Homeostasis Model Assessment as a Clinical Index of Insulin Resistance in Type 2 Diabetic Patients Treated With Sulfonylureas

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OBJECTIVE — To investigate whether the insulin resistance index (IR) assessed by homeostasis model assessment (HOMA) is associated with the insulin resistance index assessed by euglycemic-hyperinsulinemic clamp (clamp IR) in type 2 diabetic patients who received sulfonylureas (SUs), as well as in those treated by diet alone.

RESEARCH DESIGN AND METHODS — Retrospectively, the association between HOMA IR and clamp IR was analyzed in 80 type 2 diabetic subjects (53 subjects treated with SUs and 27 subjects treated with diet alone). The 80 subjects, selected because they had not received insulin therapy, were among 111 diabetic participants in a clamp study for evaluation of insulin resistance from May 1993 to December 1997 in Osaka City University Hospital.

RESULTS — The HOMA IR showed a hyperbolic relationship with clamp IR. The log-transformed HOMA IR (all subjects, $r = -0.725$, $P < 0.0001$; SU group, $r = -0.727$, $P < 0.0001$; diet group, $r = -0.747$, $P < 0.0001$) correlated more strongly with clamp IR than did HOMA IR per se (all subjects, $r = -0.594$, $P < 0.0001$; SU group, $r = -0.640$, $P < 0.0001$; diet group, $r = -0.632$, $P = 0.0004$). The univariate regression line between log-transformed HOMA IR and clamp IR in the SU group did not differ from that in the diet group (slope, -6.866 vs. -5.120, $P > 0.05$; intercept, 6.566 vs. 5.478, $P > 0.05$). Stepwise multiple regression analyses demonstrated that the log-transformed HOMA IR was the strongest independent contributor to clamp IR ($R^2 = 0.640$, $P < 0.0001$).

CONCLUSIONS — The HOMA IR strongly correlated with the clamp IR in type 2 diabetic patients treated with SUs as well as in those treated with diet alone.

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Insulin resistance is an important mechanism for the development and progression of diabetes and atherosclerotic disease, a common cause of mortality in diabetic patients (1,2). It is important to evaluate insulin resistance for the prevention and treatment of type 2 diabetes. Recently, the oral insulin-sensitizing agent troglitazone has been used clinically for glycemic control in diabetic patients (3). Diabetologists thus need a simple, precise, and easily repeatable index of insulin resistance, since the glucose clamp—the gold standard—is time-consuming, costly, and complex (4,5).

To date, several methods for evaluating insulin resistance in humans have been reported (4): fasting plasma insulin (FIRI) levels in epidemiologic studies (6,7), homeostasis model assessment (HOMA) (8,9), insulin tolerance test (10), insulin suppression test (11), steady-state plasma glucose method (12), and minimal model technique (13). Among these indexes, FIRI and the insulin resistance index (IR) by HOMA, calculated from FIRI and fasting plasma glucose (FPG) levels, are likely to be the most simple and repeatable indexes in diabetic outpatient clinics. In their initial report, Matthews et al. (8) demonstrated that HOMA IR highly correlated with the insulin resistance index assessed by euglycemic-hyperinsulinemic clamp (clamp IR) in a small number of type 2 diabetic subjects treated with diet alone. Anderson et al. (14) have reported that HOMA IR did not show a significant strength or consistency of association with clamp IR in type 2 diabetic subjects. To our knowledge, there are no reports on the validity of substituting HOMA IR for clamp IR in a large series of type 2 diabetic patients treated by oral hypoglycemic agents (OHA), although HOMA IR has been adopted as an index of insulin resistance in recent clinical studies (15–17). In a clinical use, the degree of association between HOMA IR and clamp IR even in type 2 diabetic patients receiving OHA remains unclear.

The present study investigated whether HOMA IR is associated with clamp IR in a retrospective analysis in type 2 diabetic patients treated with sulfonylureas as well as those treated with diet alone. We demonstrate the strong correlation between HOMA IR and clamp IR in 80 type 2 diabetic subjects treated with both sulfonylureas and diet alone.

