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The Threshold Value of Homeostasis Model Assessment for Insulin Resistance in Qazvin Metabolic Diseases Study (QMDS): Assessment of Metabolic Syndrome

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ABSTRACT

Background: The homeostasis model assessment of insulin resistance (HOMA-IR) is a useful model for application at large epidemiologic studies. The aim of this study was to determine the HOMA cut off values to identify insulin resistance (IR) and metabolic syndrome (MS) in Qazvin, central Iran.

Methods: Overall, 480 men and 502 women aged 20-72 yr attended in this cross sectional study from September 2010 to April 2011. The diagnostic criteria proposed by national cholesterol education program third adult treatment panel (ATPIII), International Diabetes Federation (IDF) and new Joint Interim Societies (JIS); were applied to define MS. Lower limit of the top quintile of HOMA values in normal subjects was considered as the threshold of IR. The receiver operating characteristic (ROC) curves of HOMA for MS diagnosis were depicted. The optimal cut point to determine MS was assessed by maximum Youden index and the shortest distance from the point (0, 1) on the ROC curve.

Results: The threshold of HOMA for IR was 2.48. Fifty one percent of the subjects were insulin resistant. The cut point for diagnosis of JIS, IDF, ATP III and Persian IDF defined MS was 2.92, 2.91, 2.49 and 3.21, respectively. Sensitivity and specificity of ATP III defined MS to diagnose IR was 33.95% and 84.78%, of IDF defined MS was 39.13%, 81.29% and of JIS defined MS was 43.77% and 78.11% and of Persian IDF defined MS was 27.32% and 88.76%, in that order.

Conclusions: The high prevalence of IR in the present study warns about the future burden of type 2 diabetes. Only the ATP III criteria introduced more specific cut point for putative manifestations of IR.

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Introduction

The metabolic syndrome (MS) is a modern epidemic that refers to a cluster of risk factors, including abdominal obesity, high blood pressure, dyslipidemia and increased plasma glucose. MS is strongly associated with the development of cardiovascular disease, Insulin Resistance (IR) and diabetes mellitus[1]. The prevalence of MS has been increasing worldwide.

IR is a major risk factor in the etiology of metabolic disorders includes type 2 diabetes, metabolic syndrome and cardiovascular diseases[2,3]. The gold standard for assessing IR is the euglycemic hyperinsulinemic clamp but due to complicated nature, cost and invasiveness of the method, a large number of simple alternatives have been created [4]. Various combinations of insulin and glucose level alongside other metabolic variables like triglycerides have been used to produce equivalent IR indices[2]. However, the homeostasis model assessment of insulin resistance (HOMA-IR) is still the most commonly used surrogate measure of IR.

HOMA-IR is a useful model with a simple formula and a single fasting measurement for application in large epidemiologic studies [5]. Nevertheless, no reference value has been concluded for the HOMA-IR worldwide and its cut point to diagnose IR may vary from race to race. In a study on 1327 subjects in Tehran, HOMA-IR cut off to detect IR was 1.8 [6]. The optimal HOMA-IR cut-off for the diagnosis of MS in non-diabetic individuals was set to be 1.775 (sensitivity: 57.3%, specificity: 65.3%, with National Cholesterol Education Program Third Adult Treatment Panel criteria; sensitivity: 55.9%, specificity: 64.7%, with International Diabetes Federation criteria)[3]. Reference interval for HOMA-IR was 0.63–2.68 in the Tehran Lipid and Glucose Study [7]. Limited population-based studies have been focused on defining cut-off values of HOMA-IR for diagnosis of MS.

The aim of this study was to determine the HOMA-IR cut off values to identify IR and metabolic syndrome in subjects without diabetes in Qazvin, Iran.

Methods

Subjects

This study was a cross sectional population based study performed on a representative sample of residents of Mindoodar district of Qazvin, located 150 km northwest of Tehran, the capital city of Iran. The Ethics Committee of Qazvin University of Medical Sciences approved the study.

