Determination of biological reference intervals for cardiometabolic risk factors in a population of young Mexican adults

Determinación de intervalos de referencia biológica para factores de riesgo cardiometabólicos en una población de adultos jóvenes mexicanos

Angélica M. Ortiz-Bueno¹, María E. Hernández-Hernández¹, Patricia López-Moreno¹,
María E. Blásquez-Gutiérrez¹, María de L. Martínez-Montañón¹, and Ashuin Kammar-García^{1,2,3*}

¹Department of Biochemistry, Medicine School, Benemérita Universidad Autónoma de Puebla, Puebla de Zaragoza, Puebla; ²Postgraduate Studies and Research Section, Higher School of Medicine, Instituto Politécnico Nacional, Mexico City; ³Department of Emergency, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico

Abstract

Background: The biological reference intervals (BRI), for the diagnosis of metabolic syndrome for the Mexican population, are mainly proposed by panels of experts for an adult population over 20 years of age. The diagnostic age ranges between 30 and 35 years, however, due to the tendency toward a diagnosis in increasingly younger stages. **Objective:** The objective of the study was to determine the BRI for cardiometabolic risk factors in the population of young Mexican adults. **Materials y methods:** A cross-sectional, descriptive study of 444 apparently healthy individuals (no biochemical changes) was performed. To describe the results of the biochemical parameters, measures of central tendency, dispersion, position, and form or distribution were used; for the description of the position and distribution, the coefficient of Fisher's asymmetry and kurtosis coefficient were calculated, respectively. Parametric comparisons were made using Student's t-test for independent samples and a one-way ANOVA, and BRI were calculated in the total population, by sex, and by nutritional status. **Results:** The distribution of the biochemical parameters has symmetry and propping like normality, with the exception of high-density protein-associated cholesterol (HDL-c). Comparisons of the values of the parameters between sex, showed that triglycerides, HDL-c, ureic acid (UA), and sistolic blood preasure present differences, as well as UA and blood pressure in the nutritional states. **Conclusions:** It was found that the BRI, for the biochemical parameters considered as cardiometabolic risk factors, are below those generally used, which suggests rethinking the values considered normal in this age stratum of young Mexican adults.

Key words: Biological reference intervals. Cardiometabolic risk factors. Metabolic syndrome. Young adults.

Resumen

Antecedentes: Los intervalos de referencia biológica (BRI) para el diagnóstico del síndrome metabólico en población mexicana son propuestos principalmente por paneles de expertos en población adulta mayor de 20 años. Sin embargo, la edad de diagnóstico oscila entre 30 y 35 años, debido a la tendencia hacia un diagnóstico en etapas más jóvenes. **Objetivo:** Determinar los BRI para los factores de riesgo cardiometabólico en la población de adultos jóvenes mexicanos.

Correspondence to:

Ashuin Kammar-García

E-mail: kammar_nutrition@hotmail.com

Date of reception: 08-11-2019

Date of acceptance: 03-02-2020

DOI: 10.24875/RHJM.20000036

Available online: 19-06-2020

Rev Hosp Jua Mex. 2020;87(2):74-80

www.revistahospitaljuarez.com

1405-9622/© 2020 Sociedad Médico-Quirúrgica del Hospital Juárez de México, A.C. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Materiales y métodos: Estudio descriptivo transversal de 444 individuos aparentemente sanos (sin cambios bioquímicos). Los resultados de los parámetros bioquímicos se describieron por medidas de tendencia central, dispersión, posición y forma o distribución. Para la descripción de la posición y distribución, se calcularon el coeficiente de asimetría de Fisher y coeficiente de curtosis. Se realizaron comparaciones paramétricas utilizando la prueba t de Student y un ANOVA de una vía, y se calculó el BRI en la población total, por sexo y estado nutricional. **Resultados:** La distribución de los parámetros bioquímicos tiene simetría y apuntalamiento como la normalidad, con la excepción del colesterol asociado a lipoproteínas de alta densidad (HDL-c). Las comparaciones de los valores de los parámetros entre sexos, mostraron que los triglicéridos, HDL-c, ácido úrico (UA) y la tensión arterial sistólica (TAS) presentaban diferencias, así como el UA y la presión arterial en los estados nutricionales. **Conclusiones:** Se encontró que los BRI, para los parámetros bioquímicos considerados como factores de riesgo cardiometabólico, están por debajo de los generalmente utilizados, lo que sugiere repensar los valores considerados normales en este estrato de edad de adultos jóvenes mexicanos.