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Abbreviations: CV, coefficient of variance; FIRI, fasting plasma insulin; FPG, fasting plasma glucose; HOMA, homeostasis model assessment; IR, insulin resistance index; OHA, oral hypoglycemic agents; SSPI, steady-state plasma insulin; SU, sulfonylurea.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

— There were 80 type 2 diabetic patients treated with sulfonylureas or diet alone who were retrospectively selected according to mode of glycemic control from the 111 diabetic subjects who underwent a euglycemic-hyperinsulinemic clamp for the evaluation of insulin resistance from May 1993 to December 1997 in Osaka City University Hospital. The diagnosis of diabetes was based on a previous history of diabetes or on World Health Organization criteria (18). The mean age of the 80 diabetic subjects, 51 men and 29 women, was 53.0 ± 12.9 years (mean ± SD), ranging from 19 to 74 years. The known duration of diabetes ranged from 1 to 26 years, with a mean of 8.6 ± 7.2 years. The numbers of subjects with normoalbuminuria, microalbuminuria, overt proteinuria, and chronic renal failure were 48, 18, 8, and 6, respectively. Blood pressure was measured three times using a mercury sphygmomanometer on the right arm after a 15-min rest in the supine position. BMI was calculated by dividing body weight (kilograms) by the square of the height (meters).

None of the 80 diabetic subjects had been treated with insulin therapy before the clamp study. The subjects were divided into two groups: 53 treated with sulfonylureas and 27 with diet alone. The clinical characteristics in the sulfonylurea (SU) and diet groups are shown in Table 1. No subjects were treated with insulin-sensitizing agents, troglitazone, or biguanides, before the clamp study.

Study design

All 80 type 2 diabetic subjects were admitted to our diabetes ward 1 week before the clamp study. During the admission, diet therapy was undertaken for all patients; the diet contained 30 kcal/kg of ideal body weight, 50% carbohydrate, 30% fat, and 20% protein. Sulfonylureas were taken until the day before the clamp study. After a 10- to 12-h overnight fast, a fasting blood sample was taken for the determination of FPG and FIRI levels.

The insulin resistance index assessed by the homeostasis model assessment was calculated as follows (8):

$$\text{HOMA IR} = \text{FIRI} \times \text{FPG}/22.5$$

where FIRI is fasting plasma insulin level (μU/ml) and FPG is fasting plasma glucose level (mmol/l).

To estimate the reproducibility of HOMA IR, we analyzed the second HOMA IR in 45 diabetic subjects evaluated on a separate occasion within 2 weeks of the first HOMA IR. The coefficient of variance (CV) for the two HOMA IRs was calculated as follows:

$$CV = (SD/\sqrt{2}) \times 100/\bar{x}$$

where SD is standard deviation for difference between the two HOMA IRs and $\bar{x}$ is the pooled mean value for HOMA IR. The CV for HOMA IR was 11.7%, and the correlation coefficient (r) between the two HOMA IRs was 0.958 ($P < 0.0001$).

The clamp study was performed using an artificial pancreas model STG 22 (Nikkiso, Tokyo) according to the method of DeFronzo et al. (5). We previously described the details of the study protocols, including the clamp (19–22). In brief, insulin (Humulin; Eli Lilly, Indianapolis, IN) was infused in a continuous fashion at a rate of 1.25 mU · kg^{-1} · min^{-1} after the priming insulin infusion during the first 10 min of the clamp at the same doses as previously reported (5). Blood glucose levels were determined every 5 min during the 120–min clamp study, and euglycemia (5.0 mmol/l) was maintained by infusion of variable amounts of 20% glucose solution. 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 insulin resistance index by the clamp (clamp IR) was calculated by dividing the mean glucose infusion rate by the steady-state plasma insulin (SSPI) levels during the last 30 min of the clamp.

Plasma glucose levels were measured by the glucose oxidase method, HbA_{1c} by high-pressure liquid chromatography (normal range 4.0–5.5%), and plasma insulin levels by immunoradiometric assay (Insulin Riabead II kit; Dainabot, Tokyo). Serum creatinine, serum total cholesterol, triglyceride, HDL cholesterol, and free fatty acid levels were measured by enzymatic methods adapted to an autoanalyzer (Hitachi 7450; Hitachi, Tokyo) .