All households had health profiles and contact information at Minoodar Health Center since a population research center was located in the district. The sampling unit was the household and the inclusion criterion was age ≥ 20 yr. The Minoodar district was divided into four main clusters according to the population size. The households were selected by multistage cluster random sampling methods. Firstly, subjects were invited by phone call to attend the study at Minoodar Health Center, and after face-to-face explanation of the study details, they were free to participate. All subjects in the selected households participated in the study and gave their written informed consent. Overall, 1107 people aged ≥ 20 yr were evaluated from September 2010 to April 2011.

Data collection

Social and demographic data were self-reported in the questionnaire given to the subjects. Two general practitioners recorded past medical history, family medical conditions, current medication and physical examination using an organized questionnaire. Anthropometric data were obtained after a 12 – 14 hours over night fast. Complete details of the methods have been described elsewhere[8]. Body weight, height and waist circumference (WC) were measured. WC was measured to the nearest 0.1 cm using a flexible, non-elastic measuring tape without any pressure on the tissue and halfway between the costal margin and the iliac crest at the end of normal expiration. Body mass index (BMI) was calculated as weight (kg) divided by the height (m) squared. Blood pressure (BP) was measured three times – on a single occasion – in a seated position using a mercury sphygmomanometer after a 15 min rest.

Laboratory Tests

A venous blood sample of the subjects was taken after a 12 – 14 hour overnight fast. All the samples were analyzed at the same laboratory on the day of blood collection. The serum was used for all laboratory measurements. Blood levels of glucose, insulin, total cholesterol (Chol), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) were measured in all subjects. Insulin levels were measured by ELISA using reagent (Monobind Company, USA) and Awareness stat Fax ELISA reader. A within-run precision coefficient of variation (CV) was 4.9 and total (within-laboratory) precision CV was 4.9. The cross reaction with proinsulin was less than 1%. The assay sensitivity (detection limit) was 0.75 μIU/ml. An oral glucose tolerance test (OGTT) was performed on every subjects who had never been diagnosed with diabetes.

Definitions

Diabetes mellitus was defined as fasting blood sugar (FBS) ≥126 mg/dl or 2-h post load glucose ≥200 mg/dl during OGTT or previous diagnosis of diabetes. Subjects with known or new diabetes were excluded from the present study. Participants with BMI ≤25 kg/m^2, systolic blood pressure <130 mmHg, diastolic blood pressure <85 mmHg, total cholesterol ≤200 mg/dL, HDL-C ≥40 mg/dL in males, ≥ 50 mg/dL in females, FBS<100 mg/dL and TG <150 mg/dL were defined as normal subjects (without metabolic abnormality). The diagnostic criteria of MS proposed by national cholesterol education program third Adult treatment panel (ATPIII)[9], International Diabetes Federation (IDF)[10] and the last Joint Interim Society criteria (JIS)[11] were applied (Table 1). Moreover, Persian IDF criteria were defined using WC cut-off point proposed by the Iranian National Committee of Obesity (WC ≥95 cm in both genders) as obesity domain[12]. Insulin resistance was estimated by the homeostatic model assessment (HOMA-IR), as fasting serum insulin (μIU/ml) × fasting blood sugar (mmol/L)/22.5[5].

Data analysis

Shapiro-Wilk test was used to examine the normality of the variables of interest and all of them had non-normal distribution. Data were recorded as median (interquartile range) or as number (percent). Categorical variables were analyzed by chi square test, *t*-test was used for analysis of continuous variables and non-normally distributed variables were compared by Mann Whitney U test. *P*-values less than 0.05 were considered statistically significant.

