doi: 10.4183/aeb.2018.330

CARDIOVASCULAR RISK FACTORS IN ADOLESCENTS: ROLE OF INSULIN RESISTANCE AND OBESITY

J. Lopez-Sandoval[1], S. Sanchez-Enriquez[2], E.A. Rivera-Leon[2], B.E. Bastidas-Ramirez[2], M.R. Garcia-Garcia[3], M.E. Gonzalez-Hita[2,*]

[1]"Fray Antonio Alcalde" Hospital Civil de Guadalajara, Department of Pediatric Endocrinology, Universidad de Guadalajara Centro Universitario de Ciencias de la Salud, [2]Molecular Biology and Genomics, [3]Health Science, Guadalajara, Jalisco, Mexico

Abstract

Introduction. Childhood obesity is a public health problem characterized by early insulin resistance (IR), inflammation, and oxidative stress. The presence of an uninterrupted low-grade inflammatory state impairs metabolic and cardiovascular health. The population is particularly susceptible to develop metabolic disorders related to increased body fat.

Methods. Eighty-three adolescents were recruited and grouped according to HOMA-IR and BMI in either with or without IR and obese or normal-weight respectively. Anthropometric, biochemical, immunological and hormonal variables were determined. Transverse Analytical Study.

Results. Obesity, dyslipidemia, IL-6, and C-reactive protein were significantly higher in the IR group than in the non-IR group. Obese adolescents showed increased insulin levels, HOMA-IR, inflammatory markers, and triglycerides; while having lower HDL-C, and adiponectin when compared to normal-weight adolescents. As expected, obesity-related anthropometric markers positively correlated with IR and inflammatory markers while negatively correlated with adiponectin levels.

Conclusions. Early IR, subclinical inflammation, dyslipidemia, and hypoadiponectinemia characterize obesity in adolescents. These factors may increase the risk of future coronary heart disease (CHD) and diabetes mellitus development (DM) in early adulthood.

Key words: adolescents, obesity, body fat, cardiovascular risk, adiponectin.

INTRODUCTION

Childhood obesity is a complex multifactorial public health problem (1), where both inherited predisposition and early-life unhealthy behavior are associated with the pathophysiologic process that excess body fat triggers. The effect of the genetic factors on the body fatness remains controversial, while there is consensus on the critical role of the environment as a predisposing factor to obesity and cardiac-related illnesses (2, 3). In 2012, the prevalence of obesity in Mexican children was 14% (5-11 years) and 13.3% among adolescents (12-19 years) (4). Early insulin resistance (IR) seems to be a prominent feature of obesity that promotes chronic systemic inflammation, and increased oxidative stress (OS) (5). IR and chronic inflammation play a major role in the pathogenesis of comorbid conditions associated with obesity such as type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD) (6).

Obesity during childhood is strongly related to adult obesity and thus increases the risk of chronic disease development as obesity, type 2 diabetes mellitus and atherosclerotic cardiovascular disease (7). Early signs and predictors of CHD and T2DM are present in obese young individuals (7, 8). CHD predictors include: IR, hypertension, dyslipidemia, elevated circulating inflammatory molecules, and elevated levels of oxidized low-density lipoprotein (ox-LDL) (9). The association between the factors that promote obesity and cardiovascular risk is not fully understood. New biomarkers that identify cardiovascular risk in adults and adolescent obese patients, such as decreased circulating adiponectin and increased C-reactive protein (CRP) have been recognized (10, 11). Adiponectin is a protein expressed and secreted from adipose tissue; it is a potent regulator of glucose and lipid metabolism with anti-atherogenic and anti-inflammatory properties (12). Adiponectin levels and IR differ significantly among ethnic groups (12). Mexican-Americans present more severe IR with lower adiposity when compared with Caucasians and this is

*Correspondence to: Mercedes Elvira Gonzalez-Hita PhD, Universidad de Guadalajara Centro Universitario de Ciencias de la Salud, Molecular Biology and Genomics, Sierra Mojada 950, Col. Independicencia, Guadalajara, 44340, Mexico, E-mail: mhita@hotmail.com

associated with worse cardiovascular risk profiles (3). In the Mexican adolescent population, there is limited use of biomarkers as cardiovascular risk factors (CVR). The aim of the present study was to assess the relationship between obesity, insulin resistance, inflammation and oxidative stress in adolescents. In the current study, we analyze the association between IR and the circulatory levels of interleukin-6 (IL-6), hs-CRP, adiponectin, and plasma levels of ox-LDL in order to contribute to the understanding of the mechanisms underlying the effect of obesity on cardiovascular outcomes at early stages of life, and to identify early risk factors of atherosclerotic CVD in obese Mexican adolescents

MATERIALS AND METHODS

Subjects

We conducted a cross-sectional study in 83 adolescents (47 boys and 36 girls), aged 10 to 16 years old. At the time of measurements, adolescents showed Tanner stages II or III.

Subjects with diabetes, malnutrition, or under medication affecting blood pressure (BP), glucose, or lipid metabolism were excluded from the study.

