Serum concentrations of adiponectin and ultrasensitive C-REACTIVE PROTEIN in obese adolescents

Concentraciones séricas de adiponectina y proteína C REACTIVA ultrasensible en adolescentes obesos

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Abstract

Introduction: adiponectin is a cytokine secreted into the adipocytes, which produces an anti-inflammatory effect in metabolism. **Objective**: to determine the serum concentrations of adiponectin and ultrasensitive C-reactive protein (hs-CRP) in adolescents and their relationship with anthropometric variables. **Subjects and methods:** This no experimental descriptive, cross-sectional study and non-experimental, in 250 obese adolescents and a control group, in the period from April 2020 to April 2021, Ambato-Ecuador. Anthropometric evaluation was performed with: weight, height, body mass index (BMI) and waist circumference (WC). Serum concentrations of adiponectin and hs-CRP were determined by ELISA. In the statistical analysis, the following were used: Student's t-test, Pearson's correlation and linear regression models, taking 95% as the statistical reliability index and p<0.05 as statistical significance. **Results**: obese male adolescents presented greater anthropometric and laboratory changes with a significant difference in weight: 76.73±8.4 kg, BMI 32.08±3.3 kg/m2 and WC: 101.7±4.6 cm, adiponectin concentrations with a significant negative correlation with BMI (r=-0.949, p<0.001) and WC (r=-0.958, p<0.001). Also, a significant positive correlation in the elevation of hs-CRP in relation to BMI (r=0.931, p <0.001) and WC (r=0.929, p<0.001). The linear regression model (R2) was 0.94, indicating that BMI and WC have a great effect on adiponectin and hs-CRP concentrations, contributing significantly (p=0.001) as predictors of serum concentrations. **Conclusion**: Hypoadiponectinemia and increased hs-CRP are metabolic biomarkers that correlate significantly with BMI and WC in obese adolescents.

Keywords: adiponectin, C-reactive protein, adolescents, obesity.

Resumen

Introducción: la adiponectina es una citocina secretada en los adipocitos que produce un efecto antiinflamatorio en el metabolismo. **Objetivo**: determinar las concentraciones séricas de adiponectina y proteína C reactiva ultrasensible (PCR-us) en adolescentes y su relación con variables antropométricas. **Sujeto y métodos:** Estudio descriptivo, transversal y no experimental en 250 adolescentes obesos y un grupo control, en el periodo de abril de 2020 a abril de 2021, Ambato-Ecuador. La evaluación antropométrica se realizó con: peso, talla, índice de masa corporal (IMC) y circunferencia de cintura (CC). Las concentraciones séricas de adiponectina y PCR-us se determinaron mediante ELISA. En el análisis estadístico se utilizaron: prueba T de Student, correlación de Pearson y modelos de regresión lineal, tomando el 95% como índice de confiabilidad estadística y p<0,05 como significancia estadística. **Resultados**: los adolescentes obesos del sexo masculino presentaron mayores alteraciones antropométricas y de laboratorio con una diferencia significativa en: peso:76.73±8.4 kg, IMC 32,08±3,3 kg/m^2 y CC: 101,7±4,6 cm, concentraciones de adiponectina con una correlación negativa significativa con el IMC (r=-0,949, p<0,001) y la CC (r =-0,958, p<0,001); también una correlación positiva significativa en la elevación de PCR-us en relación con el IMC (r=0,931, p <0,001) y la CC (r=0,929, p<0,001). El modelo de regresión lineal (R^2) fue 0.94 señalando que el IMC y la CC tienen un gran efecto sobre las concentraciones de adiponectina y PCR-us, contribuyendo significativamente (p=0,001) como predictores de las concentraciones séricas. **Conclusión**: La hipoadiponectinemia y el aumento de PCR-us son biomarcadores metabólicos que se correlacionan significativamente con el IMC y la CC en adolescentes obesos.

Palabras clave: adiponectina, proteína C reactiva, adolescentes, obesidad

Introduction

According to the World Health Organization (WHO), in recent decades, the prevalence of obesityand its metabolic complications have considerably increased in adults and infants. This tendency indicates that obesity could affect 60% of the adult world population by the year 2030[1]. Similarly, in the last fifty years, childhood obesity has risen by approximately 5% per decade, and has been causing overweight or obesity in almost a quarter of the children on the planet. This increase in pediatric adiposity has created a relevant public health problem[2]. There are comorbidities such as dyslipidemia, hypertension, glucose intolerance, and hepatic steatosis. In the long run, these overweight children may become obese adults with an increased risk to present some cardiovascular diseases[3].

