Surrogate index for insulin sensitivity composed of factors not using glucose and insulin in Japanese patients with diabetes

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ABSTRACT

Introduction: The aim of the present study is to propose a novel index of insulin sensitivity instead of homeostasis model assessment of insulin resistance (HOMA-IR), which has a fundamental limitation of validity when applied to subjects with lower insulin secretions or high fasting plasma glucose (FPG) levels.

Materials and Methods: A total of 25 apparently healthy subjects and 24 patients with type 2 diabetes participated in the study. We assessed relationships of glucose infusion rate (GIR), obtained by using the euglycemic hyperinsulinemic glucose clamp technique, with other measurements of metabolic and anthropometric parameters.

Results: In multiple regression analysis, a model including log-transformed (log) triglyceride/log high-density lipoprotein cholesterol and waist circumference as predictive variables showed the strongest contribution rate to explain GIR as an outcome variable ($R^2 = 0.710$). The validity of estimated GIR (EGIR) calculated from the regression equation composed of these factors was further tested in another group of patients including type 1, type 2 and pancreatic diabetes in whom HOMA-IR could not be used as a result of either high FPG or low fasting insulin level, or both. Even in those patients, EGIR showed a good positive relationship with measured GIR ($r = 0.681$, $P < 0.0001$).

Conclusions: The proposed index without HOMA-IR can adequately show insulin sensitivity in Japanese diabetic patients, even in cases with the limitation of HOMA-IR application. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00076.x, 2011)

KEY WORDS: Insulin resistance, Glucose clamp, Surrogate index

INTRODUCTION

So far, homeostasis model assessment of insulin resistance (HOMA-IR)[1] and quantitative insulin sensitivity check index (QUICKI)[2] have been proposed and widely used as surrogate indexes of insulin resistance in clinical practice. These parameters are simply calculated from fasting plasma glucose (FPG) and fasting insulin resistance index (FIRI), and show a high correlation with the indexes of insulin resistance assessed by euglycemic hyperinsulinemic glucose clamp (GC-IR), the gold standard technique for the estimation of insulin resistance[3]. However, these indexes sometimes failed to a show close relationship with GC-IR, especially in subjects with a lower body mass index (BMI), a lower beta β-cell function and high fasting glucose levels, such as lean type 1 or type 2 diabetic patients with insulin secretory defects[4]. The limitation of the validity of the HOMA-IR should be carefully taken into account for the estimation of insulin resistance.

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The ratio of triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) concentrations has been recognized as a marker of atherosclerosis and a strong predictor for future cardiovascular disease (CVD)[5]. The TG/HDL-C ratio has also been reported to be a useful metabolic marker to identify insulin resistance in healthy subjects[6] and overweight individuals[7]. Furthermore, it is often documented that subjects with non-alcoholic fatty liver disease (NAFLD) and elevated alanine aminotransferase (ALT) levels are at an increased risk of developing diabetes and metabolic syndrome[8]. This might be because of the relationship between elevated liver enzyme and insulin resistance as reflected by HOMA-IR[9], and it has been clinically shown that ALT level is related to decreased insulin sensitivity measured by GC-IR[10]. Thus, it is plausible that the TG/HDL-C ratio and/or liver enzyme, such as ALT, could be a candidate parameter for the estimation of insulin sensitivity instead of HOMA-IR.

In contrast, body composition, such as visceral or subcutaneous fat (F) amount and skeletal muscle (M) amount, has a pivotal role in whole body insulin sensitivity. Increased visceral or subcutaneous F is negatively correlated with GC-IR[11,12] in non-diabetic obese subjects. It has been proven that waist circumference (WC) has a close relationship with visceral fat in both

sexes and increased WC is related to the occurrence of obesity-related disorders indicative of future CVD events[13]. Conversely, decreased M, especially in the elderly, could diminish insulin sensitivity and consequently impair glucose uptake, storage and use in peripheral tissues[14]. Thus, body composition also plays an important role in accounting for individual insulin sensitivity, together with the metabolic factors aforementioned.

The aim of the present study was to propose a surrogate index for the estimation of insulin sensitivity in Japanese diabetic patients, even if their HOMA-IR was not adequately applied as a result of either high fasting blood glucose or low insulin level, or both.