Anthropometric parameters

All anthropometric measurements were determined by the same researcher (trained nutritionist). Body weight (kg), height (cm), and waist circumference (WC) (cm) were measured using standard techniques. Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m^2); also, the BMI Z-score was calculated. Body fat percentage (BFP) was obtained by body composition analysis using a bioelectrical impedance scale (TBF-300A-8447 Tanita, Tokyo, Japan). Subjects were divided into two categories according to the presence or absence of IR. Also, adolescents were classified according to BMI in either obese (OB) (n= 39) or normal weight (NW) (n=44). Obesity and NW were defined according to BMI classification of the World Health Organization (WHO), BMI > 95th percentile and BMI< 85th percentile, respectively. Abdominal obesity was defined with WC > 90th percentile (13).

Biochemical variable determination

Blood samples were drawn after an overnight fast. The determination method for each of the measured variables was as follows: Insulin was quantified by immunoradiometric assay (Immunotech Beckman Coulter Company, Brea CA, USA), IL-6 by enzyme-linked immunosorbent assay (ELISA) (Quantizing R&D Systems, USA), hs-CRP by a latex high sensitivity kit (hs-CRP Bio Systems, Barcelona, Spain), total human adiponectin using Acrp 30 ELISA (R&D Systems, Minneapolis MN, USA), ox-LDL by ELISA (Cat. No. BI-20042 Biomedica Gruppe, Vienna, Austria), fasting plasma glucose (FPG), triglycerides, total cholesterol, cholesterol bound to low density lipoproteins (LDL-C), and high density lipoproteins (HDL-C) were determined by dry chemistry (Vitros). The homeostatic model assessment for IR (HOMA-IR) was calculated as the concentration of fasting insulin (μU/mL) multiplied by the concentration of fasting glucose (mmol/L), divided by 22.5. HOMA values >3.16 were considered as IR (14).

Ethical considerations

All children and their parents provided written informed consent. The study was approved by the Ethics Committees of all participating institutions, and it complied with the Declaration of Helsinki (Fortaleza, Br. 2013 revised), following the Good Clinical Practice recommendations of the CEE (Document 111/3976/88 July 1990) and the legal Enforce Spanish Regulation, which all regulate clinical investigations in human subjects (RD 223/04 about Clinical Assays).

Statistical analysis

Two-sided Student's t test for independent samples was used for the comparison of means between groups. Mann-Whitney U test was used for non-parametric variables. Difference between the expected and observed frequencies was calculated using the Chi-square test (X^2). Pearson correlation analysis was used to evaluate the association between anthropometric and biochemical variables. P values <0.05 were considered statistically significant.

RESULTS

Demographic, anthropometric, and biochemical variables from the 83 adolescents grouped by IR status are shown in Table 1. The mean age of all participants was 11.8 ± 1.3 years, no sex differences in anthropometric and biochemical parameters were found. The mean, standard deviation and p values for girls and boys, respectively are as follows: IL-6 (1.59 ± 0.97 ng/mL *vs.* 1.43 ± 1.64 ng/mL; p =0.602), ox-LDL (1.39 ± 0.47 mg/dL *vs.* 1.25 ± 0.37 mg/dL; p=0.139), Adiponectin (4.93 ± 2.1 μg/mL *vs.* 4.90 ± 3.15 μg/mL; p =0.958). The prevalence of IR was 43%. Adolescents

Table 1. Demographic, anthropometric, and biochemical characteristics in adolescents according to insulin resistance

Variable	IR (-) n = 47	IR (+) n = 36	*p* Value
Age (years)	11.5 ± 1.78	12.18 ± 1.95	0.114
BMI (kg/m^2)	20.6 ± 5.3	28.7 ± 6.3	**0.0001**
BMI Z-score	0.38 ± 1.45	2.65 ± 1.78	**0.0001**
Body weight (kg)	43.7 ± 13	77.7± 22	**0.0001**
Body fat (%)	25.6 ± 10.9	40.17 ± 8.33	**0.0001**
WC (cm)	74.1 ± 14.6	89.2 ± 11.9	**0.0001**
Glucose (mg/dL)	88.7 ± 8.09	87.03 ± 9.2	0.379
Insulin (µU/mL)	9.42 ± 5.54	23.7 ± 14.9	**0.0001**
HOMA-IR	2.06 ± 1.24	7.23 ± 7.63	**0.0001**
Triglycerides (mg/dL)	84.2 ± 34.7	123.4 ± 55.3	**0.0001**
Cholesterol (mg/dL)	161.7 ± 27.3	163.1 ± 33.6	0.832
HDLC (mg/dL)	47.05 ± 11.4	40.4 ± 9.18	**0.006**
LDLC (mg/dL)	101.2 ± 26.5	112.5 ± 28.8	0.072
Hs-CRP (mg/L)	0.969 ± 2.04	2.93 ± 3.04	**0.001**
IL-6 (ng/ml)	1.23 ± 1.32	2.30 ± 3.11	**0.046**
Ox-LDL (mg/dL)	1.33 ± 0.39	1.29 ± 0.46	0.699
Adiponectin (µg/mL)	5.19 ± 2.87	4.19 ± 1.96	0.730

Values are means ± SD. Comparisons were performed with t test for independent samples and U de Mann Whitney between groups. IR (-): no insulin resistance; IR (+): insulin resistance; BMI: body mass index; WC: waist circumference; HOMAR-IR: Homeostasis Model Assessment for insulin resistance; HDL- c: high-density lipoprotein; LDL- c: low-density lipoprotein; Hs-CRP: high sensitive C reactive protein; IL-6: Interleukin 6; ox-LDL: Oxidized low density lipoproteins.