Palabras clave: Intervalos de referencia biológica. Factores de riesgo cardiometabólico. Síndrome metabólico. Adultos jóvenes.

Introduction

For the interpretation for diagnostic purposes of the measured value of a biological magnitude, it is necessary to know one or more values of that magnitude but measured in individuals of similar characteristics and makes a comparison with the biological reference intervals (BRI).

The BRI are defined as the intervals where 95% of the measured values are in a reference population¹. The Institute of Clinical and Laboratory Standards² and the International Federation of Clinical Chemistry³, are instances, which have developed different guidelines where methodologies are proposed, defined, and stipulated for calculation of the BRI in the Clinical Laboratory; however, it is important to note that the determination of the BRI is the competence of the laboratories and must be established according to the population that directs their services^{3,4}.

The BRI are usually taken from the inserts that accompany the reagents with which the different tests are processed; whose values correspond to a population other than that where the tests are carried out, with an ethnic mixture different from that corresponding to the insert⁴.

Having the BRI of a specific population is essential when issuing an interpretation, because the parameters that are measured may vary in relation to certain characteristics such as age, physical activity, environment, and height above the level of sea of the place of residence of the population under study^{5,6}.

In the area of clinical chemistry, BRI have been estimated for various analytes such as glucose, urea, uric acid, creatinine, cholesterol, triglycerides, bilirubin, amylase, gamma glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and total proteins⁷⁻¹⁰ and have allowed

both to identify a risk threshold (values of lipids or glycosylated hemoglobin), and the limits for classifying a pathology.

The results of studies carried out in the Mexican population have shown variations between the reference intervals calculated for the population evaluated on a daily basis and the intervals provided in the test inserts⁴, which correspond to different racial populations and even these data. They suggest that the BRI obtained may differ from the values suggested by official Mexican standards¹¹.

The pathophysiology of the metabolic syndrome (MS) has described risk factors such as an increase in fasting blood glucose, an increase in triglycerides, a decrease in high-density lipoprotein cholesterol (HDL-c), an increase in low-density lipoprotein cholesterol (LDL-c), and among others¹². The age of diagnosis of people with MS has progressively decreased, being considered an age of 50 years or more, at an interval of 30-35 years the population at a highest risk¹³; currently, the most used definitions for diagnosis of MS are those of the International Diabetes Federation and the Adult Treatment Panel III (ATP III) in its modified version¹⁴, who propose the BRI, for the population over 20 years. With respect to adolescents and young adults, ATP III defines MS in the same way, when at least three of any of the following five criteria are met: central or abdominal obesity (defined by the waist circumference greater than the 90th percentile for age and sex), triglycerides above 110 mg/dl (or 95th percentile), HDL-cholesterol below 40 mg/dL (or 5th percentile), blood pressure (already either systolic or diastolic) >90th percentile, and the presence of alterations of the carbohydrate metabolism (altered basal glycemia, >100 mg mg/dl, and glycemia >140 mg/dL 2 h after oral glucose overload). However, due to the increase in obesity and MS in young people and the tendency

toward poor diet (fast food, excess consumption of refined flour, and sugary drinks) and poor physical activity in the general population from early stages¹⁵, as results from it, the aim of this study is to determine the BRI for cardiometabolic risk factors in the population of young Mexican adults.

