Homeostasis Model Assessment Is a Reliable Indicator of Insulin Resistance During Follow-up of Patients With Type 2 Diabetes

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OBJECTIVE — To investigate the usefulness of the homeostasis model assessment as an index of insulin resistance (HOMA-IR) for evaluating the clinical course of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — The usefulness of HOMA-IR and its relationship with insulin resistance assessed by the hyperinsulinemic-euglycemic clamp study (clamp IR) were evaluated in 55 Japanese patients with type 2 diabetes before and after treatment. The patients were subjected to diet (~1,440–1,720 kcal/day) and exercise therapy (walking 10,000 steps daily) for 6 weeks during their hospitalization.

RESULTS — Univariate regression analysis disclosed a significant correlation between log-transformed HOMA-IR and log-transformed clamp IR before ($r = -0.613$, $P < 0.0001$) and after ($r = -0.734$, $P < 0.0001$) treatment. Neither the slopes (-0.71 ± 0.12 vs. -0.79 ± 0.09, $F = 0.25$, $P = 0.61$) nor the intercepts (y-intercept = 1.67 vs. 1.70, x-intercept = 2.36 vs. 2.15, $F = 0.02$, $P = 0.88$) of the regression lines between HOMA-IR and clamp IR were significantly different before and after treatment. There was a significant correlation between the decrease in log-transformed HOMA-IR and the increase in clamp IR during treatment ($r = -0.617$, $P < 0.0001$).

CONCLUSIONS — HOMA-IR may constitute a useful method not only for diagnosing insulin resistance, but also for follow-up during the treatment of patients with type 2 diabetes.

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Insulin resistance is currently being measured by using the glucose clamp technique (1). Although this method is highly sensitive and shows high reproducibility, it is time-consuming and very expensive. A rapid, accurate, and low-cost method for assessing insulin resistance would be very useful in clinical practice.

To date, several methods for evaluating insulin resistance have been proposed, including homeostasis model assessment (HOMA-IR), continuous infusion of glucose with model assessment, calculations of sensitivity indexes using insulin and glucose in the post–oral glucose load state, fasting insulin levels, and serum levels of sex hormone–binding globulin (SHBG) (2–10). Recently, the usefulness of HOMA-IR as an indicator of insulin resistance in diabetic patients has been the focus of much attention (11–13). A significant correlation has been reported between the insulin resistance index calculated by HOMA and the hyperinsulinemic-euglycemic clamp (clamp IR) (11,12).

We previously reported that the serum levels of SHBG may be an index of insulin resistance only in the hyperinsulinemic state (before treatment) (7). The usefulness of HOMA as an index of insulin resistance during therapy of diabetes has not been as yet evaluated. To evaluate this, in the present study, we investigated whether HOMA-IR is correlated with clamp IR before and after treatment.

RESEARCH DESIGN AND METHODS

— A total of 55 patients with type 2 diabetes treated with diet alone and with sulfonylureas were enrolled in the present study (Table 1). BMI was estimated by dividing the body weight (in kilograms) by the square of the height (in meters).

Diabetes was diagnosed according to the criteria of the American Diabetes Association (14). Subjects with fasting plasma glucose levels ≥7.0 mmol/l were provisionally diagnosed as having diabetes. Thereafter, the subjects underwent a 75-g oral glucose tolerance test (OGTT) (Trelan G 75; Shimizu, Shizuoka, Japan), and those with fasting plasma glucose levels ≥7.0 mmol/l or 2-h plasma glucose levels ≥11.1 mmol/l were diagnosed as having diabetes. Type 2 diabetes was defined according to the grade of insulin secretion, the age, the pattern of onset, and the existence of family history of diabetes.

On admission, 50 patients were treated with diet alone and 5 with sulfonylureas (glibenclamide 2.5–5.0 mg/day). None of the patients was being treated with insulin or insulin-sensitizing agents. Fifteen patients had peripheral neuropathy and simple diabetic retinopathy and 10 had

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Abbreviations: clamp IR, insulin resistance assessed by the hyperinsulinemic-euglycemic clamp; HOMA-IR, homeostasis model assessment of insulin resistance; OGTT, oral glucose tolerance test; SHBG, sex hormone–binding globulin.

