

Insulin and HOMA-IR in Healthy Young Mexicans: A Cut-off Points Proposal

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Abstract

Background: Insulin resistance is recognized as impairment subjacent in many metabolic disorders, most of them conditioning the development of diabetes mellitus type II. Cut-off points for clinical parameters such as glucose or HDL cholesterol have been established; however there is no consensus for cut-off points for two of the most used parameters to detect insulin resistance: insulin and homeostasis model assessment of insulin resistance (HOMA-IR). The aim of this study is to propose cut-off points for normal blood levels of insulin and HOMA-IR for young Mexicans.

Methods: A sample of 1,359 young Mexicans (17-24 years old) was studied. The set of metabolic alterations related to metabolic syndrome (MetS) was identified, forming two groups of young: 'Healthy' and 'Non-Healthy', whether or not they presented one or more of the five alterations according to an international definition of MetS. The cut-off points were calculated using two statistical methods, applying sensitivity analysis, and calculating the percentile 95 of 'Healthy' young to obtain normal ranges, and the 'probability of a correct diagnosis' was used to assess its efficacy.

Results: The cut-off point values proposed for young Mexicans are, for insulin 14.0 μ U/ml for women and 11.0 μ U/ml for men and for HOMA-IR 2.9 for women and 2.3 for men.

Conclusions: These upper limits could be useful to detect high risk or presence of metabolic alterations related to the MetS in young Mexicans.

Keywords: HOMA-IR; Insulin; Metabolic syndrome; Young Mexicans; Sensitivity analysis

Introduction

Insulin resistance (IR) is a metabolic alteration related to metabolic syndrome (MetS), indeed, it has been argued that IR has a stronger relation to MetS than even obesity [1,2]. Thus, to prevent the epidemic of degenerative diseases that MetS intend to predict, such as diabetes type II (DM2), cardiovascular diseases (CVD), and atherosclerosis, IR is a valuable tool to predict or even prevent MetS, and thus, those impairments putatively related to it. In this regard, several methods have been developed to measure IR ranging from very complex, like the hyperinsulinemic-euglycemic glucose clamp (involving many considerations and highly trained personnel to perform the measurement), to a more simple like homeostasis model assessment (HOMA) [3], or the oral glucose tolerance test (OGTT) [4]; however, the OGTT involves at least 2 hours of measurements and is not easily affordable for large number of individuals. In contrast, HOMA needs the measurement of both fasting plasma insulin and glucose to make an estimation of IR in steady state conditions [4]. On the other hand, it has recently been found that Mexican population has genetic factors that make them vulnerable to MetS related impairments [5], which may underlie the high prevalence of MetS in the young adult population [6,7]. Hence, to know the risk of young Mexicans to develop MetS may help prevent, in a more efficient way, the chronic diseases that follow after MetS. Since pancreatic β cells produce insulin to abate high glucose levels, in early stages of MetS, i.e., the Mexican young population, it is more probable to detect altered values in insulin than in glucose, and hence a tool to detect IR with high sensitivity became very relevant. Even though the high prevalence of MetS among Mexicans [8], and particularly among the young population [6,7], to date no studies have been reported to establish cut-off points for insulin neither for insulin resistance model assessment (HOMA-IR) [3] in Mexican young

population, thus a cut-off point to detect IR in young Mexicans with high sensitivity is needed. The objective of this study was to establish, and then propose cut-off points for normal values of insulin and HOMA-IR in young Mexicans.

Materials and Methods

Study participants

We invited undergraduate students of two universities of the Mexico City metropolitan area: Facultad de Estudios Superiores Iztacala (UNAM) in the north, and two campuses of the Universidad Autónoma de la Ciudad de México (UACM) in the east, to participate in the project. A total of 1,359 students (17-24 years old; 949 women, 410 men) of first grade were included in the sample. All students accepted to participate in the project and signed an informed consent. Inclusion criteria were: 17-24 years old; student of first grade of college; no previous clinically diagnoses of neither dyslipidemia nor hyperglycemia; no pregnancy.

