Sensitivity, Specificity and cut-off values for HOMA formula; insulin resistance diagnostic tool in Aguascalientes

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Abstract

Objective. To determine the sensitivity, specificity and cut-off values for indices derived from the homeostasis model assessment (HOMA) formula, to diagnosis of insulin-resistance using the glucose tolerance curve and serum fasting insulin detection in the municipality of Aguascalientes, Mexico. Research design and methods: A representative sample of the population in the municipality of Aguascalientes, Mexico, within a 95% CI (n=548), was studied using a validated standard (the glucose tolerance test with insulin determinations performed every hour), and a total of 1096 subjects were categorized into healthy and sick patients. Measures of central tendency, percentiles, ROC curve, Dunnett's comparison test and Pearson's correlation test were used, and the differences were considered significant if p < 0.05. The mean plus two standard deviations was considered the upper limit for HOMA-IR, and the 25th percentile was considered the upper limit for HOMA-%BS. Results: The HOMA-IR cut-off value was 2.49, and HOMA-%BS was 72%. The diagnostic test sensitivity was 95.8%, and the specificity was 97.62%. A positive correlation was found (r = 0.0199, P < 0.0001). Glucose intolerance is considered to be present when the HOMA-IR ranges from 3.8–5.78, and diabetes mellitus is considered to be present when the percentile correlation is greater than 5.8. Conclusions: The HOMA formula applied to the population of the municipality of Aguascalientes is a diagnostic test with good sensitivity and specificity for the early diagnosis of insulin resistance using 2.49 as the cut-off point. **LUXMÉDICA, AÑO 10, NÚMERO 31, SEPTIEMBRE-DICIEMBRE 2015, PP 73-85**

Keywords: Insulin resistance, HOMA,cut-off point, sensitivity, MeSH

Resumen

Objetivo. Determinar la sensibilidad, especificidad y valores de corte para los índices derivados de la fórmula de evaluación (HOMA) del modelo de homeostasis, para diagnóstico de resistencia a la insulina mediante la curva de tolerancia de glucosa en suero en ayuno para la detección de insulina, en el municipio de Aguascalientes, México. Diseño de la investigación y métodos: Se estudió una muestra representativa de la población en el municipio de Aguascalientes, México, dentro de un IC del 95% (n = 548), utilizando un estándar validado (la prueba de tolerancia a la glucosa con las determinaciones de insulina realizados cada hora), y un total de 1096 sujetos fueron categorizados en pacientes sanos y enfermos. Se utilizaron medidas de tendencia central y porcentajes, curva ROC, la prueba de comparación de Dunnett, prueba de correlación de Pearson, y las diferencias se consideraron significativas si p < 0.05. La media más dos desviaciones estándar era considerado el límite superior de HOMA-IR, y el percentil 25 fue considerado el límite superior para el HOMA-% BS. Resultados: El valor de corte de HOMA-IR fue de 2.49, y HOMA-% BS fue 72%. La sensibilidad diagnóstica fue de 95.8% y la especificidad fue del 97.62%. Se encontró una correlación positiva (r = 0.0199, P < 0.0001). Intolerancia a la glucosa se considera presente cuando la HOMA-IR oscila entre 3,8 - 5,78, y la diabetes mellitus se considera presente cuando la correlación de percentil es mayor que 5.8. CONCLUSIONES: La fórmula HOMA aplicada a la población del municipio de Aguascalientes es una prueba diagnóstica con buena sensibilidad y especificidad para el diagnóstico precoz de la resistencia a la insulina usando 2.49 como punto de corte. **LUXMÉDICA, AÑO 10, NÚMERO 31, SEPTIEMBRE-DICIEMBRE 2015, PP 73-85**

Palabras clave: resistencia a la insulina, HOMA, punto de cohorte, sensibilidad

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Introducción and theoretical

Diabetes mellitus is a metabolic disorder that follows the dysfunction of the secretion and/or action of insulin, resulting in hyperglycemia [1]. It is a disease that causes various disabling complications, even when proper medical treatment is undertaken, and it is accompanied by deterioration in the quality of life [2]. There were 171 million people with diabetes mellitus in 2000, and it is estimated that there will be 366 million people with the disease by 2013 [3], which explains the greater impetus in the development and implementation of early diagnostic techniques in recent years.

Insulin resistance has become a significant issue at the preventive level. In 1988, Raeven proposed that insulin resistance, together with glucose intolerance, hyperinsulinemia, abnormal plasma lipids and arterial hypertension, formed the X syndrome [4], and later called insulin resistance syndrome and more commonly known as metabolic syndrome.

