Optimal cut-off point for homeostasis model assessment of insulin resistance to discriminate metabolic syndrome in non-diabetic Japanese subjects

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ABSTRACT

We have recently established a 'health-associated' reference interval of homeostasis model assessment of insulin resistance (HOMA-IR) between 0.4 and 2.4. In the present study, the aim was to establish a 'decision-based' limit of HOMA-IR for the discrimination of metabolic syndrome (MetS) in non-diabetic Japanese subjects. The receiver–operating characteristic curve of HOMA-IR for detecting MetS was developed using data from 6868 non-diabetic subjects (3727 men, 3141 women). The optimal cut-off point was determined based on the point that yielded the minimum value of the square root of $[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]$. HOMA-IR = 1.7 was determined as the optimal cut-off value, with a sensitivity and specificity of 73.4% and 70.5% for men, and 81.5% and 77.0% for women, respectively. In conclusion, the optimal cut-off value for HOMA-IR to discriminate MetS in non-diabetic Japanese subjects appears to be 1.7. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00194.x, 2012)

KEY WORDS: Cut-off point, Homeostasis model assessment of insulin resistance, Metabolic syndrome

INTRODUCTION

Insulin resistance (IR) plays a crucial role in the pathophysiology of metabolic syndrome (MetS)[1], which is associated with an increased risk of cardiovascular disease and type 2 diabetes. From the standpoint of primary prevention, it is important to identify the patients at risk of MetS, especially at an early stage when IR contributes to the clustering of borderline metabolic risk factors.

Homeostasis model assessment of IR (HOMA-IR) is a useful model for assessing IR in large-scale clinical research[2,3], and it has been validated by the gold standard method – the hyperinsulinemic-euglycemic clamp technique[4]. We have recently determined a 'health-associated' reference interval of HOMA-IR, which covers the central 95% of 2153 healthy Japanese subjects, by applying the stringent C28-A3 document from the Clinical and Laboratory Standards Institute[5]. 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 IR in a Japanese population as recommended by The Japan Diabetes Society[6]. In contrast, there is another type of reference range or limit, termed 'decision-based', which should be distinguished from a 'health-associated' reference interval and is defined for use by clinicians to diagnose or manage patients[7].

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The present study focused on IR as a marker of early-stage MetS and aimed to establish a 'decision-based' limit of HOMA-IR for detecting MetS. An optimal cut-off point for HOMA-IR to discriminate MetS in non-diabetic Japanese subjects was determined by receiver–operating characteristic (ROC) curve analysis.

MATERIALS AND METHODS

Of the 7305 health-check examinees (4042 men and 3263 women) who first visited the Health Evaluation and Promotion Center at Tokai University Hachioji Hospital between April 2007 and March 2011, 6868 examinees (3727 men and 3141 women) were included in the present study after exclusion of those with fasting plasma glucose (FPG) ≥126 mg/dL and those on medication for diabetes. The present study was cross-sectional in design, and was approved by The Ethics Committee of Tokai University School of Medicine (11R-096) and complied with the Helsinki Declaration.

Anthropometric measurements and blood sampling were carried out after overnight fasting. Waist circumference (WC) was assessed at the end of expiration, measuring the minimum circumference at the level of the umbilicus to the nearest 0.1 cm. Blood pressure (BP) was measured at the right upper arm with the patient in a sitting position. Fasting serum immunoreactive insulin (IRI) was measured by fluorescence-enzyme immunoassay (ST AIA-PACK IRI; Toso, Tokyo, Japan). The intra- and interassay 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: FPG (in mg/dL) × IRI (in μU/mL)/405[2]. MetS was diagnosed if subjects had increased waist circumference (≥85 cm for men and 90 cm for women) plus at least two of the following criteria[8]: FPG 110–125 mg/dL, hypertension (systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg, or on medication) and dyslipidemia (TG ≥ 150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or on medication).

The ROC curve of HOMA-IR for detecting MetS was produced, and the area under the curve (AUC) with its 95% confidence interval (CI) was calculated. To determine the optimal point, the square root of [(1 – sensitivity)^2 + (1 – specificity)^2] was calculated[9], which is the point on the ROC curve with the shortest distance from the upper left corner. The data are reported as means ± standard deviation (SD). SPSS Statistics version 19.0 software (SPSS, Chicago, IL, USA) was used for statistical analyses.

