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Changes in C-reactive protein and biochemical profile in preschool children with obesity

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Abstract

Introduction: **the childhood obesity is a serious public health problem because if weight gain continues, complications such as insulin resistance, dyslipidemia, orthopedic disorders, sleep apnea, and metabolic syndrome may occur in other stages of child development.**

Objective: **the objective of this study was to evaluate C-reactive protein (CRP) concentrations, lipid profiles, and glucose levels in obese children three to five years of age and compare them to eutrophic children.**

Methods: **in this study, 100 children aged three to five years were selected and divided into two groups (*n = 50 per group*): a group of eutrophic children (< 84th percentile) and a group of obese children (> 95th percentile). An anthropometric evaluation and quantification of plasma levels of ultrasensitive CRP, triglycerides, cholesterol, LDL-C, HDL-C, and glucose were performed.**

Results: **the data showed a significant increase in obese children with regard to height ($p < 0.005$), weight ($p < 0.0001$), body mass index ($p < 0.0001$), ultrasensitive CRP ($p < 0.0001$), triglycerides ($p < 0.0001$), LDL ($p < 0.0001$), and glucose levels ($p < 0.0001$) as well as decreased levels of HDL ($p < 0.0001$) compared to eutrophic children.**

Conclusions: **metabolic changes that occur in obese preschool children are characterized by increases in inflammatory markers and lipid profiles. Considering that during preschool age the programming and number of adipocytes that will remain with the individual for the rest of their life are determined, this stage is crucial in the development of complications associated with obesity.**

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Key words: *Ultrasensitive C reactive protein. Lipid profile. Preschool age. Childhood obesity. Body mass index.*

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CAMBIOS EN LA PROTEÍNA C REACTIVA Y PERFIL BIOQUÍMICO EN NIÑOS PREESCOLARES CON OBESIDAD

Resumen

Introducción: **la obesidad infantil es un grave problema de salud pública, ya que si el aumento de peso continúa, pueden producirse complicaciones tales como resistencia a la insulina, dislipidemia, trastornos ortopédicos, apnea del sueño y síndrome metabólico en otras etapas del desarrollo del niño.**

Objetivo: **el objetivo de este trabajo fue estudiar las concentraciones de proteína C reactiva, perfil de lípidos y glucosa en niños de 3-5 años con obesidad, y compararlos con niños eutróficos.**

Métodos: **para dicho fin, cien niños de 3 a 5 años de edad fueron seleccionados y divididos en dos grupos (*n:50 por grupo*); un grupo de niños eutróficos (percentil < 84) y un grupo de niños con obesidad (percentil > 95). Se realizó una evaluación antropométrica y una cuantificación en plasma de proteína C reactiva ultrasensible, triglicéridos, colesterol, LDL-C, HDL-C y glucosa.**

Resultados: **los datos obtenidos muestran un aumento significativo en los niños que presentan obesidad en relación a la talla ($p < 0,005$), peso ($p < 0,0001$), índice de masa corporal ($p < 0,0001$), proteína C reactiva ultrasensible ($p < 0,0001$), triglicéridos ($p < 0,0001$), LDL ($p < 0,0001$) y glucosa ($p < 0,0001$), así como una disminución en los niveles de HDL ($p < 0,0001$), comparados con los niños eutróficos.**

Conclusiones: **los cambios metabólicos presentes en los niños preescolares obesos son caracterizados por un incremento en los marcadores inflamatorios y del perfil de lípidos. Tomando en consideración que durante la edad preescolar se determinan la programación y el número de adipocitos que se tendrán en la vida del individuo, esta etapa es clave en el desarrollo de las complicaciones asociadas a la obesidad.**

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Palabras clave: Proteína C reactiva ultrasensible. Perfil de lípidos. Edad preescolar. Obesidad infantil. Índice de masa corporal.

Abbreviators

WHO: World Health Organization.
ENSANUT: National Survey of Health and Nutrition.
BMI: body mass index.
IL-6: interleukin-6.
CRP: C reactive protein.
CDC: Centers for Disease Control and Prevention.
HDL: High-density lipoprotein.
LDL: Low-density lipoprotein.

