COMMENT

Quantitative Insulin Sensitivity Check Index and the Reciprocal Index of Homeostasis Model Assessment Are Useful Indexes of Insulin Resistance in Type 2 Diabetic Patients with Wide Range of Fasting Plasma Glucose

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The purpose of the study was to investigate whether quantitative insulin sensitivity check index (QUICKI) and the reciprocal index of homeostasis model assessment (1/HOMA-IR) are excellent surrogate indexes of insulin resistance in type 2 diabetic patients with various ranges of fasting plasma glucose. One hundred eight type 2 diabetic patients were divided into tertiles according to fasting levels of plasma glucose ranging from 4.2 to 11.1 mmol/liter, i.e. T1 (4.2 ≤ FPG < 6.5, n = 36); T2: 6.5 ≤ FPG < 8.1, n = 36; T3: 8.1 ≤ FPG ≤ 11.1, n = 36). The association between QUICKI or 1/HOMA-IR and insulin resistance index assessed by euglycemic hyperinsulinemic clamp (Clamp-IR) was investigated in each group. QUICKI was strongly correlated with Clamp-IR in all groups (r = 0.615 in T1, r = 0.659 in T2, and r = 0.788 in T3; all subjects, r = 0.691; all P < 0.001). Reciprocal of HOMA-IR also highly correlated with Clamp-IR in all groups (r = 0.600, r = 0.721, and r = 0.730, respectively; all subjects, r = 0.685; all P < 0.001). In conclusion, QUICKI and the reciprocal index of HOMA were highly correlated with Clamp-IR in type 2 diabetic patients with relatively wide ranges of fasting plasma glucose. (J Clin Endocrinol Metab 89: 1481–1484, 2004)

Insulin resistance not only induces hyperglycemia in type 2 diabetes (1) but also plays important roles in the pathogenesis of cardiovascular diseases (2). Furthermore, oral insulin sensitizers such as thiazolidinediones and biguanides have been developed for clinical availability (3, 4). Therefore, it is important to evaluate insulin resistance simply and accurately in clinical settings.

To date, it has been shown that homeostasis model assessment (HOMA-IR) (5–7), reciprocal of HOMA-IR (8), or quantitative insulin sensitivity check index (QUICKI) (9), which is calculated from fasting plasma glucose (FPG) and insulin (FIRI), is useful surrogate index of insulin resistance in healthy and diabetic subjects because of their high correlation with the indexes assessed by euglycemic hyperinsulinemic clamp (Clamp-IR), the gold standard technique for estimation of insulin resistance (10).

Because hyperglycemia affects insulin secretion from pancreatic β-cell, a phenomenon known as so-called glucotoxicity, fasting levels of plasma glucose do not necessarily correlate linearly with fasting levels of insulin (11). Therefore, there is a possibility that surrogate indexes of insulin resistance fail to strongly correlate with Clamp-IR in fasting hyperglycemia. In fact, Katsuki et al. (12) recently reported that neither QUICKI nor HOMA-IR could predict insulin resistance in elderly poorly controlled type 2 diabetic subjects. There are no reports that ascertain whether fasting hyperglycemia affect the availability of QUICKI, reciprocal of HOMA-IR, or HOMA-IR in type 2 diabetic patients.

In the present study, we investigated whether QUICKI, reciprocal of HOMA-IR, or HOMA-IR is a useful index of insulin resistance in type 2 diabetic patients with various fasting levels of plasma glucose in comparison with Clamp-IR.

Subjects and Methods

Subjects

One hundred eight type 2 diabetic patients, 74 men and 34 women, participating in diabetes education programs, were selected for the present study from among patients attending our diabetes center at Osaka City University Hospital. The diagnosis of diabetes was based on a previous history of diabetes or the American Diabetes Association criteria (13). The diabetic patients treated with any insulin therapy were excluded because fasting plasma insulin level, an essential component for the calculation of the QUICKI or HOMA-IR as described below, may be affected by insulin therapy. The patients were divided into tertiles according to their fasting levels of plasma glucose ranging from 4.2 to 11.1 mmol/liter, i.e. T1 (4.2 ≤ FPG < 6.5, n = 36), T2 (6.5 ≤ FPG < 8.1,
n = 36), and T3 (8.1 ≤ FPG ≤ 11.1, n = 36). Fifty-one subjects were treated with sulfonylureas, five with α-glucosidase inhibitors, and seven with combination of these drugs. Uremic subjects with serum creatinine levels greater than 176 μmol/liter and other active medical disease were excluded.