RESULTS

The subjects' background characteristics are shown in Table 1. The average HOMA-IR was 1.63 for men and 1.36 for women. Among the 3727 men and 3141 women, MetS was diagnosed in 594 men (15.9%) and 81 women (2.6%). HOMA-IR values were significantly higher in MetS subjects (2.68 ± 1.70 for men and 3.21 ± 2.44 for women) compared with non-MetS subjects (1.43 ± 0.90 for men and 1.31 ± 0.83 for women). Figure 1 shows the ROC curve of HOMA-IR for detecting MetS. The AUC (95% CI) was 0.794 (0.775–0.813) for men and 0.883 (0.852–0.913) for women. The optimal point of HOMA-IR yielding the minimum value of the square root of [(1 – sensitivity)^2 + (1 – specificity)^2] was 1.7 for both sexes, which was lower than the upper limit of the reference interval. A HOMA-IR value of 1.7 was also the point that maximized the product of sensitivity and specificity, with a sensitivity and specificity of 73.4% and 70.5% for men, and 81.5% and 77.0% for women, respectively. The prevalence of HOMA-IR ≥ 1.7 was 36.5% in men and 24.5% in women. The positive predictive value was 32.1% for men and 8.6% for women.

Table 1 | Background characteristics of study subjects

	Men	Women
n	3727	3141
Age (years)	49.7 ± 12.1	49.3 ± 11.7
BMI (kg/m^2)	23.7 ± 3.1	21.7 ± 3.2
Waist circumference (cm)	84.8 ± 8.5	78.4 ± 9.0
FPG (mg/dL)	99.8 ± 8.7	94.5 ± 8.4
FIRI (μU/mL)	6.51 ± 4.31	5.70 ± 3.64
HOMA-IR	1.63 ± 1.16	1.36 ± 0.96
Systolic BP (mmHg)	119.7 ± 16.9	113.8 ± 17.6
Diastolic BP (mmHg)	76.6 ± 12.4	70.0 ± 11.7
HDL-C (mg/dL)	57.6 ± 14.3	72.2 ± 16.3
TG (mg/dL)	123.3 ± 85.7	79.8 ± 47.1
FPG 110–125 mg/dL (%)	13.8	5.6
Hypertension (%)	39.0	24.4
Dyslipidemia (%)	30.3	10.8
MetS (%)	15.9	2.6

Data are means ± SD. Hypertension is defined as systolic blood pressure (BP) ≥ 130 mmHg, diastolic BP ≥ 85 mmHg, or on medication. Dyslipidemia is defined as triglycerides (TG) ≥ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, or on medication.
BMI, body mass index; FIRI, fasting immunoreactive insulin; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome.

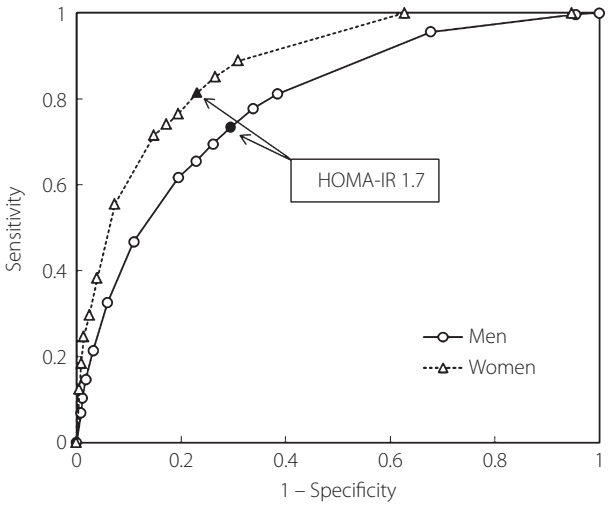

Figure 1 | The receiver–operating characteristic curves of homeostasis model assessment of insulin resistance (HOMA-IR) for detecting metabolic syndrome in men and women. The optimal points were determined by calculating the square root of [(1 – sensitivity)^2 + (1 – specificity)^2].

DISCUSSION

The present study aimed to determine the optimal cut-off point for HOMA-IR to discriminate MetS, and the proposed optimal cut-off value was 1.7, based on the point producing the greatest discriminatory ability on ROC analysis.

