Endocrine (2011) 40:117–123
DOI 10.1007/s12020-011-9447-4

ORIGINAL ARTICLE

Leptin cut-off values for determination of metabolic syndrome: third national surveillance of risk factors of non-communicable diseases in Iran (SuRFNCD-2007)

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Received: 16 January 2011 / Accepted: 22 February 2011 / Published online: 8 March 2011

Abstract Leptin is strongly contributed to the clustering of metabolic syndrome (MetS) components and potentially can be regarded as a single predictor of MetS. This population-based study, for the first time, reports the diagnostic accuracy of different leptin cut-points for determining MetS. Further, the current study compares the predictive ability of the appropriate threshold of leptin with insulin resistance. Data of the individuals without history of known diabetes mellitus, aged 25–64 years, from the third national surveillance of risk factors of non-communicable diseases (SuRFNCD-2007) were analyzed. MetS was defined due to either adult treatment panel III (ATPIII) or the modified international diabetes federation (IDF) criteria. Receiver-operating characteristic (ROC) curves were depicted to define cut-off of serum leptin, using the maximum Youden index and the shortest distance methods. Further, the values of leptin cut-offs in prediction of MetS were compared with those of insulin resistance (defined as homeostasis model assessment of insulin resistance >1.775). In men, the optimal cut-offs of leptin for IDF- and ATPIII-defined MetS were 3.6 ng/ml (positive predictive value, PPV: 56.5%; negative predictive value, NPV: 72.7%) and 4.1 ng/ml (PPV: 49.6%; NPV: 78.1%), respectively. In women, the optimal threshold was equal to 11.0 ng/ml (PPV: 53.8%; NPV: 73.0% for IDF criteria and PPV: 60.1%; NPV: 64.9% for ATPIII criteria). The diagnostic accuracy of these values in identifying MetS was similar to that of insulin resistance. Therefore, leptin is comparable to insulin resistance in identifying MetS and can be used as single predictor of MetS.

Keywords Leptin · Insulin resistance · Metabolic syndrome · Receiver operating characteristic curve

Abbreviations

ATPIII	Adult treatment panel III
AUC	Area under the ROC curve
CDC	Center for disease control
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
IDF	International diabetes federation
MetS	Metabolic syndrome
NLR	Negative likelihood ratio
NPV	Negative predictive value
PLR	Positive likelihood ratio
PPV	Positive predictive value
ROC curve	Receiver operating characteristics curve
SuRFNCD	Surveillance of risk factors of non-communicable diseases
TG	Triglycerides

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Introduction

Adipose tissue, which has been traditionally regarded as a passive site of lipid storage, is now known as an active

organ regulating appetite, insulin sensitivity, energy expenditure, inflammation, and immunity [1]. Leptin is a circulating peptide hormone produced by adipocytes, which reflects body fat content [2]. Leptin resistance reflected by hyperleptinemia is suggested to play a key role in the development of adverse outcomes of obesity such as hypertension, impaired glucose metabolism, and atherosclerosis [3]. Leptin is directly correlated with insulin concentration independent of anthropometric measures (e.g., body mass index and waist to hip ratio) [4–6]. In men, leptin is also associated with increased likelihood of diabetes after adjusting for possible confounding factors [7, 8]. In addition, in a large prospective study, leptin was reported as an independent predictor of coronary artery disease [9].

Metabolic syndrome (MetS) refers to the co-occurrence of coronary artery disease and diabetes risk factors, including abdominal obesity, glucose intolerance, dyslipidemia, and elevated blood pressure [10]. Insulin resistance or hyperinsulinemia is suggested to be the underlying characteristic of MetS, although its central role in the development of MetS is still obscure [11]. Along with insulin resistance, leptin is also crucially involved in the constellation of MetS features [12]. In line with some previous studies, recently we have shown that leptin exhibits the potential to be included as a component of MetS or utilized as a single predictor of MetS [13–16].

