Original Article

Diagnostic Values of Metabolic Syndrome Definitions for Detection of Insulin Resistance: Tehran Lipid and Glucose Study (TLGS)

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Abstract

Background: This study examines the characteristics and agreement between different definitions of metabolic syndrome (MetS) and insulin resistance (IR).

Methods: A total of 347 non-diabetic individuals who were ≥ 20 years of age were selected from the Tehran Lipid and Glucose Study (TLGS). Subjects were categorized as having MetS by the Adult Treatment Panel III (ATP III) and the Joint Interim Statement (JIS). IR was estimated by using the homeostasis model assessment (HOMA-IR).

Results: According to ATP III and JIS criteria 38.9% and 38.2% of subjects had MetS respectively. The sensitivity of ATP III was 52.3% and specificity was 65%; for JIS the sensitivity was 52.3%, with a specificity of 66.5%. Kappa between ATP III or JIS and HOMA-IR was 0.14 and 0.16, respectively. Based on receiver operating characteristic (ROC) analysis, the use of waist circumference (WC) and fasting plasma glucose (FPG) for the diagnosis of IR in women showed a diagnostic accuracy equal to or instead of counting MetS components using modified ATP III or JIS. WC optimal cut points for prediction of IR were 93.5 cm for men and 92.5 cm for women.

Conclusions: ATP III and JIS definitions have low sensitivities and specificities for detecting IR. There is poor agreement between these criteria and IR.

Keywords: Body mass index, insulin resistance, metabolic syndrome, waist circumference

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Introduction

Insulin resistance (IR) refers to decreased stimulatory effect of insulin in glucose disposal on peripheral target tissues.[1–3] It may be one of the fundamental metabolic disorders associated with aging and obesity that drives abnormal levels of blood pressure, lipids and glucose; therefore, it should be beneficial to discover individuals with IR in its primary stages.

Since it is not cost-effective to screen all individuals for IR by laboratory tests, several organizations such as the Adult Treatment Panel III (ATP III) or Joint Interim Statement (JIS) have proposed clinical criteria for the diagnosis of metabolic syndrome (MetS) which is closely linked to IR according to strong accumulative evidence.[4]

The main goal of definitions for MetS is to detect IR individuals and prevent its cardiovascular consequences. However studies have not shown good sensitivity and/or specificity for MetS in the identification of people with IR.[5–7] In the US, Cheal et al.[7] have reported that although IR and presence of MetS (by ATP III definition) were significantly associated, there was only a sensitivity of 46% and positive predictive value of 76% for MetS to identify IR individuals.

The aim of the present study was to assess the level of agreement between two definitions of MetS and IR in an adult Tehranian population and to disclose diagnostic accuracy of each of the MetS components in identifying individuals with IR. We also aimed to determine the optimal waist circumference (WC) cut-off point to detect IR.

Materials and Methods

This study was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS), a prospective study conducted on a representative sample of Tehran residents, with the aim of determining the prevalence of non-communicable disease risk factors and developing a healthy lifestyle to improve these risk factors.[8] From 15005 people aged 3 years and older residing in district 13 of Tehran, we randomly selected 347 adults (140 men and 207 women) aged ≥ 20 years, without histories of diabetes or taking any medications that could affect lipids, carbohydrate metabolism or increase IR (e.g., steroids or metformin). Those with histories of cardiovascular, renal, hepatic or thyroid disorders were excluded; also pregnant or lactating women were not enrolled. The study was approved by the local Ethics Committee of the Research Institute for Endocrine Sciences and all participants signed an informed consent before enrolling into the study.