The concept of IR as a common etiology of MetS, proposed around 1990 and given various names including 'syndrome X'[1] and 'the insulin resistance syndrome'[10], was included in the first diagnostic criteria for MetS by the World Health Organization in 1998[11]. However, in the later MetS definitions[8,12–14], the central feature of the syndrome has shifted entirely away from IR to a collective of metabolic abnormalities that have better predictive value for cardiovascular disease, perhaps because there has been hardly any consensus on the cut-off points for the classification of IR.

It is also problematic that the types of range or limit for HOMA-IR (i.e. 'health-associated' or 'decision-based') have often been confused. Unlike a 'health-associated' reference interval that is derived from the central 95% of a normal distribution

Table 2 | Summary of reports on cut-off values for homeostasis model assessment of insulin resistance for the discrimination of metabolic syndrome in different populations

Reference number	Subjects' characteristics and MetS diagnostic criteria	HOMA-IR cut-off value	Sensitivity, %	Specificity, %
15	4624 non-diabetic Koreans, BMI 26.5–27.1 kg/m^2 (MetS), 23.5–23.6 kg/m^2 (non-MetS), AHA/NHLBI and IDF	1.22 (M)	76.1 (AHA/NHLBI) 76.7 (IDF)	65.0 (AHA/NHLBI) 63.2 (IDF)
		1.28 (W)	67.2 (AHA/NHLBI) 67.4 (IDF)	77.3 (AHA/NHLBI) 75.8 (IDF)
16	3071 non-diabetic Iranians, BMI 25.4 kg/m^2 (M), 27.5 kg/m^2 (W), ATP III and IDF	1.775	57.3 (ATP III) 55.9 (IDF)	65.3 (ATP III) 64.7 (IDF)
17	1203 non-diabetic Brazilians, BMI 29.6 kg/m^2, IDF	2.3	76.8	66.7
18	976 non-diabetic Koreans, BMI 24.5 kg/m^2 (M), 24.9 kg/m^2 (W), ATP III	2.34	62.8	65.8
Present study	6868 non-diabetic Japanese, BMI 23.7 kg/m^2 (M), 21.7 kg/m^2 (W), Japanese criteria	1.7 (M) 1.7 (W)	73.4 81.5	70.5 77.0

AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; ATP III, Adult Treatment Panel III; HOMA-IR, homeostasis model assessment of insulin resistance; IDF, International Diabetes Federation; M, men; W, women.

of healthy reference individuals, there is no single standard method to determine a 'decision-based' range or limit[7]. Rather, it depends on the type of decision to be made, such as screening, assessment of risk, diagnosis of disease or disease management. ROC analysis was used in the present study, which is one of the most useful approaches to specify the cut-off points that have the greatest clinical value in discrimination.

In the present study, the optimal cut-off value for HOMA-IR to discriminate MetS was 1.7, as determined by ROC analysis using 6868 non-diabetic Japanese subjects. To the best of our knowledge, this is the first study to determine a cut-off point for HOMA-IR to discriminate MetS in a Japanese population. Several reports have determined HOMA-IR cut-off points for the diagnosis of MetS as 1.22[15], 1.7[16], 2.3[17] and 2.34[18] by ROC analysis in other ethnic populations (Table 2). The possible reasons for the inconsistency might be the differences in ethnicity and clinical backgrounds, including body mass index. Therefore, the cut-off value specific for the Japanese population is needed, and the present result shows higher sensitivity and specificity than the values of the other studies.

The prevalence of HOMA-IR ≥ 1.7 was 36.5% in men and 24.5% in women, whereas 15.9% of men and 2.6% of women had MetS. The discrepancy between the prevalence of HOMA-IR ≥ 1.7 and that of MetS was larger in women than in men. When maximal sensitivity, as well as maximal specificity, is to be prioritized, the issue of a high false-positive rate is inevitable. From the standpoint of primary prevention, we consider that it is much more important not to overlook MetS than to exclude non-MetS, and to give advice on lifestyle modifications to as many people as possible. In addition, we consider that it is not appropriate to diagnose MetS by HOMA-IR, because the prevalence of MetS was 32.1% for men and just 8.6% for women, even in the subjects with HOMA-IR ≥ 1.7.

In conclusion, HOMA-IR = 1.7 was determined as the optimal cut-off value for identifying subjects at high risk for MetS. With the aim of health guidance for MetS, we propose that HOMA-IR < 1.7 should be considered as a target.

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