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COMMENT

Neither Homeostasis Model Assessment nor Quantitative Insulin Sensitivity Check Index Can Predict Insulin Resistance in Elderly Patients with Poorly Controlled Type 2 Diabetes Mellitus

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To clarify whether homeostasis model assessment (HOMA IR) and quantitative insulin sensitivity check index (QUICKI) may be indicators of insulin resistance in elderly patients with type 2 diabetes mellitus, their relationship with the glucose infusion rate during the euglycemic hyperinsulinemic clamp study (clamp IR) was assessed. This study comprised 56 Japanese patients with type 2 diabetes mellitus; of these, 28 were 70 yr of age or older (group 1) and 28 were less than 70 yr of age (group 2). Their blood sugars were in poor control (fasting plasma glucose levels: group 1, 9.0 ± 2.6 mmol/liter; group 2, 8.9 ± 2.3 mmol/liter; hemoglobin A1c: group 1, 9.5 ± 2.0%; group 2, 9.2 ± 1.7%).

Log-transformed HOMA IR was significantly correlated with the clamp IR in group 2 patients ($r = -0.51$, $P < 0.01$), but not in group 1 patients ($r = -0.28$, $P = 0.15$). There was a significant positive correlation between QUICKI and clamp IR in group 2 patients ($r = 0.50$, $P < 0.01$). However, no significant correlation was observed between QUICKI and clamp IR in group 1 patients ($r = 0.31$, $P = 0.12$). There was a significant correlation between log-transformed HOMA IR ($r = -0.37$, $P < 0.01$) or QUICKI ($r = 0.37$, $P < 0.01$) and clamp IR when both groups were combined.

In conclusion, neither HOMA IR nor QUICKI should be used as an index of insulin resistance in elderly patients with poorly controlled type 2 diabetes mellitus. The results of this study suggest the need for developing a new noninvasive method for evaluating insulin resistance in those patients. (*J Clin Endocrinol Metab* 87: 5332–5335, 2002)

AGING IS ASSOCIATED with insulin resistance (1). In Japan, elderly patients with type 2 diabetes mellitus are gradually increasing due to a long life span (2). The number of patients needing insulin-sensitizing agents is also increasing. Thus, a simple, accurate, and reproducible index is necessary for the diagnosis of insulin resistance in elderly patients with type 2 diabetes mellitus.

To date, several methods for evaluating insulin resistance have been developed (3–7). Of these, homeostasis model assessment (HOMA IR) has been reported to be unable to evaluate insulin resistance in elderly individuals at risk of having impaired glucose tolerance (8), however, its applicability in elderly patients with type 2 diabetes mellitus has not been studied as yet. The quantitative insulin sensitivity check index (QUICKI) has been recently reported to be a useful marker of insulin resistance in patients with type 2 diabetes mellitus (5, 9), but its usefulness in elderly patients with type 2 diabetes mellitus has not been evaluated as yet.

Abbreviations: ALT, Alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; clamp IR, euglycemic hyperinsulinemic clamp study; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index.

In the present study, we investigated whether HOMA IR or QUICKI is correlated with the index of the euglycemic hyperinsulinemic clamp study (clamp IR) in elderly patients with type 2 diabetes mellitus.

Subjects and Methods

Subjects

This study comprised 28 Japanese patients with type 2 diabetes mellitus (group 1) who were 70 yr of age or older (range, 70–81 yr). Data obtained in 28 patients with type 2 diabetes mellitus (group 2) who were less than 70 yr of age were used as control (range, 30–68 yr). The duration of diabetes mellitus, obesity, and glycemic control were matched with those of group 1 patients (Table 1). We recruited patients treated with only diet and exercise to exclude the influence of oral hypoglycemic agents.

Body mass index (BMI) was calculated as the body weight (in kilograms) divided by the square of the height (in meters).