Introduction

The World Health Organization (WHO) estimates that there are approximately 42 million obese preschoolers, of which 38% live in developing countries[1]. In the case of Mexico, the National Survey of Health and Nutrition in 2012 (Encuesta Nacional de Salud y Nutrición - ENSANUT) reported a 25% prevalence of obesity in children under 5 years of age[2]. Therefore, it can be stated that childhood obesity is a serious public health problem because if weight gain continues, complications such as insulin resistance, dyslipidemia, orthopedic disorders, sleep apnea, and metabolic syndrome may occur in other stages of child development[3,4].

Preschool age, which is between three to five years of age, is crucial in the development of obesity because, in this age group, the genesis, development, and programming of adipose tissue occurs and will be retained for life[5,6,7]. If a preschooler gains an additional 2 or more kilograms of weight per year[3,5], which is expressed as an increased body mass index (BMI), this will cause an increase in interleukin-6 (IL-6) secretion by hypertrophic adipocytes, resulting in the stimulation of liver production of C reactive protein (CRP)[8]. This 118 kDa molecular weight globulin is composed of 5 subunits and plays a key role in the adipocytes by promoting infiltration, polarization, and recruitment of monocytes and preadipocytes to form macrophages and thus initiate the process of low grade subclinical inflammation[3,8,9,10,11].

Another risk factor that contributes to weight gain in preschool age children is the increased consumption of saturated fats from the diet, which will cause adipocytes to store more triglycerides and esterified cholesterol, resulting in hyperplasia of the tissue[12,13]. With the adipocyte unable to continue to store fatty acids, these fatty acids are released into the extracellular space, generating lipotoxicity. Coupled with a decrease in blood supply, adipose tissue necrosis will occur and cause changes in the physiology of adipocytes. During necrosis, monocytes are attracted from the circulation and are polarized by CRP to form M2 macrophages. In addition, fibroblasts and preadipocytes will also be polarized to M1 macrophages[10], causing a loss of regulation of the inflammatory response, which leads to a vicious cycle that is perpetuated as long as weight gain is maintained.

Despite the importance of CRP and lipid profile due to their involvement in chronic degenerative diseases, there are still no studies that clearly indicate which parameters are adequate for children from three to five years of age, given the importance of this age in the pathogenesis of obesity.

Therefore, the objective of this study is to evaluate CRP concentrations, lipid profiles and glucose levels in obese three- to five-year-old children compared to eutrophic children.

Material and methods

This study was approved by the Bioethics Committee of the School of Medicine of the National Autonomous University of Mexico, the Secretary of Health of the Federal District, and the Xochimilco Pediatric Hospital.

A prospective cohort study was conducted in Mexico City in the Xochimilco Maternal Pediatric Hospital of the Ministry of Health of the Federal District. The study was conducted from March to December 2013 in a population of children that attended the pediatric outpatient clinic for child health. The parents of the children were informed of the study procedures before they signed the letter of informed consent, following the agreement established in the protocol of the Helsinki declaration.

Selection of the sample was intentional and consisted of forming two unpaired groups: the eutrophic or control group, which consisted of children with weights between the 50th to 84th percentile, and the group of obese children with weights greater than the 95th percentile (n = 50 per group). Additionally, children from both groups had to meet the following inclusion criteria: age between three to five years, apparently healthy, with no anatomical malformations, family history of dyslipidemia, or heart disease, and permission from the parents to participate in the study.

Determination of nutritional status

An anthropometric evaluation of weight and height was conducted in the presence of the parents (with patients barefoot, standing upright with arms straight on both sides of the body, and in underwear) using the Tanita BF-2000 children's scale. The recorded value was expressed in kilograms. Height was determined by the plumb technique and is expressed in centimeters. Subsequently, to determine the nutritional status, BMI was calculated based on the formula weight/height^2 and is expressed in kg/m^2. From the-

se measurements, the BMI percentiles for each child based on age and sex were determined according to a chart from the Centers for Disease Control and Prevention (CDC), updated in 2006 (CDC-WHO 2006). The Z-score was determined according to the WHO criteria.