The role of adipose tissue goes beyond the simple storage of lipids and energy supply when it mobilizes free fatty acids during fasting[4]. It is a complex endocrine organ characterized by the adipokines secretion, which is a key modulator of the storage of visceral and subcutaneous adipose tissues[5]. Serum levels of adipokines are mainly influenced by obesity. They are products of adipose tissue expansion through adipocyte hypertrophy and infiltration of macrophages predominantly of visceral adipose tissues. These unleash an imbalance in the synthesis of proinflammatory/anti-inflammatory adipokines, with a decrease in anti-inflammatory adipokines: adiponectin and omentin-1, causing a low-grade chronic inflammation that determines the fundamental mechanism in obesity[6].

Adiponectin preferentially promotes the storage of fat in adipocytes of the subcutaneous adipose tissue, instead of visceral or ectopic adipose tissue in the liver. Circulating levels of adiponectin and infiltration of macrophages in adipose tissue are among the most potent clinical predictors for insulin sensitivity in obese individuals[7].

Obesity is associated with increased concentrations of circulating proinflammatory cytokines andproteins of the acute phase such as C-reactive protein (CRP), with a decrease in adiponectin[8]. Apositive association between BMI and CRP has been observed in adults and children. The mechanisms by which obesity leads to elevated CRP have not been fully clarified, but it has been established that C-reactive protein is a sensitive marker of systemic inflammation produced mainly by the liver under the stimulation of proinflammatory cytokines derived from adipocytes[9].

Most of the research completed on low-grade chronic inflammation of obesity and adiponectin comes from a population of adults. For this reason, this study aims to determine the concentrations of adiponectin and ultrasensitive C-reactive protein (hs-CRP) and how these relate to some anthropometric variables in adolescents.

Subjects and methods

This no experimental, cross-sectional and descriptive study included 350 adolescents between 12 and 17 years of age, from April 2020 to April 2021. They attended, together with their representative, the Technical University of Ambato to the project office “Learning Strategies with Social Relevance for the Prevention of Childhood Diseases”, Ambato-Ecuador. All met the following inclusion criteria: adolescents between 12 and 17 years of age, males or females, no smoking habits or alcohol abuse, and no acute or chronic pathologies. They were discarded through their medical history, a complete physical examination, and laboratory tests, taken before the study.

The group of 350 adolescents included 250 adolescents of both genders, with BMI: >2 standard deviations (SD) and 100 adolescent as a control group with a BMI/age between -1.0 and + 0.9 SD[10]. There were no patients lost in the investigation. The measurements were taken by two pediatricians trained in anthropometry.

For height, the following technique was applied: the patient standing so that his heels, buttocks, andhead were in contact with the vertical surface; shoulders relaxed and both arms on the side of the body to minimize lordosis. The head was held so that the lower edge of the orbit was in the same horizontal plane as the external auditory meatus (Frankfurt plane).

Their weight was recorded using a digital scale (Tanita, TBF-310 GS Body Composition Analyzer; Tokyo - Japan). The patients wore light clothing and no shoes. For the evaluation of obesity, the body mass index (BMI), known as the Quetelet index, was used. This index is defined as the ratio between the weight (in kilograms) of the individual and the square of his height in meters (BMI = Weight/ height^2). The WHO 2007 BMI reference criteria for age and gender in children 5- 19 years is the following: obese: >2 SD (equivalent to BMI 30 kg/m^2 at

19 years) and normal-weighted with a BMI/age between -1.0 and + 0.9 SD.

For waist circumference (WC), an equidistant reference point was used. It was measured from thelower edge of the last rib to the upper part of the iliac crest and marked equally on both sides byusing a non-elastic tape measure (flexible with precision of 1 mm). It was used around the waist of the adolescent passing between both positions while he/she completed a not forced exhalation. Threemeasurements were made, and an average was obtained. They included Ecuador´s national reference, where a WC above the 90th percentile is considered central adiposity[11].

The study was approved by the Bioethics Committee of the Technical University of Ambato, Ecuador. Parents and legal representatives of the adolescents were informed and gave their verbal and written consent. Therefore, the adolescents were allowed to participate in the study.