Table 2. Anthropometric, clinical, and biochemical characteristics of the studied sample of adolescents grouped by nutritional status

	Normal weight n = 44	Obese n = 39	*p* value
Age (years)	11.5 ± 1.78	12.18 ± 1.95	0.114
Weight (kg)	43.7 ± 13.3	77.7 ± 22.1	0.000*
Height (cm)	150.4 ± 14.1	154.9 ± 19.3	0.231
BMI (kg/m^2)	18.8 ± 3.10	30.06 ± 5.27	0.000*
BMI Z-score	-0.091 ± 0.86	3.01 ± 1.46	0.000*
Body fat (%)	22.5 ± 8.5	42.4 ± 4.8	0.000*
WC (cm)	69.1 ± 8.1	93.6 ± 10.6	0.000*
Glucose (mg/dL)	88.7 ± 8.09	87.03 ± 9.2	0.379
HOMA-IR	2.0 ± 1.24	7.3 ± 7.63	0.000*
TG (mg/dL)	88.7 ± 36.4	115.6 ±56.6	0.013*
Cholesterol (mg/dL)	160.7 ± 29.1	164.07 ±31.4	0.626
HDL-C (mg/dL)	46.8 ± 10.7	41.15 ±10.4	0.018*
LDL-C (mg/dL)	101.2 ± 26.5	112.5 ±28.8	0.072
Hs-CRP (mg/L)	0.245± 0.5	3.42 ± 3.06	0.000*
IL-6 (ng/mL)	1.14 ± 1.24	2.30 ± 3.02	0.030*
Ox-LDL (mg/dL)	1.38 ± 0.33	1.23 ± 0.49	0.097
Adiponectin (µg/mL)	5.69 ± 2.78	3.73 ±1.8	0.001*

Values are means ± SD. Comparisons were performed with t test for independent samples and U de Mann Whitney between groups. BMI: body mass index; WC: waist circumference; HOMA-IR: Homeostasis Model Assessment for insulin resistance; HDL- c: high-density lipoprotein; LDL- c: low-density lipoprotein; Hs-CRP: high sensitive C reactive protein; IL-6: Interleukin 6; ox-LDL: Oxidized low density lipoproteins. *p value statistical significance.

with IR presented higher anthropometric parameters of adiposity, as well as increased plasma levels of inflammatory cytokines (IL-6 and hs-CRP), and lower plasma level of adiponectin when compared to non-IR individuals. In the same way, the lipid alteration profile in the IR group was with high levels of plasma triglycerides and low levels of HDL-C.

Both IR and non-IR groups were similar in age, height and gender distribution. Body weight, BFP, and WC were significantly higher in the IR group than in the non-IR group (77.7 ± 22 kg *vs.* 43.7 ± 13 kg, $p < 0.001$; 40.17 ± 8.33% *vs.* 25.6 ± 10. 9%, $p < 0.001$; and 89.2 ± 11.9 cm *vs.* 74.1 ± 14.6 cm, $p < 0.001$, respectively). The prevalence of abdominal obesity was 75% in the IR group *vs.* 23% in the non-IR group. Both groups had normal levels of FPG. There were non-significant differences between groups when analyzing total cholesterol and LDL-C. However, plasma TG levels were significantly higher and HDL-C levels significantly lower in the IR group compared

to the non-IR. Regarding the inflammatory variables, adolescents with IR exhibited significantly higher plasma IL-6 levels (2.30 ± 3.11 ng/mL *vs.* 1.23 ± 1.32 ng/mL, p = 0.046), and hs-CRP (2.93 ± 3.04 mg/L *vs.* 0.969 ± 2.04 mg/L, p = 0.001) when compared to the non-IR group. Plasma levels of adiponectin seemed decreased in the IR group while the levels of ox-LDL were slightly higher in the same group; nonetheless, no significant differences were found when comparing to non-IR subjects.

According to BMI, 47% (n = 39) of the subjects were classified as obese. Table 2 shows that obese adolescents displayed significantly elevated mean insulin (p<0.0001), HOMA-IR (p<0.0001), TG (p=0.013), IL-6(p=0.030) and hs-CRP (p<0.0001) levels when compared to normal weight individuals. FPG, total cholesterol, LDL-C, and ox-LDL were not different between groups. Obese adolescents showed significantly lower plasma adiponectin than normal weight adolescents (3.73 ± 1.8 µg/mL *vs.* 5.69 ±2.78 µg/mL; p= 0.001). The most frequent metabolic alterations observed in the obese adolescents were low plasma adiponectin concentrations (75%), IR (72%), low HDL-C (50%), hypercholesterolemia (38%), and hypertriglyceridemia (25%).