Details of the TLGS protocol and all laboratory procedures have been published elsewhere.[8] In brief, demographic data collection and anthropometric examination was undertaken by trained personnel. Weight was measured while the subjects were minimally clothed, without shoes, by using digital scales and recorded to the nearest 100 g. Height was measured in a standing position, without shoes, using a tape measure while the shoulders were in a normal position. Body mass index (BMI) was calculated by di-

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viding weight (in kilograms) by height squared (in meters). WC was measured at the narrowest level over light clothing by using an unstretched tape measure with no pressure to the body's surface; measurements were recorded to the nearest 0.1 cm. A qualified physician measured blood pressure twice with the subject in a seated position during the physical examinations. After one initial measurement for determining the peak inflation level by using a standard mercury sphygmomanometer; the mean of two measurements was considered to be the participant's blood pressure. Fasting blood samples for the measurement of glucose and lipid concentrations were drawn after the subjects had fasted overnight. Fasting plasma glucose (FPG) was measured on the day of blood collection by the enzymatic colorimetric method that used glucose oxidase. Serum total cholesterol and triglyceride (TG) concentrations were measured by commercially available enzymatic reagents (Pars Azmoon, Tehran, Iran) adapted to a Selectra autoanalyzer. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungstic acid. Low-density lipoprotein cholesterol was calculated from serum total cholesterol, TG and HDL-C, except when TG concentration was 400 mg/dL. Concentration of serum insulin was measured by the ultrasensitive enzyme-linked radioimmunoassay method (Mercodia, Uppsala, Sweden) with a covariance <4%.

Definition

Patients were assessed for having MetS according to ATP III and JIS definitions. Per the ATP III definition,[9] MetS can be identified by the existence of three or more of the following components: high WC (> 102 cm in men and > 88 cm in women), FPG ≥ 100 mg/dL, low levels of HDL-C (< 40 mg/dL in men and < 50 mg/dL in women), high TG ≥ 150 mg/dL and high blood pressure [systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg].

MetS was defined according to JIS,[10] as the presence of any three of the following five risk factors: 1) abdominal obesity with a WC ≥ 95 cm for women according to population- and country-specific cut-off points for Iranians[11]; 2) FPG ≥ 100 mg/dL or drug treatment; 3) fasting TG ≥ 150 mg/dL or drug treatment; 4) fasting HDL-C < 50 mg/dL in women or drug treatment; 5) raised blood pressure defined as SBP ≥ 130 mmHg, DBP ≥ 85 mmHg or antihypertensive drug treatment. Diabetes was considered present if the participant was under treatment with insulin or oral hypoglycemic agents, or if FPG was > 126 mg/dL and/or if the two-hour post-glucose load (2-hPG) was > 200 mg/dL.[12] IR was estimated by the homeostasis model assessment (HOMA) as an imperfect reference standard for measurement of IR according to the formula[13]:

$$\text{HOMA-IR} = [(\text{Fasting insulin level (mU/L)} \times \text{FPG (mmol/L)}]/ 22.5$$

To determine the IR cut-off value, 80 subjects with BMI of 18.5–25 kg/m^2, FPG < 100 mg/dL and 2-hPG < 140mg/dL, aged 25–84 years (mean ± SD; 45.3 ± 15.5 years) were selected in whom HOMA-IR distribution had some skewness. The 95th percentile was considered for the definition of IR (2.50 mol × μU/L^2).

Statistical analysis

Data are summarized as means ± SD for quantitative variables and numbers or percentages for categorical variables. Continuous variables were checked for normality using the one-sample Kolmogorov-Smirnoff test. The sensitivity, specificity and positive and negative predictive values were calculated for evaluating the diagnostic accuracy of MetS. The agreement between different definitions of MetS has been determined by the kappa statistic and receiver operating characteristic (ROC) curves which are constructed to provide a graphical representation of the relationship between false positive (specificity) and true positive (sensitivity) detection rates for the counting of categorical MetS components. The appropriate optimum value for diagnostic accuracy of MetS components can be defined using the formula: $(1\text{-sensitivity})^2 + (1\text{-specificity})^2$.

Statistical software SPSS (version 16.0; SPSS Inc., Chicago, IL, USA) was used for analysis and ROC curves were compared using STATA (version 9.0; STATA College Station, TX). $P < 0.05$ was considered significant.

Results

A total of 347 subjects (40.3% men and 59.7% women) aged 21–84 years (mean age: 47.8 ± 13.2 years) were included in the study (Table 1). Men had higher weight and TG levels but lower HDL-C. However, women had higher 2-hPG, serum insulin levels and HOMA-IR ($P < 0.05$). Of 347 subjects, 86 (24.8%) were IR based on HOMA-IR, and the prevalence of MetS was 38.9% based on the modified ATP III and 38.2% based on JIS. MetS was more common in women ($P = 0.01$). In addition, the prevalence of central obesity was 41.2% (18.6% in men and 56.5% in women, $P < 0.001$) using the modified ATP III and 35.3% (36.7% in men and 34.3% in women, P = NS) using JIS criteria.