Type 2 diabetes mellitus was diagnosed in our patients at a local clinic 14.8 ± 9.1 (group 1) or 14.2 ± 5.4 (group 2) years before the beginning of this study. All patients received dietary (1,440–1,720 kcal/d) and exercise (walking 7,000–10,000 steps/d) therapy. Their blood sugar was in good control [hemoglobin A1c (HbA1c), ≤6.5%] at the beginning of their disease, but thereafter their blood sugar gradually increased (HbA1c, ≥8%) because of overeating and inactivity about several months before admission. They were admitted in our clinical department for glycemia control. We categorized them as having type 2 dia-

TABLE 1. Clinical and laboratory characteristics of patients with type 2 diabetes mellitus

	Group 1 (age ≧70 yr)	Group 2 (age <70 yr)
No.	28	28
Sex (M/F)	15/13	17/11
Age (yr)	73.3 ± 3.0	55.4 ± 8.9[a]
Duration of diabetes (yr)	14.8 ± 9.1	14.2 ± 5.4
BMI (kg/m^2)	21.2 ± 2.2	22.0 ± 1.4
Visceral fat area (cm^2)	82.2 ± 42.1	82.9 ± 24.8
Subcutaneous fat area (cm^2)	109.6 ± 46.1	111.1 ± 36.7
HbA1c (%)	9.5 ± 2.0	9.2 ± 1.7
Fasting plasma glucose (mmol/liter)	9.0 ± 2.6	8.9 ± 2.3
Fasting serum insulin (pmol/liter)	34.2 ± 22.2	39.0 ± 34.2
Total cholesterol (mmol/liter)	5.0 ± 1.0	5.0 ± 1.0
Triglyceride (mmol/liter)	1.4 ± 0.5	1.7 ± 0.8
HDL cholesterol (mmol/liter)	1.3 ± 0.5	1.2 ± 0.4
AST (IU/liter)	20.0 ± 4.9	21.3 ± 5.6
ALT (IU/liter)	21.8 ± 6.8	19.0 ± 7.1
Creatinine (μmol/liter)	85.2 ± 17.1	80.8 ± 14.9
Systolic blood pressure (mm Hg)	135.0 ± 17.8	135.2 ± 15.7
Diastolic blood pressure (mm Hg)	73.7 ± 10.4	76.4 ± 9.4
Clamp IR (μmol/kg·min)	36.1 ± 13.0	41.6 ± 17.5
HOMA IR	2.3 ± 1.9	2.4 ± 1.8
Log-transformed HOMA IR	0.256 ± 0.306	0.300 ± 0.268
QUICKI	0.353 ± 0.039	0.347 ± 0.031

Data are means ± SD. M, Male; F, female.
[a] $P < 0.01$; group 1 *vs.* group 2.

betes mellitus based on the diagnostic criteria of the American Diabetes Association (10). In group 1, there were 16 patients with peripheral neuropathy, 12 with background diabetic retinopathy, 14 with macroproteinuria, 7 with lacunar stroke, 9 with hypertension (of these, 5 were receiving 5 mg/d enalapril maleate and 4 were receiving 5 mg/d amlodipine besilate), and 7 with hyperlipidemia treated with 10 mg/d pravastatin sodium. None of them had ischemic heart disease or arteriosclerosis obliterans. In group 2, there were 16 patients with peripheral neuropathy, 14 with background diabetic retinopathy, 10 with macroproteinuria, 5 with hypertension (of these, 3 were receiving 5 mg/d enalapril maleate and 2 were receiving 5 mg/d amlodipine besilate), and 3 with hyperlipidemia treated with 10 mg/d pravastatin sodium. None of them had macrovascular complications.

Informed consent was obtained from all subjects before the beginning of the study.

Study protocol and methods

The blood levels of glucose, HbA1c, insulin, total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine and the values of HOMA IR, QUICKI, clamp IR, body fat area, and blood pressure were measured in all patients with type 2 diabetes mellitus. To evaluate the insulin secretion ability, a 75-g oral glucose tolerance test (Trelan G 75; Shimizu, Shizuoka, Japan) was performed in 20 group 1 (age, 73.1 ± 2.4; male/female, 13/7; BMI, 21.2 ± 2.3) and 20 group 2 (age, 53.8 ± 9.7; male/female, 13/7; BMI, 22.3 ± 1.2) patients.