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Clinical data

The metabolic alterations related to metabolic syndrome (MetS) were taken as dependent variables to adjust cut-off points for insulin and HOMA-IR, i.e., the cut-off points searched intend to detect young Mexicans with MetS, or one or two impairments related to it. The MetS definition was according to an international panel [9] (Table 1).

Waist circumference and blood pressure were taken to each student by physicians specialized in Internal Medicine of our team. A sample of blood was taken at morning and laboratory analysis were made for fasting glucose, HDL cholesterol, triglycerides, and insulin, performed by Grupo Diagnóstico Médico PROA, S.A. de C.V. (CARPERMOR), an international reference laboratory. The samples were collected in years 2009, 2010, and 2011.

Statistical data analyses

The young were classified into two groups: (a) 'Healthy', those young with no metabolic alterations (Table 1), and (b) 'Non-Healthy', those young with one or more metabolic alterations related to metabolic syndrome, in this group are included also the young with MetS. We considered 'Non-Healthy' to all individuals with 1 to 5 alterations of the MetS, since MetS, as a multifactorial process, is a continuum between 'Healthy' and 'Non-Healthy' status, and we suggest that if an individual presents one or more alterations related to MetS it is sufficient evidence for considering a process of loss of health. Notice that the 'Healthy' label used in this study strictly refers to the absence of evidence of an impairment related to MetS, and thus, Non-Healthy on a broad context. We preferred to analyze to all young with one or more alterations as a whole group, since below the cut-off points values are included only healthy young and above them will include 1 to 5 alterations. A Student's *t*-test was applied to compare averages of clinical parameters of 'Healthy' vs. 'Non-Healthy' young, and also to compare means of insulin and HOMA-IR of young with no metabolic alterations vs. young with 1, 2, 3, 4 and 5 alterations of MetS parameters.

In order to compare and select the best option, the cut-off points were calculated using two statistical methods, applying sensitivity analysis, and calculating the percentile 95 of 'Healthy' young to obtain normal ranges.

For cut-off points obtained with sensitivity analysis, the probability of a correct diagnosis was calculated as follows [10]:

$Probability (correct\ diagnosis) = PREV \times sensitivity + (1 - PREV) \times specificity$

Where *PREV* is the prevalence of the alteration in the sample, in the case the percentage of 'Non-Healthy' young, i.e., young with one or more metabolic alterations related to MetS.

In order to contextualize the insulin and HOMA-IR cut-off points into metabolic alterations of young Mexicans, average values of MetS parameters by 'Healthy' and 'Non-Healthy' young were calculated. Also, we calculated average values of insulin and HOMA-IR by group of young according to the number of MetS parameters altered; six groups were formed: from zero to five parameters altered. All those average values and cut-off points were calculated separately for women and men. The statistical tests were performed using the R language [11].

Finally, in order to evaluate the cut-off points proposed, average values of the MetS parameters were obtained for the young grouped in classes, according to ranges based on the cut-off points.

Results

Parameter values of 'Healthy' and 'Non-Healthy' young:

Overall, 32.8% (446/1359) of the students are 'Healthy', i.e., they presented no alterations related to MetS; however, the proportion are unbalanced between women and men, since 26.8% (254/949) of women were in the 'Healthy' group, whereas 46.8% (192/410) of men were 'Healthy', i.e., the prevalence of 'Non-Healthy' young was 73.2% (695/949) for women, and 53.2% (218/410) for men.

All the parameters of MetS, and insulin and HOMA-IR showed differences ($P < 0.001$) between the average values of 'Healthy' vs. 'Non-Healthy' young (Table 2). The average values of insulin and HOMA-IR by group of young, according with the number of MetS parameters altered showed a tendency to increase (Figure 1); the low average values are those for 'Healthy' group of young, i.e., for those young with none parameter altered; whereas the higher average values were for the group of young with five parameters altered. The average values are higher for women compared with men, for all the six groups, for both, insulin and HOMA-IR, from zero to five altered parameters.