Laboratory analyses

The following procedure was performed to determine the adiponectin serum concentrations. After

a 12-hour overnight fast, a 5 ml venous blood sample was taken by an antecubital venipuncture invacutainer tubes without anticoagulant. Then, it was centrifuged for 10 minutes at 300 revolutionsper minute (rpm) to obtain serum. Samples were frozen at 70ºC until processed.

A Human Adiponectin Enzyme Immunoassay kit SPI-BIO (Société de Pharmacologie et d'Immunologie – BIO, France) # A05185 was used. According to the manufacturer's instructions,the normal adiponectin values for men with a BMI under 25 Kg/m² is 10,9 ±4 µg/mL while for women with a BMI under 25 Kg/m² is 13,6±5,4 µg/mL.

A hs-CRP Cat # 1668Z kit was used to determine serum concentrationsof the hs-CRP. The limit of hs-CRP detection is 0.1 mg/L.

Statistical analyses

The statistical analysis of the data was carried out with the use of statistical software (SPSS Statistics 20.0 for Windows). Data was organized by using contingency tables. The Student-T testwas applied to calculate the average of independent samples. Likewise, Pearson correlation analysis and linear regression models were used with 95% as an index of statistical reliability, anda statistical significance at p<0.05. Quantitative data was shown as average values ± standard deviation (DS).

Results

Table 1 shows the anthropometric variables of normal-weighted and obese adolescents. In obese adolescents, the female gender (n=138, 55.2%) prevailed with significant differences in the anthropometric variables of weight, body mass index, and waist circumference when comparing obese adolescents with the control group. The greatest difference was found in the waist circumference of male adolescents, (101.7±4.6 cm), while females was (94.5 ± 5.7 cm).

Table 1. Anthropometric variables according to sex

Anthropometric variables	Normal-weighted Females (n:50)	Obese Females (n=138)	Normal-weighted Males (n:50)	Obese Males (n=138)
Age (years)	13,8±1,3	13,4±1,8	14±1,4	14,71±2,1
Weight (Kg)	49,1±4,5	73,30±9,1*	52±5,7	76,73±8,4*
Height (m)	1,6 ± 0,06	1,5±0,1	1,6±0,04	1,5±0,06
BMI (Kg/m²)	18,6 ± 0,8	31,6±4,2*	19.4±1,6*	32,08±3,3*
WC (cm)	68,4±3,4	94,5±5,7*	70,4±4,6*	101,7±4,6*

*(p<0,001) obese and normal-weighted. Table expressed as media ± D.S. BMI= body mass index. WC=waist circumference.

Table 2 shows the concentrations of adiponectin and hs-CRP in normal- weighted and obese adolescents. In the determination of the levels of adiponectin and hs-CRP, the obese adolescents presented reduced adiponectin concentrations (5.0±0.8) and increased serum levels of hs-CRP (4.0±1.6), both significant observations, when compared to normal-weighted adolescents.

Table 2. Determination of concentrations of Adiponectin and hs-CRP in Normal-Weighted and Obese Adolescents

Variables	Normal-weighted (n:100)	Obese (n=250)	p
Adiponectin (µg/mL)	10,0 ± 1,0	5,0 ± 0,8	0,001
hs-CRP (mg/L)	0,2 ± 0,0	4,0 ± 1,6	0,001

Table expressed as media ± D.S., hs-CRP: ultrasensitive C-reactive protein. *T-student (p<0,05)

Table 3 shows the correlation analysis of adiponectin and hs-CRP concentrations associated with anthropometric indicators of adiposity in adolescents. The correlation analysis of adiponectin and hs-CRP concentrations associated with anthropometric indicators of adiposity in adolescents evidenced that adiponectin concentrations showed a significant negative correlation between body mass index (r = -0.949, p<0.001) and waist circumference (r = -0.958, p<0.001). It also showed a significant positive correlation between the serum elevation of hs-CRP and the body mass index (r = 0.931, p <0.001) and waist circumference (r = 0.929; p <0.001).