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

Table 1—*Clinical characteristics of patients with type 2 diabetes before and after treatment*

	Before treatment	After treatment
n	55	—
Sex (M/F)	44/11	—
Age (years)	54.7 ± 10.6	—
Duration of diabetes (years)	8.3 ± 6.7	—
BMI (kg/m^2)	23.6 ± 3.2	22.3 ± 2.9*
Visceral fat area (cm^2)	109.2 ± 50.9	96.1 ± 49.5*
Subcutaneous fat area (cm^2)	121.9 ± 55.3	111.9 ± 54.4
Systolic blood pressure (mmHg)	131.5 ± 22.0	128.3 ± 17.1
Diastolic blood pressure (mmHg)	79.4 ± 11.7	78.9 ± 10.7
Fasting plasma glucose (mmol/l)	8.7 ± 2.6	6.4 ± 1.6*
HbA_{1c} (%)	9.5 ± 2.4	8.2 ± 1.5*
Fasting serum insulin (pmol/l)	39.0 ± 22.2	34.8 ± 23.4
Clamp IR (μmol · kg^{-1} · min^{-1})	35.4 ± 16.9	50.1 ± 13.6*
HOMA-IR	2.4 ± 1.6	1.7 ± 1.2*

Data are *n* or means ± SD. *$P < 0.01$ vs. before treatment.

microalbuminuria. Macrovascular complications were not detected.

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

Study design

After admission, the patients were subjected to diet and exercise therapy for 6 weeks. The dietary treatment was as follows: 1,440–1,720 kcal/day with a diet consisting of 20% (energy) protein, 25% fat, and 55% carbohydrates. The compliance of dietary therapy was checked by a dietitian twice a week. During the exercise therapy, the patients walked about 10,000 steps daily; the number of steps per day was counted using a pedometer, and the count was checked by a nurse on each day. Diet and exercise therapies were not modified during the course of the treatment.

The blood levels of glucose, HbA_{1c}, and insulin; the values of clamp-IR, HOMA-IR, and the simple indexes of insulin sensitivity (the 30-min and 2-h glucose, 30-min and 2-h insulin, and 30-min and 2-h insulin sensitivity index [10^4/(insulin ± glucose)] obtained during a 75-g OGTT) (9,10); and body fat area and blood pressure were measured in all subjects within 1 week after admission and 1 week before discharge. Sulfonylureas were withdrawn 1 day before the clamp study; none of the patients received any drug after the first clamp study during treatment.

The plasma glucose level was measured by an automated enzymatic method. The HbA_{1c} (normal value 4.3–5.8%) was measured by high-performance liquid chromatography. Serum insulin was measured using an immunoradiometric assay kit (Insulin Riabead II kit; Dainabot, Tokyo). This kit included ^{125}I-labeled and unlabeled anti–human insulin mouse monoclonal antibodies. The intra- and interassay coefficients of variation of the assay were 1.9 and 2.0%, respectively.

Clamp IR was evaluated by the hyperinsulinemic-euglycemic clamp technique using the artificial pancreas (STG-22; Nikkiso, Tokyo) (1,7,15–18). In brief, at 8:00 A.M., two Teflon-coated cannulae were inserted; one was inserted into the left antecubital vein for infusion of insulin (Humulin R; Eli Lilly, Indianapolis, IN) and 10% glucose, and the other was inserted into the right contralateral heated hand vein for arterialized blood sampling. After baseline blood collections for glucose and insulin determinations, a priming dose of insulin was administered during the initial 10 min in a logarithmically decreasing manner to raise serum insulin rapidly to the desired level (1,200 pmol/l); this level of insulin was then maintained by a continuous insulin infusion at a rate of 13.44 pmol · kg^{-1} · min^{-1} for 120 min. The mean insulin level reached a stable level between 90 and 120 min after starting the clamp study (before treatment 1,224.0 ± 208.8 pmol/l; after treatment 1,177.2 ± 232.8 pmol/l). Blood glucose was monitored continuously and maintained at the desired level (5.24 mmol/l) by infusing 10% glucose. The mean amount of glucose given during the last 30 min was considered as the glucose infusion rate, which was taken as the value of the clamp IR.