Insulin resistance can be defined as a reduced response of target tissues to insulin, as insulin resistance is linked to hyperinsulinemia. Insulin regulates the sensitivity of its target tissues, and high insulin levels decrease the tissue response. This insensitivity disappears upon removing excess hormone [5].

Other studies have shown that insulin resistance and the impairment of β-cell function are among the first disorders in the pathogenesis of type 2 diabetes. Both of these symptoms can be found in people with impairment of glucose tolerance and fasting glucose [6,7]. Therefore, various methodologies have been developed to facilitate the measurement of these parameters, which include insulin resistance, insulin sensitivity and the β-cell secretion rate.

The hyperglycemic clamp is considered the "gold standard" technique by which calculate insulin sensitivity [8,9]. It is a complicated technique that seeks to raise fasting glucose to 125 mg/dl and maintain this glucose concentration for two hours using continuous glucose infusion with constant monitoring. It is a difficult method to implement due to the limited availability of the appropriate instruments, and it is only performed in specialized medical centers.

The glucose tolerance test with serum insulin determinations is another method for estimating insulin sensitivity and resistance [10,11]. The test consists of a continuous intravenous glucose infusion; blood samples are drawn at 60, 120 and 180 minutes, and the glucose and insulin concentrations are measured in each sample. Once the values are obtained, the data are analyzed automatically by Bergman's Minimal Model program [12].

There are simple methods for the calculation of insulin sensitivity, insulin resistance and even the percentage of functional pancreatic β-cells up on measuring only fasting glucose and insulin blood levels.

The first method developed is the Homeostasis Model Assessment (HOMA) index described by Turner 13 in 1985, which is an accurate calculation that has been validated against hyperglycemic clamp studies and is therefore widely used. Although the HOMA index initially only calculated insulin resistance (HOMA-IR), later, with the use of computer technology, Levy, Matthews et al.[14] refined the calculation, making it possible to calculate the tissue sensitivity to insulin ratio (HOMA-%S) and the Beta-secretion ratio (HOMA-%B). The University of Oxford has software available on the website of the diabetes tests unit (available online at http://www.dtu.ox.ac.uk) that performs the improved calculation, which is known as HOMA[2].

The glucose tolerance test with serum insulin determinations still is the gold standard to determinate insulin resistance. HOMA's formula is faster, economical and can be considered as screening test, the test is performed by the serum determination of a fasting glucose and insulin, HOMA-IR, HOMA-%BS and HOMA-%IS are obtained using three mathematical calculations. Therefore it was decided to conduct a study to determinate the precision of this test in the diagnosis of insulin resistance, considering that this manifestation is the pre pathogenic state of type 2 diabetes.

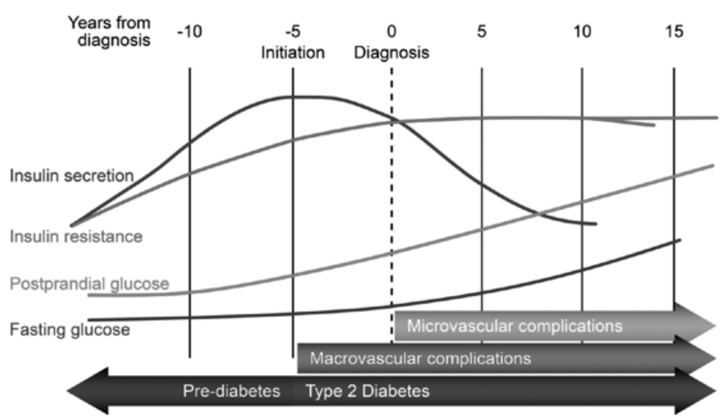

Figure 1.- Shows such plots the natural history of disease.

The aim of our study was to determine the sensitivity, specificity and cut-off values for indices derived from the HOMA formula in the municipality of Aguascalientes. Because the HOMA formula is considered a diagnostic test for insulin resistance, and thus an early diagnostic tool for type 2 diabetes, it can also be considered a method for assessing the response to treatment with oral hypoglycemic agents and insulin in patients who have diabetes or are glucose intolerant.

Research design and methods

Population Selection

The study was conducted prospectively with support from the company CMQ L.C. pharmaceuticals in Aguascalientes, Ags, México .It was used to create a database with a youth-adult population aged between 20 and 65 years. The participants underwent glucose tolerance tests, tolerance tests with insulin as control and regular checkups. Their family history and likelihood of having diabetes, among other factors, were recorded.