SUBJECTS AND METHODS

Subjects

A total of 25 healthy volunteers (Group C: 21 men and four women) with a mean (±SD) age of 37 ± 9 years and body mass index (BMI) of 21.7 ± 2.4 kg/m^2 participated in the present study. None of the subjects had a family history of diabetes. Diabetic patients were randomly selected from admitted patients to the endocrinology and metabolism ward in Kurume University Hospital, Kurume, Japan, from November 2007 to December 2009. Patients with excessive alcohol consumption (more than 120 g of ethanol per day), severe liver dysfunction (viral hepatitis or liver cirrhosis), renal dysfunction (serum creatinine concentration over 132.6 μmol/L), known malignant disease and chronic inflammatory disease (e.g. rheumatoid arthritis) were excluded from the study. After the stabilization period for metabolic parameters (7 ± 2 days after admission), such as blood glucose, blood pressure and lipid profile, the eligibility of each patient was evaluated. Because of the comparison of a current index with HOMA-IR, patients with type 2 diabetes who had both FPG of 8.8 mmol/L or less and fasting plasma insulin level (FIRI) of 18 pmol/L or over were initially enrolled (Group DM1: nine men and 15 women, 60 ± 11 years, BMI 25.5 ± 5.2), because the accuracy of HOMA-IR has been proposed in diabetic patients within this cut-off value of FPG and FIRI[7]. In contrast, another group of diabetic patients with either FPG more than 8.8 mmol/L or FIRI <18 pmol/L or both were further recruited to confirm the validity of a surrogate index derived from the data of both group C and DM1. These patients were those with type 2 diabetes (Group DM2: 15 men and seven women, 59 ± 12 years, BMI 24.2 ± 4.4) and those with type 1 diabetes or diabetes as a result of pancreatic disease, such as chronic pancreatitis or pancreatectomy (Group DM3: 14 men and seven women, 14 type 1 and seven pancreatic diabetes, 42 ± 20 years, BMI 19.1 ± 3.1). Diagnosis of type 1 diabetes was carried out by the positive anti-glutamic acid decarboxylase antibody or the abrupt onset of diabetes with symptoms or signs such as thirst, polyuria, weight loss or ketoacidosis.

Six DM1 patients had not been given any medication for diabetes, five patients had been treated with sulfonylurea, eight had been treated with biguanide, four had been treated with α-glucosidase inhibitor, one had been treated with glinide and two had been treated with insulin. Four DM2 patients had not been given any medication for diabetes, eight had been treated with sulfonylurea, five had been treated with biguanide, three has been treated with α-glucosidase inhibitor and eight had been with insulin. All patients in group DM3 had been treated with multiple injections of insulin. Patients treated with oral hypoglycemic agents were instructed to cancel their medications for the day before GC (for at least 24 h) according to the half-life of each drug indicated in its instructions of the pharmaceutical company. Patients treated with long-acting or intermediate-acting insulin in the evening or before bedtime were instructed to cancel it the day before GC, because FIRI level, an essential component for the calculation of HOMA-IR, might be affected by those insulin injections. Among DM1 patients, statin was given in eight patients for the treatment of dyslipidemia, including one patient further treated with fibrate. Among the DM2 and DM3 patients, eight patients were treated with statin and one with fibrate. Both healthy subjects and diabetic patients were on their usual diet before the study day and none were engaged in heavy exercise. All subjects gave their written consent after being informed. The study was carried out in accordance with the Declaration of Helsinki and approved by the ethics committee of Kurume University School of Medicine.

Blood Sampling and Measurements

After an overnight fast without any medication, including oral hypoglycemic agents or insulin in the morning, bodyweight, waist circumference and blood pressure were measured, and blood samples were obtained from the antecubital vein into fluoride tubes for analysis of FPG, into EDTA-2Na for hemoglobin A_{1c} (HbA_{1c}), and into a plain siliconized tube for other measurements. Blood samples were then immediately centrifuged at 4°C and stored at −70°C until the assays.