Parameter	Categorical cut-off point
HDL Cholesterol	<50 mg/dL in women
	<40 mg/dL in men
Waist circumference	≥80 cm in women;
	≥90 cm in men
Triglycerides	≥150 mg/dL
Blood pressure	≥130 mm Hg systolic;
	≥85 mm Hg diastolic
Fasting glucose	≥100 mg/dL

Table 1: Parameters of metabolic syndrome [9] and the cut-off points used to define 'Healthy' and 'Non-Healthy' young. A young was classified as 'Healthy' if all out of the five parameters were into the not altered values, whereas a young was classified as 'Non-Healthy' if presented one or more parameters altered.

Parameter	'Healthy' young	'Non-Healthy' young
Women	n=254	n=695
Waist circumference (cm)	71.28 ± 5.56	84.05 ± 11.48
HDL cholesterol (mg/dL)	58.86 ± 7.57	46.67 ± 8.72
Diastolic blood pressure (mmHg)	67.4 ± 8.0	71.9 ± 8.9
Systolic blood pressure (mmHg)	100.2 ± 10.3	105.8 ± 11.6
Triglycerides (mg/dL)	81.61 ± 24.36	121.28 ± 60.05
Glucose (mg/dL)	84.38 ± 7.34	87.75 ± 8.80
Insulin (μU/ml) [5-95%]	7.90 ± 3.08 [3.9-14.0]	12.12 ± 7.76 [4.8-25.5]
HOMA-IR (mg/dL μU/ml) [5-95%]	1.65 ± 0.66 [0.8-2.9]	2.67 ± 1.83 [1.0-5.5]
Men	n=192	n=218
Waist circumference (cm)	76.95 ± 6.64	90.18 ± 12.10
HDL cholesterol (mg/dL)	51.03 ± 7.96	42.54 ± 9.48
Diastolic Blood pressure (mmHg)	72.7 ± 7.2	79.8 ± 9.5
Systolic Blood pressure (mmHg)	108.0 ± 9.8	118.5 ± 11.3
Triglycerides (mg/dL)	88.90 ± 24.84	154.69 ± 75.34
Glucose (mg/dL)	85.29 ± 8.35	89.62 ± 12.28
Insulin (μU/ml) [5-95%]	6.25 ± 2.37 [3.0-10.8]	10.64 ± 5.66 [4.4-21.8]
HOMA-IR (mg/dL μU/ml) [5-95%]	1.33 ± 0.56 [0.6-2.3]	2.37 ± 1.32 [0.8-4.8]

Table 2: Average values of MetS parameters, insulin and HOMA-IR of 'Healthy' and 'Non-Healthy' groups in the sample of young Mexicans. Values are mean ± SD; [5-95%] represents percentiles 5 and 95, respectively; $P < 0.001$ for all averages, differences with Student's *t*-test between 'Healthy' and 'Non-Healthy' young.