Statistical analyses

Statistical analyses were performed with the Statview IV system (Abacus Concepts, Berkeley, CA) for Apple computer. Unpaired Student's t tests and χ^2 tests were used where appropriate for the comparisons of clinical parameters between the SU and diet groups. Univariate regression analyses and stepwise multiple regression analyses were performed to evaluate the relationships among clamp IR and various clinical factors including HOMA IR. A P value <0.05 was considered significant.

Table 1—*Clinical characteristics of 80 type 2 diabetic subjects*

	SU group	Diet group	P value
n	53	27	—
Sex (M/F)	34/19	17/10	0.917
Age (years)	54.7 ± 10.1	49.6 ± 16.7	0.096
Duration of diabetes (years)	8.5 ± 6.3	9.1 ± 8.7	0.716
BMI (kg/m^2)	22.7 ± 3.4	24.6 ± 3.2	0.016*
Blood pressure (mmHg)			
Systolic	129 ± 24	128 ± 23	0.968
Diastolic	73 ± 11	71 ± 9	0.682
FPG (mmol/l)	7.7 ± 2.1	7.3 ± 2.3	0.612
HbA_{1c} (%)	9.0 ± 2.2	7.8 ± 1.9	0.021*
Fasting plasma insulin (pmol/l)	40.5 ± 28.8	32.5 ± 19.4	0.145

Data are n or means ± SD. SU group, subjects treated with sulfonylureas; diet group, subjects treated with diet alone. *$P < 0.05$, SU group vs. diet group.

RESULTS — In simple regression analyses, HOMA IR highly correlated with clamp IR in both SU and diet groups (all subjects, $r = -0.594$, $P < 0.0001$; SU group, $r = -0.640$, $P < 0.0001$; diet group, $r = -0.632$, $P = 0.0004$). Since the visual inspection suggested a skewed hyperbolic relationship between HOMA IR and clamp IR, the log-transformed HOMA IR was analyzed (Fig. 1). The log-transformed HOMA IR (all subjects, $r = -0.725$, $P < 0.0001$; SU group, $r = -0.727$, $P < 0.0001$; diet group, $r = -0.747$, $P < 0.0001$) correlated

