Prediction of Homeostasis Model Assessment of Insulin Resistance in Japanese Subjects

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Objective: In our previous study, multivariate analysis showed that body mass index (BMI), triglycerides (TG) levels, and systolic blood pressure (SBP), in addition to fasting plasma glucose (FPG) levels, significantly correlated with homeostasis model assessment of insulin resistance (HOMA-IR). Our aim was to develop a predictive tool for HOMA-IR using tests of the specific health examinations.
Methods: We enrolled 7,248 Japanese adults (3,793 men, and 3,455 women) in this cross-sectional study. A multiple regression model for predicting HOMA-IR was created using laboratory tests and lifestyle habits in the specific health examination.
Results: HOMA-IR prediction index was developed using routinely measured parameters (BMI; levels of FPG, TG, and high-density lipoprotein cholesterol; BP; exercise; and physical activity), and did not require measurement of immunoreactive insulin levels. The prediction accuracy of the model was considered good, as indicated by R^2 values (men, 0.465; women, 0.405).
Conclusion: The predictive tool for HOMA-IR using specific health examination tests allows healthcare professionals to estimate an individual's overall risk of metabolic syndrome (MetS). We propose that this tool can be used as an aid in health guidance for MetS.

Key words: insulin resistance, HOMA-IR, prediction, health guidance, metabolic syndrome

INTRODUCTION

Resistance to insulin develops as a result of unhealthy lifestyles, and obesity is a key event in the origin and progression of the metabolic syndrome (MetS) [1–3]. For primary prevention of the Mets, it is important to identify subjects at risk of MetS, namely, those with insulin resistance.

Homeostasis model assessment of insulin resistance (HOMA-IR) is a useful model for assessing insulin resistance by a single measurement of fasting plasma glucose (FPG) and immunoreactive insulin (IRI) levels [4]. HOMA-IR has been validated using the euglycemic hyperinsulinemic clamp method [5, 6], which is an expensive and invasive gold-standard method. We have previously identified anthropometric and metabolic parameters other than FPG in a non-diabetic Japanese population that showed a significant correlation with HOMA-IR on multivariate analyses [7]. Body mass index (BMI), triglycerides (TG) levels, and systolic blood pressure (SBP) significantly correlated with insulin resistance in men and women. High-density lipoprotein cholesterol (HDL-C) levels were found to be correlated with insulin resistance by multiple logistic regression analysis in men. Insulin measurement is still expensive and difficult to perform in some healthcare settings. In Japan, basic health examinations were performed in April 2008 with specific health examination and guidance aimed for subjects, aged between 40 and 74, who are covered by health insurance. This examination and guidance includes advice to prevent MetS and detect lifestyle-related diseases at an early stage; however, this examination does not include measurement of insulin levels. Therefore, development of a predictive tool for HOMA-IR that estimates insulin resistance using routinely measured parameters will be clinically useful.

The aim of the present study was to propose a predictive tool for determining insulin resistance to efficiently identify subjects at a risk of MetS. A multiple regression model for predicting HOMA-IR was created using tests of specific health examinations.

METHOD

Subjects

Between April 2007 and March 2012, 9,150 people (men, 5,028 and women, 4,122) underwent a first annual health examination at the Health Evaluation and Promotion Center at Tokai University Hachioji Hospital. Of these, 7,248 adults (men, 3,793 and women, 3,455) were enrolled in this study after excluding subjects with an FPG level ≥ 126 mg/dL; those on medication for diabetes, hypertension, and dyslipidemia; or those with a history of coronary artery disease, cerebrovascular disease and chronic renal failure. The medical history of subjects was assessed using self-administered questionnaires and interviews by nurses. Verbal consent was obtained from the subjects for using their health records for analysis. Our study was a cross-sectional study approved by the Ethics Committee of Tokai University School of Medicine; further, our study conforms to the principles outlined in the Declaration of Helsinki.

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Measurements

Anthropometric measurements and blood sampling were performed after overnight fasting. Blood pressure was measured using an automatic blood pressure monitor (TM-2655P; A&D Co., Ltd., Tokyo, Japan) on the right upper arm in a sitting position. BMI was calculated by dividing weight (kg) by height squared (m^2). Waist circumference (WC) was measured at the level of the umbilicus while standing, and during slight expiration. Serum levels of low-density lipoprotein cholesterol (LDL-C), HDL-C, and TG were measured by visible spectrophotometry (Determiner L LDL-C, Determiner L HDL-C, Determiner L TG II; Kyowa Medex Co., Ltd., Tokyo, Japan). Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (γ-GT) were measured using an automatic analyzer (JCA-BM2250; JEOL, Tokyo, Japan). All measurements were included in the routine health examinations.