Determination of biochemical profile

For the laboratory tests, blood samples were obtained in the laboratory of the Xochimilco Pediatric Maternal Hospital by qualified staff, and 10 ml of blood was obtained by venipuncture after fasting for 12 hrs. Serum quantification of ultrasensitive CRP was performed by a Siemens model BNII nephelometer with a detection limit of 0.1 mg/dl according to the manufacturer's instructions. Subsequently, the lipid profile, triglycerides, total cholesterol, LDL, HDL, and glucose levels were analyzed with a SYNCHRON CX7 blood chemistry analyzer (Beckman Coulter, Inc. Fullerton, California, USA) based on the manufacturer's indications.

The results were compared between the group of eutrophic children (control group) and the obese group of children (n = 50 per group) because there are no data regarding normal levels of these parameters for the Mexican population in this age group.

According to the data distribution, nonparametric statistical tests using the Mann-Whitney U test were conducted for comparisons between groups. Graph-Pad Prism VI® software was used for the statistical analyses.

Results

The children who participated in this study were distributed as follows: 48% were female and 52% male, with a mean age of 4.1 years. Regarding their nutritional status, 50% were between the 50th and 84th percentile, indicating a normal weight for their age (control group), and the remaining 50% were above the 95th percentile, which corresponds to obesity (obese group).

The results indicated that the group of obese children showed a statistically significant increase in the concentrations of ultrasensitive CRP, triglycerides, HDL-C, LDL-C, and glucose compared to the children in the control or eutrophic group.

Mann-Whitney U tests were performed to compare the biochemical parameters. The CRP level in obese children ($\bar{x}$ = 0.66 mg/dl ± 0.1) showed a statistically significant increase ($p < 0.0001$) compared to control children ($\bar{x}$ = 0.0 mg/dl ± 0.0). The triglyceride levels in obese children ($\bar{x}$ = 116 mg/dL ± 1.6) showed a significant increase ($p < 0.0001$) compared to control children ($\bar{x}$ = 85 mg/dl ± 5.2). The LDL-C levels showed a significant difference ($p < 0.0001$) between obese children ($\bar{x}$ = 86.3 mg/dL ± 3.1) and control children ($\bar{x}$ = 103.1 mg/dl ± 7.6). Finally, the glucose levels showed a significant difference ($p < 0.0001$) between obese children ($\bar{x}$ = 98 mg/dl ± 2.8) and control children ($\bar{x}$ = 86.06 mg/dl ± 1.0). For the other biochemical markers, no statistically significant differences were observed. In addition, no statistically significant correlation was found between the parameters evaluated (Fig. 1).

Discussion

The results from this study show that obese preschoolers presented inflammatory and metabolic alterations in very early stages of life, as evidenced by the levels of CRP, lipid profile (triglycerides, HDL-C and LDL-C), and glucose levels, which were compared with eutrophic children from the same population. These changes indicate the beginning of chronic degenerative diseases at school age and during adolescence, as demonstrated by multiple studies in different populations around the world.

The increase in the serum concentration of ultrasensitive CRP in obese children compared to eutrophic children is of utmost importance because CRP is involved in the acute phase of the immune response, which appears after an imbalance in the innate immune system occurs. Thus, CRP is used as an inflammatory marker and is regulated by transcriptional factors of IL-6, which are secreted directly by adipocytes[9,14,15]. Another action that can directly impact the levels of CRP is related to the type of diet consumed. A diet high in sweeteners, semi-synthetic sweeteners, and saturated fats increases plasma concentrations of CRP in obese patients. However, if lifestyle is modified, if the consumption of fruits, vegetables, and bioactives derived from milk is increased, and if a diet high in antioxidants is consumed, the concentrations of CRP will decrease independently of BMI[8,16,17,18,19].

The concentrations of triglycerides and LDL-C were higher in obese children than in eutrophic children, and the HDL-C concentrations were lower. If this metabolic modification of lipids continues, adipocyte dysfunction will be stimulated, causing the accumulation of fatty acids in muscle (intramyocellular), resulting in insulin resistance. However, if this phenomenon occurs at an early age, the effect will be more severe[18] (Table I).