Although several studies have demonstrated that leptin is strongly contributed to the clustering of MetS components [17–19], no study is available to report the diagnostic accuracy of different cut-off points of leptin in prediction of the risk of MetS. In this study, for the first time, we determined the appropriate cut-offs of leptin for MetS, defined by two different conventional criteria. Also, we compared the predictive value of leptin in identifying MetS with that of a reliable surrogate measure of insulin resistance, i.e., the homeostasis model assessment [20–22], in a large national representative sample of Iranian men and women.

Methods

Participants

Data of the third national surveillance of risk factors of non-communicable diseases (SuRFNCD-2007) in Iran were used in this study. Details of the survey have been reported previously [23]. Briefly, a total number of 4233 individuals as a representative sample of 25–64 years old Iranian adults were enrolled using a cluster sampling design. The data were obtained and recorded in standardized questionnaires by trained healthcare professionals in line with WHO recommendations. After excluding pregnant women, individuals with self-reported diabetes, individuals with missing data and those with body mass index <18.5 kg/m^2, analyses were performed on the remaining 2660 subjects. The survey received ethics approval from the Center for Disease Control (CDC) of Iran, and all participants gave verbal informed consent before study commencement.

Procedures and definitions

Weight and height of participants were determined in light clothing and without shoes. Waist circumference was measured at the end of a normal expiration with arms relaxed at the sides, at mid-distance between iliac crest, and rib cage on the mid-axillary line. Three blood pressure measurements with 5 min intervals were obtained after the participants had been relaxed for at least 5 min. The average of these three measurements was used for the analyses. Venous blood samples were collected after 12 h overnight fast. Fasting plasma glucose was assessed by glucose oxidize test (intra- and inter-assay coefficients of variation less than 2.1 and 2.6, respectively). Insulin was measured by radioimmunoassay, using an antibody with no cross-reaction against pro-insulin and C-peptide (Immunotech, Prague, Czech Republic). The intra- and inter-assay coefficients of variation were lower than 4.3 and 3.4, respectively. Triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were determined by enzymatic methods (Parsazmun, Karaj, Iran). Serum leptin concentration was determined by an enzyme-linked immunosorbent assay (DRG Instruments GmbH, Germany) with an intra-assay coefficient of variation of 5.9–6.9% and an inter-assay coefficient of variation of 8.6–11.5%.

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (U/l) $\times$ fasting plasma glucose (mg/dl)/405, as described by Matthews et al. [24]. MetS was defined due to either ATPIII declaration or IDF criteria modified by the waist circumference cut-point recommended for Iranian population. ATPIII criteria allow the diagnosis of MetS when three or more of the following conditions are satisfied: presence of the abdominal obesity (waist circumference $\geq$102 cm and $\geq$88 cm in men and women, respectively), elevated blood pressure (systolic blood pressure $\geq$130 mmHg and/or diastolic blood pressure $\geq$85 mmHg), low HDL-C ($<$40 and $<$50 mg/dl in men and women, respectively), TG $\geq$ 150 mg/dl and fasting plasma glucose $\geq$100 mg/dl [10, 25]. According to the modified IDF criteria, a person with MetS must have abdominal obesity (waist circumference $\geq$90 cm for both men and women) plus any two or

more of the following conditions: elevated blood pressure (see above) or treatment of previously diagnosed hypertension, low HDL-C (see above) or on HDL-C therapy, TG ≥150 mg/dl or on TG therapy and fasting plasma glucose ≥100 mg/dl [26, 27].

