CLINICAL STUDY

Distribution of the homeostasis model assessment of insulin resistance in Mexican children and adolescents

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Abstract

Objective: Several cutoff points of the homeostasis model assessment of insulin resistance (HOMA-IR; varying from 2.5 to 4.0) have been suggested for diagnosing IR in youth. In this study, we determined the distribution of the HOMA-IR in Mexican children and adolescents.

Design and methods: A total of 6132 children and adolescents from San Luis Potosí, León, Queretaro, and Durango, which are cities in central and northern Mexico, were enrolled in a population-based cross-sectional study. Eligible participants were apparently healthy children and adolescents aged 6–18 years. Pregnancy and the presence of chronic illnesses were exclusion criteria.

Results: A total of 3701 (60.3%) girls and 2431 (39.7%) boys were included in this study. In the overall population, the mean body mass index, insulin levels, and fasting glucose levels were 21.8 ± 1.3 kg/m², 7.1 ± 3.2 µU/ml, and 86.2 ± 10.0 mg/dl respectively. The concentrations of insulin and fasting glucose gradually increased from 6 to 12 years of age, whereas the concentrations tended to plateau in the 13- to 18-year-old population. The absolute mean of the HOMA-IR was 2.89 ± 0.7 . The HOMA-IR gradually increased with age and reached a plateau at 13 years of age.

Conclusions: Because the insulin concentrations, glucose levels, and HOMA-IR exhibited a gradual increase with age that was not related to obesity, our results suggested that the evaluation of IR in children should be based on percentiles of the HOMA-IR rather than a dichotomous value derived from a single cutoff point.

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Introduction

The emergence of type 2 diabetes in children and adolescents has been recognized as a potential public health problem (1) and emphasizes the need for increasing the efforts of public health policies that focus on primary prevention.

Although several clinical features, such as obesity, acanthosis nigricans, and polycystic ovary syndrome, are indicative of insulin resistance (IR) in children and adolescents, a diagnosis of decreased insulin sensitivity requires a laboratory assessment.

The standard technique for assessing insulin sensitivity is the hyperinsulinemic euglycemic clamp; however, it is expensive and too invasive for epidemiological studies. Alternatively, the homeostasis model assessment of IR (HOMA-IR), which only requires fasting glycemia and insulin measurements (2), has been validated as a surrogate measure of IR in

non-diabetic children and shows a high correlation with clamp measurements (3, 4). Thus, the HOMA-IR emerged as an acceptable and useful tool to evaluate IR in epidemiological studies focused on children and adolescents (5).

Using the adult cutoff values of the HOMA-IR for children and adolescents might be inappropriate because insulin levels significantly vary during childhood and adolescence (6). Furthermore, studies have shown that the prevalence of type 2 diabetes and its risk factors vary widely according to gender and ethnicity. Among adolescents aged 12–19 years who participated in the National Health and Nutrition Examination Survey 1999–2002, the girls exhibited a higher HOMA-IR than the boys (2.97, 95% confidence interval (CI)=2.82–3.11; and 2.74, 95% CI=2.61–2.89, $P=0.02$), and Mexican-American children showed a higher HOMA-IR (3.08, 95% CI=2.94–3.23) than Afro American (2.90, 95% CI=2.76–3.05) and Caucasian

(2.76, 95% CI=2.63–2.91) children (7). In 9-, 13-, and 16-year-old Canadian youths, the mean values for the HOMA-IR were similar in age-matched boys and girls, except for the 13-year-old girls (1.90, 95% CI=1.73–2.06), who showed higher values than the boys (1.66, 95% CI=1.50–1.82) (8). In Latin American children and adolescents from Brazil, the HOMA-IRs for 11- to 12.9-year-old children (1.03 ± 0.81 and 1.44 ± 0.79 , $P=0.003$) and 15- to 17.9-year-old children (1.05 ± 0.67 and 1.49 ± 0.70 , $P=0.003$) were significantly higher in the girls compared with the boys. Interestingly, there were not significant differences in the other age strata (9). These results strongly support the previous studies, which suggested that insulin sensitivity varies according to gender and ethnicity.

Studies focused on determining a cutoff point for the HOMA-IR that could be applied for children and adolescents are scarce (5, 7, 8, 9, 10, 11). To the best of our knowledge, the HOMA-IR has not been previously evaluated over an age continuum from childhood to adolescence. Thus, the objective of this study was to evaluate the distribution of the HOMA-IR in Mexican children and adolescents.