Materials and methods

Study design and participants

A cross-sectional study, in apparently healthy young, was carried out in the Department of Biochemistry of the School of Medicine of the BUAP. This study was approved by the Ethics and Research Committee of School of Medicine of the Benemérita Universidad Autónoma de Puebla, with the number 279.

Between 2011 and 2018, annual samples were collected from Mexican-mestizo individuals with an age of 18-22 years, without a pathological history of metabolic alterations in the past year, who were not receiving a pharmacological treatment for chronic or metabolic diseases or with a specific diet. Subjects who did not have fasting longer than 12 h, who reported metabolic alteration in the past year or who decided not to participate were excluded from the study. A sample of 1535 individuals was obtained, of which 1059 were eliminated for presenting metabolic alterations (Glucose ≥ 110 mg/dL, triglycerides ≥ 150 mg/dL, total cholesterol ≥ 200 mg/dL, LDL cholesterol ≥ 100 mg/dL, HDL cholesterol ≤ 50 mg/dL in men and ≤ 40 mg/dL in women, and UA ≥ 6 or 7 in women and men, respectively).

The individuals showed up at the facilities of the Department of Biochemistry of the School of Medicine of the Benemérita Universidad Autónoma de Puebla, where they underwent somatometry (weight, height, waist, and hip circumference), clinical assessment (blood pressure), and obtaining a sample of peripheral blood by venipuncture, clinical history, and biochemical analysis that included quantification of glucose, total cholesterol, triglycerides, UA, and high lipoprotein cholesterol (HDL-c), low (LDL-c), and very low-density (VLDL-c).

A certified anthropometrist collect all the anthropometric measurements in standard conditions and with instruments certified by the International Society for the advancement of Kinanthropometry using a standardized portable scale and a metallic measuring tape. The blood pressure measurement was performed by a standardized clinician in the technique and procedures recommended by the American Heart Association using a

mercury sphygmomanometer and a medical-grade digital monitor (Omron HEM-907xL).

The concentrations of UA, glucose, triglycerides, and total cholesterol were measured using colorimetric enzymatic methods. HDL-c was determined by colorimetric enzymatic method with prior precipitation separation of LDL-c and VLDL-c using dextran sulfate (PM 50000) and magnesium chloride. LDL-c concentrations were determined by Friedewald's formula. The samples were processed in a VITROS DT60 II analyzer (Johnson Medical, Ortho-Clinical Diagnostics, Raritan, NJ, United States), with normal and pathological commercial control calibrators and serums. The intralaboratory variation coefficients were the following: 2.1 for total cholesterol, 1.4 for glucose, 2.3 for triglycerides, 4.0 for HDL-c, and 1.8 for UA.

Statistical methods

The variables are presented as mean $\pm$ standard deviation and as frequencies and proportions. A normality test was performed using the Kolmogorov-Smirnov statistic.

A population of 444 apparently healthy individuals was delimited (they did not present any biochemical alteration). To describe the results of the biochemical parameters, measures of central tendency, dispersion, position, and shape or distribution were used; for the description of the position and distribution, Fisher's asymmetry coefficient and kurtosis coefficient were calculated, respectively, values of 0 ± 0.5 were considered to define the distribution as symmetric and mesokurtic.

An identification of the extreme and atypical values was made by means of distribution of the data in graphic methods (Box-Plot). Likewise, the Grubbs test was performed, in which a $Z = 3.27$ was taken, with each test, each of the outliers was eliminated.