Table 1: Diagnostic criteria for the metabolic syndrome

Components	Adult treatment panel III (2004)	International Diabetes Federation	Joint Interim Societies
Glucose	FBS ≥100 mg/dl (includes diabetes)	FBS ≥100 mg/dl (includes diabetes)	FBS ≥100 mg/dl (includes diabetes)
Obesity	WC ≥102 cm (men) / ≥88 cm (women)	WC ≥94 cm (men) / ≥80 cm (women)	WC ≥94 cm (men) / ≥80 cm (women)
Triglycerides	TGs ≥150 mg/dl	TGs ≥150 mg/dl or receiving treatment	TGs ≥150 mg/dl or receiving treatment
HDL -C	HDL <40 mg/dl (men) / <50 mg/dl (women)	HDL <40 mg/dl (men) / <50 mg/dl (women) or receiving treatment	HDL <40 mg/dl (men) / <50 mg/dl (women) or receiving treatment
Blood Pressure	SBP ≥130 mmHg or DBP ≥85 mmHg	SBP ≥130 mmHg or DBP ≥85 mmHg or receiving treatment	SBP ≥130 mmHg or DBP ≥85 mmHg or receiving treatment
Definition of metabolic syndrome	Any 3 of the above components	Obesity domain plus any 2 of the above components	Any 3 of the above components

FBS: Fasting blood sugar; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TGs: triglycerides; HDL-C: high density lipoprotein cholesterol

The optimal cut point of HOMA-IR to determine IR was evaluated by lower limit of top quintile of HOMA-IR values in normal subjects [6, 13]. The 75th and the 90th percentile of HOMA–IR values were also calculated. The Receiver

operating characteristic (ROC) curve of HOMA–IR for the diagnosis of ATP III, IDF and JIS defined MS in the study subjects was depicted separately. The optimal cut point to determine the MS was assessed by maximum Youden index [sensitivity – (1- specificity)] and the shortest distance from the point (0, 1) [(1- sensitivity) ^{2} + (1- specificity) ^{2}] on the ROC curve[14]. Positive likelihood ratio [sensitivity/ (1- specificity)] (PLR) and negative likelihood ratio [(1- sensitivity)/ specificity] (NLR) for every suggested cut point by the above approaches were also calculated. When the maximum Youden index and the shortest distance from the point (0, 1) indicated different cut points for diagnosis of MS, diagnostic odds ratio (DOR) was calculated as PLR/ NLR. DOR value ranges from 0 to infinity and higher values indicate better discrimination of applied test [15]. The cut point with higher DOR was considered as the proper cut point value.

Results

The study was performed on a total of 480 men and 502 women between 20-72 yr (39.20 ±10.16). Table 2 presents clinical and biochemical characteristics of the subjects. Men had more WC and higher blood pressure, FBS, TGs, and LDL-C. Women had more BMI and higher 2-h post-load glucose and HDL-C. No significant differences according to gender were found for fasting insulin, Total Cholesterol, and HOMA-IR. The prevalence of MS was 24.9% according to ATP III (24.7% in men vs. 25.1% in woman; *P*=0.470), 29.1% according to IDF (26.5% in men vs. 31.5% in woman; *P*=0.092), 33.2% according to JIS (33.2% in men vs. 33.3% in woman; *P*=0.518), and 19.3% according to Persian IDF (26.3% in men vs. 12.7% in woman; *P*<0.001).

Table 2: Clinical and biochemical characteristics of the study subjects

	Total		Men (n=480)		Women (n=502)		
Variables	**Median**	**IQR***	**Median**	**IQR**	**Median**	**IQR**	**P value**
Body mass index (kg/m^2)	25.65	5.76	25.01	5.30	26.22	5.95	0.001
Waist Circumference (cm)	89.00	14.00	92.00	12.00	86.00	15.25	0.001
Systolic Blood Pressure (mmHg)	110.00	20.00	110.00	20.00	110.00	20.00	0.001
Diastolic Blood Pressure (mmHg)	70.02	20.00	70.00	15.00	70.00	15.00	0.001
Fasting blood sugar (mg/dL)	93.00	11.57	94.30	12.55	92.00	11.00	0.001
Blood glucose after 2 hours (mg/dL)	102.00	33.45	98.00	31.70	105.00	33.72	0.001
Fasting Insulin (µIU/mL)	11.00	7.30	10.60	7.60	11.30	7.05	0.118
Triglycerides (mg/dL)	118.00	86.00	134.00	93.25	103.00	69.12	0.001
Total Cholesterol (mg/dL)	180.00	47.00	182.00	49.00	179.00	46.50	0.155
HDL-C (mg/dL)	41.30	13.90	37.70	12.30	45.00	13.98	0.001
LDL-C (mg/dL)	104.30	31.50	107.45	31.70	101.00	30.55	0.001
HOMA-IR	2.50	1.77	2.43	1.87	2.55	1.70	0.475