Figure 1 shows the association between anthropometric measurements (BMI-Z score, and WC), and biochemical variables (HOMA-IR, IL-6, adiponectin, and triglycerides). A significant positive correlation between the parameters of adiposity and IR was observed. BMI-Z score was positively correlated with HOMA-IR index (r = 0.551, p < 0.0001) (Fig. 1A). Similarly, WC was positively correlated to HOMA-IR (r = 0.434, p < 0.0001) (Fig. 1B). WC, correlated significantly with plasma IL-6 (r = 0.4178, p = 0.001) (Fig. 1C). On the other hand, a significant inverse association was found between serum concentrations of adiponectin and WC (r = -0.393, p < 0.0001) (Fig. 1D). HOMA-IR was inversely associated with adiponectin (r = - 0.246, p = 0.013) (Fig. 1E), and directly related to plasma TG (r = 0.366, p = 0.009). Finally, significant associations between BMI, WC and hs-CRP, or ox-LDL, were not found.

DISCUSSION

Pediatric obesity is a major public health problem in Mexico. Mexicans are susceptible to develop obesity and T2DM, particularly if they live in an adverse environment (15). Many of the changes leading to obesity start *in-utero* or at a very early age, and studies acknowledge the first 5 years of life as relevant in establishing the course of obesity over the years that will follow (16). Information regarding obesity and its relationship to adipokines and markers of CVR in Mexican adolescents is still limited. In the present study we have found that obese Mexican adolescents, even though not severely obese, do present metabolic alterations such as IR, subclinical inflammation, dyslipidemia, and low plasma adiponectin levels. These adolescents might be at high risk of developing other chronic diseases mainly CHD and T2DM. We consider that low plasma adiponectin and high hs-CRP are biomarkers to identify obese Mexican adolescents at risk to become obese adults that will potentially suffer from metabolic or cardiovascular diseases.

Our results are consistent with previous findings in other Mexican pediatric groups, in obese Mexican-American children, as well as in other ethnic population (17-19). We found that fasting insulin and HOMA-IR, both markers of IR, are significantly associated with anthropometric parameters of excess body fat, such as BMI-Z score, BFP, and WC. WC is a marker of intra-abdominal visceral adipose tissue (VAT), and an independent risk factor for CHD. According to WC, in the present study, 82% of the obese adolescents showed visceral obesity. Excessive VAT has been associated with IR, dyslipidemia, hypertension, atherosclerosis, and nonalcoholic fatty liver disease (7, 17). Thus, the increase in VAT in obese Mexican adolescents may explain most of the metabolic alterations observed.

Adipocyte hypertrophy is linked to increased inflammation in adipose tissue of obese children (18). This provides evidence that obesity-associated adipose tissue dysfunction develops in early childhood and is related to IR due to production of free fatty acids (FFA), hs-CRP, and inflammatory cytokines (20). Systemic inflammation in obesity is originated by the increased expression and secretion of IL-6, TNFα, and monocyte chemoattractant protein 1 (MCP-1) from adipocytes; this in turn generates inflammatory infiltration of the adipose tissue by chemoattracting monocytes and macrophages (21). In our study, obese adolescents with IR clearly presented subclinical systemic inflammation by showing IL-6 levels almost two times higher than non-IR adolescents (see Table 1). Also, IL-6 was positively associated with all adiposity indicators. These findings are consistent with a basal inflammatory state in the group of Mexican obese adolescents.

Longitudinal studies have demonstrated that pediatric obesity and the metabolic abnormalities displayed by obese children persist over time and