BRI were calculated from the following formula¹⁶:

$$\bar{X} \pm [Z_{\alpha} \left(\frac{SD}{\sqrt{n}} \right)]$$

The BRI were calculated in the total population, as well as by sex and nutritional status. For the bivariate comparison for BRI, it was carried out by means of the Student's *t*-test, and in comparisons of more than two groups by ANOVA one-way, and a *post hoc* Tukey analysis. It was necessary to treat each reference interval as a series of grouped data, using the mean and standard deviation; therefore, the arithmetic mean of

Table 1. Descriptive analysis of the metabolic parameters of cardiovascular risk

Metabolic parameters	Mean $\pm$ SD	Median (IQR)	Rank	Asymmetry	Kurtosis
Glucose	86.1 $\pm$ 7.9	87 (81-92)	59-100	-0.56	0.16
Triglycerides	90.7 $\pm$ 27.4	87 (71-110)	33-150	0.32	-0.66
Cholesterol	159.7 $\pm$ 21	161 (144-175)	93-200	-0.23	-0.43
HDL-c	57.2 $\pm$ 9.6	56 (51-62)	40-101	1.02	2.38
LDL-c	84.4 $\pm$ 19	85 (71-98)	18-130	-0.28	-0.13
Uric acid	5.2 $\pm$ 1.3	5.2 (4.3-6.1)	1.8-6.8	0.18	-0.25

SD: standard deviation, IQR: interquartile range, HDL-c: high-density cholesterol, LDL-c: low-density cholesterol

each reference interval was calculated again, as well as its standard deviation by the following formulas:

$$\mu = \frac{\sum_{i=1}^n f_i X_i}{n}$$

$$s = \sqrt{\frac{\sum_{i=1}^n f_i * (x_i - \mu)^2}{n - 1}}$$

Linear regression analyzes were performed to observe if there was an influence of anthropometry on the values of each metabolic parameter. All analyzes were performed with the statistical software R.

Results

The study included 444 individuals, young adults, who did not present any altered biochemical parameters, 56% (n = 248) were women and 44% (n = 196) were men. The mean age was 18.8 $\pm$ 1.7 years, with an interquartile range of 1 in men and women.

Table 1 shows the statistics, such as measures of central tendency, distribution, and position of the metabolic parameters associated with the MS. It was observed that the distribution of biochemical parameters has symmetry and underpinning like normal, except for HDL cholesterol. Most metabolic parameters showed symmetry, except for glucose and HDL-c.

During the analysis of outliers, the Grubbs test was found mainly in glucose and triglycerides, after its elimination indicated that there were no outliers that exceeded the critical Z = 3.27.

Table 2 shows the comparisons of the values of metabolic parameters between sex and nutritional status, triglycerides, HDL-c, and AU had differences between men and women, while VLDL-c, UA present differences by nutritional status.

The BRI are shown in **table 3**, it is observed that the BRI are below those used for the general population. The biological intervals were very short, having an average range of 2 units. The comparison of the BRI of women with those calculated in the total population only differed in the HDL-c (p = 0.02) and UA (p = 0.01), while in men they differed in triglycerides (p = 0.03) and HDL-c (p = 0.001). No different BRI were found for the state of nutrition than those of the general population (all p > 0.05).

The results of the linear regression analyses are shown in **table 4**. It is observed that none of the metabolic parameters are influenced by weight or waist circumference.

Discussion

The BRI calculated in this study are completely different and lower than those suggested by the different international associations¹⁷, this is very important since the population of this study is an age group in which the primary prevention of alterations can be performed metabolic factors such as dyslipidemia and MS, if the BRI suggested are considered as cutoff points to determine the risk of an alteration. It is necessary to emphasize that the BRI proposed in this study do not serve as a diagnostic criterion but rather as an alert for a future metabolic alteration¹⁶.

The differences in BRI in men and women were found mainly in triglycerides, HDL-c, and UA, with triglycerides being the most important finding since this difference in population BRI does not exist.