HOMA was used to evaluate insulin resistance before and after treatment (2). Assuming that normal subjects aged <35 years with normal weight have an IR of 1, the values for a patient can be calculated from the fasting concentrations of insulin and glucose using the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5. Blood samples for HOMA-IR measurements were drawn from each subject from 8:00 A.M. after an overnight bed rest. We examined three separate insulin samples taken 15 min apart, and the averaged insulin level was used for the HOMA-IR calculation. To estimate the reproducibility of HOMA-IR, we analyzed a second HOMA-IR in all patients on another occasion within 5 days of the first HOMA-IR before and after treatment. The coefficient of variation for HOMA-IR before treatment was 10.2% and 9.8% after treatment.

The 75-g OGTT was started from 8:00 A.M. after an overnight bed rest (hunger for 11:00 h). Blood was taken at 0, 30, and 120 min, and plasma glucose and serum insulin levels were evaluated.

The body fat area was evaluated as previously described (19). The total cross-sectional area, the intra-abdominal visceral fat area, and the subcutaneous fat area were measured by abdominal computed tomography taken at the umbilical level. Any intraperitoneal region having the same density as the subcutaneous fat layer was defined as a visceral fat area.

Blood pressure was determined three times in the supine position after a 5-min rest.

Statistical analyses

Data are expressed as means ± SD. Student's *t* test was performed to compare the means of variables measured before and after treatment. The relationship of clamp IR with several clinical indexes of insulin sensitivity was evaluated by univariate regression analysis. Comparison of the regression lines, with respect to slopes and intercepts, between HOMA-IR and clamp IR before and after treatment was conducted by analysis of covariance; in this analysis, the *F* test was used to evaluate the difference between two regression coefficients. To approach normal distribution, the values of HOMA-IR and clamp IR were all transformed logarithmically before regression and covariance analysis. Student's *t* test and correlations were carried out using the StatView 4.0 software program (Abacus Concepts, Berkeley, CA) for the Macintosh. Analysis of covariance and regression analysis were performed using

the PRISM 2.0 software program (GraphPad software, San Diego, CA) for the Macintosh. A probability value of $P < 0.05$ on two-sided tests was considered statistically significant.

RESULTS — The univariate regression analysis showed that HOMA-IR is significantly correlated with clamp IR ($r = -0.625$, $P < 0.0001$). Log-transformed HOMA-IR also significantly correlated with log-transformed clamp IR ($r = -0.613$, $P < 0.0001$) (Fig. 1).

Concomitant to the improvement in the blood concentrations of glucose and HbA_{1c} and to the decrease in BMI and visceral fat areas, a significant increase in clamp IR and a decrease in HOMA-IR were observed (Table 1). Patients walked a mean of 10,200 ± 1,200 steps/day during the whole treatment.

After therapy, HOMA-IR was inversely and significantly correlated with the clamp IR ($r = -0.726$, $P < 0.0001$). Similarly, there was also a significant correlation between log-transformed HOMA-IR and log-transformed clamp IR after treatment ($r = -0.734$, $P < 0.0001$) (Fig. 1). The analysis of covariance showed that neither the slopes (-0.71 ± 0.12 vs. -0.79 ± 0.09, CI = -0.96 ± -0.45, $F = 0.25$, $P = 0.61$) nor the intercepts (y-intercept = 1.67 vs. 1.70, x-intercept = 2.36 vs. 2.15, $F = 0.02$, $P = 0.88$) of the regression lines between log-transformed HOMA-IR and log-transformed clamp IR before and after treatment were statistically different in magnitude.

There was a significant correlation between the change in log-transformed HOMA-IR and that in clamp IR ($r = -0.617$, $P < 0.0001$).

Significant correlations were observed between clamp IR and fasting serum insulin levels before ($r = -0.444$, $P < 0.01$) and after ($r = -0.524$, $P < 0.0001$) treatment. No significant correlations were observed between clamp IR and other simple indexes of insulin sensitivity during the oral glucose load before and after treatment.

CONCLUSIONS — The present study clearly demonstrated that HOMA-IR correlates significantly with clamp IR, not only before, but also after treatment in type 2 diabetic patients.