Informed consent was obtained from all participants in the present study, and the study including clamp protocol was approved by the local Ethics Committee.

Study protocol and methods

After admission, all subjects were under medical nutritional therapy (energy 25–30 kcal/kg ideal body weight) and euglycemic hyperinsulinemic clamp (clamp study) was performed within 1–2 wk after admission as described below. Oral hypoglycemic agents were taken until the day before the clamp study. After a 12-h overnight fast, a fasting blood sample was taken for the determination of FPG and FRI levels.

QUICKI was calculated from FPG and FRI levels according to the report by Katz et al. (9) with the formula: QUICKI = 1/(log (FIRI in μU/ml) + log (FPG in mg/dl)). The HOMA-IR was calculated from FPG and FRI according to the report by Matthews et al. (5) with the formula: HOMA-IR = FIRI in μU/ml × FPG in mg/dl/405. The reciprocal index of HOMA-IR was also calculated.

Clamp study was performed according to the method of DeFronzo et al. (10) using an STG 22 artificial pancreas model as described in our previous study (6, 7, 14, 15). Insulin (Humulin R, Eli Lilly & Co., Indianapolis, IN) was loaded during the first 10 min of the clamp in priming ass as reported previously followed by infusion in a continuous fashion at a rate of 1.25 mU/kg/min. The total-body glucose disposal rate was evaluated as the mean of the glucose infusion rate during the last 30 min of the clamp. The mean plasma insulin level during the steady-state was 647 ± 191 μU/ml in all diabetic subjects. The insulin sensitivity index (Clamp-IR) derived from the clamp study was calculated by dividing the mean glucose infusion rate by the plasma insulin level during the steady-state level during the last 30 min of the clamp and multiplying by 600.

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<th>TABLE 1. Clinical characteristics of the subjects</th>
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All values are means ± sd, unless otherwise indicated. Statistical analysis was performed by the Stat View 5 system (SAS Institute Inc., Cary, NC) on a Windows computer (Microsoft Co., Redmond, WA). Student’s t test or the χ² test was appropriately used for comparisons of groups. Simple linear regression analysis was performed for analysis of associations between Clamp-IR and clinical covariates including QUICKI, 1/HOMA-IR, or HOMA-IR. P < 0.05 was considered statistically significant.

Results

Table 1 shows clinical characteristics of all type 2 diabetic subjects. There were no significant differences in gender, age, duration of diabetes, systolic and diastolic blood pressure, body mass index, FIRI, triglyceride, high-density lipoprotein-cholesterol, or free fatty acid level among the three groups. The means of hemoglobin A1c were significantly higher in T2 and T3 than in T1, and the means of serum creatinine were significantly lower in T3 than in T1.

QUICKI was significantly lower in T3 than in T1 and HOMA-IR was significantly higher in T3 than in T1.

Simple linear regression analysis demonstrated that QUICKI was highly correlated with Clamp-IR in all groups (r = 0.615 in T1, r = 0.659 in T2, and r = 0.788 in T3; all subjects, r = 0.691; all P < 0.001, Fig. 1A). Reciprocal of HOMA-IR had almost equally high correlation with Clamp-IR in all groups (r = 0.600, r = 0.721, and r = 0.730, respectively; all subjects, r = 0.685; all P < 0.001, Fig. 1B). HOMA-IR and FRI were also significantly correlated with Clamp-IR in all groups, but the correlation coefficients were lower than those for QUICKI or 1/HOMA-IR (Table 2).