The plasma glucose level was measured by an automated enzymatic method. The HbA1c (normal value, 4.3–5.8%) was measured by HPLC. Serum insulin was measured using an immunoradiometric assay kit (Insulin Riabead II kit; Dainabot, Tokyo, Japan). The intra- and interassay coefficients of variation of the assay were 2.0% and 2.1%, respectively. No significant cross-reactivity or interference was observed between insulin and proinsulin, C-peptide, glucagon, secretin, or gastrin-I.

Serum levels of total cholesterol, triglyceride, HDL cholesterol, AST, ALT, and creatinine were measured by enzymatic methods using an autoanalyzer (TBA60M; Toshiba, Tokyo, Japan).

HOMA IR and QUICKI were calculated from the fasting concentrations of insulin and glucose using the following formula: HOMA IR = fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/liter)/22.5 (4), QUICKI = 1/[log fasting serum insulin (μU/ml) + log fasting plasma glucose (mg/dl)] (5). clamp IR was evaluated by the euglycemic hyperinsulinemic clamp technique using an artificial pancreas (STG-22; Nikkiso, Tokyo, Japan) (3, 7, 11, 12). At 0800 h, a priming dose of insulin (Humulin R; Eli Lilly Japan, Kobe, Japan) was administered during the initial 10 min in a logarithmically decreasing manner to rapidly raise serum insulin to the desired level (1200 pmol/liter); this level was then maintained by continuous infusion of insulin at a rate of 13.44 pmol/kg·min for 120 min. The mean insulin level from 90–120 min after starting the clamp study was stable (group 1, 1380.0 ± 426.0 pmol/liter; group 2, 1339.8 ± 371.4 pmol/liter). The clamp study was started at the fasting levels of glucose (group 1, 9.0 ± 2.6 mmol/liter; group 2, 8.9 ± 2.3 mmol/liter). Blood glucose was monitored continuously and decreased to normoglycemic levels within 50 min; thereafter it was maintained at the target clamp level (5.24 mmol/liter) by infusing 10% glucose. The mean amount of glucose given during the last 30 min was defined as the glucose infusion rate , and it was used as a clamp IR.

The capacity to secrete insulin in response to oral glucose stimulation was estimated by the ratio of ΔI_{30} to ΔG_{30} ($\Delta I_{30}/\Delta G_{30}$; calculated as: increment of serum insulin from 0–30 min/increment of plasma glucose from 0–30 min), and the insulin area under the curve (AUC). Blood was taken at 0, 30, 60 and 120 min.

Body fat area was evaluated by a previously described method (13). The intra-abdominal visceral fat and sc fat areas were measured in all subjects by abdominal computed tomography scanning taken at the umbilical level. Any ip regions having the same density as the sc fat layer were defined as a visceral fat area; this area was measured by tracing object contours on films using a computerized planimetric method.

In addition, we measured blood pressure in the supine position after a rest of 5 min.

Statistical methods

Data were expressed as the means ± SD. Differences between groups were determined by unpaired *t* tests after checking the normal distribution of the data. The relationship of HOMA IR or QUICKI with clamp IR was evaluated by univariate regression analysis. Unpaired *t* tests and correlations were carried out using the StatView 4.0 software program (Abacus Concepts, Berkeley, CA) for the Macintosh computer. A *P* value less than 0.05 was considered as statistically significant.

Results

Type 2 diabetic patients were in poor glycemic control (fasting plasma glucose levels: group 1, 9.0 ± 2.6 mmol/liter;

group 2, 8.9 ± 2.3 mmol/liter; HbA1c: group 1, 9.5 ± 2.0%; group 2, 9.2 ± 1.7%; Table 1).