Statistical analysis

Data were weighted for sex, age, and residential area (urban/rural) strata, according to the population of Iran (National Census, 2006). Complex sample survey analysis was performed based on the clusters of sampling protocol, strata (age groups, sex, and residential area) and the determined weights, using SPSS software (version 16.0; SPSS Inc., Chicago, IL). National estimates, made in the complex survey analysis mode, are expressed as mean ± standard error of the mean (SEM). In order to improve the normality of skewed variables, natural log transformations were used in the subsequent analyses as appropriate. Leptin cut-offs from the 50th to the 95th percentile along with their corresponding sensitivity and specificity for diagnosis of ATPIII- and IDF-defined MetS in men and women were determined. The receiver-operating characteristic (ROC) curves of leptin for ATPIII- and IDF-defined MetS were depicted, and the areas under the curves (AUC) were estimated for men and women separately. To determine the optimal thresholds of leptin, the points on the ROC curves with maximum Youden index [sensitivity − (1 − specificity)]), and the points with shortest distance value form the point (0,1) [$(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$] were identified. The positive and negative predictive values (PPV and NPV) along with the positive and negative likelihood ratios (PLR and NLR) of optimal cut-points of leptin for MetS were calculated and compared with that of optimal HOMA-IR cut-off (i.e. 1.775 unites [28]) in Iranian population. Sensitivities and specificities were compared using McNemar test.

Results

Table 1 summarizes general characteristics of the study population. The plasma leptin levels were more than two times higher in women ($P < 0.001$). The prevalence of IDF-defined MetS was similar in men and women (39.1 and 37.8%, respectively). However, a higher proportion of women had ATPIII-defined MetS compared to men (45.3 vs. 29.9%, respectively, $P < 0.001$).

Sex-specific distribution of leptin cut-offs from the 50th to the 95th percentile along with their corresponding sensitivity and specificity for diagnosis of IDF- and ATPIII-defined MetS are shown in Table 2. This table presents the sensitivity and specificity of different leptin cut-points for identifying MetS in different clinical situations. For instance, in relation to IDF-defined MetS if >80% sensitivity is regarded acceptable, the appropriate cut-off value for leptin will be around 2.85 ng/ml in men (corresponding to the 34th percentile with specificity of 43.2%) and 6.55 ng/ml in women (corresponding to the 33rd percentile with specificity of 39.9%). However, the leptin cut-off value that yielded >80% specificity was 3.9 (i.e. 68th percentile) and 13.9 (i.e. 72nd percentile) in men and women, respectively. The sensitivities of these cut-offs were 50 and 41.1%, respectively, in men and women.

Youden index values and the distance from the top left corner of the ROC curve of leptin for diagnosis of MetS are depicted in Fig. 1. In men for IDF-defined MetS, leptin showed a plateau on the top of Youden index curve, and at the bottom of distance curve ranged from 3.3 to 4.0 (corresponding to the 53rd to 70th percentile). The best cut-off point in this range was 3.6 (i.e. 60th percentile). The appropriate cut-off point for ATPIII-defined MetS was 4.1 (i.e. 71st percentile). In women, the optimal threshold was equal to 11.0 (61st percentile) for both MetS definitions.

Table 3 compares the diagnostic accuracy of the optimal leptin cut-off points with that of HOMA-IR to predict MetS. McNemar analysis revealed that for diagnosis of

Table 1 Principal characteristics of the study population

	Men ($n = 1245$)	Women ($n = 1415$)
Age (years)	43.4 ± 0.3	43.0 ± 0.3
BMI (kg/m^2)	25.8 ± 0.1	28.1 ± 0.1
Waist circumference (cm)	90.1 ± 0.3	90.3 ± 0.3
TG (mg/dl)	158.9 ± 2.9	140.4 ± 2.1
HDL-C (mg/dl)	34.7 ± 0.3	39.1 ± 0.3
Fasting plasma glucose (mg/dl)	91.9 ± 0.9	90.2 ± 0.6
Systolic blood pressure (mmHg)	127.1 ± 0.4	124.2 ± 0.5
Diastolic blood pressure (mmHg)	81.0 ± 0.3	82.4 ± 0.3
Leptin (ng/ml)	4.1 ± 0.1	11.0 ± 0.2
IDF defined MetS (%)	39.1	37.8
ATPIII defined Mets (%)	29.9	45.3

Variables are expressed as percentage or mean ± SEM

Table 2 Sex-specific distribution of leptin cut-offs with their corresponding sensitivity and specificity for diagnosis of IDF- and ATPIII-defined metabolic syndrome