Sensitivity and specificity of ATP III and JIS were relatively low for the diagnosis of IR [sensitivity: 52.3 for both; specificity: 65.5 (ATP III) and 66.5 (JIS)], which was lower in women than men. The kappa values for agreement among different definitions were low (Table 2) at 0.14 for ATP III and 0.16 for JIS. Kappa values were also lower in women compared to men.

Curves were constructed based combined counts of MetS components in addition to each of the MetS components individually to compare diagnostic accuracy between them. The area under the ROC curve based on counting MetS components was 0.62 (ATP III) and 0.64 (JIS), which was greater in men than women (Table 3). The area under the ROC curve for FPG (0.65) and WC (0.62) were equivalent to counting MetS components in ATP III and JIS. Among men, the area under the ROC curves for FPG was 0.70 and for WC, it was 0.73, which meant that above variables could individually discriminate IR subjects from insulin sensitive with accuracy of 70%. The area under the ROC curve for FPG was 0.68 and 0.57 for WC in women (Table 3).

To identify the optimum cut-off point for each component of MetS that detected IR subjects we used ROC analysis with a WC cut-off of 93.5 cm for men and 92.5 cm for women (Table 4).

Discussion

The present population-based study demonstrates that defining MetS by using ATP III and JIS criteria that identifies IR lacks sensitivity and is poorly specific; moreover, there is no significant agreement between MetS and IR. In addition, these results suggest that a single measurement of WC or FPG alone may provide the same or even greater accuracy than whole components for the

Table 1. Descriptive characteristics of participants.

Variable	Total *n* = 347	Male *n* = 140	Female *n* = 207
Age (years)	47.8 ± 13.2	49.7 ± 14.2	46.4 ± 12.3
Height (cm)	161.2 ± 8.6	168 ± 6.5	156 ± 5.6*
Weight (cm)	72.8 ± 13.1	75.8 ± 13	69.5 ± 12.5*
BMI (kg/m^2)	27.8 ± 4.7	26.6 ± 4	28.6 ± 5
WC (cm)	90.9 ± 10.6	91.4 ± 10.9	90.5 ± 11.8
FPG (mg/dL)	91.4 ± 9.8	93.6 ± 9.6	90 ± 9.6
2-hPG (mg/dL)	110 ± 26.8	105.4 ± 28.3	113.9 ± 25.2*
TG (mg/dL)	176.3 ± 120	194.3 ± 153	164 ± 90.9*
HDL-C (mg/dL)	41.7 ± 11	37.6 ± 9.3	44.5 ± 11.3*
SBP (mmHg)	122.2 ± 19.6	122.8 ± 17.9	121.8 ± 20.6
DBP (mmHg)	79.6 ± 11	79.4 ± 10.3	79.8 ± 11.5
Hypertension (%)	41.5	40	42.5
IFG (%)	15	21.4	10.6
IGT (%)	8.1	7.9	8.2
IFG + IGT (%)	3.5	2.1	4.3
Serum insulin (μg/ml)	8.2 ± 7.3	7.2 ± 7.2	8.9 ± 7.2*
HOMA-IR index	1.88 ± 1.69	1.68 ± 1.61	2.01 ± 1.73*
IR (%)	24.8	20.7	27.5

All values are mean ± SD. BMI= Body mass index; WC= Waist circumference; FPG= Fasting plasma glucose; 2h-PG= 2-h post-glucose load; TG= Triglycerides; HDL-C= High-density lipoprotein cholesterol; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; IFG= Impaired fasting glucose; IGT= Impaired glucose tolerance; IR= Insulin resistance; Hypertension is defined as SBP/DBP ≥ 130/85. IFG and IGT are defined according American Diabetes Association criteria (ADA) 2003.[12] *$P < 0.05$ is significant between genders.