In addition, the glucose concentrations of the children studied showed statistically significant differences between groups; these figures may be related to the age that children begin to consume bottled juices sweetened with high fructose corn syrup, which is approximately 3.2 years of age in different populations[20].

The results from this study coincide with those of Lo et al., who conducted a therapeutic intervention

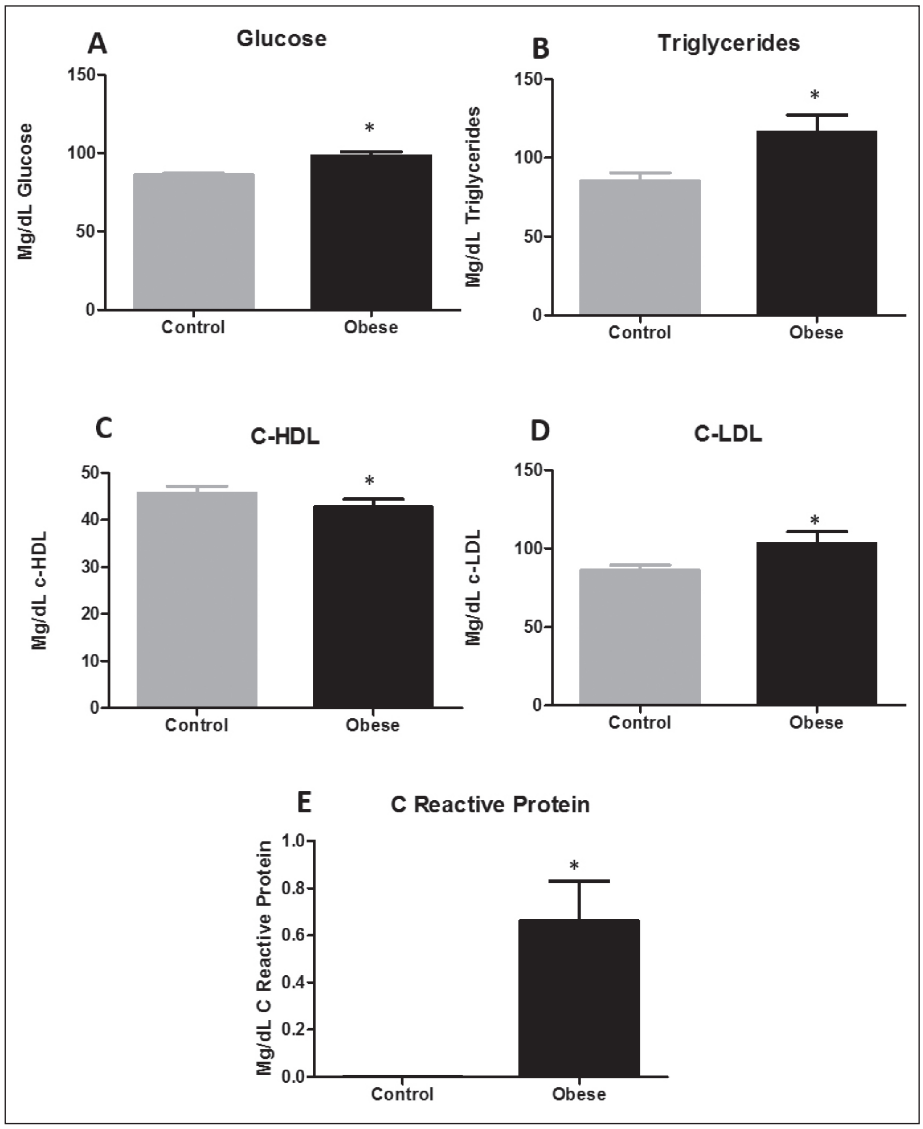

Fig. 1.—Effect of early obesity in children aged 3-5 years graphics for levels of glucose (A), triglyceride (B), HDL-c (C), LDL-C (D), C-reactive protein (E), note the increase of glucose, triglycerides, LDL-C, C-reactive protein and decrease in HDL-C of the children who had obesity.