	Percentiles of leptin									
	50th	55th	60th	65th	70th	75th	80th	85th	90th	95th
Men										
Cut-off	3.2	3.4	3.6	3.8	4.0	4.4	4.9	5.8	6.8	9.0
Sen%/spe% for IDF-defined MetS	66.1/62.4	63.3/66.7	58.4/71.1	53.7/77.5	48.0/82.0	42.9/85.7	35.5/89.8	28.6/93.6	19.8/95.6	9.0/97.5
Sen%/spe% for ATPIII-defined MetS	64.9/58.4	62.1/61.6	57.4/67.1	53.2/73.5	48.8/78.7	44.9/83.1	38.2/87.9	29.9/91.5	21.0/94.3	10.1/97.2
Women										
Cut-off	9.0	9.9	10.9	12.0	13.1	14.4	15.4	17.8	20.0	25.0
Sen%/spe% for IDF-defined MetS	66.2/60.5	62.1/64.8	58.7/69.4	51.5/75.0	44.2/78.2	36.9/81.7	29.3/85.2	23.0/89.2	16.1/93.5	8.4/96.9
Sen%/spe% for ATPIII-defined MetS	62.4/60.9	57.8/64.7	54.7/69.8	47.5/75.1	41.0/78.4	34.1/81.9	27.4/85.1	21.6/89.6	14.6/93.5	7.5/97.0

Sen sensitivity, *Spe* specificity

IDF-defined MetS, there is not significant difference between sensitivities and specificities of the proposed leptin and HOMA-IR cut-off values, except for specificity of leptin in women which was higher than the specificity of HOMA-IR ($P < 0.001$). For ATPIII-defined MetS, the sensitivities and specificities of leptin cut-offs were, respectively, weaker and stronger compared to those seen with HOMA-IR values ($P < 0.001$). The PPV and NPV of leptin cut-offs were comparable or slightly better than HOMA-IR especially in diagnosis of IDF-defined MetS. In addition, leptin had more satisfactory PLR and NLR compared to HOMA-IR.

Discussion

This study inspects the suitability of using leptin as an indicator of MetS in Iranian men and women. We found that in men the optimal cut-offs of leptin for diagnosis of IDF- and ATPIII-defined MetS were 3.6 and 4.1, respectively. In women, the optimal leptin threshold for both MetS definitions was estimated to be 11.0. Although the serum leptin concentration in women was remarkably higher than men, our results showed that leptin can be considered as a marker of MetS regardless of gender. In this study, we demonstrated that the risk of MetS increases with rising leptin percentiles, and we determined the sensitivity and specificity of different leptin cut-points for prediction of MetS. The rational behind maximum Youden index and shortest distance from (0,1) is to identify an optimal cut-off that would have both a large sensitivity and a large specificity. However, reporting the sensitivity and specificity of different leptin percentiles would be beneficial for prediction of MetS risk in an individual patient with a certain value of serum leptin. Additionally, for different clinical and research situations, different cut-off points might be selected. For instance, high sensitivity is necessary for a screening test, while a diagnostic test requires a much higher specificity.

Leptin modulates mass of adipose tissue and body weight by regulating food intake and energy expenditure [2, 3]. It has been speculated that some underlying processes may link leptin to insulin resistance and different MetS features. For instance, impaired leptin action precedes accumulation of TG in non-adipose tissue organs such as skeletal muscles, which may be responsible for impairment of glucose metabolism [3]. It has been shown that leptin is an independent positive predictor of type 2 diabetes in men after controlling for confounding factors [7, 8]. Serum leptin is positively correlated with TG [4, 14]. Likewise, leptin is directly associated with blood pressure [12]. Leptin through its vascular, renal, and sympathetic actions may influence blood pressure [29–31]. In this respect, increase in the number of metabolic abnormalities enhances serum leptin levels [32]. Leptin is also regarded as an indicator of MetS after adjusting for possible confounding factors such as BMI [12].