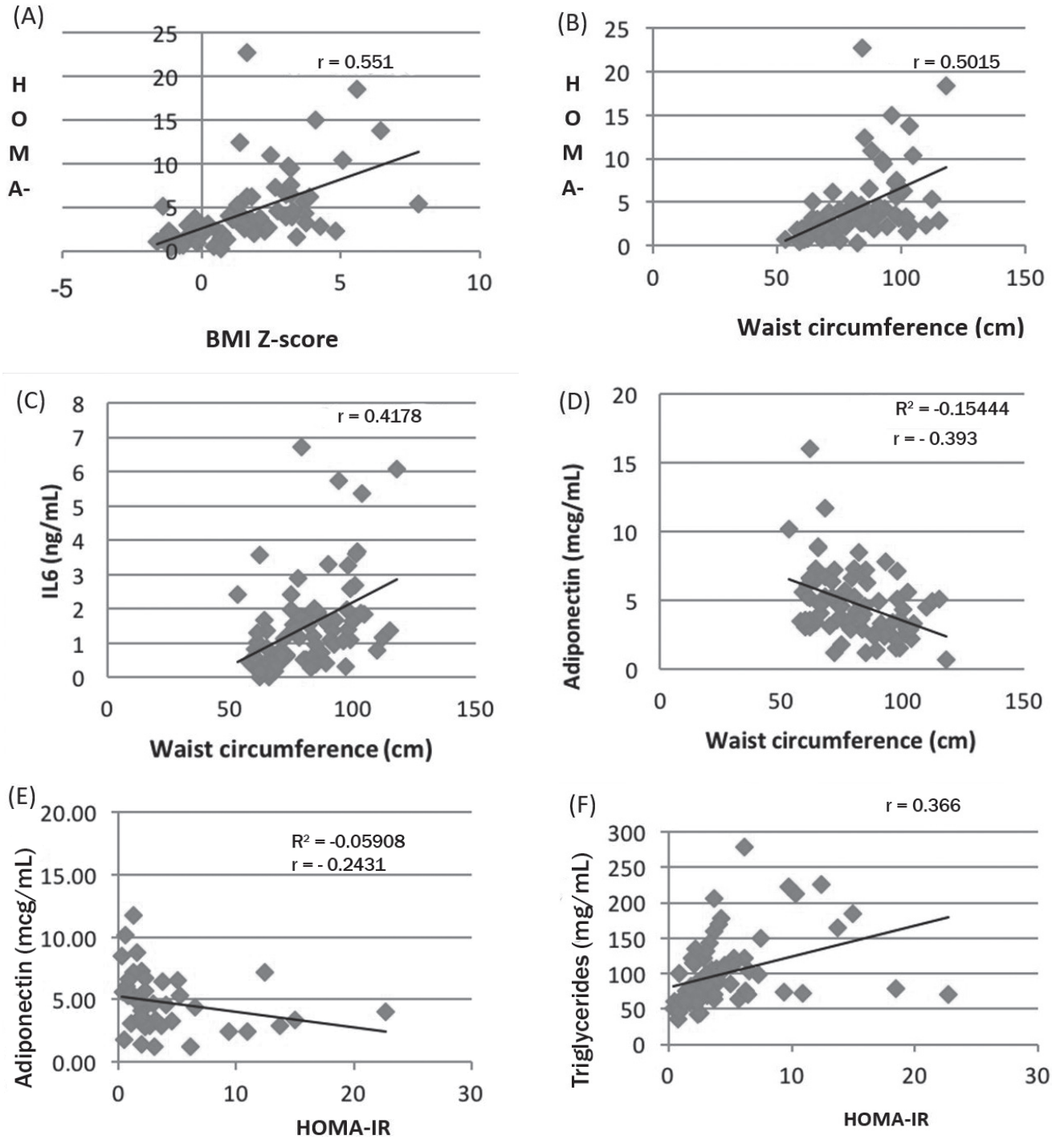

Figure 1. Correlations between BMI Z-score and HOMA-IR (r =0.551, p =0.000) (A), waist circumference (WC) and HOMA-IR (r = 0.5015, p = 0.000) (B), WC and interleukin 6 (IL6, r = 0.4178; p = 0.01) (C), WC and adiponectin (r = - 0.393; p = 0.000) (D), HOMA-IR and adiponectin (r = - 0.2431; p = 0.013) (E), HOMA-IR and serum triglycerides (r = 0.366, p = 0.009) (F) in obese adolescents (n= 83).

may worsen through adulthood (22). Inflammation accompanies obesity as well, leading to endothelial damage (22). Hs-CRP is an extensively studied acute phase reactant known to be a sensitive marker for systemic inflammation and an independent predictor factor of future cardiovascular events (11). Additionally, the relevance of hs-CRP as a CVR equals that of the metabolic syndrome-associated dyslipidemia (23,24). In the present study, besides the elevation of plasma IL-6; obese adolescents with IR showed a significantly increased serum hs-CRP concentration, three times higher than the non-IR group (see Table 1). IL-6 and TNFα increase the synthesis of hs-CRP in the liver and adipocytes (25). Thus, in our study, elevated levels of

serum hs-CRP in IR obese adolescents could be explained in part by the increase in plasma IL-6 concentration. Considering the significant elevation of hs-CRP in adolescents with IR and its known role as a risk factor for the development of CVD and T2DM, Mexican obese adolescents with this biochemical abnormality are at risk of CVD and endocrine diseases development as compared to those not exhibiting these alterations.

In addition to inflammation, low plasma adiponectin concentration was another important obesity-related alteration found in our sample. There is evidence of an inverse association of adiponectin levels with metabolic alterations, vascular inflammatory changes, adiposity, and fasting plasma insulin in obese children and adolescents (26-28). Adiponectin is a product of the ADIPOQ gene that is highly expressed in adipose tissue, and has potent anti-inflammatory effects on endothelial cells (12). Furthermore, adiponectin is an endogenous hormone that increases insulin sensitivity (29). Plasma adiponectin concentration and its mRNA expression decrease significantly in obese subjects (29). This is due, at least in part, to an inhibition of adiponectin gene expression originated by elevation of IL-6 and TNFα (30). In our study, the findings of elevated IL-6 in the obese group are consistent with lower serum adiponectin concentrations. We observed that adiponectin inversely correlates with anthropometric markers of excess body fat. In our sample, we found a stronger correlation between adiponectin levels and WC than with HOMA-IR. This is consistent with previous findings that postulate hypoadiponectinemia as a consequence of obesity in childhood and that adiponectin has no independent effect on markers of IR in young individuals. Stefan N *et al.* (12), found in 10-year-old Pima Indian children that BFP but not fasting plasma insulin was independently associated with fasting plasma adiponectin concentrations. Punthakee *et al.* (31) reported similar results in French Canadian children aged 9-16 years, supporting that total fat mass is the major determinant of adiponectin concentrations in growing youth. It has been reported that hypoadiponectinemia may result in metabolic syndrome (32); on the other hand, high adiponectin plasma concentrations predict lower prevalence of T2DM independently of BMI in Mexican children (32). Our data supports that low plasma adiponectin concentration is a consequence of obesity. We consider low adiponectin plasma concentration as a useful biomarker for predicting the development of cardiovascular diseases. Although the relationship between hypoadiponectinemia and CVD remains unclear, research has linked both entities trough molecular pathways. It has been postulated that adiponectin has anti-inflammatory and anti-atherogenic effects through activation of the AMP–activated protein kinase (AMPK), the peroxisome proliferator-activated receptor (PPAR) and the p38 mitogen-activated protein kinase (MAPK) signaling pathways. In addition, adiponectin appears to be protective against endothelial dysfunction, plaque formation, and thrombosis on the vascular endothelium (33,34). In this regard, hypoadiponectinemia may be a factor related to the development of CVD in obese subjects. Thus, adiponectin might serve as a useful biomarker for CVD. However, more epidemiological research is needed.