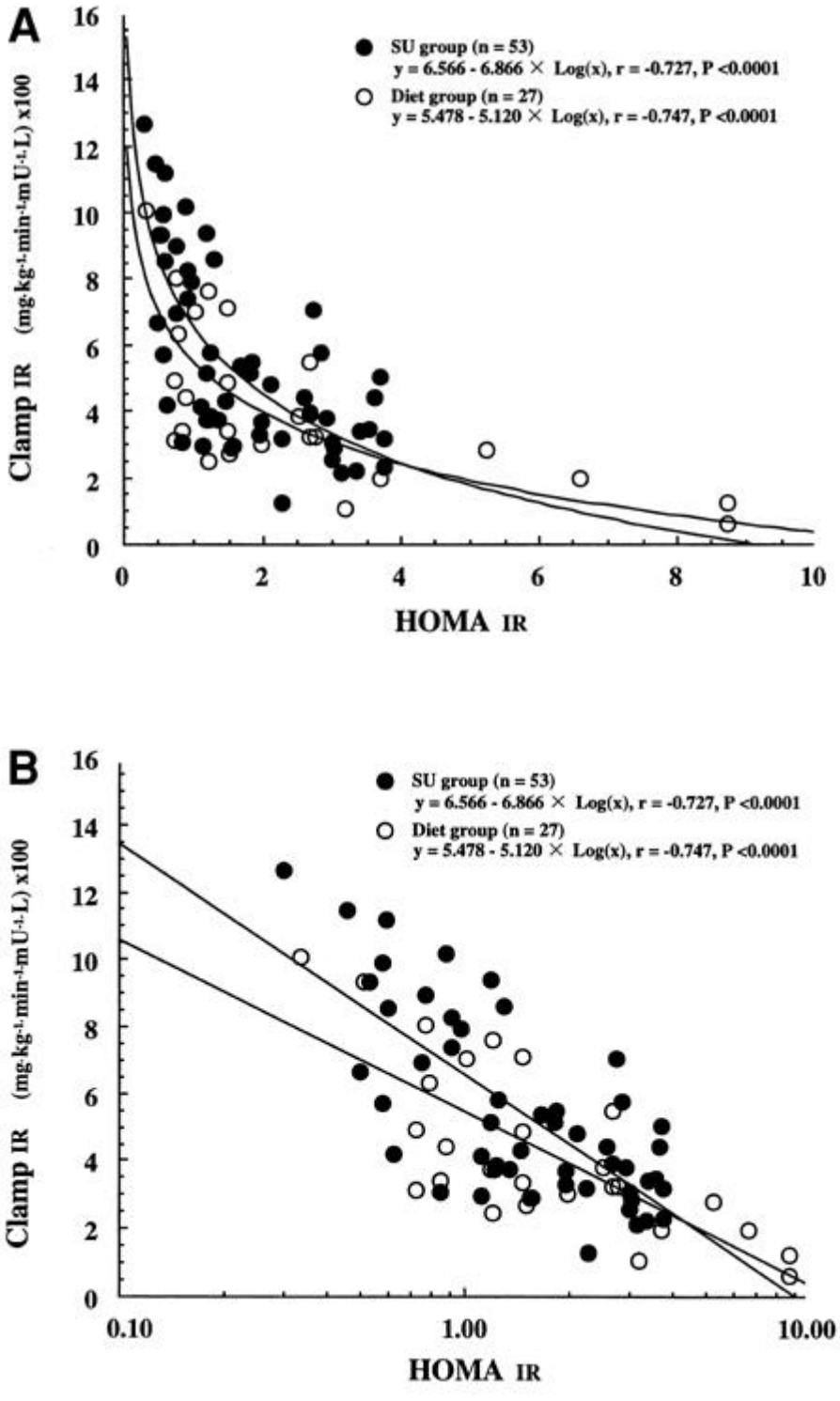

Figure 1—*The relationship between HOMA IR and clamp IR in 80 type 2 diabetic subjects. The univariate regression lines between HOMA IR and clamp IR are shown on the x-axis of the real (A) and the log (B) scales. HOMA IR showed the skewed hyperbolic relationship with clamp IR, and the nonlinear lines fitted the data better than linear lines in both SU (●) and diet (○) groups. The log-transformed HOMA IR highly correlated with clamp IR in both SU and diet groups (all subjects,* r = −*0.725,* P < *0.0001; SU group,* r = −*0.727,* P < *0.0001; diet group,* r = −*0.747,* P < *0.0001). The univariate regression line between log-transformed HOMA IR and clamp IR in the SU group did not differ from that in the diet group (slope,* −*6.866 vs.* −*5.120,* P > *0.05; intercept, 6.566 vs. 5.478,* P > *0.05).*

Table 2—*Correlation coefficients by simple linear regression analyses between clamp IR and clinical variables in 80 type 2 diabetic subjects*

	r value	*P* value
Age	0.034	0.767
Duration of diabetes	0.076	0.505
BMI	0.570	<0.0001*
Systolic blood pressure	0.205	0.108
Diastolic blood pressure	0.101	0.431
HbA_{1c}	0.043	0.705
Total cholesterol	0.298	0.007
Triglyceride	0.182	0.107
HDL cholesterol	0.052	0.644
Free fatty acid	0.346	0.002*
1/Creatinine	0.036	0.752

*$P < 0.05$.

more strongly with clamp IR than did HOMA IR per se in both SU and diet groups. Therefore, the nonlinear lines fitted the data better than linear lines in both SU and diet groups. The regression line between HOMA IR and clamp IR in the SU group did not significantly differ from that in the diet group (slope, −6.866 vs. −5.120, $P > 0.05$; intercept, 6.566 vs. 5.478, $P > 0.05$). FIRI also showed a strong correlation with clamp IR (all subjects, $r = -0.628$, $P < 0.0001$) as did HOMA IR, although FPG did not (all subjects, $r = -0.211$, $P = 0.060$). Table 2 demonstrates the correlation coefficients between clamp IR and the other clinical variables by simple linear regression analyses. There were significant inverse correlations between clamp IR and BMI, serum total cholesterol, and free fatty acid levels.

Since these clinical variables were expected to be mutually associated, stepwise multiple regression analyses were performed, in which clamp IR was included as a dependent variable and significant variables in simple regression analyses as independent variables (Table 3). The highest value of the coefficient of determinations (R^2) among the models was 0.640 in model 3, which included the log-transformed HOMA IR as a dependent variable ($P < 0.0001$).