Assessment of insulin resistance

Fasting serum IRI levels were measured by fluorescence-enzyme immunoassay (ST AIA-PACK IRI; Toso Co., Ltd., Tokyo, Japan). The intra- and inter-assay coefficients of variation were 1.4–2.3% and 2.6–4.6%, respectively, and cross-reactivity with proinsulin molecules was 2.0%. HOMA-IR was calculated as follows: fasting plasma glucose level (mg/dL) × IRI level (μU/mL)/405 [4].

Statistical analysis

To design a dummy-variable multiple regression model, a series of binary (ie, dummy) variables was created that identify whether or not an observation belongs to a specific category. Binary variables were coded as 1 or 0. BMI was classified into 5 categories: < 22 kg/m^2, 22 to < 24 kg/m^2, 24 to < 26 kg/m^2, 26 to < 28 kg/m^2, or ≥ 28 kg/m^2. FPG levels were classified into 3 categories: < 100 mg/dL, 100 to < 110 mg/dL, or ≥ 110 mg/dL. TG levels were classified into 3 categories: < 150 mg/dL, 150 to < 300 mg/dL, or ≥ 300 mg/dL. HDL-C levels were classified into 3 categories: ≥ 50 mg/dL, 40 to < 50 mg/dL, or < 40 mg/dL. SBP was classified into 2 categories: < 130 mmHg or ≥ 130 mmHg. Diastolic blood pressure (DBP) was classified into 2 categories: < 85 mmHg or ≥ 85 mmHg. ALT levels were classified into 3 categories: < 31 U/L, 31 to < 51 U/L, or ≥ 51 U/L. If there were 4 categories, 3 dummy variables were created. The lowest category was used as a reference for BMI, FPG levels, TG levels, SBP, DBP and ALT levels, and the highest category was used as a reference for HDL-C levels. Multiple linear regression analysis was performed to find significant determinants of HOMA-IR, including BMI, FPG levels, TG levels, HDL-C levels, SBP, DBP, ALT levels, exercise (≥ 30 min a time, ≥ 2 times/week), physical activity (≥ 1 h/day), fast walker, fast eater, eating supper within 2 h before bedtime, snacking after supper, and skipping breakfast. Variables were selected in a stepwise procedure ($p < 0.1$). Data are presented as the mean ± standard deviation (SD). SAS Software version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses. All p values were two-tailed, and $p < 0.05$ was considered significant.

RESULTS

The clinical characteristics of the subjects are shown in Table 1. The mean values of HOMA-IR were 1.55 for men and 1.28 for women.

On the basis of our previous study [7], BMI was used as a variable related to insulin resistance as an index for obesity. Table 2 shows the results of multivariate analyses including BMI, FPG levels, TG levels, HDL-C levels, SBP, DBP, ALT levels, exercise, physical activity, fast walker, fast eater, eating supper within 2 h before bedtime, snacking after supper, and skipping breakfast as independent variables. Stepwise multiple linear regression analysis was performed to find significant determinants for HOMA-IR. Although BMI, FPG, TG, HDL-C, ALT, SBP, exercise, and physical activity were selected, DBP was included only in women. The regression coefficients for each variable are shown in Table 2, where BMI, < 22 kg/m^2; FPG level, < 100 mg/dL; TG level, < 150 mg/dL; SBP < 130 mmHg, DBP < 85 mmHg; ALT level, < 31 U/L; and HDL-C level, ≥ 50 mg/dL were used as references. If the subject was a man with BMI of 25 kg/m^2, FPG level of 105 mg/dL, ALT of 40 U/L, HDL-C level of 55 mg/dL, TG level of 125 mg/dL, SBP of 140 mmHg, and no exercise and no physical activity, the predicted probability is calculated as follows: 0.462 + 0.356 + 0.259 + 0 + 0 + 0.137 + 0 + 0 + 0.815 = 2.331. R^2 (coefficient of determination) showed a good predictive efficacy (men, 0.465; women, 0.405).

DISCUSSION

We developed a method for predicting HOMA-IR using BMI, FPG levels, TG levels, HDL-C levels, ALT levels, SBP, exercise, and physical activity (and DBP for women only). One of the main strengths of our model is that it enables us to predict insulin resistance using routinely measured parameters, without having to measure IRI.