Materials and methods

A total of 6132 Mexican children and adolescents aged 6–18 years, which represent ~93% of the children and adolescents that were invited to participate in the study, were enrolled in a multicenter, population-based, cross-sectional study that was carried out from May 2008 to July 2010.

The protocol was previously approved by the Institutional Research Boards of the institutions involved in the study, and the appropriate written informed consent of the children and at least one of their parents was obtained.

The sample to be studied was determined according to a two-stage cluster sampling as described previously (12). Briefly, a sample of elementary and middle schools that represented the different social, economical, and cultural characteristics of the targeted population from the cities of San Luis Potosí, León, and Querétaro in central Mexico and Durango in northern Mexico was randomly obtained. Children and adolescents aged 6–18 years were randomly selected from the schools and invited to participate in the study. All of the participants were Latin American Mexican children. According to the sampling strategy and the sample size, the cohort in this study was representative of the 6- to 18-year-old population from northern and central Mexico for both genders.

Pregnancy, diabetes, hypertension, chronic illnesses, the use of contraceptives, and hormonal replacement were exclusion criteria.

Measurements

The HOMA-IR was calculated using the following formula: (fasting insulin ($\mu\text{U/ml}$) $\times$ fasting glucose (mmol/l))/22.5 (2).

The heights and weights were assessed with a stadiometer using a fixed scale. The increments of the weight and height measurements were 0.1 kg and 0.01 m respectively. All of the measurements were performed with the children standing in light clothing without shoes under fasting conditions, which were confirmed by a direct interview with the parents of the children and the adolescents. The inter-assay coefficients of variation (CV) were 1.4 and 0.6% for height and weight respectively. The body mass index (BMI) was calculated as the weight (kilograms) divided by the height (meters) squared. All of the measurements were performed by trained personnel from the participating centers.

Obesity was defined by a BMI $\geq$ 95th percentile by age and gender, and being overweight was defined by a BMI $\geq$ 90th percentile but $<$ 95th percentile (13).

Assays

Whole blood samples were collected from an antecubital vein after an 8–10 h overnight fast. Serum glucose was measured using the glucose oxidase method (Sigma Diagnostics), and the intra- and inter-assay CV for the glucose measurements were 1.1 and 1.5% respectively. The insulin levels were measured by a microparticle enzyme immunoassay (Abbott AxSYM System, Alameda, CA, USA), and the intra- and inter-assay CV were 4.5 and 6.9% respectively. Samples were frozen at -20°C until their analysis, which was performed in the Central Laboratory of the Biomedical Research Unit at Durango.

Statistical analysis

The numerical values are reported as the mean $\pm$ s.d., and the categorical variables are presented as proportions. For the bivariate analysis, the comparison between the girls and the boys was performed by an unpaired Student's *t*-test.

Using a parametric procedure, the distribution of the HOMA-IR was tabulated for the values corresponding to the 5th, 25th, 50th, 75th, and 95th percentiles.

The distribution of the HOMA-IR was plotted using the LOWESS method. A LOWESS fit was calculated at each data point in the dataset, and a local polynomial was fit to a local region of data using a linear least squares regression. The LOWESS method has two inputs, the smoothing parameter and the degree of the local polynomial.

The data were analyzed using the statistical package SPSS for Windows 15.0 (Chicago, IL, USA), and a *P* value ≤ 0.05 defined statistical significance.

Results

A total of 6616 children and adolescents were invited to participate in this study, but 484 (7.3%) children and adolescents with an average age and BMI of 11.1 ± 1.4 years and 22.0 ± 1.2 kg/m², respectively, were not included in the study because they had diabetes ($n=29$ (0.4%)), a previous diagnosis of chronic illnesses ($n=411$ (6.2%)), or they refused to participate ($n=44$ (0.7%)).

Thus, 6132 children and adolescents (3701 (60.3%) girls and 2431 (39.7%) boys) were enrolled in this study. The mean age was 11.1 ± 3.0 years, and there was no significant difference between the ages of the girls (11.0 ± 3.0 years) and the boys (11.2 ± 3.2 years; $P=0.09$).

The mean insulin level in the overall group was 7.1 ± 3.2 µU/ml. The insulin levels between 6 and 12 years of age and at 18 years of age were significantly higher in the girls compared with the boys. Interestingly, there were no significant differences in the insulin levels of the other age groups (Fig. 1A). In both the girls and the boys, the insulin levels showed a gradual increase with age and reached a maximum peak at 13 years of age.