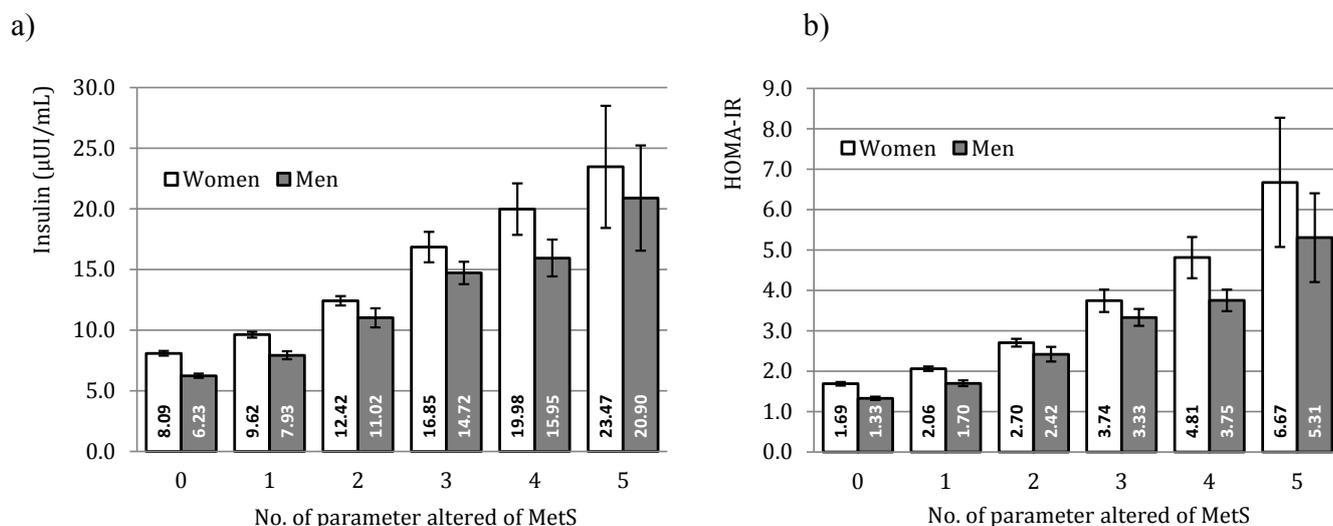


Figure 1: Average values (mean ± SEM) of (a) insulin and (b) HOMA-IR in young Mexicans by number of altered MetS parameters (listed in Table 1). P<0.001 for Student's t-test comparing the group of young with 0 alterations vs. each other group: 1, 2, 3, 4 and 5 alterations, for both women and men, and for insulin and HOMA-IR.

Sensitivity analysis

The optimal cut-off points from the sensitivity analysis for insulin were 8.4 µU/ml for women, with 68.9% [95 CI, 65.3-72.3%] of sensitivity, and 60.1% [95 CI, 54.3-66.6%] of specificity; and 7.3 µU/ml for men, with 67.9% of sensitivity [95 CI, 61.2-74.0%], and 72.4% [95 CI, 64.4-78.5%] of specificity. The optimal cut-off points for HOMA-IR were 1.87 for women, with 66.0% [95 CI, 61.3-68.6%] of sensitivity, and 68.1% [95 CI, 61.9-73.3%] of specificity; and 1.55 for men, with 68.8% of sensitivity [95 CI, 62.1-74.8%], and 76.8% [95 CI, 71.0-81.8%] of specificity. The probabilities of a correct diagnosis if used the sensitivity analysis cut-off points are 65% (women), and 69% (men) for insulin, and 68% (women), and 69% (men) for HOMA-IR.

Percentile 95 of insulin and HOMA-IR

The percentile 95 for insulin of 'Healthy' young was 14.0 µU/ml for women and 10.8 µU/ml for men (that could be rounded to 11.0 µU/ml); for HOMA-IR they were 2.9 for women and 2.3 for men (Table 2). The average values of the MetS parameters showed differences (P<0.05) when young were grouped, whether the insulin and HOMA-IR percentiles fall in the ranges >95% or 5-95% (Table 3).

Discussion

CARPERMOR, the reference laboratory, established a normal range up to 21 µU/ml for insulin, which compared with that proposed in this study (14 µU/ml women, 11 U/ml men), seems too high when evaluating young population. It is unclear if in 'Healthy' adults, the percentile 95% will stay near to the one found in young in this study.

Based on a sensitivity analysis, a study [12] proposed a cut-off point for HOMA-IR for adult Iranian population (25-64 years old) of 1.8. This value is consistent with that found in our sensitivity analysis; nevertheless, the specificity of 65% implies a high error in detect people that actually present IR.