Table I
Distribution of data by age and body mass index with the biochemical parameters studied (Group control children <85 percentile group of obese children and ≥ 95 percentile)

Variables n = *100*	*Control* n = *50*	*Obeses* n = *50*
	Mean ± std error	*Mean ± std error*
Size (cm)	104.5 ± 1.05	108.62 ± 1.12
Weight (kg)	15.64 ± 0.32	23.07 ± 0.82
BMI (kg/m^2)	14.78 ± 0.13	18.13 ± 0.30
Glucose (mgs/dl)	86.06 ± 1.05	98 ± 2.81
Cholesterol (mgs/dl)	148.3 ± 3.93	153.1 ± 4.56
Tryglicerides (mgs/dl)	85.46 ± 5.28	116.42 ± 11.05
LDL-C (mgs/dl)	86.32 ± 3.12	103.12 ± 7.12
HDL-C (mgs/dl)	45.64 ± 1.51	42.71 ± 1.69
C reactive Protein us (mgs/L)	0.00 + 0.00	0.66 + 0.16

(lifestyle change) in morbidly obese North American preschoolers (three to five years old) and concluded that these children are more likely to present metabolic diseases at earlier ages[21]. However, perhaps one of the important findings of our study is that when we compared obese children with eutrophic children, we found statistically significant differences between groups in the serum concentrations of CRP, triglycerides, LDL-C, HDL-C, and glucose. It is essential to perform biochemical profiles that include CRP, lipids, and glucose early in preschool children that present obesity, as the relationship between these markers is a strong predictor of insulin resistance and metabolic syndrome in later stages of life[21,22].

Conclusions

It can be concluded that children that are obese during preschool age have alterations in CRP concentrations and lipid profiles compared to eutrophic children and that the continued elevation of these biochemical parameters creates more severe clinical consequences at later ages in child development.

We suggest performing anthropometric and biochemical evaluations of all obese preschool age children because this age is critical to the development of obesity and its complications, which can occur in the pediatric stage and develop into chronic degenerative diseases during young adulthood.

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Conflict of interests

The Author(s) declare(s) that there is no conflict of interest.