Although this study considered the inclusion of only apparently metabolically healthy subjects, after the elimination of individuals with altered metabolic parameters it was observed that 17% of the individuals had overweight and obesity, these patients were included

Table 2. Comparison of demographic characteristics and metabolic parameters by sex and nutritional status

Variables	Total	Women	Men	p	Normal weight	Overweight	Obesity	p
n (%)	444	248 (56)	196 (44)		365 (82.2)	68 (15.3)	11 (2.5)	
Age, years	18.8 ± 1.7	18.8 ± 1.7	19 ± 1.6	0.2	18.8 ± 1.4	19.3 ± 2.7	18.8 ± 1	0.05
Weight, Kg	60.1 ± 10	56.1 ± 9	65.4 ± 9.6	< 0.0001	57.3 ± 8	71.6 ± 7	84.9 ± 9	< 0.0001
Height, cm	164 ± 0.8	159 ± 0.6	170 ± 0.6	< 0.0001	164 ± 0.8	163 ± 0.7	160 ± 0.5	0.2
Waist circumference, cm	78.7 ± 9	75.9 ± 9	82.3 ± 9	< 0.0001	76.5 ± 8.1	87.7 ± 8.1	97.3 ± 6.7	< 0.0001
Hip circumference, cm	95 ± 8	93.8 ± 8	96.7 ± 8	< 0.0001	93 ± 6.8	102 ± 6.8	111 ± 9.2	< 0.0001
BMI	22 ± 3.3	21.9 ± 3.4	22.6 ± 3.3	0.06	21.1 ± 2.1	26.5 ± 1.1	33.1 ± 4	< 0.0001
SBP, mmHg	111.2 ± 10.3	109.3 ± 10	113.6 ± 9	< 0.0001	110.4 ± 10.5	114.4 ± 8.9	116.5 ± 6	0.003
DBP, mmHg	66.7 ± 8.1	67.2 ± 8.6	68.4 ± 7.5	0.1	67.2 ± 8.2	69.4 ± 7.4	72.8 ± 8.3	0.01
Glucose, mg/dL	86.1 ± 7.9	84.9 ± 8	87.5 ± 7.3	0.001	86.2 ± 8.1	85.3 ± 7.5	87 ± 8.4	0.6
Triglycerides, mg/dL	90 ± 27	88 ± 26	94 ± 28	0.02	89.7 ± 27	95.9 ± 29	93.1 ± 23	0.2
Cholesterol, mg/dL	159.7 ± 21	159 ± 21	159 ± 20	0.8	159 ± 20	162 ± 23	159 ± 10	0.4
HDL-c, mg/dL	57.2 ± 9.6	59.9 ± 8.5	53.9 ± 9	< 0.0001	57.7 ± 9.8	55.4 ± 8.6	53.4 ± 6	0.1
LDL-c, mg/dL	84.4 ± 19	83.4 ± 19	86 ± 19	0.01	83.8 ± 19	87 ± 22	85 ± 11	0.4
Uric acid, mg/dL	5.2 ± 1.3	4.8 ± 1.1	5.7 ± 1.4	< 0.0001	5.1 ± 1.3	5.5 ± 1.3	6 ± 1.3	0.01

Mean ± SD. Data compared by Student's t-test for independent samples and ANOVA one-way. HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table 3. IBR of cardiovascular risk parameters in young adults according to sex and nutritional status

Metabolic parameters	Total	Women	Men	Normal weight	Overweight	Obesity
n	444	248	196	365	68	11
Glucose, mg/dL	85.4-86.8	83.9-85.9	86.5-88.5	85.4-87.0	83.5-87.1	82.0-92
Triglycerides, mg/dL	87.5-92.5	84.8-91.2	90.1-97.9	86.9-92.5	89.0-102.8	79.5-106.7
Cholesterol, mg/dL	157.7-161.7	156.4-161.6	156.2-161.8	156.9-161.1	156.5-167.5	153.1-164.9
HDL-c, mg/dL	56.3-58.1	58.8-61.0	52.6-55.2	56.7-58.7	53.4-57.4	49.9-56.9
LDL-c, mg/dL	82.6-86.2	81.0-85.8	83.3-88.7	81.9-85.7	81.8-92.2	78.5-91.5
Uric acid, mg/dL	5.1-5.3	4.7-4.9	5.5-5.9	5.0-5.2	5.2-5.8	5.2-6.8

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol.

to determine their BRI and observe if there was any difference from those and the general population or subjects with normal weight. When the values of the metabolic parameters were compared by nutritional status, no difference was found from the main components of the MS, which would indicate that the metabolic alterations were not present even in overweight or obese patients.