* IQR: interquartile range.

Distribution of HOMA–IR in all subjects and normal subjects are shown in Table 3. The lower limit of the top quintile of HOMA–IR in normal subjects was 2.48. About 51% of all subjects were insulin resistant. With respect to the 75th and 90th percentiles of HOMA–IR, the prevalence of IR was 54.1% and 31.7%.

Table 3: Distribution of homeostasis model assessment (HOMA) values in the study subjects

Groups	Mean	SD	Median	Min	Max	75th percentile	Lower limit of top quintile	90th percentile
All subjects								
All	2.77	1.90	2.50	0.11	35.69	3.47	3.72	4.59
Men	2.76	2.10	2.44	0.32	35.69	3.49	3.78	4.76
Women	2.77	1.70	2.54	0.11	20.81	3.46	3.66	4.52
Normal subjects								
All	1.88	1.22	1.68	0.11	8.58	2.37	2.48	3.11
Men	1.83	0.97	1.68	0.51	4.71	2.36	2.44	2.93
Women	1.92	1.43	1.68	0.11	8.58	2.39	2.63	3.41

Normal: Subjects with BMI ≤25 kg/m^2, systolic blood pressure <130 mmHg, diastolic blood pressure <85 mmHg, total cholesterol ≤200 mg/dL, HDL-C ≥40 mg/dL in males, ≥ 50 mg/dL in females, FBS<100 mg/dL and TGs <150 mg/dL

AUC of HOMA–IR for ATP III defined MS was 0.663 (95% CI: 0.623, 0.703), for IDF defined MS was 0.663 (95% CI: 0.625, 0.701), for JIS defined MS was 0.662 (95% CI: 0.626, 0.699) and for Persian IDF defined MS was 0.680 (95% CI: 0.636, 0.723). Sensitivity, specificity, Youden index, shortest distance, PLR, NLR and DOR of HOMA–IR cut points to detect subjects with MS by 4 mentioned criteria are shown in Table 4. The cut point for diagnosis of ATP III defined, IDF defined, JIS defined and Persian IDF MS was 2.49, 2.91, 2.92 and 3.21, respectively. The cut-off points at fixed sensitivity of 75% for diagnosis of ATP III defined and JIS defined MS was 2.23 and for diagnosis of IDF defined, and Persian IDF MS was 2.24 and 2.34, respectively.

IR and MS were significantly associated. The prevalence of IR among subjects with and without ATP III defined MS was 70.1 % and 45% (*P*<0.001). The prevalence of IR among subjects with and without IDF defined MS was 68.5% and 43.8% (*P*<0.001). The prevalence of IR among subjects with and without JIS defined MS was 67.8 % and 43.2% (*P*<0.001). The prevalence of IR among subjects with and without Persian IDF defined MS was 71.7 % and 46.1% (*P*<0.001). 43.2% of the subjects who did not meet ATP III, IDF, JIS or Persian IDF criteria were insulin resistant. Sensitivity and specificity of ATP III defined MS to diagnose IR was 33.95% and 84.78%, of IDF defined MS was 39.13% and 81.29%, of JIS defined MS was 43.77% and 78.11% and of Persian IDF defined MS was 27.32% and 88.76%.