The overall mean glucose level was 86.2 ± 10.0 mg/dl. The boys aged 6–9, 15, and 17 years exhibited higher glucose concentrations than the girls of the same age. The other age strata did not show any gender differences. Similar to the insulin levels, the glucose concentrations gradually increased with age and reached a plateau at 12 years of age (Fig. 1B).

In the overall group, the mean HOMA-IR index was 2.89 ± 0.7 . The HOMA-IR gradually increased with age and reached a plateau at 13 years of age in both the girls and the boys (Fig. 1C). The HOMA-IR was significantly higher in the girls who were 12 years old

or younger and the 14-year-old girls compared with the boys of the same ages (Table 1).

The prevalence of obesity and being overweight in the study population was 28.0%, which was similarly distributed in both genders. The mean BMI in the overall group was 21.8 ± 1.3 kg/m². From 6 to 12 years of age, both the girls and the boys showed similar BMIs; however, the 13- to 18-year-old boys exhibited a higher BMI than the girls (Fig. 1D). For the girls, the BMI did not show significant changes with age, whereas the boys showed a significant increase in BMI from 16 to 18 years of age.

Interestingly, in 15- and 17-year-old participants, a total of 13 (3.5%) and seven (4.4%) participants, respectively, were classified as metabolically healthy obese individuals. A higher proportion of the boys fitted this criterion compared with the girls (6.6 vs 1.35%, $P=0.008$; and 4.3 vs 0.6%, $P=0.04$, for 15 and 17 years of age respectively). In the 17-year-old participants, the means $\pm$ s.d.s of BMI, glucose, insulin, and the HOMA-IR for the boys and the girls were 34.3 ± 3.4 and 30.2 ± 2.7 kg/m² ($P=0.11$); 91.0 ± 5.6 and 89.5 ± 3.0 mg/dl ($P=0.66$); 10.6 ± 2.1 and 9.7 ± 2.1 µU/ml ($P=0.58$); and 2.4 ± 0.5 and 2.1 ± 0.5 ($P=0.52$) respectively. In the 15-year-old participants, the means $\pm$ s.d.s of BMI, glucose, insulin, and HOMA-IR for the boys and the girls were 32.0 ± 4.8 and 32.9 ± 4.0 kg/m² ($P=0.83$); 79.8 ± 10.0 and 94.0 ± 6.3 mg/dl ($P=0.06$); 9.8 ± 1.8 and 10.5 ± 1.7 µU/ml ($P=0.55$); and 1.9 ± 0.4 and 2.4 ± 0.5 ($P=0.15$) respectively. The phenotype of metabolically healthy obese individuals was identified in boys and girls from 14 to 18 years, but not in the participants that were younger than 14 years of age. In the 16-year-old participants, 4.6% of the boys and 1.3% of the girls ($P=0.18$) exhibited a metabolically healthy obese phenotype. Between the 14- and 18-year-old participants, only one boy and one girl in each age group exhibited the metabolically healthy obese phenotype.

Figure 2 shows the percentiles of the HOMA-IR by gender and age and highlights the small differences between the 5th and 25th percentiles and the 75th and 95th percentiles for both genders.

Figure 1 The mean $\pm$ s.e.m. for insulin (A), fasting glucose (B), HOMA-IR (C), and BMI (D) in girls (white circles) and boys (black circles). * P value ≤ 0.05 .

Discussion

This study reported the distribution of the HOMA-IR with age in a representative population-based sample of Mexican children and adolescents. The mean HOMA-IR gradually increased with age and was significantly higher in the girls who were 12 years old or younger compared with the boys. In participants between the ages of 13 and 18 years old, we only observed a significant difference in the HOMA-IR between the 14-year-old boys and girls. Independent of changes in BMI, the present results showed that the insulin levels, the glucose levels and, consequently, the HOMA-IR,

Table 1 Distribution of HOMA-IR ($n=6132$).