The control group included volunteers who met the inclusion criteria mentioned below. Each patient was examined, and the following data were collected: age, weight, sex, height, BMI, blood pressure, history of type 2 diabetes, obesity and hypertension. The total population for the municipality of Aguascalientes was analyzed according to the 2010 survey conducted by the Mexican National Institute of Statistics, Geography and Informatics (INEGI, for its initials in Spanish) (available online at http://www.inegi.org.mx/).The survey included 797,010 people of all ages. The population sample for the age range of the study population was obtained, which consisted of 247,010 people. In total, 48% of the participants were women, and 52% were men with a 95% confidence interval and an accepted error of 0.05. A population prevalence of 8% for type 2 diabetes was estimated according to the 2012 National Survey of Health and Nutrition for Aguascalientes (available online at http://www.ensanut.insp.mx/), resulting in a proportional sample of 548 +/- 54 patients.

The study subjects were informed of the use of their data in the project through an informed consent procedure. The participants were classified as healthy patient (548) and patient with insulin-resistance (548), as determined by a validated standard and performing the glucose tolerance test with insulin determinations. These patients were newly diagnosed and therefore had not received any treatment. The total population sample was 1,096 patients.

The inclusion criteria were as follows: voluntary participation, BMI from 20 to 30 kg/m2, waist circumference according to ATP III criteria < 103cm for men and < 88cm for women, blood pressure < 135/85 mmHg; no presence of diabetes mellitus by a validated standard and fasting glucose and post-load glucose within 75g at 120 min in control subjects; and alterations in the validated standard showing clear signs of disease in sick patients.

In all cases, the patients underwent an unrestricted carbohydrate diet (minimum 300g/day) for three days prior to the test according to the WHO standards. They arrived at the lab after a 12hour fast at 08:00 to undergo a glucose tolerance test with a determination of insulin in three hours. Waist diameter was measured below the costal margin and above the iliac crest, and blood pressure was measured by personnel trained according to the technique proposed by the WHO with a manual sphygmomanometer. A blood sample was drawn, in which fasting insulin and glucose were analyzed at 60, 120 and 180 min after glucose load of 75g in 375 ml of water was ingested over 5 to 10 minutes. The patients remained at rest and seated in the area designed for glucose tolerance tests developed by CMQ L.C. pharmaceuticals in Aguascalientes.

Analytical Methodology

Clinical chemistry determinations were performed on an auto-analyzer (A 25 BioSystems).The glucose levels were determined using a glucose oxidase colorimetric method with SPIN reagents (ISO 9001 validated and certified trademark:2008).This method was calibrated with the SPINTROL multi-calibrator and validated with normal and pathological controls (SPIN). Insulin blood levels were measured by a chemiluminescence immunoassay with an Abbott Architect i 1000 (Abbott Diagnostic) autoanalyzer and an Inmuno Assay Plus (Bio-Rad, USA) internal quality control.

The population mean plus two standard deviations was used as the upper cut-off value for IR and Youden index using ROC curve. For the ß-secretion rates, we used the 25th percentile as the lower cut-off value in the same population, we used the Dunnett test to compare sex and age, using the GraphPad Prism 5.01 data analysis system.

The values were validated using the following HOMA formula: HOMA-IR = ((glucose mg/dl)/180) (10) (insulin uU/ml))/22.4, HOMA-%BS = ((Insulin uU/ml)(360))/((glucose mg/dl-63)), HOMA-%IS = ((1)/(HOMA-IR))(100). The cutoff values calculated according to whether they were upper or lower cut-off values are shown below.

Results

Table I

General characteristic of the study population in Aguascalientes.

N=1096 pacientes	VALUE			
	Healtly patient (n=548)		Insulin-resistance patient (n=548)	
	MEAN	*SD	MEAN	*SD
Age (years)	40	18.62	42	19.98
Waist diameter (cm)	74.5	6.9	88.5	14.5
HDL Cholesterol (mg/dl)	45	13.6	32	12.1
Weight (kg)	70.6	10.9	87	19.8
High (m)	1.66	0.20	1.69	0.22
Diastolic blood pressure (mmHg)	80	2	90	5.9
Sistolic blood pressure (mmHg)	110	10.5	135	14.5
Triglycerides (mg/dl)	139	25	198	35
Basal glucose (mg/dl)	89	5	120	23.1
Glucose at 60 min (mg/dl)	125	10.8	169	25.7
Glucose at 120 min (mg/dl)	101	9.6	132	20.1
Glucose at 180 min (mg/dl)	85	8.7	120	18.6
Insulina basal (uU/ml)	8.5	2.1	21	7.9
Insulina 60 min (uU/ml)	48.0	7.7	80.5	17.0
Insulina 120 min (uU/ml)	25.4	4.9	69.5	32.0
Insulina 180 min (uU/ml)	6.8	5.0	25	19.8