Insulin resistance is supposed to be the possible underlying pathophysiologic mechanism which contributes to the appearance of MetS [11]. For this reason, MetS is also called insulin resistance syndrome. HOMA-IR has been widely used as an estimate of insulin resistance in both non-diabetic and diabetic individuals [20–22]. It has been demonstrated that there is a good correlation between estimates of insulin resistance derived from HOMA-IR and from the euglycemic clamp [33]. The results of the present study demonstrated that the predictive values of leptin cut-offs for identifying MetS are similar or slightly better than

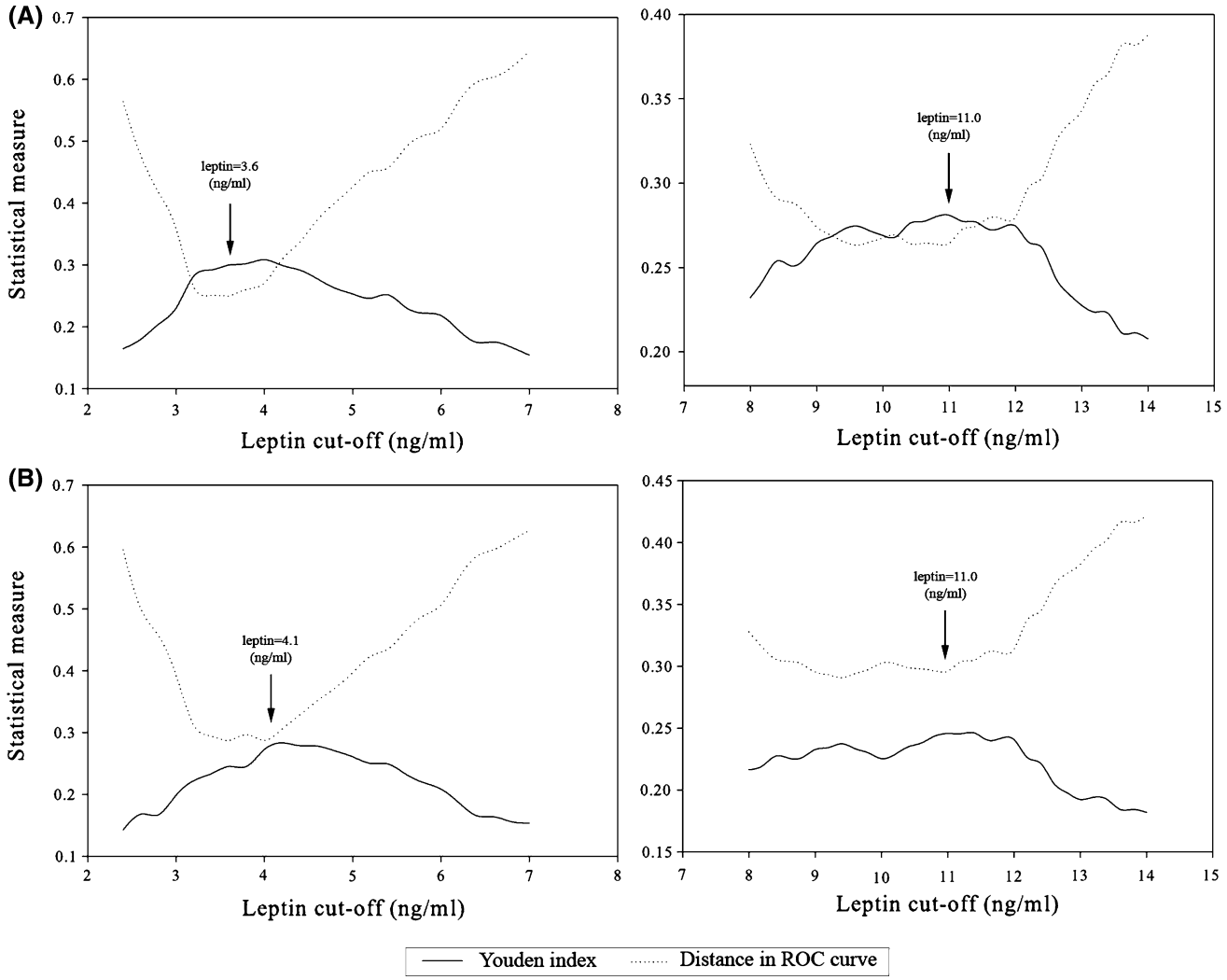

Fig. 1 The optimal cut-offs of leptin for diagnosis of IDF-defined (**a**) and ATPIII-defined (**b**) metabolic syndrome. The *left column* shows the results in men and the *right column* refers to women

HOMA-IR especially in diagnosis of IDF-defined MetS. This finding emphasizes on the prominent role of leptin in clustering of MetS components, and places leptin beside insulin resistance as a key feature of MetS. This is also in line with the findings of our previous study, which showed that inclusion of leptin as a component of MetS does not interfere with the theory of one-factor structure of MetS [16].

Limitations in the current study warrant discussion. First we used a cross-sectional study design, which confines our ability to infer a causal relationship between leptin and MetS development. Since the analyses were performed on a representative sample of Iranian population, the emerged cut-offs cannot be used in people with lipodystrophy (hereditary and acquired) who typically have low leptin levels but are at high risk of having MetS. Ethnicity would most likely influence leptin normative values and their correlation with MetS. Therefore, similar studies are required in different ethnic groups for validating the use of leptin measures as a clinical risk calculator across different ethnicities. Further, although the predictive ability of leptin values for MetS were close to those of insulin resistance reflected by HOMA-IR, it cannot be considered as a strong indicator of