CONCLUSIONS — The present study demonstrated the strong association between HOMA IR and clamp IR, the gold standard of insulin resistance, in type 2 diabetic subjects. Log-transformed HOMA IR, age, and BMI were independent con-

Table 3—*Stepwise multiple regression analyses of HOMA IR determining the clamp IR in 80 type 2 diabetic subjects*

	Model 1		Model 2		Model 3	
	β	*F*	β	*F*	β	*F*
Age	–0.318	13.728	–0.339	16.003	–0.279	14.208
Duration of diabetes	—	0.964	—	2.610	—	1.827
BMI	–0.351	13.941	–0.441	27.061	–0.308	13.898
HbA_{1c}	—	0.833	—	0.576	—	0.854
Free fatty acid	—	2.570	—	0.100	—	0.490
SU or diet group	—	0.605	—	0.226	—	–2.587
Fasting plasma insulin	–0.568	33.100				
HOMA IR			–0.550	38.163		
Log-transformed HOMA IR					–0.653	61.623
R^2	0.546	$P < 0.0001$	0.566	$P < 0.0001$	0.640	$P < 0.0001$

The *F* value to enter was set at 4.0 at each step. The SU group was entered as 1 and the diet group as 0.

tributors to clamp IR in the multiple regression models, which explained 64% of the clamp IR variability. For the first time, our results prove the validity for clinical use of the HOMA IR as an insulin resistance index in most type 2 diabetic subjects, since our type 2 diabetic subjects included patients treated with OHA.

Previous reports have not demonstrated any grounds for clinical use of HOMA IR in most type 2 diabetic patients, especially those treated with OHA. Matthews et al. (8) have demonstrated that HOMA IR closely correlated with clamp IR in 12 normal and 11 type 2 diabetic subjects. A few limitations for its clinical use were also shown in their initial report. First, HOMA IR showed a low precision in estimating from HOMA IR. Second, their data in association with clamp IR were obtained from a small number of type 2 diabetic subjects treated with diet alone. Third, clamp IR in their report was expressed by values relative to the median value from normal-weight nondiabetic subjects. Insulin sensitivity even in healthy subjects is known to vary widely (23). Thus it seems to be difficult to determine the standard values of insulin resistance in normal subjects. Anderson et al. (14) demonstrated that HOMA IR did not have significant strength and consistency of association with clamp IR in 55 subjects with normal glucose tolerance (n = 11), impaired glucose tolerance (n =20), and type 2 diabetes (n = 24). So it remains to be clarified whether HOMA IR is associated with clamp IR in type 2 diabetic patients receiving oral hypoglycemic agents.

The present study clearly demonstrated that HOMA IR was closely associated with clamp IR in the SU as well as the diet group. HOMA IR in both SU and diet groups showed a strong hyperbolic relationship with the gold standard index of insulin resistance, as do fasting plasma insulin levels in healthy subjects reported by others (7). The regression line and correlation coefficient between HOMA IR and clamp IR in the SU group did not differ from those in the diet group. Furthermore, the presence of sulfonylurea therapy did not independently contribute to clamp IR in our multiple regression analyses. Our data indicate that HOMA IR is a useful index of insulin resistance even in diabetic patients treated by OHA.

In our multiple regression analyses, log-transformed HOMA IR was shown to be the strongest contributor to clamp IR among the clinical variables. For the first time, our study demonstrates that the log-transformed HOMA IR was stronger in the contribution to clamp IR than HOMA IR per se according to the hyperbolic skewed relationship between HOMA IR and clamp IR. The formula of the estimates for clamp IR was obtained from model 3 in our multiple regression analyses, as follows: estimates of clamp IR = $14.876 - 0.059 \times$ age $- 0.243 \times$ BMI $- 5.564 \times \log$ (HOMA IR). It is noteworthy that 64% of the clamp IR variability was contributed by the three factors age, BMI, and HOMA IR, which is calculated by the data from one blood sampling. This finding from our study allows the use of HOMA IR as an insulin resistance index in outpatient clinics.

In conclusion, HOMA IR was highly associated with clamp IR in type 2 diabetic patients treated with sulfonylureas and diet alone. Therefore, it is valid that HOMA IR be used as a simple index of insulin resistance substituted for clamp IR in type 2 diabetic patients.

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