**Abbreviations: SD, Standard deviation.*

Cutoff Values

Statistical analysis resulted in cutoff for HOMA-IR (2.49), using the Youden index, the ROC curve, the average of two standard deviation and population 25th percentile, resulted en 72% for HOMA-%BS and 64% for HOMA-%IS. The selected population was distributed by sex and age range (20 to 35, 36 to 45 and 46 to 65 years), and after setting a cut-off value of the mean plus two standard deviations, the data were subjected to one-way ANOVA. To determine significance, if p ≤ 0.05 the cut-off points for the subgroup were not significant relative to the overall cut-off point for the entire population. The selected population was distributed by sex and age range to establish the 25th percentile as the lower cut-off point for %BS. These data were subjected to one-way ANOVA to determine significance at p ≤ 0.05, and the subgroup cut-offs were not significantly different from the population cut-off point.

Calculated Values for the Construction of a Theoretical Chart to Classify Patients in Aguascalientes

To classify patients undergoing a HOMA test as proposed by Graciela Buccini et al. [15], different combinations of glucose and insulin determinations were performed to attain the same HOMA-IR. Thus, calculations were obtained for five iso-HOMA: two were below the cut-off (2.49), and two were above it. We calculated the 4 iso-% BS series in the same manner. One had a %BS below the cut-off (72%), and two were above it. All calculations were grouped in Figure 3, and we constructed a chart that classifies patients receiving the HOMA test in Aguascalientes.

Table 2

Tables showing several constant iso-HOMA-IR for the construction of a theoretical chart that will be used to classify patients.

	GLU	INS	%BS	%IS
HOMA 0.59	70	3.3984	174.774857	169.491525
	80	2.9736	62.9703529	169.491525
	90	2.6432	35.2426667	169.491525
	100	2.37888	23.1458595	169.491525
	110	2.16261818	16.564735	169.491525
	120	1.9824	12.5204211	169.491525
	130	1.82990769	9.83233984	169.491525
	140	1.6992	7.94431169	169.491525
	150	1.58592	6.56242759	169.491525
	160	1.4868	5.51802062	169.491525
	170	1.39934118	4.70806377	169.491525

	GLU	INS	%BS	%IS
HOMA 1.61	70	9.2736	476.928	62.1118012
	80	8.1144	171.834353	62.1118012
	90	7.2128	96.1706667	62.1118012
	100	6.49152	63.1607351	62.1118012
	110	5.90138182	45.2020735	62.1118012
	120	5.4096	34.1658947	62.1118012
	130	4.99347692	26.8306223	62.1118012
	140	4.6368	21.6785455	62.1118012
	150	4.32768	17.9076414	62.1118012
	160	4.0572	15.0576495	62.1118012
	170	3.81854118	12.8474283	62.1118012

	GLU	INS	%BS	%IS
HOMA 2.49	70	14.3424	737.609143	40.1606426
	80	12.5496	265.756235	40.1606426
	90	11.1552	148.736	40.1606426
	100	10.03968	97.683373	40.1606426
	110	9.12698182	69.9087969	40.1606426
	120	8.3664	52.8404211	40.1606426
	130	7.72283077	41.4958071	40.1606426
	140	7.1712	33.5276883	40.1606426
	150	6.69312	27.695669	40.1606426
	160	6.2748	23.2879175	40.1606426
	170	5.90569412	19.8696251	40.1606426

	GLU	INS	%BS	%IS
HOMA 3.94	70	22.6944	1167.14057	25.3807107
	80	19.8576	420.513882	25.3807107
	90	17.6512	235.349333	25.3807107
	100	15.88608	154.567265	25.3807107
	110	14.4418909	110.618739	25.3807107
	120	13.2384	83.6109474	25.3807107
	130	12.2200615	65.6600321	25.3807107
	140	11.3472	53.0518442	25.3807107
	150	10.59072	43.823669	25.3807107
	160	9.9288	36.8491546	25.3807107
	170	9.34475294	31.4402903	25.3807107

	GLU	INS	%BS	%IS
HOMA 5.49	70	31.6224	1626.29486	18.2149362
	80	27.6696	585.944471	18.2149362
	90	24.5952	327.936	18.2149362
	100	22.13568	215.374184	18.2149362
	110	20.1233455	154.136263	18.2149362
	120	18.4464	116.503579	18.2149362
	130	17.0274462	91.4907555	18.2149362
	140	15.8112	73.9224935	18.2149362
	150	14.75712	61.0639448	18.2149362
	160	13.8348	51.3456495	18.2149362
	170	13.0209882	43.8089324	18.2149362

Table 3

Tables showing several constant iso-HOMA-%BS for the construction of a theoretical chart that will be used to classify patients.