Table 2. Test characteristics and agreement between deferent definitions of metabolic syndrome (MetS) and insulin resistance (IR).

MetS	Modified ATP III criteria			JIS criteria		
	Total	Male	Female	Total	Male	Female
Sensitivity	52.3 (41.7–62.9)	58.6 (40.7–76.5)	49.0 (36.1–62.1)	52.3 (45.2–68.8)	65.5 (46.2–80.1)	45.6 (29.1–58.8)
Specificity	65.5 (59.3–70.9)	73.6 (65.4–81.8)	58.8 (51.9–66.7)	66.5 (56.1–67.2)	67.6 (69.4–84.2)	65.8 (52.4–70.8)
PPV	33.3 (25.3–41.2)	37.2 (23.1–51.4)	31.5 (21.8–41.2)	34.1 (26.9–48.2)	34.5 (21.8–48.2)	33.8 (24.7–42.3)
NPV	80.4 (75.2–85.8)	87.4 (80.3–93.9)	75.5 (67.1–82.9)	80.8 (74.9–86.1)	88.2 (81.3–94.8)	76.0 (67.5–85.1)
Kappa	0.14	0.26	0.11	0.16	0.25	0.10

Values in parentheses represent 95% confidence interval. PPV = positive predictive value; NPV = negative predictive value.

Table 3. Area under the curve (AUC) of metabolic syndrome (MetS) with different definitions and individual metabolic components.

	Total *n* = 347	Male *n* = 140	Female *n* = 207
MetS as ATP III criteria	0.62 (0.57–0.70)	0.67 (0.56–0.80)	0.59 (0.52–0.67)
MetS as JIS criteria	0.64 (0.57–0.71)	0.69 (0.57–0.81)	0.62 (0.53–0.70)
WC (cm)	0.62 (0.55–0.69)	0.71 (0.61–0.81)	0.57 (0.48–0.66)
FPG (mg/dL)	0.65 (0.59–0.72)	0.70 (0.59–0.81)	0.68 (0.57–0.74)
TG (mg/dL)	0.60 (0.53–0.66)	0.64 (0.53–0.76)	0.58 (0.50–0.67)
HDL-C (mg/dL)	0.43 (0.36–0.50)	0.48 (0.37–0.60)	0.37 (0.29–0.45)
SBP (mmHg)	0.60 (0.52–0.66)	0.68 (0.59–0.78)	0.55 (0.46–0.63)
DBP (mmHg)	0.55 (0.49–0.62)	0.61 (0.50–0.72)	0.52 (0.44–0.61)

MetS = metabolic syndrome; ATP III = adult Treatment Panel III; JIS = joint Interim Statement; WC = waist circumference; FPG = fasting plasma glucose; SBP = systolic blood pressure; DBP = diastolic blood pressure.

diagnosis of IR.

Despite several evidences that consider IR to be an effective predictor of cardiovascular risk,[14] measuring IR is not simple. Special and sophisticated techniques such as the euglycemic hyperinsulinemic clamp are needed; thus, other methods should be defined to enable easier diagnosis of IR. Simpler and easier-to-calculate indices such as HOMA-IR, as an imperfect reference standard, have been used in large population-based epidemiological studies. It has been shown that there is a good correlation between estimates of IR derived from HOMA-IR and the euglycemic clamp technique.[15] In order to achieve more simplicity, different criteria for defining MetS have been proposed to identify individuals with IR. MetS is believed to be a reliable indicator of IR,[4] although there is some disagreement over current definitions of MetS and IR.[5–7]

In view of our data based on the HOMA-IR value as an imperfect reference standard and a cut-off point equal to 2.5 based on the 95th percentile, it was shown that 24.8% of subjects were IR, with no difference between genders. The sensitivity of ATP III and JIS definitions was 52.3% for both and their specificity was 65% (ATP III) and 66.5% (JIS); there was poor agreement between IR and ATP III (kappa = 0.14) or JIS (kappa = 0.16) definitions. In line with our study, Sierra-Johnson et al.,[5] studied 256 non-diabetic individuals for IR using a minimal model in which 26% were IR. In their study, ATP III had a sensitivity of 42% and specificity of 94%. Another study on 74 non-diabetic individuals for IR that used the euglycemic hyperinsulinemic clamp method found 33.8% IR subjects with an ATP III sensitivity of less than 50% and specificity equal to 90%.[6] A study by Cheal et al.[7] on 443 healthy volunteers used the steady state plasma glucose concentration (SSPG) method and have reported 20% IR subjects with 46% sensitivity and 93% specificity for ATP III. Considering the

Table 4. Optimum cut-off points for each component of metabolic syndrome (MetS) using the ROC curve.