On the basis of our previous study, BMI, levels of FPG, TG, and HDL-C, and SBP were used as variables related to insulin resistance for men, and BMI, levels of FPG, and TG, and SBP were used for women by multiple linear regression analysis including 4 components of MetS (obesity, glucose, blood pressure, and lipid) as independent variables [7]. The selected components were similar to the existing MetS criteria, except for the measure of obesity, for which BMI had a stronger association than WC with insulin resistance. Therefore, BMI was used as an index of obesity in this study too.

In addition, it is noteworthy that MetS risk factors were stratified using dummy variables, but not contentious variables in the HOMA-IR prediction index, and that ALT levels, exercise and physical activity were selected in addition to the components of MetS for the index.

Adipose tissue-derived secretory proteins are collectively named adipocytokines. Obesity and mainly visceral fat accumulation impair adipocyte function and adipocytokine secretion [8]. Impaired adipocytokine secretion promotes hepatic steatosis and development of nonalcoholic steatohepatitis [9]. Adiponectin directly regulates glucose metabolism and insulin

Table 1 Background characteristics of study subjects

	Men (n = 3,793)	Women (n = 3,455)	p^*
Age (years)	47.6 ± 11.2	47.3 ± 11.0	0.253
Height (cm)	170.6 ± 6.1	157.4 ± 5.6	< 0.01
BMI (kg/m^2)	23.5 ± 3.1	21.4 ± 3.1	< 0.01
WC (cm)	84.0 ± 8.5	77.3 ± 8.8	< 0.01
SBP (mmHg)	117.6 ± 16.2	111.4 ± 16.7	< 0.01
DBP (mmHg)	75.3 ± 12.2	68.7 ± 11.4	< 0.01
FPG (mg/dL)	99.1 ± 8.4	93.9 ± 8.1	< 0.01
F-IRI (μU/mL)	6.23 ± 4.08	5.43 ± 3.45	< 0.01
HOMA-IR	1.55 ± 1.09	1.28 ± 0.90	< 0.01
LDL-C (mg/dL)	123.3 ± 31.1	116.0 ± 32.5	< 0.01
HDL-C (mg/dL)	57.9 ± 14.2	72.9 ± 16.5	< 0.01
TG (mg/dL)	121.9 ± 97.0	76.9 ± 45.0	< 0.01
AST (U/L)	22.7 ± 10.4	19.7 ± 10.7	< 0.01
ALT (U/L)	27.1 ± 19.6	17.0 ± 14.0	< 0.01
γ -GT (U/L)	46.9 ± 58.9	22.2 ± 27.2	< 0.01
Exercise (≥ 30 min at a time, ≥ 2 times/week)	22.0%	18.0%	< 0.01
Physical activity (≥ 1 h/day)	41.0%	42.6%	0.181
Fast walker	59.3%	47.7%	< 0.01
Fast eater	47.4%	33.9%	< 0.01
Eating supper within 2 h before bedtime	43.3%	18.2%	< 0.01
Snacking after supper	15.2%	18.3%	< 0.01
Skipping breakfast	20.6%	12.5%	< 0.01

Data are means ± standard deviation (SD).

*: t-test or chi-square test

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIRI, fasting immunoreactive insulin; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C cholesterol, low-density lipoprotein cholesterol; HDL-C cholesterol, high-density lipoprotein cholesterol; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ -GT, γ -glutamyl transpeptidase.

sensitivity in the liver and skeletal muscle [10]. Thus, accumulation of visceral fat accompanied by reduced levels of adiponectin clearly explains complication of insulin resistance and fatty liver. Therefore, ALT levels selected in the HOMA-IR prediction index would express accumulation of fat in the liver. In addition, our previous study showed that including measurement of ALT levels as an additional parameter was useful for the diagnosis of early-stage MetS [11].

Moreover, exercise and physical activity were selected in this index because insulin resistance is improved by exercise training without weight loss [12, 13].

Insulin resistance plays a crucial role in the pathophysiology of MetS [1–3], which is a complex of interrelated risk factors for cardiovascular disease. It is important to identify subjects at risk of MetS, especially in the pre-atherogenic stage, when insulin resistance contributes to the clustering of borderline metabolic risk factors. Reference values are of 2 types, the most common one referred to as "health-associated," which is derived from a reference sample of individuals who are in good health. The other type is referred to as "decision-based," and defines specific medical decision limits that are used by clinicians to diagnose or manage patients. We have established the reference interval for HOMA-IR as between 0.4 and 2.4, and proposed that HOMA-IR ≥ 2.5 be considered a reasonable indicator of insulin resistance in a Japanese population [14]. Further, we reported that the optimal cut-off value for HOMA-IR for diagnosing MetS in non-diabetic Japanese subjects is 1.7 [15].