The lack of differences in BRI by nutritional status may be due to the wide range in the metabolic parameters; therefore, many of the general population intervals are within the intervals by nutritional status and vice versa.

Linear regression analyzes did not show an influence of anthropometric parameters on changes in metabolic parameters, indicating that regardless of body composition,

Table 4. Linear regression models for metabolic parameters by weight and waist circumference

Metabolic parameters	B	B1 (Weight)	p	B2 (Waist-C)	p
Glucose	79.7	0.013	0.8	0.071	0.3
Triglycerides	138.9	-0.022	0.9	0.283	0.1
Cholesterol	62.4	0.253	0.2	0.167	0.4
HDL-c	68.2	-0.146	0.04	-0.027	0.7
LDL-c	59.5	0.074	0.6	0.26	0.1
Uric acid	2.45	0.019	0.05	0.021	0.04

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol.

it is extremely interesting since in other investigations^{18,19} it has been observed that body composition, even in this age group, influences metabolic alterations, although it is necessary to mention that there is a possibility that these changes have not been observed since the population was selected from the beginning without any metabolic alteration.

The BRI calculated in this study are different from those generally used in the adult population. This is one of the main findings, suggesting that more research is needed in larger and widely dispersed populations in the age to determine whether BRI change depending on age alone or influence other variables in the development of these intervals. Other studies¹⁶ with populations widely dispersed in age show some BRI different from those found by this study, but equally different from those used for general populations.

The BRI calculated in specific populations should not be used as delimiters of any condition that requires medical-pharmacological treatment, but rather as tools to make population comparisons that allow to support certain recommendations of preventive clinical intervention and that may be supportive of metabolic alterations preventive programs.

Population estimates, multivariate and without temporal specification should be considered as the main limitations of this study, since these considerations can cause a specific tendency to certain values^{7,20,21}.

Another limitation in the study is that the calculated BRI allude to the finding of a value in a subject would depend on what can be considered as a good state of health according to the methodological definition of the study itself²⁰⁻²³. In this regard, it should be noted that

the definition of a healthy person in this study has limitations related to the fact of not making explicit the physiological states (menarche, pregnancy, lactation, altered blood pressure, or nutritional status) or certain risk factors as obesity, alcoholism, and smoking, since these entities were not considered as factors to eliminate the individual from the study. However, these omissions do not affect the validity of the results, as the inclusion criteria directly considered the values of the metabolic profiles.

The international recommendations of the reference intervals are based on the results of multicentric studies and with heterogeneous populations; but the exploration of specific populations allows to expand the panorama for future recommendations in which they consider different levels in the cutoff points, it is paramount the increase of investigations that address the generation of new cutoff points for prevention and treatment in different populations.

Conclusion

The BRI of the main parameters used for the determination of metabolic alterations, obtained for a population of young Mexican adults, are below those generally used in clinical practice, which suggest rethinking the values considered normal in this stratum age, and thus achieve a better prevention of future metabolic disorders that lead to the development of cardiovascular diseases.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Funding