Discussion

HOMA–IR was introduced in 1985 by Matthews et al. It is a simple method for identification of IR in epidemiological

studies where complexity and cost of euglycemic glucose clamp technique makes it difficult to apply [5]. There is a good correlation between HOMA-IR method and the euglycemic clamp technique[5]. A single fasting plasma glucose and insulin level is necessary for this method. The HOMA-IR has been used worldwide but there is no consensus on its cut off to predict insulin resistance because of differences between ethnic groups in insulin resistance and β-cell function [6]. On the other hand, application of the suggested cuts in clinical practice is limited.

Table 4: Optimal HOMA–IR Cut Points to detect metabolic syndrome based on Adult treatment panel III (ATP III), International Diabetes Federation (IDF), Joint Interim Societies (JIS) and Persian IDF criteria in subjects without diabetes

Metabolic syndrome	Method	Cut Point	Sensitivity	Specificity	Youden Index	Shortest Distance	PLR	NLR	DOR[a]
ATP III									
All	Method 1	2.49	70.30	55.80	0.261	0.284	1.590	0.532	2.988
	Method 2	2.75	61.20	64.30	0.255	0.277	1.714	0.603	2.841
	Method 3	2.48	70.70	55.30	0.26	0.286	1.582	0.530	-
Men	Method 1	3.05	57.40	75.57	0.329	0.241	2.349	0.564	4.164
	Method 2	2.76	65.20	67.00	0.323	0.229	1.979	0.519	3.813
	Method 3	2.48	72.20	59.10	0.313	0.245	1.764	0.471	-
Women	Method 1	2.31	72.30	47.30	0.196	0.354	1.371	0.586	2.339
	Method 2	2.80	54.60	63.30	0.179	0.341	1.488	0.717	2.075
	Method 3	2.48	68.10	51.00	0.191	0.342	1.389	0.625	-
IDF									
All	Method 1	2.91	55.70	71.00	0.267	0.280	1.921	0.624	3.078
	Method 2	2.75	60.40	65.80	0.262	0.274	1.766	0.602	2.935
	Method 3	2.48	68.90	56.50	0.254	0.286	1.584	0.550	-
Men	Method 1	2.99	59.70	75.40	0.351	0.223	2.429	0.534	4.548
	Method 2	2.82	64.50	69.90	0.344	0.216	2.146	0.507	4.232
	Method 3	2.48	70.20	59.50	0.296	0.252	1.733	0.501	-
Women	Method 1	2.31	72.40	49.70	0.220	0.329	1.438	0.556	2.586
	Method 2	2.36	71.10	50.60	0.216	0.327	1.438	0.571	2.518
	Method 3	2.48	67.10	52.75	0.198	0.331	1.420	0.623	-
JIS									
All	Method 1	2.92	54.20	71.60	0.258	0.290	1.908	0.640	2.984
	Method 2	2.76	59.10	66.30	0.254	0.281	1.754	0.617	2.843
	Method 3	2.48	68.20	57.10	0.253	0.285	1.590	0.557	-
Men	Method 1	3.05	54.50	78.40	0.329	0.253	2.523	0.580	4.350
	Method 2	2.51	68.20	63.50	0.317	0.234	1.868	0.501	3.728
	Method 3	2.48	68.80	61.30	0.301	0.247	1.777	0.508	-
Women	Method 1	2.31	72.00	49.40	0.213	0.334	1.421	0.567	2.506
	Method 2	2.36	70.70	50.30	0.210	0.332	1.422	0.582	2.443
	Method 3	2.48	66.90	52.50	0.193	0.335	1.408	0.630	-
Persian IDF									
All	Method 1	3.21	53.30	76.60	0.299	0.273	2.277	0.609	3.739
	Method 2	2.82	62.00	65.90	0.279	0.261	1.818	0.576	3.156
	Method 3	2.48	71.70	53.80	0.255	0.293	1.551	0.526	-
Men	Method 1	2.99	59.70	75.40	0.350	0.223	2.422	0.535	4.527
	Method 2	2.82	64.50	69.90	0.343	0.216	2.140	0.507	4.220
	Method 3	2.48	70.20	59.40	0.295	0.253	1.728	0.502	-
Women	Method 1	3.24	51.70	74.30	0.260	0.299	2.013	0.650	3.096
	Method 2	3.24	51.70	74.30	0.260	0.299	2.013	0.650	3.096
	Method 3	2.48	75.00	49.40	0.244	0.318	1.482	0.506	-

PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic Odds ratio. Method 1: maximum Youden index; Method 2: shortest distance from the (0, 1) point on the ROC curve; Method 3: lower limit of top quintile (80^{th} p).
[a] When method 1 and method 2 indicated different cut points, DOR was calculated as PLR/ NLR.

In the present study, the threshold of HOMA-IR values to diagnose IR is set to be 2.48. As a result, the prevalence of insulin resistance was more than 50% in the study population. This value is close to the result of some non-Iranian studies[13,16] but it is higher than two previous studies in Tehran [6,17]. In Esteghamati et al. study, the participants were not a representative sample and were enrolled from individuals taking health examinations, or those who accompanied patients [6]. In Hosseinpanah et al. study, the 95th percentile of HOMA-IR was considered for the definition of IR [17].

However, the HOMA-IR cut off values in other studies are not similar [13, 16, 18-20]. These differences may be due to various applied methods to determine HOMA-IR cut points and ethnic diversity in studied populations. Moreover, there is not a standard assay for insulin measurement. Present methods cause different results for HOMA-IR and affect the comparability of suggested cut points. Not only different criteria have been used to define IR, but also different statistical approaches have been used to determine cut off values.

For the first time, Matthews et al. proposed the HOMA-IR cut point value of 2.5 and evaluated the accuracy of this value by comparison with euglycemic hyperinsulinemic clamp method [5]. Some researchers have used ROC curve to determine the cut point [19, 20]. Youden index and shortest distance from the (0, 1) point of the ROC curve are more common methods in previous studies. Some other methods consist of estimation of cut point values by means of median[21], the 75th percentile [16], lower limit of top quintile[6,13],

the 90th percentile[18], or tertile[22] of HOMA-IR in total population or non-obese subjects without any metabolic disorders. Evaluating the sensitivity and specificity of different HOMA-IR cut points and selecting the cut point based on the epidemiologic purposes has also been tried by Esteghamati et al[3]. Cut point values from 1.7 to 3.8 have been proposed by above-mentioned methods in previous studies.

Since HOMA-IR cut point to diagnose insulin resistance may vary from race to race, differences in HOMA-IR cut point with the same method in various population is not surprising. The results of the present study are not consistent with Esteghamati et al. study in Tehran [6]. As mentioned above, the participants were not a representative sample and subjects with diabetes were not excluded. On the other hand, the lower limit of top quintile of HOMA-IR in the present study was approximately equal to the 90th percentile and the 95th percentile of HOMA-IR (2.5) in Meshkani et al. and Hosseinpanah et al. studies, respectively [17, 23]. Although these studies have been conducted in two close areas in Iran, their results are very different. The subjects of the present study had higher values of HOMA-IR that is relevant with the point that Qazvin is one of the areas of Iran that has the highest prevalence of diabetes [24]. In addition, our results are less than those proposed in the Bruneck study [13]. Comparing the results by hyperinsulinemic euglycemic clamp method would improve the value of the study.

The prevalence of MS in the present study was more than 20% by all applied criteria except the Persian IDF in women. That is partly because of lifestyle changes in past decade. WC is a mandatory component to meet the IDF criteria [10] and the Persian IDF definition consists of a higher cut off point for WC in women. Therefore, a remarkably decrease in prevalence of MS in women was found in the present study using the Persian IDF criteria and resulted in significantly difference between men and women. Other components of MS may be present in subjects who do not have central obesity and the individuals who meet the other criteria without central obesity would be omitted [25]. There is a possibility of underestimation using IDF criteria especially Persian IDF.