Our model can be particularly useful when subjects have multiple mild abnormalities that act synergistically to increase insulin resistance. Another advantage of our model is that it enables us to assess an individual's overall metabolic status by a single indicator, insulin resistance.

Our study had some limitations. First, our model has not been externally validated, and whether our model can be applied to other groups that show considerably different degrees of insulin resistance remains to be clarified. Another limitation of this study is that HOMA-IR was used as an index of insulin resistance, because it sometimes fails to show a close relationship with whole body insulin resistance assessed using the euglycemic clamp method, especially in subjects with high FPG levels [5, 16]. Because of the cross-sectional nature of the present study, a prospective study is required to show the risk of MetS in future. Finally, our model includes parameters that require fasting, such as FPG and TG. If a model could be created using parameters without using fasting values, it might be of greater utility not only in hospitals but also in community or industrial health care settings.

In conclusion, HOMA-IR prediction index was developed using routinely measured metabolic parameters that allows healthcare professionals to estimate an individual's overall MetS risk. We propose that this

Table 2 Results of multivariate linear regression analyses

(A) Men

		Coefficient	SE	F-value	*p*
BMI	< 22	0			
(kg/m^2)	22 to < 24	0.219	0.034	40.81	< .0001
	24 to < 26	0.462	0.039	140.65	< .0001
	26 to < 28	0.764	0.050	236.18	< .0001
	≥ 28	1.491	0.060	622.29	< .0001
FPG	< 100	0			
(mg/dL)	100 to < 110	0.356	0.030	142.79	< .0001
	≥ 110	0.839	0.044	364.44	< .0001
ALT	< 31	0			
(U/L)	31 to < 51	0.259	0.037	49.08	< .0001
	≥ 51	0.804	0.053	228.83	< .0001
HDL-C	≥ 50	0			
(mg/dL)	40 to < 50	0.246	0.033	56.66	< .0001
	< 40	0.294	0.056	27.56	< .0001
TG	< 150	0			
(mg/dL)	150 to < 300	0.129	0.035	13.40	0.0003
	≥ 300	0.285	0.076	14.05	0.0002
SBP	< 130	0			
(mmHg)	≥ 130	0.137	0.033	17.17	< .0001
Exercise	< 2 times/week	0			
	≥ 30 min at a time, ≥ 2 times/week	- 0.191	0.032	35.75	< .0001
Physical activity	< 1 h/day	0			
	≥ 1 h/day	- 0.075	0.027	7.75	0.0054
Intercept		0.815	0.031	680.82	< .0001

SE, standard error; BMI, body mass index; FPG, fasting plasma glucose; ALT, alanine aminotransferase; HDL-C cholesterol, high-density lipoprotein cholesterol; TG, triglyceride; SBP, systolic blood pressure.

(B) Women

		Coefficient	SE	F-value	*p*
BMI	< 22	0			
(kg/m^2)	22 to < 24	0.241	0.032	58.12	< .0001
	24 to < 26	0.439	0.042	111.39	< .0001
	26 to < 28	0.830	0.064	168.38	< .0001
	≥ 28	1.613	0.068	563.81	< .0001
FPG	< 100	0			
(mg/dL)	100 to < 110	0.435	0.033	171.01	< .0001
	≥ 110	0.912	0.058	243.61	< .0001
ALT	< 31	0			
(U/L)	31 to < 51	0.455	0.057	63.07	< .0001
	≥ 51	0.473	0.104	20.59	< .0001
HDL-C	≥ 50	0			
(mg/dL)	40 to < 50	0.236	0.054	19.19	< .0001
	< 40	0.329	0.125	6.94	0.0084
TG	< 150	0			
(mg/dL)	150 to < 300	0.302	0.055	30.07	< .0001
	≥ 300	1.332	0.225	35.07	< .0001
SBP	< 130	0			
(mmHg)	≥ 130	0.084	0.041	4.08	0.0434
DBP	< 85	0			
(mmHg)	≥ 85	0.183	0.049	14.01	0.0002
Exercise	< 2 times/week	0			
	≥ 30 min at a time, ≥ 2 times/week	- 0.150	0.031	23.03	< .0001
Physical activity	< 1 h/day	0			
	≥ 1 h/day	- 0.042	0.024	3.06	0.0801
Intercept		0.946	0.020	2259.46	< .0001

SE, standard error; BMI, body mass index; TG, triglyceride; FPG, fasting plasma glucose; ALT, alanine aminotransferase; HDL-C cholesterol, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

model can be used as an aid in health guidance for MetS.

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