Age (years)	Girls							Boys							<i>P</i> value ^a
	<i>n</i>	Mean±s.d.	Percentiles					<i>n</i>	Mean±s.d.	Percentiles					
			5th	25th	50th	75th	95th			5th	25th	50th	75th	95th	
6	259	1.04±0.46	0.39	0.68	0.97	1.40	1.85	247	0.86±0.51	0.39	0.47	0.64	1.12	2.07	0.03
7	321	1.17±0.45	0.43	0.86	1.12	1.52	1.96	285	0.99±0.47	0.35	0.59	0.91	1.35	1.87	0.002
8	321	1.19±0.48	0.42	0.81	1.17	1.57	1.99	105	1.03±0.44	0.40	0.66	0.95	1.38	1.80	0.002
9	304	1.25±0.46	0.52	0.90	1.23	1.65	2.0	109	1.05±0.41	0.42	0.73	0.95	1.38	1.86	<0.0005
10	407	1.28±0.46	0.44	0.92	1.32	1.63	1.98	135	1.17±0.49	0.44	0.77	1.11	1.58	2.0	0.02
11	388	1.56±0.58	0.55	1.15	1.51	2.04	2.44	132	1.41±0.60	0.42	0.90	1.47	1.89	2.34	0.02
12	298	1.88±0.70	0.72	1.31	1.94	2.41	2.96	266	1.49±0.77	0.50	0.84	1.31	1.99	2.97	<0.0005
13	328	1.97±0.66	0.83	1.46	1.97	2.45	3.09	289	1.98±0.72	0.96	1.35	1.95	2.64	3.15	0.98
14	335	1.88±0.76	0.64	1.28	1.79	2.50	3.2	290	1.70±0.72	0.66	1.18	1.60	2.13	3.35	0.048
15	221	1.90±0.79	0.85	1.28	1.76	2.51	3.48	150	1.99±0.85	0.72	1.29	1.79	2.64	3.46	0.50
16	176	1.84±0.85	0.76	1.19	1.57	2.48	3.51	129	1.85±0.95	0.39	1.27	1.66	2.75	3.73	0.95
17	171	1.79±0.74	0.65	1.25	1.82	2.25	3.30	139	2.01±0.75	0.94	1.29	1.95	2.63	3.39	0.13
18	172	1.75±0.76	0.72	1.15	1.60	2.28	3.37	155	1.53±0.86	0.50	0.90	1.30	2.10	3.46	0.13
Total	3701							2431							

^aBetween mean $\pm$ s.d. by girls and boys within each stratum.

exhibited a gradual increase from 6 to 13 years of age. These results strongly suggest that an appraisal of HOMA-IR in children should be based on a percentile distribution rather than a dichotomous value derived from a single cutoff point.

The prevalence of obesity and being overweight was 28.0%, which was similar to previous values reported for Mexican children (26.8%) and adolescents (30.9%) (14). Because the prevalence of obesity and being overweight in childhood and adolescence has significantly increased in recent decades (15), and obesity is closely related with IR, the emergence of type 2 diabetes and cardiovascular diseases in youth is not surprising. Because diabetes in children and adolescents is a public health challenge (16), non-invasive tests for the early identification of IR in childhood and adolescence are necessary. The results of this study highlight that an early recognition of IR in children and adolescents is possible using a percentile distribution rather than cutoff points for the HOMA-IR.

In this study, the mean HOMA-IR in the girls was significantly higher than the boys for all ages between 6 and 12 years old. Our findings agreed with previous studies that showed that prepubertal girls are less insulin sensitive than boys (10); however, some studies have not shown significant differences in the HOMA-IR between genders (5, 9). Among adolescents (youths from 13 to 18 years of age), we only found a significant difference for the HOMA-IR for the 14-year-old participants (i.e. the HOMA-IR was significantly higher in the girls compared with the boys). Our finding disagreed with the report by Lee *et al.* (7), which showed that 14- and 15-year-old boys who participated in the National Health and Nutrition Examination Survey 1999–2002 exhibited a higher HOMA-IR than the girls, whereas the 16- and 18-year-old girls had a higher HOMA-IR compared with the boys. In youths from

southeast Brazil, however, Almeida *et al.* (9) did not find significant differences in the HOMA-IR between girls and boys aged 13–14.9 years, but the 15- to 18-year-old girls exhibited a higher HOMA-IR. The inconsistencies between these studies could be attributed to ethnicity, and these studies highlight the need for further population-based studies that include children with different racial backgrounds.