Discussion

In the present study, we demonstrated no effects of FPG on correlation coefficients between QUICKI, the reciprocal

Statistical methods

All values are means ± sn, unless otherwise indicated. Statistical analysis was performed by the Stat View 5 system (SAS Institute Inc., Cary, NC) on a Windows computer (Microsoft Co., Redmond, WA). Student’s t test or the χ² test was appropriately used for comparisons of groups. Simple linear regression analysis was performed for analysis of associations between Clamp-IR and clinical covariates including QUICKI, 1/HOMA-IR, or HOMA-IR. P < 0.05 was considered statistically significant.
index of HOMA-IR and Clamp-IR in type 2 diabetic patients, at least with maximum range of FPG, approximately 11.1 mmol/liter. These results indicated that QUICKI and the reciprocal index of HOMA-IR were useful surrogate indexes of insulin resistance in type 2 diabetic patients with wide range of fasting levels of plasma glucose.

Matthews et al. (5) originally reported the clinical usefulness of HOMA-IR as an index of insulin resistance in type 2 diabetes with the mean FPG of 6.6 ± 1.5 mmol/liter. We also previously showed the validity of HOMA-IR in 80 type 2 diabetic patients in which their mean FPG was 7.7 ± 2.1 mmol/liter (6). In each of the two studies, plasma glucose levels were relatively well controlled, and the subjects with marked fasting hyperglycemia were not included.

In 2000, Katz et al. (9) proposed QUICKI as an excellent insulin sensitivity index according to the strong correlation with Clamp-IR, in which the mean FPG of 15 type 2 diabetic subjects was 8.9 ± 0.8 mmol/liter. Additionally, Mather et al. (16) reported significant correlation between QUICKI and Clamp-IR in 11 type 2 diabetic patients with relatively high mean FPG level, 10.4 mmol/liter. In contrast, Katsuki et al. (17) recently reported that neither HOMA nor QUICKI significantly correlated with Clamp-IR in poorly controlled (the mean of FPG was 9.0 ± 2.6 mmol/liter) elderly type 2 diabetic patients. They showed insulin secretion evaluated by Δplasma insulin/Δplasma glucose in oral glucose tolerance test was decreased in such patients. Impaired insulin secretion may affect the relation between hepatic (i.e. HOMA-IR or QUICKI) and peripheral (i.e. Clamp-IR) insulin resistance. In the present study, it is likely that the ability of insulin secretion was more preserved in our patients who have shorter duration of diabetes, although we did not directly evaluated insulin secretion of each subjects. Thus, QUICKI or HOMA-IR may be suitable for estimating insulin resistance in type 2 diabetes with relatively high FPG, in case enough insulin secretion is preserved. In addition, differences in characteristics of study subjects or in clamp method may affect the correlation between surrogate indexes and Clamp-IR.

There were no reports that examined the validity of simple indexes of insulin resistance in various ranges of FPG, separately, except for the report by Ono et al. (18), in which they demonstrated that HOMA-IR was suitable for evaluating insulin resistance in obese type 2 diabetic subjects with fasting glucose levels 170 mg/dl or less and that HOMA-IR did not significantly correlate when examined including subjects with fasting glucose more than 200 mg/dl. Our data demonstrated that QUICKI and the reciprocal index of HOMA-IR, a simpler and more convenient index than QUICKI, may be more preferable than HOMA-IR when estimating insulin resistance in subjects with higher fasting plasma glucose than in previous reports (9, 19, 20), which indicate the possibility of more extensive application in clinical settings. It should be kept in mind, however, that QUICKI, the reciprocal index of HOMA-IR, and HOMA-IR are not independent to each other because of their common origin (i.e. all of them consist of fasting levels of plasma glucose and insulin).

In conclusion, QUICKI and the reciprocal index of HOMA-IR were highly correlated with Clamp-IR in type 2 diabetic patients in which their mean FPG was 7.7 ± 2.1 mmol/liter (6). In each of the two studies, plasma glucose levels were relatively well controlled, and the subjects with marked fasting hyperglycemia were not included.

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