In another report [13], a cut-off point of 2.5 for HOMA-IR to detect MetS in Brazilian children (6.5 ± 2.3 years old) using ROC curve is proposed. The sensitivity (61%) and specificity (74%) found were as

low as those found in this study (66% and 68% for women, and 69% and 77% for men, respectively). The higher value reported for HOMA-IR (2.5), compared with those found in this study means that lower ROC curves (1.87 women, 1.55 men) could be explained by two facts: first, the detection of MetS in different ages (children or young), and second, in our study the young with one or two metabolic alterations were included in the 'Non-Healthy' group. In other study [14], using a machine learning algorithm involving several parameters related to MetS, including among them the serum aminotransferases, proposed a HOMA-IR cut-off point of 2.6 (and hence with 83% sensitivity, 54% specificity) for Americans of Mexican ascent. Furthermore, in one study [15] based on a sample population of 22 Japanese of 22-24 years old, set an upper threshold of 2.5 for HOMA-IR. They used the criteria of the mean plus one standard deviation, that could be interpreted (when applying the empirical rule) as the specificity of such cut-off point is 84% (mean+SD, implies, according to the empirical rule, an area under the normal curve of 68%+(32%/2)), i.e., 16% (100-84%) of healthy young will be misclassified when evaluated with HOMA-IR. In that regard, it is preferable to use the percentile 95 and not the percentile 84 (as it is mean+SD). While Aguilar-Salinas et al. [16] used the percentile 90 of HOMA-IR to establish a cut-off point of 2.4, based on a sample of 2,256 Mexican adults (20-69 years old); they argued that this value is quite similar to the 2.5 used by Taniguchi et al. [15] Clearly both values were set based on non-compatible premises and populations: first, the age group in the Japanese sample were older than in the Mexican sample; second, the study of Taniguchi et al. [15] set the cut-off point based on percentile 84, whereas the study of Aguilar-Salinas et al. [16] set the cut-off point based on percentile 90; and third, the Japanese population was selected based in a healthy condition, i.e., within normal BMI and fasting blood glucose, whereas in the Mexican sample of this study no restriction was imposed on clinical parameters. Comparing the cut-off point used by Aguilar-Salinas et al. [16] for Mexican population and the one proposed in this study, two issues can be discussed: (1) Our study is centered to detect early (i.e., before the evolution of MetS) the metabolic alterations related to MetS, then the cut-off points should be used in this context; whereas the cited study was framed in a very wide context: Mexican adults with no restrictions in clinical parameters, and hence the HOMA-IR threshold is biased

Percentile		Insulin percentile		
		<5%	[5-95%]	>95%
Insulin cut-off point (µUI/mL)		<3.9	[3.9-14.0]	>14.0
Women	n (number of young)	21	741	194
	HDL cholesterol (mg/dL) [2]	52.33 ± 10.20	50.81 ± 9.70	45.94 ± 9.95
	Waist circumference (cm) [1,2]	73.43 ± 7.98	78.40 ± 10.43	89.77 ± 11.70
	Triglycerides (mg/dL) [1,2]	82.76 ± 50.13	101.15 ± 43.57	150.58 ± 79.69
	Diastolic Blood pressure(mmHg) [2]	67.6 ± 8.1	69.6 ± 8.5	74.63 ± 9.1
	Systolic Blood pressure (mmHg) [2]	100.8 ± 11.0	102.6 ± 10.9	110.32 ± 11.6
	Glucose (mg/dL) [1,2]	81.38 ± 6.36	86.13 ± 12.86	90.65 ± 10.13
Insulin cut-off point (µUI/mL)		<3.0	[3.0-10.8]	>10.8
Men	n (number of young)	9	315	90
	HDL cholesterol (mg/dL) [2]	46.89 ± 4.68	47.53 ± 9.87	42.30 ± 8.54
	Waist circumference (cm) [2]	79.11 ± 7.03	80.69 ± 9.34	96.54 ± 12.48
	Diastolic Blood pressure(mmHg) [2]	79.6 ± 4.1	75.07 ± 8.7	80.7 ± 10.0
	Systolic Blood pressure (mmHg) [2]	113.6 ± 8.3	111.36 ± 11.5	121.3 ± 10.0
	Triglycerides (mg/dL) [1,2]	74.89 ± 23.08	110.28 ± 50.16	174.37 ± 87.36
	Glucose (mg/dL) [2]	82.33 ± 10.33	86.58 ± 10.82	91.06 ± 10.28
Percentile		HOMA percentile		
		<5%	[5-95%]	>95%
HOMA-IR cut-off point		<0.8	[0.8-2.9]	>2.9
Women	n (number of young)	25	711	220
	HDL cholesterol (mg/dL) [2]	52.12 ± 10.45	50.93 ± 9.55	46.12 ± 10.29
	Waist circumference (cm) [1,2]	74.16 ± 7.15	78.20 ± 10.35	89.08 ± 11.88
	Triglycerides (mg/dL) [1,2]	76.72 ± 26.28	99.45 ± 41.44	151.25 ± 78.71
	Diastolic blood pressure(mmHg) [2]	68.8 ± 7.8	69.4 ± 8.3	74.8 ± 9.3
	Systolic blood pressure(mmHg) [2]	100.5 ± 1.0	102.3 ± 10.8	110.4 ± 11.5
	Glucose (mg/dL) [1,2]	78.60 ± 5.82	85.33 ± 7.67	93.09 ± 20.53
HOMA-IR cut-off point		<0.6	[0.6-2.3]	>2.6
Men	n (number of young)	9	292	113
	HDL cholesterol (mg/dL) [2]	48.11 ± 3.69	48.20 ± 9.72	41.54 ± 8.40
	Waist circumference (cm) [2]	76.56 ± 7.56	80.10 ± 8.99	95.00 ± 12.27
	Triglycerides (mg/dL) [1,2]	72.00 ± 23.43	107.01 ± 46.46	169.99 ± 84.65
	Diastolic blood pressure (mmHg)[2]	79.1 ± 4.3	74.7 ± 8.8	80.6 ± 9.2
	Systolic blood pressure (mmHg) [2]	115.3 ± 7.2	110.4 ± 11.2	121.5 ± 10.1
	Glucose (mg/dL) [1,2]	79.33 ± 11.07	85.28 ± 8.32	93.74 ± 13.73