	GLU	INS	HOMA	%IS		GLU	INS	HOMA	%IS
%BS 40	70	0.77777778	0.13503086	740.571429	%BS 72	70	1.4	0.24305556	411.428571
	80	1.88888889	0.37477954	266.823529		80	3.4	0.67460317	148.235294
	90	3	0.66964286	149.333333		90	5.4	1.20535714	82.962963
	100	4.11111111	1.01962081	98.0756757		100	7.4	1.83531746	54.4864865
	110	5.22222222	1.4247134	70.1895551		110	9.4	2.56448413	38.9941973
	120	6.33333333	1.88492063	53.0526316		120	11.4	3.39285714	29.4736842
	130	7.44444444	2.4002425	41.6624569		130	13.4	4.32043651	23.1458094
	140	8.55555556	2.97067901	33.6623377		140	15.4	5.34722222	18.7012987
	150	9.66666667	3.59623016	27.8068966		150	17.4	6.47321429	15.4482759
	160	10.7777778	4.27689594	23.3814433		160	19.4	7.6984127	12.9896907
	170	11.8888889	5.01267637	19.9494228		170	21.4	9.02281746	11.0830126
	GLU	INS	HOMA	%IS		GLU	INS	HOMA	%IS
%BS 100	70	1.94444444	0.33757716	296.228571	%BS 150	70	2.91666667	0.50636574	197.485714
	80	4.72222222	0.93694885	106.729412		80	7.08333333	1.40542328	71.1529412
	90	7.5	1.67410714	59.7333333		90	11.25	2.51116071	39.8222222
	100	10.2777778	2.54905203	39.2302703		100	15.4166667	3.82357804	26.1535135
	110	13.0555556	3.56178351	28.0758221		110	19.5833333	5.34267526	18.7172147
	120	15.8333333	4.71230159	21.2210526		120	23.75	7.06845238	14.1473684
	130	18.6111111	6.00060626	16.6649828		130	27.9166667	9.00090939	11.1099885
	140	21.3888889	7.42669753	13.4649351		140	32.0833333	11.1400463	8.97662338
	150	24.1666667	8.9905754	11.1227586		150	36.25	13.4858631	7.41517241
	160	26.9444444	10.6922399	9.35257732		160	40.4166667	16.0383598	6.23505155
	170	29.7222222	12.5316909	7.9797691		170	44.5833333	18.7975364	5.31984607

By plotting each of the calculated values, we obtained a similar chart to that presented by Buccini et al.[15] The area considered normal is delimited by (*).The upper cut-off point for HOMA-IR = 2.49, and the lower value of 72% was used for HOMA-%BS (green line). Several areas have been marked with a black frame.

In these areas, sector 1 is above the red line representing the highest HOMA-IR and above the line representing HOMA-%BS. This pattern corresponds to increased insulin resistance with increasing %BS or compensatory insulin secretion; this is the first manifestation of insulin resistance and suggest that it is important to pay more attention in the patients whose HOMA measurement is in this area.

In sector 2, insulin resistance is observed with diminishing beta secretion, and three subtypes can be identified based on the degree of hyperglycemia; the diminishing beta secretion in combination with insulin resistance appears in advanced stages before diabetes mellitus, and it is caused for a direct damage in beta cell produced by toxic effects of glucose and lipids. Sector 3 corresponds to compensatory increased beta-secretion but with normal insulin resistance; this increase even with normal glycemia and insulin appears in the inicial stages of truly insulin resistance.

Finally, sector 4 is delimited by normal insulin resistance but decreased beta-secretion, and means hyperglycemia. This sector may be classified depending on the degree of hyperglycemia(4a, 4b and 4c).A sub sector (4d) was found that has regular insulin resistance without hyperglycemia as well as decreased beta secretion, which is considered a state of pre-diabetes or high insulin sensitivity.