FPG, HbA_{1c}, low-density lipoprotein cholesterol (LDL-C), HDL-C, TG, ALT, aspartate aminotransferase (AST) and uric acid (UA) levels were measured according to the standard procedures. FIRI was measured by an enzyme-linked immunosorbent assay. Systolic (SBP) and diastolic blood pressure (DBP) were measured by an automatic electronic sphygmomanometer (BP-103i II; Colin Medical Technology, Komaki, Japan) in the sitting position after resting for at least 5 min. Waist circumference (WC) was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest according to the guideline of IDF[15]. The HOMA-IR was calculated from FPG and FIRI according to the report by Matthews *et al.*[1] with the formula:

$$\text{HOMA-IR} = \text{FIRI (pmol/L)} \times \text{FPG (pmol/L)}/135.$$

Euglycemic Hyperinsulinemic Glucose Clamp Study

After blood sampling, a clamp study was carried out according to the method of DeFronzo *et al.*[3] using a STG 22 artificial pancreas model (Nikkiso, Tokyo, Japan) as described in a previous

report[16]. Briefly, insulin (Humulin R; Eli Lilly & Co., Indianapolis, IN, USA) was loaded during the first 10 min of the clamp in priming doses followed by infusion in a continuous fashion at a rate of 1.25 mU/kg per min. Blood glucose levels were determined every 5 min during the 120-min clamp study, and euglycemia (5.6 mmol/L) was maintained by infusion of variable amounts of 25% glucose solution, which were determined by the built-in computer program according to the control algorithm. The whole body glucose disposal rate was evaluated as the mean of the glucose infusion rate (GIR) during the last 30 min of the clamp study. The mean glucose concentration was 5.4 ± 0.4 mmol/L and the coefficient of variation for GIR was 5.3 ± 0.3% during this period. The mean plasma insulin level during the steady-state was 460.2 ± 128.4 pmol/L in group C, 651 ± 198.6 pmol/L in group DM1, 668.4 ± 169.2 pmol/L in group DM2 and 461.4 ± 95.4 pmol/L in group DM3. These insulin concentrations are reported to be high enough to efficiently suppress hepatic glucose output[17].

Evaluation of Body Compositions

Regional body composition of diabetic patients was determined by INBODY720 (Japan Biospace, Tokyo, Japan) after an overnight fast and urination in the morning. Bioelectrical impedance analysis (BIA) is a widely used method for estimating body composition. The measurement was carried out in an upright position based on the 8-point tactile electrode, multifrequency and segmental measurement method[18]. The validity of this method has been established by comparison with the results derived from dual-energy X-ray absorptiometry (DXA)[19,20]. Skeletal muscle amount (M), percentage of M for bodyweight (M%), fat mass (F) and percentage of F for bodyweight (F%) were estimated as items to assess body composition.

Statistical Analysis

All tests were carried out using SPSS 11.0J for windows (SPSS, Chicago, IL, USA). Because TG, HDL-C, TG/HDL-C, AST, ALT and HOMA-IR values didn't show normal distribution according to the Kolmogorov–Smirnov test, logarithms of these values were used instead for further analyses. For comparisons of baseline values among groups C, DM1, DM2 and DM3, one-way ANOVA was used for parametric data and χ^2-test was used for non-parametric data. Univariate analysis of GIR with metabolic or anthropometric parameters was carried out using Pearson's correlation coefficient in each group of subjects. For multivariate analysis of each parameter on GIR as an outcome variable, multiple regression analysis was used. A P-value <0.05 was considered to be statistically significant.

RESULTS

Characteristics in Each Group of Subjects

Characteristics of healthy subjects and diabetic patients are summarized in Table 1. Subjects in groups C and DM3 were

Table 1 | Characteristics of subjects

	Group C (n = 25)	Group DM1 (n = 24)	Group DM2 (n = 22)	Group DM3 (n = 21)	P
Age (years)	37 ± 9	60 ± 11	59 ± 12	42 ± 20	<0.0001
Male	21 (84)	9 (38)	15 (68)	14 (67)	<0.01
Duration of diabetes (years)	–	8.9 ± 7.5	11.2 ± 8.4	4.8 ± 5.5	<0.05
Family history of diabetes (+)	–	14 (58)	12 (55)	5 (24)	N.S.
BMI	21.7 ± 2.4	25.5 ± 5.2	24.2 ± 4.4	19.1 ± 3.1	<0.0001
WC (cm)	76.3 ± 8.5	87.0 ± 12.1	86.3 ± 10.5	67.7 ± 6.5	<0.0001
SBP (mmHg)	114 ± 13	120 ± 19	122 ± 20	105 ± 13	<0.05
DBP (mmHg)	71 ± 10	74 ± 12	73 ± 11	68 ± 12	N.S.
FPG (mmol/L)	4.8 ± 0.6	7.2 ± 1.1	9.1 ± 2.0	10.3 ± 4.3	<0.0001
HbA_{1c} (%)	–	7.4 ± 1.8	8.7 ± 2.5	9.6 ± 3.5	<0.0001
LDL-C (mmol/L)	2.87 ± 0.71	3.08 ± 0.93	2.87 ± 0.72	2.48 ± 0.80	N.S.
HDL-C (mmol/L)	1.67 ± 0.55	1.16 ± 0.16	1.07 ± 0.21	1.40 ± 0.31	<0.0001
TG (mmol/L)	0.86 ± 0.44	1.60 ± 0.72	1.29 ± 0.52	0.99 ± 0.35	<0.0001
AST (U/L)	13.4 ± 6.7	27.0 ± 16.2	25.9 ± 13.8	24.6 ± 14.8	<0.001
ALT (U/L)	7.6 ± 6.1	18.3 ± 16.2	17.1 ± 14.4	14.7 ± 13.3	<0.01
FIRI (pmol/L)	34.8 ± 19.8	61.2 ± 43.2	15.5 ± 9.3	9.5 ± 4.8	<0.0001
HOMA-IR	1.26 ± 0.80	3.19 ± 2.25	1.73 ± 0.87	1.21 ± 0.56	<0.001
GIR (mg/kg per min)	8.44 ± 2.78	4.71 ± 2.33	5.23 ± 1.92	6.53 ± 1.56	<0.0001