Several reports demonstrate that obese children have abnormal lipid profiles (36). In addition, it has been reported that 40% to 55% of children with elevated lipid levels continued with this alteration up to 15 years later (35). In our study, the main lipid alterations exhibited in obese IR-adolescents were low levels of HDL-C (50%), hypercholesterolemia (40%), and hypertriglyceridemia (25%). Also, a significant positive association between IR and plasma TG (Fig. 1F) was appreciated. The dyslipidemia found in a high percentage of the group of obese Mexican adolescents plays a role in the development of CVD, the leading cause of death in Mexican population (37). In the present study, no significant differences were found in serum levels of total cholesterol and LDL-C between groups. These results agree with those obtained by Pinhas-Hamiel *et al.* (38) in a cross-sectional study of 181 obese children and adolescents divided into <12 years and those ≥12 years. The authors observed that subjects 12 years of age or older had lower total cholesterol and LDL-C levels than <12 years. The authors found that age and advancing sexual maturity rating were inversely correlated to total colesterol, LDL-C and HDL-C These results are explained in part by the action of the sex hormones released during puberty.

Childhood obesity is not only associated with metabolic alterations, but also increased body mass modifies the growth patterns in children of both genders. Emandi AC *et al.* evaluated how body mass is related to height gain in Romanian children of 7-18 years. The authors found that increased BMI originates taller boys at an early age, also obese girls show an early growth spurt at younger age compared with normal BMI girls. These changes may affect not only growth but also development and maturation processes (39).

Increased oxidation is another complication in the pathological process associated with obesity. Oxidative stress (OS) is explained in part by the increased oxidation of free fatty acids derived from adipose cells with excessive fat accumulation (37). OS promotes metabolic consequences, dysregulation of cytokines, and IR, being both a cause and a consequence of adipose tissue dysfunction (38, 40, 41). Ox-LDL is a novel biomarker of OS that has been used in the study of obesity-related complications in children and in adults (9). In the current study, however, levels of ox-LDL were similar between IR obese adolescents and non-IR adolescents. This result could be explained in part by the fact that both groups have normal plasma levels of LDL-C. Also ox-LDL might not be a sensible biomarker of OS in this group of subjects.

We consider that our study may contribute to improve the clinical management of these potentially future patients, as well as to the development of guidelines for the Mexican population. However, it was conducted with a small sample of individuals selected by convenience, which do not necessarily represent the entire population of Mexican adolescents. A higher group of patients should be analyzed in order to be able to establish a causal relationship.

The main limitations of the present study are: the non-probabilistic sampling and the small sample size that were used. Another limitation is the cross-sectional design of the study, which does not allow to establish causal relationships between the variables. Therefore, it is important that in future studies a longitudinal design be used in order to establish a cause-effect relationship.

The study population was obtained from a public hospital outpatients sample which may represent a bias in the characteristics of obese adolescents, a possible source of error.

The novelty of our study is the detection of cardiovascular risk factors in obese Mexican adolescents, such as elevation of levels of hs-CRP and IL-6 associated to IR; and the presence of hypoadiponectinemia associated with increase in visceral fat. The search and early detection of these alterations could be useful in clinical treatment in order to monitor and prevent CHD in the young adult.

In conclusion, our group of Mexican adolescents exhibit abdominal obesity associated to a high metabolic risk profile represented by IR, increased TG levels, low HDL-C, elevated hs-CRP and a IL-6; that is why our young population may be susceptible to develop early metabolic alterations related to increased body fat and in the long term, to have a high risk to develop clinical alterations such as hypertension, and other related cardiac diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Global Strategy on Diet, Physical Activity and Health: Childhood overweight and obesity. 2011. World Health Organization. (Accessed November 19th, 2011, at site : http://www.who.int/dietphysicalactivity/childhood/es/)

2. Butte NF, Cai G, Cole SA, and Comuzzie AG. Viva la Familia Study: genetic and environmental contributions to childhood obesity and its comorbidities in the Hispanic population. Am J Clin Nutr 2006; 84:646-654.