Among all diabetic patients (n = 56), clamp IR was significantly correlated with log-transformed HOMA IR (r = −0.37, $P < 0.01$) and QUICKI (r = 0.37, $P < 0.01$). Evaluation by age group showed that clamp IR is significantly correlated with log-transformed HOMA IR (r = −0.51, $P < 0.01$; Fig. 1, ○, *solid line*) and QUICKI (r = 0.50, $P < 0.01$; Fig. 2, ○, *solid line*) in group 2. However, neither log-transformed HOMA IR (r = −0.28, $P = 0.15$; Fig. 1, ●, *dotted line*) nor QUICKI (r = 0.31, $P = 0.12$; Fig. 2, ●, *dotted line*) was significantly correlated with clamp IR in group 1.

Log-transformed HOMA IR was strongly correlated with QUICKI in group 1 (r = −0.99, $P < 0.0001$), group 2 (r = −1.0, $P < 0.0001$), and in all patients (r = −1.0, $P < 0.0001$).

There was a significant correlation between fasting serum levels of insulin and clamp IR in group 2 patients (r = −0.39, $P < 0.05$) but not in group 1 patients (r = −0.08, $P = 0.67$).

Significant negative correlations were observed between clamp IR and visceral fat areas both in group 1 (r = −0.66, $P < 0.001$) and group 2 (r = −0.62, $P < 0.001$) patients.

The ability of insulin secretion in group 1 patients ($\Delta I_{30}/\Delta G_{30}$, 14.3 ± 10.6; AUC, 10,868.4 ± 5,905.2) was significantly decreased compared with group 2 patients ($\Delta I_{30}/\Delta G_{30}$, 17.6 ± 10.4, $P < 0.03$; AUC, 16,903.8 ± 6,527.4, $P < 0.02$).

Serum levels of AST, ALT, and creatinine in all patients were within the normal range (AST, 0–40 IU/liter; ALT, 0–35 IU/liter; creatinine, 53.0–123.8 μmol/liter; Table 1).

Discussion

The present study demonstrated that neither HOMA IR nor QUICKI is useful for assessing insulin resistance in elderly patients with poorly controlled type 2 diabetes mellitus.

Many studies have reported the usefulness of HOMA IR and QUICKI in type 2 diabetic patients (14–16). The values of HOMA IR and QUICKI depend on the fasting concentrations of insulin and glucose, and they are thought to estimate mainly hepatic insulin resistance (14). On the contrary, clamp IR reflects essentially peripheral insulin resistance (14). Peripheral insulin resistance is generally associated with decreased ability of insulin to suppress adipose tissue lipolysis (17). Insulin stimulation of lipolysis is associated with an increased flux of free fatty acids from fatty tissue to the liver and, at the same time, with decreased insulin-mediated suppression of hepatic glucose output (18). In the present study, we demonstrated a significant delayed and decreased insulin secretion in elderly patients with type 2 diabetes mellitus. This decreased ability to secrete insulin may alter the relation between peripheral lipolysis and hepatic glucose output. This alteration might explain the lack of correlation of clamp IR with HOMA IR or QUICKI in our elderly diabetic patients.

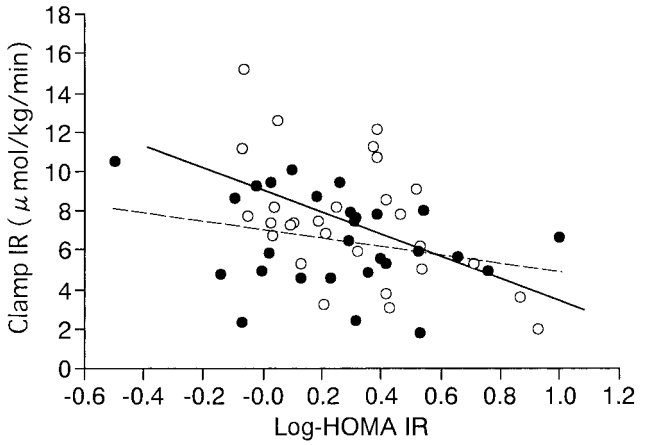

FIG. 1. Correlations between log-transformed HOMA IR and clamp IR in patients with type 2 diabetes mellitus. There was a significant negative correlation in group 2 (r = −0.51, $P < 0.01$, ○, *solid line*) but not in group 1 (r = −0.28, $P = 0.15$, ●, *dotted line*) patients.