Data are presented as means ± SD or number of subjects. Data in parentheses are the percentage of subjects. One-way ANOVA or χ^2-test was used for statistical analysis.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; C, control subjects; DBP, diastolic blood pressure; DM1, diabetes mellitus 1; DM2, diabetes mellitus 2; DM3, diabetes mellitus 3; FIRI, fasting plasma insulin; FPG, fasting plasma glucose; GIR, glucose infusion rate; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; N.S., not significant; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.

younger than groups DM1 and DM2, and a lower ratio of male participants was observed in group DM1. DM3 patients had shorter duration of diabetes compared with the other two diabetic groups of patients. Patients with type 2 diabetes (DM1 and DM2) had higher BMI and WC values than groups C and DM3. FPG and HbA_{1c} levels among the diabetic groups showed a stepwise increase in order of DM1, DM2 and DM3. In groups DM1 and DM2, lower HDL-C and higher TG, AST and ALT levels were observed compared with groups C and DM3. FIRI was markedly declined in DM2 and almost diminished in DM3 compared with DM1. HOMA-IR levels in DM1 were significantly higher than that in group C. BMI and WC in group D were significantly higher than those in group C. GIR obtained from all diabetic groups were significantly lower than that in group C, in line with previous reports[21].

Univariate Analysis Between GIR and Each Factor

Univariate analyses were carried out to explore the relationships between GIR and metabolic factors in each group of subjects (Table 2). Log HOMA-IR was excellently correlated to GIR in both groups C and DM1, whereas significant correlations were not observed in both groups DM2 and DM3. Log TG/log HDL-C showed an excellent correlation to GIR in both control and all diabetic groups. Although log AST and log ALT were moderately correlated to GIR in group C, these correlations virtually disappeared in all diabetic groups.

In contrast, regarding anthropometric factors, GIR was negatively correlated with BMI, WC, F and F%, and positively correlated with M% in groups C and DM1. These correlations were partially maintained in groups DM2 and DM3, whereas correlation coefficients were smaller than those in groups C and DM1 (Table 3).

Multivariate Analysis on GIR as an Outcome Variable

To assess the degree of contribution of each factor to account for GIR, multiple regression analysis was carried out in groups C and DM1 all together. Because each anthropometric factor correlated well with each other, it was difficult to include these

Table 2 | Univariate analysis between glucose infusion rate and metabolic factors

	Group C (n = 25)		Group DM1 (n = 24)		Group DM2 (n = 22)		Group DM3 (n = 21)	
	r	P-value	r	P-value	r	P-value	r	P-value
Log HOMA-IR	−0.868	<0.0001	−0.608	<0.01	−0.108	N.S.	−0.207	N.S.
FIRI	−0.839	<0.0001	−0.527	<0.01	−0.115	N.S.	−0.193	N.S.
FPG	−0.554	<0.01	−0.056	N.S.	−0.292	N.S.	0.057	N.S.
LDL-C	−0.49	<0.05	−0.015	N.S.	0.06	N.S.	−0.235	N.S.
Log TG	−0.636	<0.001	−0.637	<0.001	−0.479	<0.05	−0.593	<0.01
Log HDL-C	0.604	<0.01	0.262	N.S.	0.676	<0.001	0.467	<0.05
Log TG/log HDL-C	−0.703	<0.0001	−0.611	<0.01	−0.655	<0.001	−0.669	<0.01
Log AST	−0.471	<0.05	−0.212	N.S.	0.28	N.S.	0.052	N.S.
Log ALT	−0.569	<0.01	−0.284	N.S.	0.317	N.S.	0.076	N.S.