3. Mansur M, Nassef YE, Abu Shady M, Aziz AA, El Malt HA. Metabolic syndrome and cardiovascular risk factors in obese adolescent. J Med Sci. 2016; 1:118-121.

4. Instituto Nacional de Salud Pública. Encuesta Nacional de Salud y Nutrición 2012. Resultados Nacionales. 2012. Available in: http//ensanut.insp.mx/informes/ENSANUT2012Resultados. [Links].

5. Pires A, Martins P, Pereira AM, Silva PV, Marinho J, Marques M, Castela E, Sena C, Seiça R. Insulin Resistance, Dyslipidemia and cardiovascular changes in a group of obese children. Arq Bras Cardiol. 2015; 104: 266-273.

6. Sinaiko AR, Steinberger J, Moran A, Prineas RJ, Vessby B, Basu S, Tracy R, Jacobs DR Jr. Relation of body mass index and insulin resistance to cardiovascular risk factors, inflammatory factors, and oxidative stress during adolescence. Circulation. 2005; 111:1985-1991.

7. Caballero E, Bousquet-Santos K, Robles-Osorio L, Montagnani V, Soodini G, Porramatikul S, Hamdy O, Nobrega ACL, and Horton ES. Overweight Latino Children and Adolescents have Marked Endothelial Dysfunction and Subclinical Vascular Inflammation in Association with excess body fat and insulin resistance. Diabetes Care 2008:31; 576-582.

8. Breslin WL, Johnston CA, Strohacker K, Carpenter KC, Davidson TR, Moreno JP, Foreyt JP, and McFarlin BK. Obese Mexican American Children Have Elevated MCP-1, TNF-a, Monocyte Concentration, and Dyslipidemia. Pediatrics 2012; 129:e1180–e1186.

9. Norris AL, Steinberger J, Steffen LM, Metzig AM, Schwarzenberg SJ, Kelly AS. Circulating oxidized LDL and inflammation in extreme pediatric obesity. Obesity (Silver Spring). 2011; 19:1415–1419.

10. Alikaşifoğlu A, Gönç N, Özön ZA, Sen Y, Kandemir N. The Relationship between Serum Adiponectin, Tumor Necrosis Factor-Alpha, Leptin Levels and Insulin Sensitivity in Childhood and Adolescent Obesity: Adiponectin is a Marker of Metabolic Syndrome. J Clin Res Ped Endo 2009; 1(5):233-239.

11. Kelishadi R, Sharifi M, Khosravi A, and Adeli K. Relationship between C - reactive protein and Atherosclerotic Risk factors and Oxidative Stress Markers among Young Persons 10-18 Years Old. Clinical Chem 2007; 53:456-464.

12. Stefan N, Bunt JC, Salbe AD, Funahashi T, Matsuzawa Y, Tataranni PA. Plasma Adiponectin Concentrations in Children: Relationships with Obesity and Insulinemia. J Clin Endocrinol Metab 2002 87(10):4652–4656.

13. Must A, Dallal GE, Dietz WH. Reference data from obesity: 85th and 95th percentiles of body mass index and Triceps skinfold thickness. Am J Clin Nutr 1991; 53: 839-846.

14. Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis Model Assessment is more reliable than the fasting Glucose/Insulin Ratio and Quantitative Insulin Sensitivity Check index for Assessing Insulin Resistance among Obese Children and Adolescents. Pediatrics 2005; 115; 500.
15. Esparza-Romero J, Valencia ME, Urquidez-Romero R, Chaudhari LS, Hanson RL, Knowler WC, Ravussin E, Bennett PH, and Schulz LO. Environmentally Driven Increases in Type 2 Diabetes and Obesity in Pima Indians and Non-Pimas in Mexico over a 15-Year Period: The Maycoba Project. Diabetes Care 2015; 38:2075–2082.
16. Cunningham SA, Kramer MR, and Venkat Narayan KM. The incidence of obesity between the ages of 5 and 14 years was 4 times as high among children who had been overweight at the age of 5 years as among children who had a normal weight at that age. N Engl J Med 2014; 370:403-411.
17. Balas-Nakash M, Perichart-Perera O, Benitez-Arcienega A, Tolentino-Dolores M, Mier-Cabrera J, Vadillo-Ortega F. [Association between adiposity, inflammation and cardiovascular risk factors in a group of Mexican students]. Gaceta Medica de Mexico 2013; 149:196-203.
18. Sbarti A, Osculati F, Silvagni D, Benati D, Galie M, Camoglio FS, Rigotti G, Maffei C. Obesity and inflammation: Evidence for an elementary lesion. Pediatrics 2006; 117 (1): 220-223.
19. Sourani M, Kakleas K, Critselis E, Tsentidis C, Galli-Tsinopoulou A, Dimoula M, Kotsani E, Armaou M, Sdogou T, Karayianni C, Baltaretsou E, Karavanaki K. Cross-Sectional Study on Childhood Obesity and Central Obesity on A Rural Greek Island. Acta Endocrinologica-Bucharest 2015; 11(3):329-336.
20. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 444:860-867.
21. Kintscher U, Hartge M, Hess K, Foryst-Ludwig A, Clemenz M, Wabitsch M, Fischer-Posovszky P, Barth TF, Dragun D, Skurk T, Hauner H, Blüher M, Unger T, Wolf AM, Knippschild U, Hombach V, Marx N. T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. Arterioscler Thromb Vasc Biol. 2008; 28(7):1304–1310.
22. Toprak D, Toprak A, Chen W, Xu JH, Srinivasan S, Berenson GS. Adiposity in childhood is related to C-reactive protein and adiponectin in young adulthood: from the Bogalusa Heart Study. Obesity (Silver Spring). 2011; 19:185–190.
23. Ridker PM. Clinical Application of C - reactive protein for Cardiovascular Disease Detection and Prevention. Circulation. 2003; 107:363-369.
24. Michalsky MP, Inge TH, Simmons M, Jenkins TM, Buncher R, Helmrath M, Brandt ML, Harmon CM, Courcoulas A, Chen M, Horlick M, Daniels SR, Urbina EM; Teen-LABS Consortium. Cardiovascular risk factors in severely obese adoslescents: The teen longitudinal assessment of bariatric surgery (Teen-LABS) study. JAMA Pediatr. 2015;169:438-444.
25. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction, a potential role for cytokines originating from adipose tissue. Arterioscler Thromb Vas Biol 1999; 19:972-978.
26. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999; 257:79-83.
27. Asayama K, Hayashibe H, Dobashi K, Uchida N, Nakane T, Kodera K, Shirahata A, Taniyama M. Decrease in serum adiponectin level due to obesity and visceral fat accumulation in children. Obes Res 2003; 11: 1072–1079.
28. Valle M, Martos R, Gascon F, Cenete R, Zfra MA, Morales R. Low grade systemic inflammation, hypoadiponectinemia and concentration of leptin are present in very young obese children and correlate with metabolic syndrome. Diabetes Metab 2005; 31:55-62.
29. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Khan BB, Kadowaki T, Adiponectin stimulates glucose utilization and fatty acid oxidation by activating AMP-activated protein kinase. Nat Med 2002; 8:1288-1295.
30. Alikasifoglu A, Gonc N, Ozon ZA, Sen Y, Kandemir N. The Relationship between Serum Adiponectin, Tumor Necrosis Factor-Alpha, Leptin Levels and Insulin Sensitivity in Childhood and Adolescent Obesity: Adiponectin is a Marker of Metabolic Syndrome. J Clin Res Ped Endo 2009; 1(5):233-239.
31. Punthakee Z, Delvin EE, O'Loughlin J , Paradis G, Levy E, Platt WR, and Lambert M. Adiponectin, Adiposity, and Insulin Resistance in Children and Adolescents. J Clin Endocrinol Metab 91(6):2119–2125, 2006.
32. Cruz M, Garcia-Macedo R, Garcio-Valerio Y, Gutierrez M, Medina-Navarro R, Duran G, Wacher N, Kumate J. Low adiponectin levels predict type 2 diabetes in Mexican children. Diabetes Care 2004; 27:1451-1453.
33. Szmitko, PE, Teoh H, Stewart DJ, and Verma S. Adiponectin and cardiovascular disease: state of the art? American Journal of Physiology-Heart and Circulatory Physiology,2007; 292(4), H1655-H1663.
34. Lau WB, Ohashi K, Wang Y, Ogawa H, Murohara T, Ma X L, and Ouchi N. Role of Adipokines in Cardiovascular Disease. Circulation Journal, 2017; 81(7), 920-928.
35. Haney EM, Huffman LH, Bougatsos C, Freeman M, Fu R, Steiner RD, Helfand M, Nelson HD.[Internet] Screening for Dyslipidemia in children and Adolescents: Systematic evidence Synthesis. Rockville (MD): Agency for Healthcare Research and Quality (US); 2007 Jul. Report No.: 07-0598-EF-1.U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews.
36. Gishti O, Gaillard R, Durmus B, Abrahamse M, van der Beek EM, Hofman A, Franco OH, de Jonge LL, Jaddoe VW. Body mass index, total and abdominal fat distribution and cardiovascular risk factors in school-age children. Pediatric Research. 2015; 77:710-718.
37. Del Río-Navarro BE, Velázquez-Monroy O, Sánchez-Castillo CP, Lara-Esqueda A, Berber A, Fanghänel G, Violante R, Tapia-Conyer R, James WP; [National Health Survey 2000]. Working Group, National Health Survey 2000. The high prevalence of overweight and obesity in Mexican children. Obesity Research 2004; 12:215-223.
38. Pinhas-Hamiel O, Lerner-Geva L, Copperman NM, and Jacobson MS. Lipid and Insulin Levels in Obese Children Changes with Age and Puberty. Obesity. 2007; 15(11): 2825-2831.
39. Emandi A, Gafencu M, Pienar C, Puiu M. Impact of Increased Body Mass on Growth Patterns in School Children. Acta Endocrinologica-Bucharest 2012; 8(4):551-563.
40. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. Eur J Clin Invest 2002; 32(Suppl. 3):14–23.
41. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M, Shimomura I. Increased oxidative stress in obesity and its impact in metabolic syndrome. J Clin invest 2004; 114:1752-1761.