The authors received no specific funding for this work.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Aradillas C, Tenorio E, Flores J, De la Cruz E, Calderón J, Hernández H, et al. Valores de referencia de insulina y lípidos en jóvenes de 16 a 18 años de edad en la ciudad de San Luis Potosí. *Bioquímica*. 2003;28:9-13.
2. Geffré A, Friedrichs K, Harr K, Concordet D, Trumel C, Braun JP. Reference values: a review. *Vet Clin Pathol*. 2009;38:288-98.
3. Horn PS, Pesce AJ. Reference intervals: an update. *Clin Chim Acta*. 2003;334:5-23.
4. Boyd JC. Defining laboratory reference values and decision limits: populations, intervals, and interpretations. *Asian J Androl*. 2010;12:83-90.
5. Gonzales G. Hemoglobina y testosterona: importancia en la aclimatación y adaptación a la altura. *Rev Perú Med Exp Salud Pública*. 2011;28:92-100.
6. Roshan TM, Rosline H, Ahmed SA, Rapiaah M, Zai-dah AW, Khattak MN. Hematological reference values of healthy Malaysian population. *Int J Lab Hematol*. 2009;31:505-12.
7. Devez M, Sanchez D, Cuellar P, Jiménez G, Duran E. Determinación de valores de referencia en bioquímica clínica en suero de derechohabientes de la clínica hospital "B" de Guanajuato. *Cont Quím*. 2011;6:3-7.
8. Fuentes G, Díaz P, Hernández R, Cervantes D, Presno J, Alcántara L. Determinación de intervalos de referencia para química clínica en población Mexicana. *Rev Latinoam Patol Clin*. 2013;60:43-51.
9. René W, Bonneau G, Castillo M, Juárez M, Cardozo J. Valores de referencia y prevalencia de las alteraciones del perfil lipídico en adolescentes. *Arch Argent Pediatr*. 2010;108:107-15.
10. Mendoza L, Gómez T, Pérez L, Mollineda A, Salazar L, Hernandez V. Perfil bioquímico y valores de referencia en sangre del cordón umbilical. *Acta Bioquím Clín Latinoam*. 2014;48:311-7.
11. García-Jiménez S, Martínez-Salazar MF, Monroy-Noyola A, Juantorena-Ugás A, Sánchez-Alemán MA. Intervalos de referencia del perfil de lípidos en trabajadores y estudiantes de la Universidad Autónoma del Estado de Morelos, México. *Rev Biomed*. 2011;22:3-10.
12. Aguilar-Salinas CA, Gomez-Perez FJ, Rull J, Villalpando S, Barquera S, Rojas R. Prevalence of dyslipidemias in the Mexican national health and nutrition survey 2006. *Salud Pública Méx*. 2010;52:44-53.
13. Robles JC. Síndrome metabólico: concepto y aplicación práctica. *An Fac Med*. 2013;74:315-20.
14. Guzmán J, González A. Epidemiología, Diagnóstico, Control, Prevención, Tratamiento del SM en Adultos. Vol. 18. *Revista ALAD*; 2010.
15. Norma Oficial Mexicana. No. NOM-037-SSA2-2002. Para el Manejo y Control de las Dislipidemias; 2002.
16. Galvis Y, Barona J, Cardona JA. Biological reference intervals of lipid profile. *Acta Med Colomb*. 2016;41:29-35.
17. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*. 2001;16:2486-97.
18. Kammar-García A, Hernández-Hernández ME, López-Moreno P, Ortiz-Bueno AM, Martínez-Montano ML. Relation of body composition indexes to cardiovascular disease risk factors in young adults. *Semergen*. 2019;45:147-55.
19. Rodea-Montero ER, Evia-Viscarra ML, Apolinar-Jiménez E. Waist-to-height ratio is a better anthropometric index than waist circumference and BMI in predicting metabolic syndrome among obese Mexican adolescents. *Int J Endocrinol*. 2014;2014:195407.
20. Horowitz GL, Chairholder MD. Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline. 3rd ed. USA: CLSI, NCCLS; 2008. p. 1-76.
21. Solberg HE. The IFCC recommendation on estimation of reference intervals. The RefVal program. *Clin Chem Lab Med*. 2004;42:710-4.
22. Ritchie RF, Palomaki G. Selecting clinically relevant populations for reference intervals. *Clin Chem Lab Med*. 2004;42:702-9.
23. Horn PS, Pesce AJ. Effect of ethnicity on reference intervals. *Clin Chem*. 2002;48:1802-4.