Peason's correlation coefficient was used for statistical analysis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, control subjects; DBP, diastolic blood pressure; DM1, diabetes mellitus 1; DM2, diabetes mellitus 2; DM3, diabetes mellitus 3; FIRI, fasting plasma insulin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; N.S.; not significant; TG, triglyceride.

Table 3 | Univariate analysis between glucose infusion rate and anthropometric factors

	Group C (n = 25)		Group DM1 (n = 24)		Group DM2 (n = 22)		Group DM3 (n = 21)	
	r	P-value	r	P-value	r	P-value	r	P-value
BMI	−0.554	<0.01	−0.469	<0.05	−0.315	N.S.	−0.412	<0.05
WC	−0.679	<0.001	−0.484	<0.05	−0.347	<0.05	−0.474	<0.05
M (kg)	−0.125	N.S.	0.012	N.S.	0.021	N.S.	0.231	N.S.
M (%)	0.453	<0.05	0.543	<0.01	0.427	<0.05	0.395	N.S.
F (kg)	−0.599	<0.01	−0.484	<0.05	−0.373	N.S.	−0.318	N.S.
F (%)	−0.537	<0.01	−0.554	<0.001	−0.444	<0.05	−0.352	N.S.

Descriptions for each abbreviation are given in text. Peason's correlation coefficient was used for statistical analysis.
BMI, body mass index; C, control subjects; DBP, diastolic blood pressure; DM1, diabetes mellitus 1; DM2, diabetes mellitus 2; DM3, diabetes mellitus 3; F, fat mass; M, skeletal muscle; N.S.; not significant; WC, waist circumference.

Table 4 | Multiple regression analysis on glucose infusion rate as an outcome variable in the control group and diabetes mellitus 1 group

Predictive variable	Model 1		Model 2		Model 3		Model 4	
	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
	$R^2 = 0.710$		$R^2 = 0.708$		$R^2 = 0.682$		$R^2 = 0.688$	
Log TG/log HDL-C	−0.598	<0.0001	−0.56	<0.0001	−0.578	<0.0001	−0.648	<0.0001
WC	−0.367	0.0002						
F (%)			−0.384	0.0003				
M (%)					0.338	0.0021		
BMI							−0.31	0.0014

β, standard regression coefficient; BMI, body mass index; F, fat mass; HDL-C, high-density lipoprotein cholesterol; M, skeletal muscle; R^2, coefficient of determination; WC, waist circumference.

parameters into the same model in further multivariate analysis due to the multicollinearity. Instead, four separate models were constructed, with one anthropometric factor included in each model. The model including WC and log TG/log HDL-C as explanatory variables (model 1) showed the highest value in coefficient of determination ($R^2 = 0.710$) to account for GIR. An alternative model including F% instead of WC showed the similar contribution as model 1 (model 2, $R^2 = 0.708$), but models including M% (model 3) or BMI (model 4) instead of WC showed a smaller contribution than model 1. Although an adjustment of age, sex and the existence of diabetes slightly improved the R^2 values in each model, all of these variables were not significant confounders (Table 4).

An Equation for the Estimation of GIR

Using an intercept and regression coefficients of each factor obtained from model 1, an equation was built up to estimate GIR as shown below:

$$\text{Estimated GIR (EGIR)} = 25.772 - 0.101 \times \text{WC (cm)} - 9.444 \times \log \text{TG}/\log \text{HDL-C}.$$

The correlation between measured GIR and EGIR is shown in Figure 1. EGIR showed an excellent positive relationship with measured GIR either in group C ($r = 0.791$, $P < 0.0001$) or DM1 ($r = 0.702$, $P < 0.0001$). Overall correlation coefficients in groups C and DM1 was 0.843, and comparable with that between HOMA-IR and GIR in these groups of patients ($r = -0.819$).