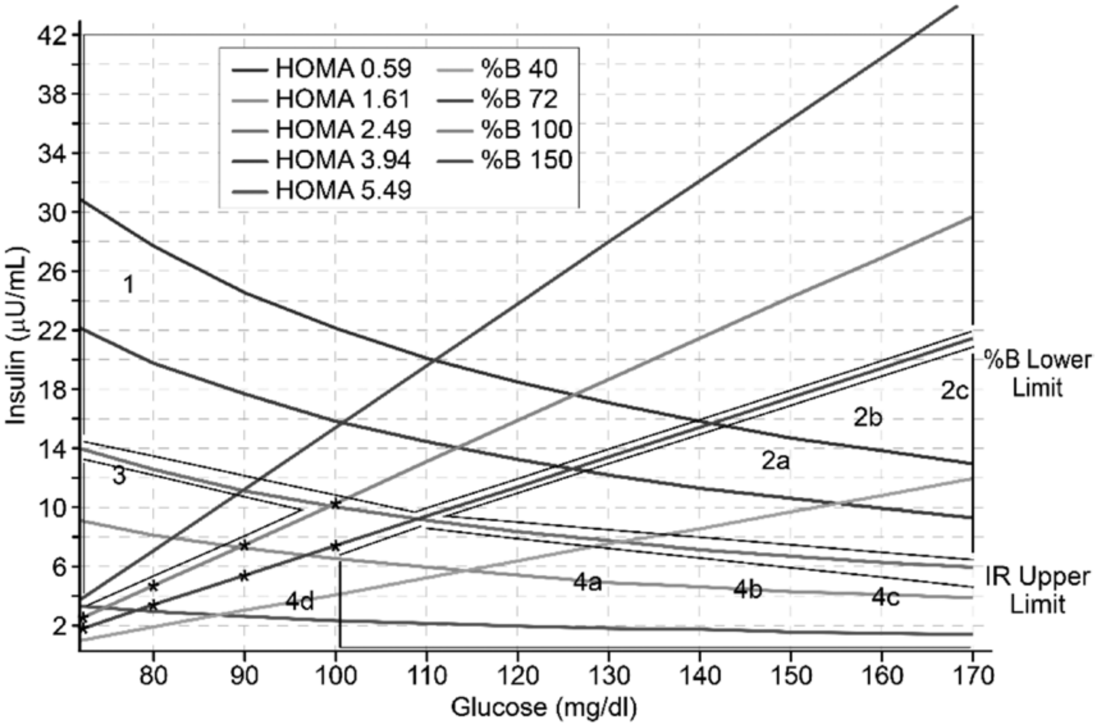

Figure 2. Chart prepared by different ISO-HOMA-IR and ISO-HOMA-%BS

Sensitivity and Specificity of the Homa Test in the Population of Aguascalientes

When analyzing the cases by a validated diagnostic test, the total population was defined in the true positive characteristic cases. Sick patients were identified by a validated standard and positive HOMA-IR (greater than 2.49), and 525cases were found. Healthy patients whose HOMA-IR was above the cut-off were considered false positives, and there were 13 such cases. Those patients who were classified as healthy by a validated standard and whose HOMA-IR was below the cut-off point established for the population were considered true negatives, and there were 535 such patients in total. Finally, those patients who showed disease evidenced by the diagnostic standard and whose HOMA-IR was below the cut-off point were considered false negatives, and there were 23 such cases. The data were entered into the GraphPad Prism 5.01 data analysis program, and the following parameters were obtained for the HOMA-IR cut-off = (mean + 2 SD) 2.[49].

We found that for our population (n = 548), all of the healthy patients in the municipality of Aguascalientes, as determined by a validated standard (glucose tolerance test with insulin determination at 60, 120 and 180 minutes) and considering a HOMA-IR cut-off point of 2.49, had95.8% sensitivity, 97.62% specificity, 97.58% positive predictive value, 95.87% negative predictive value, 40.25% positive likelihood ratio and a 0.043% negative likelihood ratio, with an area under the ROC curve of 0.9877, assuming $p \leq 0.0001$ and a 95% confidence interval from 0.982 to 0.9935.

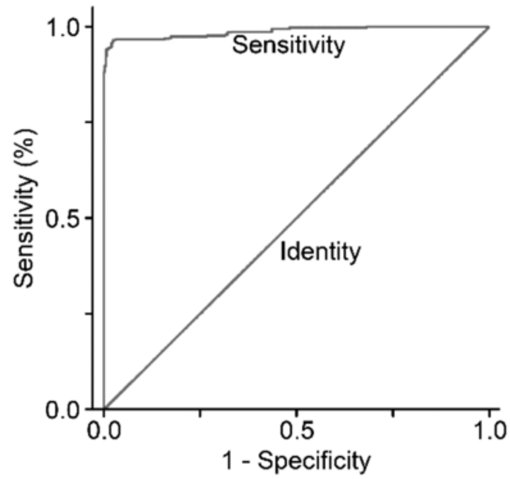

Figure 3. ROC curve showing sensitivity and specificity for the people of Aguascalientes with a cut-off point of 2.49.