MetS. In contrast, this study has several strengths. We stratified our analyses by sex and used a large representative sample of Iranian population. This is the first study reporting the cut-off of leptin for MetS defined by two widely used declarations. Since Youden Index and the shortest distance from (0, 1) compared to other methods are least dependent on the population case prevalence, they are more suitable for the determining a generalisable cut-point [34]. Further, we compared the diagnostic ability of leptin with insulin resistance reflected by a broadly accepted index (i.e. HOMA-IR).

In conclusion, we found that in men the appropriate cut-offs of leptin for IDF- and ATPIII-defined MetS were

Table 3 Comparison of optimal leptin cut-offs with HOMA-IR > 1.775 for predicting metabolic syndrome

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
IDF-defined MetS						
Men						
Leptin > 3.6	58.4	71.1	56.5	72.7	2.03	0.58
HOMA-IR > 1.775	53.7*	66.8*	50.9	69.2	1.61	0.69
Women						
Leptin > 11	57.5	70.0	53.8	73.0	1.92	0.60
HOMA-IR > 1.775	60.3*	59.0†	47.2	71.0	1.47	0.67
ATPIII-defined MetS						
Men						
Leptin > 4.1	48.0	79.2	49.6	78.1	2.31	0.65
HOMA-IR > 1.775	60.8†	67.6†	44.4	80.1	1.87	0.58
Women						
Leptin > 11	54.0	70.3	60.1	64.9	1.82	0.65
HOMA-IR > 1.775	63.5†	61.3†	57.6	66.9	1.64	0.59

*$P > 0.05$, †$P < 0.001$ for the comparison of sensitivity and specificity of leptin cut-offs with HOMA-IR > 1.775

3.6 and 4.1 ng/ml, respectively. The optimal cut-off of leptin was much higher in women and was equal to 11.0 ng/ml. The predictive values of the aforementioned leptin cut-offs were comparable to those of insulin resistance, which is thought to be the underlying characteristic of MetS. Further investigations are needed to determine how measurement of leptin can affect the approach of clinicians toward MetS and whether adding leptin to the MetS definition improves the prognostic ability and predictive power of this syndrome for development of adverse outcomes such as coronary artery disease and diabetes.

Conflicts of interest The authors declare no conflicts of interests.

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