Validity of the Surrogate Index for the Estimation of Insulin Sensitivity

By using the equation obtained from groups C and DM1, EGIR were further calculated in both DM2 and DM3 patients. As shown in Figure 2, EGIR showed a slightly scattered, but still excellent correlation with measured GIR in these groups of diabetic patients ($r = 0.681$, $P < 0.0001$). The correlation coefficient was comparable with that between HOMA-IR and GIR in DM1 shown in Table 2. The significant correlation was further maintained in each separate diabetic group ($r = 0.629$, $P < 0.01$ in DM2, $r = 0.676$, $P < 0.001$ in DM3).

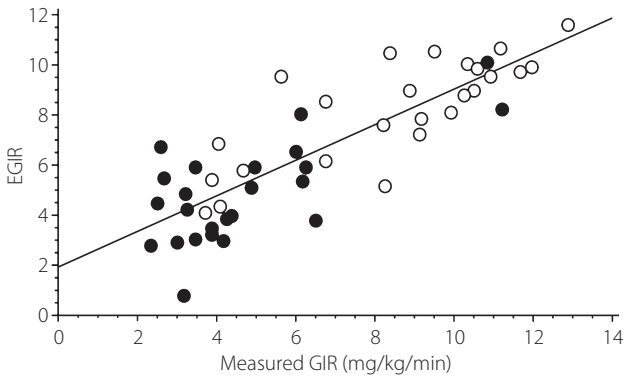

Figure 1 | Correlation between estimated glucose infusion rate (EGIR) and measured glucose infusion rate (GIR) in healthy subjects and type 2 diabetic patients. Open circles indicate group C and closed circles indicate DM1.

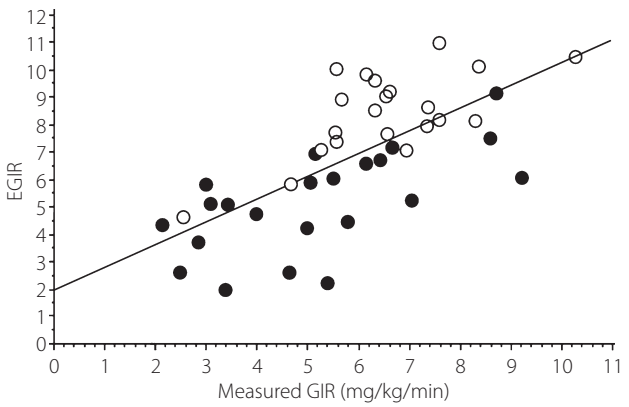

Figure 2 | Correlation between estimated glucose infusion rate (EGIR) and measured glucose infusion rate (GIR) in diabetic patients. Closed circles indicate DM2 and open circles indicate DM3.

DISCUSSION

The present investigation included some important issues. Apart from HOMA-IR, some of the metabolic and anthropometric factors were significantly correlated with GIR obtained from the glucose clamp method in healthy subjects and patients with type 2 diabetes. Among these factors, TG to HDL-C ratio and WC were selected as explanatory variables and constituted a model to account for GIR by 71%. Furthermore, estimated GIR calculated from these variables were excellently correlated with measured GIR in another group of diabetic patients in whom HOMA-IR could not be applied appropriately. It is thus feasible that our surrogate index can be applied to various types of diabetic patients, even with high FPG or low FIRI levels.

Metabolic factors, such as HOMA-IR and TG to HDL-C ratio, were negatively correlated with GIR in either healthy subjects or type 2 diabetic patients. HOMA-IR is a surrogate index of insulin resistance and widely used for clinical practice[1,7]. However, the limitation of this index has often been pointed out in type 2 diabetic patients with low insulin secretion and high fasting glucose level[4], and therefore alternative indexes have been anticipated instead of HOMA-IR for the estimation of insulin resistance in such patients. Because elevated TG to HDL-C ratio has been reported to be closely related to insulin resistance[6,7], it is conceivable that these parameters could be used for a novel surrogate index.

In contrast, excessive fat mass causes insulin resistance through the modulation of adipokines secreted from adipose tissue[22]. Visceral fat, in particular, is relevant to insulin resistance and developing CVD, and central obesity is usually expressed as the measure of WC, which is an essential component for the definition of metabolic syndrome in Japan[15,23]. Conversely, reduced skeletal muscle amount, especially in lower extremities, is also an important issue in forming insulin resistance[14]. In our previous study, the sarcopenic obesity of Japanese type 2 diabetic patients expressed as excessive F, WC and reduced M is an important anthropometric feature to account for insulin resistance and future CVD risks[24].

