation coefficient ($r = 0.82$) that was comparable to that observed between QUICKI and $S_{\text{Clamp}}$. Our results with HOMA are similar to those recently reported by Lansang et al. (27), who also found significant correlations between glucose clamp results and HOMA ($r = -0.64$) in 36 hypertensive subjects. Moreover, several independent clinical studies (each with >250 subjects) have concluded that the test characteristics of QUICKI, including the coefficient of variation and discriminant ratio, are comparable to those of the glucose clamp and are superior to the test characteristics of HOMA (20, 28). Because of the close correlation between QUICKI and $1/HOMA$ or logHOMA, it is likely that QUICKI performs as well as appropriately transformed versions of HOMA.

Of note, the correlation between QUICKI and $S_{\text{Clamp}}$ in hypertensive subjects ($r = 0.84$) was substantially and significantly better than that between $S_{\text{MM}}$ and $S_{\text{Clamp}}$ ($r = 0.65$), despite the fact that QUICKI is derived from a single fasting blood sample whereas $S_{\text{MM}}$ is derived from an FSIVGTT that requires intravenous administration of glucose and insulin as well as 30 blood samples over a 3-h time period. This superior performance of QUICKI was not due to

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the fact that the FSIVGTT and clamp studies were done on separate days, since QUICKI calculated from either clamp or FSIVGTT data gave similar results. This is consistent with a similar analysis in our previous study in lean, obese, and diabetic subjects (24). Furthermore, reliable values for QUICKI could be determined for all of our subjects. By contrast, in 3 of 27 hypertensive subjects, the minimal model generated negative values for $SI_{MM}$ that are artifactual (similar to difficulties previously observed with diabetic subjects) (24). The $SI_{MM}$ tends to correlate better with glucose clamp results in normal subjects (see Table 1 in Ref. 24). Conversely, QUICKI tends to correlate better with glucose clamp results in insulin-resistant subjects (24). This may help to explain why QUICKI performs better than the minimal model in our hypertensive cohort that is insulin resistant.

Because QUICKI and HOMA are based on fasting glucose and insulin values, these indexes primarily reflect hepatic insulin sensitivity (i.e., the ability of insulin to suppress hepatic glucose production). The minimal-model-derived index of insulin sensitivity, $SI_{MM}$, lumps together the contributions of the liver and peripheral tissues (i.e., skeletal muscle and adipose tissue) to metabolic insulin sensitivity. By contrast, the glucose clamp assesses glucose disposal under hyperinsulinemic conditions, where hepatic glucose production is presumably suppressed. Therefore, $SI_{clamp}$ the clamp-derived index of insulin sensitivity, primarily reflects insulin action in peripheral tissues. Under normal conditions, changes in hepatic insulin sensitivity and changes in peripheral insulin sensitivity parallel each other. This is reflected in the excellent correlation between QUICKI and $SI_{clamp}$ in our hypertensive subjects. However, in cases where peripheral and hepatic insulin sensitivities are uncoupled, QUICKI may not be a reliable index of peripheral insulin sensitivity.

Our validation studies with QUICKI in a cohort with essential hypertension complement a number of other recent studies that have demonstrated the value of QUICKI as a useful index of insulin sensitivity in subjects with obesity, type 2 diabetes, gestational diabetes, pregnancy, PCOS, premature adrenarche, hyperandrogenism, and nonalcoholic steatohepatitis (2, 3, 5, 9, 14, 17, 19, 20, 23, 25, 26, 35, 38, 39, 41). It should be noted that one study using a steady-state plasma glucose protocol as the reference method found correlations with QUICKI in normal subjects that were comparable to those of our previous studies but slightly lower correlations for obese subjects (1).

Utility of QUICKI for following changes in insulin sensitivity after therapeutic interventions. In addition to validating QUICKI as an accurate index of insulin sensitivity in hypertensive subjects, we also evaluated the utility of QUICKI for following changes in insulin sensitivity after therapeutic interventions with various antihypertensive medications. Fourteen subjects were randomly chosen for reevaluation after they had resumed taking antihypertensive medications for 1 mo. Except for the expected reduction in blood pressure, no differences in any of the measured clinical character-

istics were observed between the original 25 subjects and the 14 subjects selected for reevaluation. The mean $SI_{Clamp}$ did not change significantly when the same subjects on and off medication were compared. This is most likely because some patients were taking antihypertensive medications predicted to increase insulin sensitivity, whereas others were taking medications predicted to decrease insulin sensitivity. For example, ACE inhibitors are known to improve insulin sensitivity, whereas β-blockers and calcium channel blockers may worsen insulin sensitivity (18). Nevertheless, positive and negative changes in $SI_{Clamp}$ observed in individual patients were tracked by similar changes in QUICKI. That is, the percent change in $SI_{Clamp}$ after patients were restarted on their medication was highly correlated with the percent change in QUICKI. There was also a comparable correlation between percent change in $SI_{Clamp}$ and percent change in HOMA. In sharp contrast, $SI_{MM}$ was unable to track changes accurately in insulin sensitivity when compared with results from the glucose clamp. These results suggest that QUICKI may be useful not only in large epidemiological studies but also for evaluating and following insulin sensitivity in individual patients after therapeutic interventions. In addition, these results highlight the importance of validating QUICKI against a reference standard. Similar results were obtained in a group of Japanese subjects with type 2 diabetes who were treated with diet and exercise (23). In that study, QUICKI was able to accurately track improvement in insulin sensitivity after therapy, as documented by changes in glucose clamp estimates of insulin sensitivity. A recent study evaluating changes in insulin sensitivity after exercise training concluded that QUICKI does not accurately reflect changes in insulin sensitivity, because changes in QUICKI did not correlate with changes in $SI_{MM}$ (11). However, that study did not include a reference standard for comparison (33). The authors of that study claim that errors in their minimal-model approach are constant and therefore unbiased with respect to determining changes in insulin sensitivity (12). However, this is clearly not the case, since the $SI_{MM}$ from the unmodified FSIVGTT that they used (without insulin infusion) does not significantly correlate with $SI_{Clamp}$ (10). As illustrated in the present study, one may observe a poor correlation between QUICKI and $SI_{MM}$ while still maintaining an excellent correlation between QUICKI and the reference glucose clamp results. It is conceivable that the two-compartment version of the minimal model may give better results than the single-compartment minimal-model results obtained here (6, 7). However, because this requires infusion of labeled glucose, we were unable to evaluate this possibility in the present study. Several other studies have also found that changes in insulin sensitivity after therapeutic interventions can be detected reliably by QUICKI in patients with PCOS and type 2 diabetes and in obese adolescents (17, 23, 26, 28). We conclude that QUICKI is a simple and robust index of insulin sensitivity in hypertensive subjects that will be a useful tool in population studies as
as well as in clinical settings where evaluation of changes in insulin sensitivity is of interest.

REFERENCES