Table 3. Correlation analysis of adiponectin and hs-CRP concentrations associated with anthropometric indicators of adiposity in adolescents				
Pearson Correlation	Adiponectin (N:250)	hs-CRP (N:250)	BMI (N:250)	WC (N:250)
Adiponectin r	1	-0,897*	-0,949*	-0,958*
p		0,001	0,001	0,001
hs-CRP r	-0,897*	1	0,931*	0,929*
p	0,001		0,001	0,001

*Significant correlation (p ˂0,01), hs-CRP: ultrasensitive C-reactive protein.

BMI= body mass index. WC=waist circumference

Table 4 shows the linear regression coefficients predictors of concentrations of adiponectin and hs-CRP according to anthropometric parameters. The BMI and waist circumference demonstrate a significant contribution (p=0.001) as predictive indicators of serum concentrations of adiponectin used as a dependent variable. The linear regression model (R^2) was 0.94, showing that BMI and waist circumference have a large effect on adiponectin concentrations. Similar observations were made regarding the concentrations of hs-CRP and anthropometric measures.

Table 4. Linear regression coefficients predictors of adiponectin and hs-CRP concentrations according to anthropometric parameters				
Variables	Non-standardized coefficients		Standardized coefficients	
ADIPONECTIN[1]	B	Standard error	Beta	p
BMI	-0,15	0,03	-0,425	0,001
CC	-0,1	0,01	-0,56	0,001
hs-CRP[2]	B	Standard error	Beta	p
BMI	0,16	0,03	0,498	0,001
CC	0,07	0,01	0,463	0,001

Predictor variables of the method: (BMI) body mass index; (WC) waist circumference (cm); hs-CRP: ultrasensitive C-reactive protein
[1](Constant)= 19,872. (R2)=0,940, [2](Constant)= -8,107. (R2)= 0,894

Discussion

The WHO has determined that obesity is a global outbreak and is considered a public health problem. When obesity is present in children over three years of age, it is associated with an increased risk of obesity in adulthood with the consequent increase in morbidity and mortality associated to metabolic, cardiovascular, respiratory, orthopedic, and psychological alterations[12].

The average age of participant adolescents was 13.9 ± 1.3 years of age, with a predominance of females. These outcomes are similar to the study completed by Pérez-Galarza., et al., but different from the results of the National Survey of Health and Nutrition of Ecuador. The report pointed out that males between 7 and 17 years of age have the highest prevalence in obesity[13].

The anthropometric variables of participants -in spite of the female predominance- evidenced a high difference in weight, BMI, and WC in males. However, it is noteworthy that the difference was more pronounced in WC. These outcomes are similar to the study completed by Trandafir et al.,which showed predominance in males with a significant difference in WC[14].

There is a sexual dimorphism in the distribution of body fat. Men have a greater fat accumulation in the upper part of the body mainly in the abdominal region (android or apple-like distribution) while women accumulate fat in the lower part of their body, at the gluteal-femoral level (a gynecoid distribution). This explains the difference in the predominance of visceral adipose tissue in men, which stores 10-20% of the total body fat[15].

Women tend to store body fat in the subcutaneous adipose tissue, particularly in the gluteal- femoral region, and to a lesser extent in the visceral adipose tissue. This explains the lower waist circumference. It should be mentioned that sex steroids influence the distribution of adipose tissue.For example, postmenopausal women show an increase in fat deposition in the abdominal region,which is reduced with estrogen replacement therapy. Besides, estrogens regulate the catalytic activity and the expression of the lipoprotein lipase mRNA, a limiting enzyme in the process of lipid storage[15,16].

Obese adolescents presented reduced adiponectin concentrations and increased serum concentrations of hs-CRP. Both observations were significant concerning normal- weighted adolescents. Similarly, the studies carried out by Magaña et al. and González-Torres et al. obtained a negative correlation among adiponectin and obesity anthropometric indicators[17,18]. Kwaifa et al., who worked with obese adolescents and compared their data with a control group, established a negative association between serum adiponectin and CRP levels. This observation confirms a negative relationship between the expression of adiponectin and CRP levels that may reflect the role of adipose tissue in the source of the circulation of CRP that would require further investigation[19].