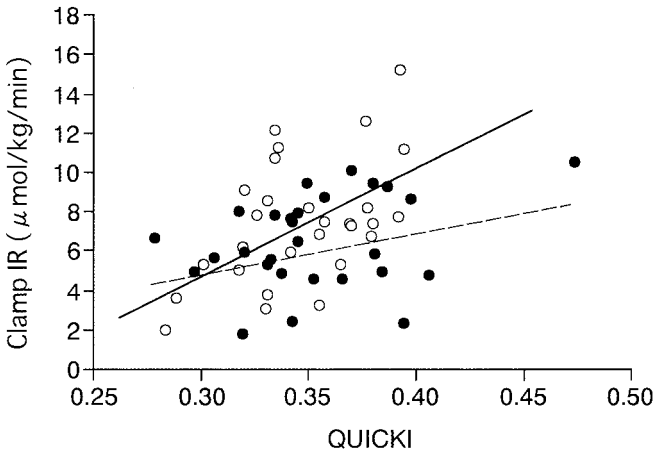

FIG. 2. Correlations between QUICKI and clamp IR in patients with type 2 diabetes mellitus. A significant positive correlation was observed in group 2 (r = 0.50, $P < 0.01$, ○, *solid line*) but not in group 1 (r = 0.31, $P = 0.12$, ●, *dotted line*) patients.

In the present study, fasting plasma levels of glucose (group 1, 9.0 ± 2.6 mmol/liter; group 2, 8.9 ± 2.3 mmol/liter) were relatively high compared with those reported in previous studies [6.6 ± 1.5 mmol/liter (4), 7.3 ± 2.3 mmol/liter (15), 7.8 ± 2.4 mmol/liter (19)]. It has been reported that fasting plasma levels of glucose may influence the correlation between HOMA IR and clamp IR; HOMA IR is suitable for evaluating insulin sensitivity in obese type 2 diabetic patients whose fasting glucose levels are 9.4 mmol/liter or less (20). Compared with data reported in previous studies [r = 0.92, $P < 0.0001$ (4); r = −0.75, $P < 0.0001$ (15); r = 0.75, $P < 0.0001$ (19)], the relationship between HOMA IR and clamp IR was relatively weak (r = −0.51, $P < 0.01$) in patients of group 2). The relatively high levels of fasting glycemia might have affected correlation between HOMA IR and clamp IR in patients of group 1.

The glucose clamp study may be performed based on different criteria; in our present study, the target blood glucose level of the clamp study was lower than the fasting level. Therefore, acute changes in insulin sensitivity judged based on changes in glucose levels may cause misinterpretation of the glucose clamp results; based on our present protocol, clamp IR may be overestimated. This factor may also explain the lack of correlation between clamp IR and HOMA IR or QUICKI in our elderly patients.

Patients of group 2 included 10 patients with macroproteinuria, but with normal serum levels of creatinine. HOMA IR has been reported to be useful in type 2 diabetic patients

with overt proteinuria and renal failure (15, 21). The defect of insulin secretion in these diabetic patients may be compensated by decreased renal clearance of insulin, and this phenomenon may contribute to maintain the relationship between hepatic and peripheral insulin resistance. Additional studies should be performed to clarify these points. Association between these insulin resistance indicators should also be assessed in patients with other vascular complications.

In conclusion, we found a limited value of HOMA IR and QUICKI for elderly patients with poorly controlled type 2 diabetes mellitus. A different index of insulin resistance should be developed for this group of patients.

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