By using these metabolic and anthropometric factors, except for HOMA-IR, multiple regression analyses showed several models for the estimation of insulin sensitivity. Among these models, the combination of log TG/log HDL-C and WC most accounted for GIR by 71%. Inclusions of F%, M% and BMI instead of WC also showed excellent, but slightly smaller contributions to GIR. It is of note that WC, TG and HDL of diabetic patients are easily available parameters in clinical practice and the novel index can be widely used by not only specialized endocrinologists, but also general practitioners.

The most important issue to be emphasized is that the novel index fitted excellently to measured GIR, even in another group of diabetic patients in whom HOMA-IR could not be applied as a result of low insulin secretion or high blood glucose level. Notably, it can be anticipated that EGIR is available for the estimation of insulin sensitivity in patients with type 1 diabetes or diabetes as a result of pancreatic disease with diminished endogenous insulin secretion. The contribution of insulin resistance to the development of type 1 diabetes has been reported[25,26], and components of the metabolic syndrome, such as central obesity and abnormal lipid profile, are positively related to insulin resistance, even in type 1 diabetic patients[27]. In contrast, insulin resistance and hyperinsulinemia have been documented in diabetic patients as a result of pancreatic cancer[28]. These findings suggest that the surrogate index of insulin resistance is necessary for clinical practice, even in patients with type 1 diabetes and pancreatic disorder.

EGIR was also well correlated to measured GIR in type 2 diabetic patients with low insulin secretion or high FPG level (DM2), but the correlation was more scattered than that of DM3. The same tendency of the relatively scattered correlation between HOMA-IR and GIR was observed in type 2 diabetic patients (DM1) compared with healthy subjects, especially in insulin resistant patients. It is thus possible that EGIR might have some limitations for the application to insulin resistant type 2 diabetic patients. Patients with type 2 diabetes are composed of rather heterogeneous populations and unknown mechanisms that underlie the heterogeneity might affect insulin sensitivity in those patients. Manifestations of type 2 diabetes and metabolic syndrome, such as high blood pressure, endothelial dysfunction, disorder of adipokine and chronic inflammation, are all able to affect insulin sensitivity. Taking the heterogeneity in type 2 diabetes into account, future investigations for the surrogate index are anticipated.

In another aspect, EGIR is composed of both metabolic and anthropometric factors. Because anthropometric features are not easily changeable for such a short period, the inclusion of these factors makes the index more robust and reproducible. However, in clinical practice, insulin sensitivity can be partially changeable in company with the change of metabolic situations, especially lipid profile[29]. Those short-term effects of metabolic derangements can also be reflected in EGIR by the inclusion of TG and HDL-C.

There are some limitations in the present study. The number of subjects investigated is rather small for the establishment of a new index of insulin sensitivity, although the reproducibility of EGIR was validated in patients with poorly controlled or insulin deficient type 2 diabetes, type 1 diabetes and pancreatic disorder. Further validation in a large number of patients reinforces the index in future studies. Because EGIR was obtained from not only mildly obese type 2 diabetic patients, but also lean healthy subjects, this surrogate index accounted well for insulin sensitivity in lean patients with type 1 diabetes and pancreatic disorder. However, another surrogate index obtained originally from those diabetic patients might be necessary in future studies. Our subjects were limited to Japanese with normal bodyweight or mild obesity. The validity of our index for other ethnic populations with more severe obesity should be further investigated

in future studies. Finally, one-third of DM1 patients had been treated with statin or fibrate, which might have affected the results of TG or HDL-C, major components of EGIR. However, multivariate analysis after the exclusion of those dyslipidemic patients showed basically the same results ($R^2 = 0.696$ using log TG/log HDL-C and WC). Furthermore, excluding nine dyslipidemic patients from groups DM2 and DM3 did not affect the correlation ($r = 0.629$, $P < 0.0001$) between GIR and EGIR calculated by the formula obtained from groups C and DM1. Because all studies were carried out after the stabilization of lipid profile as aforementioned, effects of these drugs might have been minimized. Although an appropriate use of this index for statin and fibrate users is to be further elucidated, it is plausible that this index can be applied at least to diabetic patients without statin or fibrate use.

In summary, EGIR as a novel index for insulin sensitivity can be applied in Japanese diabetic patients whose HOMA-IR is not appropriately available. The validation of this index is to be elucidated in a large number and various types of diabetic patients.

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The authors declare that they have no conflict of interest.

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