Correlation of adiponectin and hs-CRP concentrations associated with anthropometric indicators of adiposity in adolescents proved that adiponectin concentrations showed a significant negative correlation with BMI (r=-0.949, p<0.001) and WC (r=-0.958, p<0.001). Adiponectin correlates inversely with BMI and, especially, with WC due to the visceral fat accumulation, as the expansion of the adipose tissue (with hypertrophy and hyperplasia of the adipocyte) regulates the synthesis and secretion of adiponectin. Similarly, Naryzhnaya et al. showed an inverse relationship between the mean diameter of adipocytes and adiponectin segregation[20]. Regarding the correlation of hs-CRP concentrations associated with anthropometric indicators of adiposity in adolescents, a significant positive correlation was found between the serum elevation of hs-CRP in relation to BMI ($r=0.931$; $p<0.001$) and WC ($r=0.929$, $p<0.001$). Likewise, the study conducted by Pascu et al. showed a proportional increase in hs-CRP with the excess of adiposity expressed by the rise inWC and BMI[21].

Regarding the linear regression coefficients, which are predictors of adiponectin and hs-CRP concentrations, the BMI and WC demonstrate a significant contribution as predictive indicators of serum concentrations of adiponectin used as a dependent variable. The linear regression model indicated that BMI and WC have a substantial effect on the concentrations of adiponectin and hs-CRP. Jung et al. established that there is an increase in pro-inflammatory factors such as TNF-α, IL-6 in obesity, ROS that suppress the expression of adiponectin in adipocytes in rodents and obese humans[22]. Thus, adiponectin serves as a potential biomarker in Type 2 Diabetes since the low level of plasma adiponectin (<5μg/mL) is associated with obesity increased and the appearance of metabolic disorders[23]. Shklyaev et al. determined that an excess of adiposity in obesity was associated with a low regulation of adiponectin secretion (hypoadiponectinemia) and the decrease of the expression of their AdipoR1 and AdipoR2 receptors, which contributes to insulin resistance and metabolic deregulation[24].

Gariballa et al. detected that adiponectin levels and biologically active oligomers increase after weight loss. Their results proved that total adiponectin levels increased in severe obesity (BMI≥40Kg/m2) after an approximately 10% in weight loss. Thus, adiponectin can act as an endocrine protective factor to prevent the progression of complications related to obesity, due to the adiponectin effects: its anti-hyperglycemic, antiatherogenic, and anti-inflammatory properties[25]. Adiponectin exerts its anti-inflammatory effects directly on the macrophage. It changes the polarization of macrophages from the M1, pro-inflammatory category, to the M2, anti- inflammatory category. In other words, it modulates the classically activated pro-inflammatory phenotype of macrophages (M1) to alternatively activated macrophages (M2). It stimulates the expression of arginase-1 and IL-10, and it improves the ability of macrophages to eliminate apoptotic bodies early, which is crucial in the prevention of inflammation[26].

Lourenço et al. conducted a study in the Brazilian Amazon, and they established evidence that an increase in the serum concentrations of CRP triggers a low-grade inflammation that predicts changes in body mass index during childhood[27]. Obesity is considered a chronic pro-inflammatory state since it has been referred that excessive visceral fat increases the production of cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), which stimulate the production of the CRP by the liver[28-33].

In animal models and some clinical studies, it has been shown that pro-inflammatory cytokines mainly originate in the non-adipose cells that reside or infiltrate the vascular stromal fraction of fat compartments in obesity. Most part of the immune response seems to be driven mainly by macrophages and primarily by the pro-inflammatory phenotype of M1 cells[34]. Similarly, Chait et al. established that low levels of adiponectin are associated with high levels of CRP[35]. The hypothesis that adiponectin reduces the synthesis and secretion of CRP was tested by gathering new data to show that adiponectin decreases the production of IL-1 and IL-6 by rat primary hepatocytes and that this may be due to the regulation of NF-kB activities (nuclear factor kappa B). Thus, in obesity and diabetes, hypoadiponectinemia could aggravate the pro-inflammatory state by inducing the production of CRP[36].

Limitations of the reasearch:

During the reseach, there was a limitation that some parents and indigenous representatives only speak the Quichua language, without understanding Spanish. But this limitation was overcome with the help of a bilingual interpreter.

Conclusions

The changes in the anthropometric variables weight, body mass index, and waist circumference were greater in male adolescents. There was a significant difference in waist circumference.

In obese adolescents, a significant difference was found in hypoadiponectinemia and elevated serum hs-CRP levels when compared with the normal-weighted control group.

The linear regression coefficients of BMI and waist circumference presented a significant contribution as predictive indicators of serum adiponectin and hs-CRP concentrations.

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