Oral insulin-sensitizing agents have been recently used in Japan for glycemic control in patients with type 2 diabetes. Although HOMA-IR is used as an index of insulin resistance in type 2 diabetic patients (20–23), its relation with clamp IR during the clinical course of type 2 diabetic patients has not been elucidated as of yet. In the present study, the slope and intercept of the regression lines between HOMA-IR and clamp IR did not significantly differ before and after treatment; this finding suggests that HOMA-IR is a reliable index of insulin resistance for the follow-up of type 2 diabetic patients. This is the first report that shows the usefulness of HOMA-IR as an index of insulin sensitivity during the clinical course of patients with type 2 diabetes.

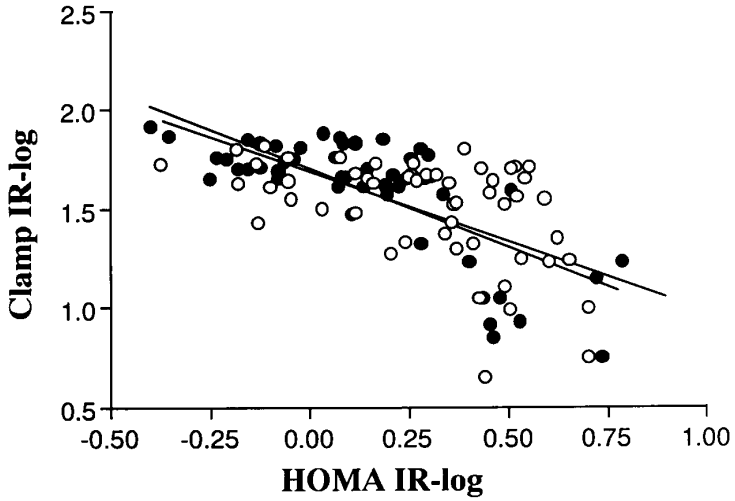

Figure 1—*Correlation between log-transformed HOMA-IR and log-transformed clamp IR before (○) and after (●) treatment. Log-transformed HOMA-IR was significantly correlated with log-transformed clamp IR before (r = −0.613, P < 0.0001) and after (r = −0.734, P < 0.0001) treatment. Neither the slopes (−0.71 ± 0.12 vs. −0.79 ± 0.09, F = 0.25, P = 0.61) nor the intercepts (y-intercept = 1.67 vs. 1.70, x-intercept = 2.36 vs. 2.15, F = 0.02, P = 0.88) of the regression lines before and after treatment were significantly different.*

Hanson et al. (9) reported that all indexes based on fasting insulin concentrations, especially HOMA-IR, show significant correlation with clamp IR in a large number of subjects with normal and impaired glucose tolerance (9). In the present study, we demonstrated similar findings in patients with type 2 diabetes. Overall, these observations illustrate the usefulness of HOMA-IR in subjects with various degrees of glucose tolerance (12).

Our present study showed improvement of clamp IR and HOMA-IR after treatment. Many studies demonstrated that daily walking in combination with diet therapy improved clamp IR in obese patients with type 2 diabetes (15,24). Although our diabetic patients were nonobese subjects based on the BMI values, they were metabolically obese with significant accumulation of visceral fat (25). Therefore, daily walking combined with diet therapy may be useful even in metabolically obese patients with type 2 diabetes (7). On the other hand, clamp IR mainly reflects peripheral insulin resistance, whereas HOMA-IR is thought to reflect essentially hepatic insulin resistance (12,26). It has been reported that exercise combined with diet therapy might improve fasting hyperglycemia caused by failure of insulin action in the liver itself (24). Thus, in our present study, improvement of HOMA-IR after treatment may be the result of improved hepatic insulin resistance. An additional finding in the present study was the significant correlation between changes in log-transformed HOMA-IR and clamp IR during treatment. The explanation for this association is not clear, but it may depend on the existence of a close relationship between the degree of lipolysis in adipose tissue and the flux of free fatty acids from adipocytes to the liver (27); however, further studies must be carried out to clarify this point.

In conclusion, our results suggest that HOMA-IR may constitute a useful method not only for diagnosing insulin resistance but also for follow-up during the treatment of patients with type 2 diabetes.

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