Study on the Population with insulin resistance

A validated standard was used to conduct a study on glucose and HOMA-IR in the population; for individuals with insulin resistance, a Pearson's test was conducted to determine the correlation between glucose and HOMA-IR, and there was a significant correlation with $r = 0.199$ and $p < 0.0001$.

The percentiles for HOMA-IR and glucose were established for the population with insulin resistance, and a percentile in which the glucose variable would meet the criteria of glucose intolerance and diabetes mellitus according to the ADA criteria was sought (125 mg/dl>glucose >100 mg/dl and glucose ≥ 126 mg/dl, respectively,). In our population, a glucose level> 100 is in the 30% percentile, and in contrast with the HOMA-IR for the population, this percentile corresponds to 3.6. Likewise, glucose ≤ 125 is in the 77% percentile, in contrast to the population HOMA-IR, which is 5.78. A glucose level ≥ 126 corresponds to the 78% percentile and is in contrast with the HOMA-IR, which corresponds to the 5.8 percentile. Therefore, we consider a patient to be intolerant to glucose when the HOMA-IR is between 3.6 to 5.78 and to have diabetes when the HOMA-IR is 5.8.

Table 4

Percentile distribution of HOMA-IR variables and glucose-insulin-resistant from a gold standard population.

	IR Female	IR Female	IR Female	IR Male	IR Male	IR Male	Population	Population
	20-34	35-49	50-65	20-34	35-49	50-65	HOMA-IR	glucose
N	91	97	145	49	79	87	548	548
22% percentil	3.225	3.533	3.141	3.25	3.498	3.448	3.404	98
25% Percentil	3.401	3.674	3.313	3.391	3.498	3.491	3.487	99
30% percentil	3.509	3.713	3.457	3.833	3.602	3.713	3.6	101
Media	3.852	4.433	3.947	4.479	4.113	4.167	4.167	108
75% Percentil	4.719	6.071	5.632	6.061	5.667	5.51	5.639	123
77% percentil	4.762	6.201	5.639	6.108	5.667	5.635	5.78	125
78% percentil	4.762	6.366	5.639	6.143	5.671	5.745	5.805	129
Multiple comparison test of Dunnett	Population HOMA-IR Vs IR Female 20-34	Population HOMA-IR Vs IR Female 35-49	Population HOMA-IR Vs IR Female 50-65	Population HOMA-IR Vs IR Male 20-34	Population HOMA-IR Vs IR Male 35-49	Population HOMA-IR Vs IR Male 50-65	-	-
Significance if P < 0.05	No	No	No	No	No	No	-	-

Discussion

The HOMA-IR model has been widely used in epidemiological studies to estimate insulin resistance. This model assumes that fasting blood glucose is regulated by the liver production of glucose, which is insulin-dependent; like wise, fasting insulin depends on the response of beta cells to glucose. The HOMA-IR formula should be validated in a population in which genetic and environmental factors are considered to take it into clinical practice 16 . The ideal method for analyzing the HOMA formula is the hyperinsulinemic-euglycemic clamp, which is difficult to use in clinical laboratories [17].

The insulin resistance measured by the HOMA formula correlates closely with cardiovascular risk factors and precedes type 2 diabetes; it is therefore a predictor of the condition. It is known that insulin levels are a good surrogate marker of insulin resistance, and a HOMA value of 2.5 is associated with cardiovascular disease risk, while a value of 3.5 is associated with a risk of type 2 diabetes [18].

The HOMA formula has been validated as determining insulin resistance, although there is no overall cut-off value. Therefore, it is necessary to validate a cut-off in each population [19]. It is important to consider the high range of cut-offs that many researchers have proposed. To compare these points extrapolated to our population with a 95% confidence interval, we should determine the sensitivity, specificity and positive likelihood ratio that these values would have in our community to classify our cut-offas reliable.

Lee et al.[20] studied 976 Korean subjects aged between 30 and 79 years and reported a cut-off of 2.34, which in our population would have 96.72% sensitivity, 95.26% specificity and a 20.38% positive likelihood ratio. These results are very similar to ours. However, our project, with a cut-off of 2.49, has a PLR of 40.26, and the age range was similar to ours. This cut-offpoint could be rated as good in our community.

Yeni-Komshian et al.[21] presented a paper studying 490 Spaniards aged between 17 and 70 years and found a cut-off of 2.7, which in our population would have 93.61% sensitivity, 99.71% specificity and good diagnostic value.It has 128.5% of the PLR, and therefore, this cut-off value is rejected as a safe cut-off option for our population.