None of the MS definitions was sensitive to detect insulin resistant subjects. JIS was more sensitive and Persian IDF and ATP III were more specific for diagnosis of IR. Decision on priority of screening or diagnosis purposes would help to select the best criteria. A screening test needs higher sensitivity while a diagnostic test needs higher specificity. Hosseinpanah et al. studied 347 non-diabetic individuals who were ≥ 20 years of age in Tehran. In their study, ATP III had a sensitivity of 52.3% and specificity of 65% and JIS had a sensitivity of 52.3% with a specificity of 66.5% [17]. In Sierra-Johnson et al. study [26], ATP III had a sensitivity of 42% and specificity of 94% for detecting IR among 256 non-diabetic individuals. Using HOMA-IR may lead to an underestimation of sensitivity and specificity since it is a surrogate measure of IR. In addition, there is no consensus on HOMA-IR cut-off points to define IR. A little change in threshold value would result in a better specificity.

Prevalence of IR was significantly higher in subjects with MS defined by all applied criteria than others in the present study. Insulin resistance has been suggested as the core pathophysiology underlying the MS [27]. The association of the four MS definitions with IR provides support for this notion. On the other hand, MS is not synonymous with IR; since more than 40% of subjects who did not meet any definitions were insulin resistant. Although IR has been assumed as the main defect leading to MS but among various definitions, only WHO and the European group for the study of insulin resistance (EGIR) definitions has been considered it as part of the criteria [28, 29]. Using putative manifestations of IR to detect subjects with MS in other definitions is based on the fact that specific measurements of IR e.g. HOMA-IR cannot predict IR in clinical practice [21].

HOMA-IR cut point for diagnosis of ATP III defined MS was lower than three other definitions. This value was very close to the value resulted from the lower limit of top quintile of HOMA-IR values for diagnosis of IR. In fact, IR and MS are synonymous in these subjects. HOMA-IR cut point for diagnosis of JIS defined MS was very close to the value of IDF defined MS. This was predictable concerning similarity of the two definitions and their related MS prevalence. Different prevalence of MS using different criteria is also results in different cut points.

The point on the ROC curve with shortest distance to (0, 1) point did not agree with Youden index to identify MS except for Persian IDF defined MS in women. In the cases of disagreement, DOR was used to select the optimal cut point in the present study. Overall, the related DOR of Youden index method was more than shortest distance to (0, 1) point. In Mathematics view, Youden index maximizes overall correct classification rates and minimizes misclassification rates, but the clinical meaning for the shortest distance from the point (0, 1) is unknown [30]. When the shortest distance from the point (0, 1) is different from the Youden index, using this method to determine the optimal cut point leads to an increased misclassification rate [30]. It seems that using Youden index has additional support and is preferable to find the optimal cut point between these two methods.

In addition, the sensitivity of HOMA-IR cut point to diagnose IR was more than both Youden index and shortest distance to (0, 1) point for detecting subjects with MS. The cut-off points at fixed sensitivity of 75% for diagnosis of ATP III, JIS defined and IDF defined MS was very close to each other. Decision on priority of screening or diagnosis purposes would help to select the best cut-off point.

The main limitation of this study was its cross sectional design and the number of studied subjects. HOMA-IR was calculated by a single test of fasting plasma glucose and insulin. Various definitions for diagnosis of IR will result in different cut points. The applied method in this study may not be the best approach and needs comparison with euglycemic clamp method.

Conclusions

Since IR is an early stage in the pathogenesis of type 2 diabetes, the high prevalence of IR in the present study warns about the future burden of type 2 diabetes. IR and MS were statistically associated, but none of the MS definitions was sensitive to detect insulin resistant subjects. Only the ATP III criteria introduced more specific cut point for putative manifestations of IR. Further cohort studies are needed to

evaluate the usage of these cut points to predict diabetes and cardiovascular diseases.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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