Table 3: Average values of MetS parameters by group of young according to insulin and HOMA-IR cut-off points proposed. Values are mean ± SD. [1] P<0.05 5% vs. [5-95%]; [2] P<0.05 [5-95%] vs. >95%.

by the insulin resistance prevalence. (2) The cut-off points proposed in this study differentiate according to sex: women 2.9, and men 2.6, the two values are higher than the one obtained by Aguilar-Salinas et al. [16].

The probability of a correct diagnosis (i.e., the probability to detect correctly that there is present an impairment related to MetS) if applied the cut-off points deduced from ROC, is under 70%, and the specificity (the probability of detect correctly positive cases) is also under 70%. On the other hand, the cut-off points based on percentile 95 (with a specificity of 95%), show higher accuracy if looking for a 'normal range'. Depending on the prevalence of MetS-related impairments, the sensitivity of this upper limit vary, i.e., the probability of correctly detect the positive cases. It is important to remark that the cut-off point set on percentile 95 in this study, for both insulin and HOMA-IR, should be used to detect alterations if it exceeds the threshold, i.e., it should be used only to detect positive cases, and not negative ones.

If the cut-off points proposed in this study, for insulin and HOMA-IR for young Mexicans, are adopted this will result in benefits at two levels, both at individual level in the clinical field, and at a population level in public health context. To account with more accurate upper limits values for insulin and HOMA-IR will result in a better health

care of young, because the physician could alert them when observing bordering values, or definitively diagnosed as an alteration when the values passed these cut-off-points. At public health level, the benefits will result in to reduce the prevalence of DM2 in later years or decades.

This study has some limitations, among them are: the participants are from Mexico city metropolitan area, thus the results should be applied with care in population of young from others regions of the country; the participants are undergraduate students, and the life habits of students are different from young that are dedicated to work. Finally, the results of this study only are valid for young from 17 to 24 years old, and should not be applied to other age group of Mexicans.

Conclusions

The upper limits for insulin of 14 µU/ml for women and 11 µU/ml for men are proposed as a recommendation for young Mexicans from 17-24 years old; for HOMA-IR the upper limits proposed are 2.9 for women and 2.3 for men. These values should be read strictly as upper limits, as many Non-Healthy young present values under such limits, and only 5% of healthy young present values over them.

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