Pozzan et al.[22] presented a study in Rio de Janeiro, in which they evaluated 2,264 Brazilian subjects aged between 4 and 93 years andreportedtwocut-off points. The first cut-off was allocated to those under 18 years of age, being 2.39 for our population. It had 96.72% sensitivity and 96.16% specificity as well as 25.24% PLR; this cut-off point would be considered excellent in our population,although the age range for this cut-offis not similar to that of our patients.

In contrast, the authors of that study described an optimal cut-off value of 3.2 for their patients more than 18 years,which would give a cut-off point sensitivity of 82.85%and 100% specificity for our population. This value is useful to diagnose patients with disease, but it would lead to patients with early stages of insulin resistance not being properly diagnosed. It is important to consider that the PLR would be> 483%, which makes it a cut-off point with low sensitivity.

The study conducted by Bonora et al.[23] was based on the analysis of 225 Italians aged between 40 and 79 years in whom, when considering the last quintile,the HOMA-IR cut-offwas 2.77.Compared to our population, this population would have 92.37% sensitivity and 99.22% specificity, which are good values. ??Even so, a 126.5% PLR should be considered, as it would not be a reliable cut-off in our population.

In Argentina, Coniglio [24] studied 135 patients aged between 40 and 60 years and reported a cut-off of 3.1.When compared to our population, it showed 86.31% sensitivity, 100% specificity and a PLR higher than 483%, which makes it inaccuratefor our population.

Esteghamati et al.[25] studied 3,071 Iranians aged between 25 and 64 and reported a cut-off of 1.8.When compared to our population, it showed 97.63% sensitivity, 71.72% specificity and a very good PLR of 3.36.This cutoff is good for defining healthy patients but not discriminating healthy patients from sick patients.

Gurmendia et al.[26] reported a cut-off of 2.5 after studying 1,003 Chilean patients older than 80 years. Their cut-off was the same as our despite the age range difference between the two studies. When compared with our population, the findings were 95.8% sensitivity, 97.81% specificity and PLR of 43.85, which is slightly higher than what wasreported by our group.

Esteghamati et al.[25] also described, in their study with 3,071 Iranian subjects, an optimal diagnostic cut-off of diabetes patients by HOMA and a proposed a cut-off of 4.33. This cut-off was 5.8 in our population based on a percentile comparison, where the existing correlation of the HOMA-IR result with glucose in a population of type 2 diabetes patients was previously confirmed by the Pearson's test ($r = 0.2$ $p < 0.0001$). Rossana [27], in their study, described a correlation between glucose and the HOMA-IR cut-off with a Pearson's correlation coefficient of ($r = 0.52$, $p < 0.0001$).

We believe that establishing a safe cut-off in the population of Aguascalientes is necessary. Currently, many people who undergo a test to diagnose type 2 diabetes mellitus choose a simple fasting glucose test, and when normal values are found, the patient trusts the outcome. It is necessary to remember, however, that abnormal fasting glucose will appear 10 years after a self-regulating mechanism such as hyperinsulinemia has been triggered.

A basal insulin study can be suggested at the same time as a fasting glucose test, and it has more diagnostic value when the HOMA formula is calculated, as indicators will give a real picture of what is happening with endogenous hepatic glucose production, insulin sensitivity in peripheral tissues, etc. However, we should remember that in the early stages of insulin resistance, aerobic exercise induces muscles to continue the carbohydrate metabolic pathway, and innovative studies report that exercise increases the amount of cAMP within the cell. This cAMP is essential in mobilizing vesicles containing the Glut-4 channels for glucose uptake into the cell [28].

Conclussions

In summary, the following conclusions can be drawn:

1. The cut-off value for the upper HOMA-IR range in our population of n = 548 patients aged between 20 and 65 years with no evidence of metabolic syndrome, and using the Youden index by ROC curve, the population mean plus two standard deviations was 2.49, and it is considered normal. The cut-offs for the lower HOMA-%BS and HOMA-%IS ranges, considering the 25th percentile, were 72% and 64%, respectively.
2. With a HOMA-IR cut-off of 2.49 in the study population, reported values were 95.8% sensitivity, 97.62% specificity, 97.58% PPV, 95.87% NPV, 40.25% PLR and 0.043% NLR with an area under the ROC curve of 0.9877.
3. Glucose intolerance is considered to exist by percentile correlation if HOMA-IR >3.6 (30% percentile) but < 5.78 (77% percentile). Diabetes mellitus is considered to exist in a patient if HOMA-IR is > 5.8 (78% percentile).
4. The HOMA formula in the study population (n = 548) is a diagnostic and screening test with good sensitivity and specificity for the diagnosis of insulin resistance.

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