Interestingly, although BMI and fasting glucose levels were significantly higher in the 15- to 17-year-old boys compared with the girls, there were no significant differences in the HOMA-IR. This finding could be explained by the presence of the phenotype of metabolically healthy obese individuals (17), which involves a large quantity of fat but a normal insulin sensitivity index and a favorable cardiovascular risk profile (18). Although the phenotype has been described in adults, the finding of metabolically healthy obese youths in our population can also explain the great

Figure 2 The percentiles of the HOMA-IR index by gender and age for Mexican girls ($n=3701$) and boys ($n=2431$).

dispersion of the data regarding the BMIs and glucose levels observed in the 15- and 17-year-old participants. Further research in the field is needed to understand the role of the metabolically healthy obese phenotype in youth.

A transitory decrease in insulin sensitivity is a physiological condition that occurs during pubertal development (19). The factors influencing insulin sensitivity during puberty, however, have not been clearly defined (6). Although IR in puberty may be exaggerated by obesity (20), the decrease in insulin sensitivity is not completely explained by differences in BMI or adiposity. Furthermore, studies have shown that neither testosterone nor estradiol levels are independently related with IR (21), and IR in normal puberty might be related to the GH/insulin-like growth factor 1 axis (6, 22). In addition, the increase in IR during puberty can also be related to a reduction in hepatic SHBG, which increases adrenocortical androgen production and sex steroid hormone bioavailability in both boys and girls (22, 23).

Currently, there is no consensus regarding cutoff points for the HOMA-IR values to define IR in children and adolescents. For example, the HOMA-IR cutoff points of 3.16 (11), 4.0 (24), 3.45 (25), 2.5 (26), and 3.8 (27) have been suggested for the diagnosis of IR in childhood and adolescence. The mean HOMA-IR in the overall population of this study was 2.89 (1.3 ± 0.6 from 6 to 12 years and 2.0 ± 0.7 from 13 to 18 years), which is similar to the HOMA-IR that has been reported in Latin American children and adolescents from the general population (25, 26). Because insulin and glucose levels gradually increase with age, our results suggested that the HOMA-IR should be considered as a continuum during childhood and adolescence, and the estimation of IR should be based on a percentile distribution of the HOMA-IR rather than a dichotomous value derived from a single cutoff point.

Several limitations of this study should be discussed. First, because fasting plasma glucose and insulin levels vary from day to day, the evaluation of the HOMA-IR using percentile charts could be controversial. Because the variability of the glucose and insulin levels also affects the insulin sensitivity measured by the clamp, and the values of the HOMA-IR and the clamp were highly correlated, this limitation did not affect our main conclusion. Secondly, we did not have any data for the Tanner stage of the target population. Because insulin sensitivity decreases during puberty and pubertal development starts at different ages, we evaluated the distribution of the HOMA-IR as a continuum through age and by gender to minimize this limitation. Thirdly, we did not measure body fat distribution, and body fat distribution may impact insulin sensitivity. Nonetheless, studies have shown that BMI is a surrogate measure of adiposity that correlates with the fat-free mass and total body fat in children (28). Therefore, the lack of body fat distribution measurements did not influence our

results. Fourthly, because we only included Mexican children and adolescents, our results cannot be extrapolated to other ethnic populations. The cutoff points of the HOMA-IR vary according to ethnicity, and further population-based studies with a wide racial background are necessary.

The main strength of this study was our sampling strategy and the sample size, which allowed the girls and boys in this study to mirror a representative population-based sample from central and northern Mexico.

In conclusion, the results of this study highlighted that the mean HOMA-IR was significantly higher in Mexican girls aged 12 years old or younger compared with the boys of the same age. Furthermore, our data showed that the HOMA-IR exhibited a gradual increase from 6 to 13 years of age, which suggested that the appraisal of the HOMA-IR in children should be based on a percentile distribution rather than a single cutoff point.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

C Aradillas-García, M Rodríguez-Morán, and F Guerrero-Romero had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. The study concept and design were performed by F Guerrero-Romero and M Rodríguez-Morán. The acquisition of the data was handled by M E Garay-Sevilla, J M Malacara, and C Aradillas-García, and the analysis and interpretation of the data were performed by F Guerrero-Romero and M Rodríguez-Morán. F Guerrero-Romero drafted the manuscript, and critical revision of the manuscript for important intellectual content was performed by C Aradillas-García, M Rodríguez-Morán, R A Rascon-Pacheco, M E Garay-Sevilla, J M Malacara, and F Guerrero-Romero. The statistical analysis was performed by F Guerrero-Romero. F Guerrero-Romero and C Aradillas-García obtained the funding for this study, and R A Rascon-Pacheco provided administrative, technical, and material support. C Aradillas-García supervised the study.

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