References

1. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation*. Geneva, Switzerland: World Health Organization; 2000. http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/. Accessed March 31, 2015.
2. Gutiérrez JP, Rivera-Dommarco J, Shamah-Levy T, Villalpando-Hernández S, Franco A, Cuevas-Nasu L, Romero-Martínez M, Hernández-Ávila M. *Encuesta Nacional de Salud y Nutrición 2012. Resultados Nacionales*. Cuernavaca, México: Instituto Nacional de Salud Pública (MX); 2012.
3. Bocca G, Stolk P, Wolffenbuttel B, Sauer P. Effect obesity intervention programs on adipokines, insulin resistance, lipid profile, and low-grade inflammation in 3-to 5-y-old children. *Pediatr. Res*. 2014;75:352-357. doi:10.1038/pr.2013.216.
4. Skinner AC, Steiner MJ, Henderson FW, Perin EM. Multiple markers of inflammation and weight status: cross-sectional analyses throughout childhood. *Pediatrics*. 2010;125:e-801-e-809. doi:10.1542/peds.2009-2182.
5. Fujiwara T, Oguni T, Unishi G, Tanabe T, Ohbayashi K, Kaneko K. Factor related of patterns of body mass index in early infancy: 18 month longitudinal study. *Pediatr. Int*. 2014;56:406-410. doi:10.1111/ped.12272.
6. Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound: causes and consequences for obesity in children and adults. *Int. J. Obes*. 2006;30:S11-S17. doi:10.1038/sj.ijo.0803514.
7. Roland-Cachera MF, Deheeger M, Bellisle F, Sempé M, Guilloud-Bataille M, Patois E. Adiposity rebound in children: a simple indicator for predicting obesity. *Am. J. Clin. Nutr*. 1984;39:129-135.
8. González-Jimenez E, Montero-Alonso M, Schmidt-Río Valle J. Proteína C reactiva como marcador bioquímico de riesgo cardiovascular. *Nutr. Hosp*. 2013;28:2182-2187. doi:10.3305/nh2013.28.6.6807.
9. Nienaber-Rousseau C, Swanepoel B, Dolman R, Pieters M, Conradie K, Towers W. Interactions between C-reactive protein genotypes with markers of nutritional status in relation to inflammation. *Nutrients*. 2014;11:5034-5050. doi:10.3990/nu6115034.
10. Yousuf O, Mohanty BD, Martin S, Joshi P, Blaha M, Blumental R, Budoff M. High-sensitive c-reactive protein and cardiovascular disease: a resolute belief or an elusive link? *J. Am. Col. Cardiol*. 2013;62:397-408. doi:10.1016/j.jacc.2013.05.016.
11. Soriano-Guillen L, Hernández-García B, Pita J, Domínguez-Garrido N. High-sensitivity C-reactive protein is a good marker of cardiovascular risk in obese and adolescents. *Eur. J. Endocrinol*. 2008;159:R1-R4. doi:10.1530/EJE-08-0212.
12. Klop B, Elte JW, Cabezas MC. Dyslipidemia in obesity: Mechanisms and potential targets. *Nutrients*. 2013;5:1218-1240. doi:10.3390/nu5041218.
13. Huh JY, Park YJ, Ham M, Kim JB. Crosstalk between adipocytes and immune cells in adipose tissue inflammation and metabolic dysregulation in obesity. *Mol. Cells*. 2014;37:365-371. doi:10.14348/molcells.2014.0074.
14. Haro-Acosta M, Ruiz Esparza-Cisneros J, Delgado-Valdez J, Ayala-Figueroa R. Proteína C reactiva ultrasensible, estado nutricional y perfil bioquímico en escolares mexicanos. *Rev. Med. Inst. Mex. Seguro Soc*. 2014;52:398-403.
15. Black S, Kushner I, Samols D. C-reactive protein. *J. Biol. Chem*. 2004;279:48487-48490. doi:10.1074/jbc.R400025200.
16. Salazar J, Martínez M, Chávez M, Toledo A, Añez R, torres Y, Apruzzese V, Silva C, Rojas J, Bermúdez V. C-reactive protein: clinical and epidemiological perspective. *Cardiol. Res. Pract*. 2014;2014:1-10. doi:10.1155/2014/605810.
17. Benozzi S, Perruzza F, Pennacchiotti G. Proteína C reactiva: un marcador bioquímico asociado con el síndrome metabólico y la obesidad abdominal. *Rev. Argent Cardiol*. 2012;80:433-435. doi:10.7775/rac.es.v80.i6.1040.
18. Nanri A, Moore M, Kono S. Impact of C-reactive protein on disease risk and its relation to dietary factors: literature review. *Asian Pac. J. Cancer Prev*. 2007;8:167-177.

19. Zhou LM, Xu JY, Rao CP, Han S, Wan Z, Qin LQ. Effect of whey supplementation on circulating C-reactive protein: A meta-analysis of randomized controlled trials. *Nutrients*. 2015;7:1131-1143. doi:10.3390/nu7021131.
20. Pérez-Morales E, Bacardí-Gascón M, Jiménez-Cruz A. Sugar-sweetened beverage intake before 6 years of age and weight or BMI status among older children; systematic review of prospective studies. *Nutr. Hosp*. 2012;28:47-51. doi:10.3305/nh.2013.28.1.6247.
21. Lo J, Maring B, Chandra M, Daniels SR, Sinaiko A, Daley MF, Sherwood NE, Kharbanda EO, Parker ED, Adams KF, Prineas RJ, Magid DJ, O´Connor PJ, Greenspan LC. Prevalence of obesity and extreme obesity in children aged 3-5 years. *Pediatr. Obes*. 2014;9:167-175. doi:10.111/j.2047-6310.2013.00154.x
22. Baughcum A, Gramling K, Eneli I. Severely obese preschoolers in a tertiary care obesity program: Characteristics and management. *Clin. Pediatr*. 2015;54:346-352. doi:10.1177/000992281455975.