Variable	Total	Male	Female
	n = 347	*n* = 140	*n* = 207
WC (cm)	93	93.5	92.5
FPG (mg/dL)	92	96	92
TG (mg/dL)	172	173	161
HDL-C (mg/dL)	—	34	42
SBP (mmHg)	122	120	115
DBP (mmHg)	80	80	79

WC = waist circumference; FPG = fasting plasma glucose; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure

above-mentioned studies, it seemed that identifying MetS using ATP III criteria was poorly sensitive but had high specificity. In comparison, we found the same sensitivity but lower specificity, however we used the HOMA-IR as an imperfect reference standard, which could have led to an underestimation of sensitivity and specificity. Another reason for low specificity in the present study might be the selected cut-off value (95th percentile of HOMA-IR distribution).In fact a little change in selected cut-off value can highly influence specificity. There is no consensus regarding cut-off points for diagnosing IR. For instance, Can et al.,[16] and Sandhofer et al.[17] selected the 75th percentile of the non-diabetic population for the IR cut-off point. However, Strazzullo et al.[18] suggested using the 80th percentile value for cut-off point in non-diabetic and non-obese populations. In a recent study of 1327 non-diabetic and non-hypertensive Tehranian subjects, HOMA-IR cut-off to determine MetS was based on the lower limit of the top quintile of HOMA-IR distribution values in normal subjects and defined as 1.8.[19] However, considering the existing controversies we arbitrarily selected the 95th percentile to identify the cut-off value to define IR.

When the ROC curve was constructed for each individual component of the MetS definition, we found that the individual components of MetS, WC and FPG were appropriate predictors for diagnosing IR with higher accuracy than the MetS components as a whole. In a Sierra-Johnson study,[5] the diagnostic accuracy of counting MetS components was 0.76 based on the ROC curve (higher in men than women); when MetS components were considered separately, the WC was reported to have more accuracy for diagnosing IR when compared with counting MetS components.

As a secondary result, we found that the best cut-off point of WC for IR in our population was 93 cm (93.5 cm in men and 92.5 cm in women). In agreement with this finding, the preceding study in the TLGS framework defined cut-off point values of WC equal to 94.5 cm for both genders to predict cardiovascular outcomes in a group of subjects aged ≥ 40 years.[20] In addition, a national study on 3024 Iranians aged 25–64 years showed that the optimal cut-off point of WC for predicting at least two other components of the MetS as defined by IDF was 89 cm for men and 91 cm for women.[21]

Our survey has both strength and limitations. First, we used the HOMA-IR method as an imperfect reference standard for identifying insulin sensitivity instead of the euglycemic hyperinsulinemic clamp method since there is good correlation between estimates of IR derived from HOMA-IR and the euglycemic clamp method (r = 0.73).[15] Second, in the present study the 95th percentile cut-off point was selected arbitrarily for defining IR using HOMA-IR but it seems reasonable to determine cut-off points for HOMA-IR based on a comparison with the euglycemic hyperinsulinemic clamp method. Moreover, it is better to define gender-specific cut-off points. The strength of this study is its determination of the 95th percentile HOMA-IR distribution value from the normal population (BMI = 18.8–25 kg/m^2; FPG < 100 mg/dl and 2h-PG < 140 mg/dL) that was derived from a large population-based study. Most studies, however, only enroll the non-diabetic and non-obese populations.

In summary, we have shown that application of ATP III and JIS definitions for identifying MetS provides poor sensitivity and specificity. There is poor agreement between these definitions and IR. It seems that measuring WC or FPG alone may provide equal or greater overall diagnostic accuracy for identification of IR than counting MetS components as advocated by ATP III or JID guidelines.

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