Obesity Medicine 5 (2017) 4–10

Contents lists available at ScienceDirect

Obesity Medicine

journal homepage: http://www.journals.elsevier.com/obesity-medicine

Original research

The impact of adiponectin levels on biomarkers of inflammation among adolescents with obesity

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ARTICLE INFO

Article history:
Received 8 October 2016
Received in revised form
27 December 2016
Accepted 30 December 2016

Keywords:
Adiponectin
Obesity
Adolescents
Cardiometabolic risk
Inflammation

ABSTRACT

Aims: Considering the protective role of adiponectin, we aimed to investigate the impact of different levels of adiponectin on biomarkers of inflammation among adolescents with obesity.
Methods: Were recruited 220 post-pubertal adolescents with obesity. Body composition, lipid profile, adiponectin and leptin concentrations were obtained. Adolescents were distributed in 3 groups (lower levels of adiponectin ≤4.85; medium levels of adiponectin >4.85 e ≤ 9.63; higher levels of adiponectin >9.63). GLM test was performed to analyze difference between groups with p level set at ≤0.05. Pathway analyze was performed.
Results: The most important find in the present low tertile has higher values of body fat compared to medium values. Interesting, insulin(μU/mL), HOMA −AD, total cholesterol (mg/dL), LDL, VLDL, Triglycerides (mg/dL), leptin and leptin/adiponectin ratio presented statistical higher values; inversely; QUICKI, HDL, and adiponectin/leptin ratio has lower when compared low with higher tertile. Analyzing the adiponectin pathway, the comportment of adiponectin was partially mediated by negative correlation with leptin/adiponectin ratio, HOMA-AD and HOMA-IR and positive correlation with HDL-col.
Conclusion: Together, these results may partly contribute to explain the role of adiponectin linking obesity whit atherosclerosis, as depended dose-response of this hormone concentration once in the lower tertile of adiponectin these results were not showed.

1. The impact of adiponectin levels on biomarkers of inflammation among adolescents with obesity

Obesity is characterized as a low-grade inflammatory disease due two varieties of pro inflammatory adipokines secreted by adipose tissue (Sanches et al., 2016). In obesity-related disorders, excess of visceral fat accumulation leads to adipose macrophage infiltration and metabolic dysfunction contributing to low-grade local and systemic inflammation, which contribute to the pathogenesis of cardiovascular complications (Deboer, 2013).

According to the World Health Organization (WHO) estimates in 2014, over 1.9 billion adults above 18 years were overweight, among them 600 million were obese. In general, the study predicts that over 13% of the population is obese. In addition, when compared with 1980 data, the worldwide prevalence of obesity has more than twice in 2014. In the United States, about a third of

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http://dx.doi.org/10.1016/j.obmed.2016.12.002
2451-8476/

children and adolescents are overweight or obese (World Health Organization, 2015). In this way, recent study reinforce that obesity and its comorbidities in childhood and adolescents leading public health problems worldwide (Atay and Kereket, 2016).

The obesity inflammatory response leads not only to increase the expression of pro inflammatory adipokines, but also to reduction with adipokines anti-inflammatory properties, as adiponectin. Adiponectin represents the most abundant protein secreted by adipose tissue. Adiponectin is considered a cardio protector adipokine, since its levels are correlated negatively with adiposity, insulin resistance, type 2 diabetes, and metabolic syndrome, yet positively correlated with markers of insulin sensitivity in frequently sampled intravenous glucose tolerance testing and clamp studies (Izadi et al., 2011).

Although adiponectin is secreted by adipose tissue, studies have showed that in obesity state, low levels of adiponectin are observed. In fact, studies have demonstrated that low levels of adiponectin are correlated with metabolic syndrome. It has anti-inflammatory action, resulting in decreased production and inhibition of TNF-α action, decreased IL-6 production, with a consequent induction of IL-l0 and antagonist of IL-l. Adiponectin is considered the major component of the adipo-vascular axis which mediates the cross-talk between adipose tissue and the vasculature. This adipokine can attenuate the atherogenic process through multiple actions on macrophages, vascular endothelial cells, and systemic inflammation (Xu and Vanhoutte, 2012; Liu et al., 2010).

On the other hand, in obesity, hyperleptinemia state characterized as leptin resistance can impair both the control of energy balance and at least contribute to a reduction of adiponectinemia. Corroborating, only after a reduction in approximately 10% leptin restart its function by upregulation of alpha-MSH, an important anorexigenic factor, and increase adiponectin concentration (Dâmaso et al., 2011; Sanches et al., 2014).

Moreover, the adiponectin/leptin concentration and vice-versa emerge as important biomarker of anti-pro-inflammatory state, respectively. However, it if these biomarkers were correlated, as dose-response manner with the low and high tertiles of adiponectin concentration were not explored in obese adolescents. Finally, considering that obesity has increased worldwide, especially among young ages, and the protective role of adiponectin, it is important to investigate the impact of different levels of adiponectin on biomarkers of inflammation among adolescents with obesity.

2. Methods

Subjects. Into this study, 220 post-puberty obese adolescents aged 15–19 years were included. Inclusion criteria were Tanner stage five (Tanner and Whithouse, 1976), primary obesity and BMI >97th percentile of the WHO reference growth charts. Non-inclusion criteria were the use of birth control pills, cortisone, anti-epileptic drugs, and history of renal disease, alcohol intake, smoking, and secondary obesity due endocrine disorders. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics committee on research at the Universidade Federal de Sao Paulo-UNIFESP (#0135/04 and 152.281), Clinical Trials.gov: NCT01358773. All procedures were clear to those responsible for the participants and an informed consent for research was obtained. The main reasons for dropping out (n = 5) in our study were financial and family problems, followed by school and job opportunities.

Anthropometric measurements. Body composition and weight were measured by plethysmography scale (BODPOD equipment), where patients wore a minimum clothing as possible and height was measured using a stadiometer (Sanny-model ES, 2030). BMI was calculated dividing the weight by height squared (kg/m^2).

Serum analysis. Blood samples were collected at the outpatient clinic at approximately 8:00 a.m. after an overnight fasting (12 h). The serum concentrations concentrations of glucose, insulin, triglycerides, total cholesterol (T-cholesterol), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and very low-density lipoprotein cholesterol (VLDL-c), were determined by enzymatic colorimetric methods (CELM, Barueri, Brazil). To identify individuals with abnormal lipid profiles, we used the reference values from the I Guideline for Preventing Atherosclerosis in Childhood and Adolescence: HDL-C (≥45), LDL-C (<100) and T-cholesterol (<150) (Giuliano et al., 2006).

Leptin and adiponectin were measured by enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems (Minneapolis, MN, USA). For this study, leptin data was analyzed according to reference values (Gutin et al., 1999). The pro-inflammatory leptin/adiponectin ratio (L/A ratio) and anti-inflammatory adiponectin/leptin ratio (A/L ratio) biomarkers were calculated. Insulin resistance was determined by the Homeostasis Model Assessment Insulin Resistance (HOMA-IR): [Fasting insulin (μU/mL) x fasting blood glucose (mmol/L)/22.5] (Matthews et al., 1985). Insulin sensitivity was determined by the Quantitative Insulin Sensitivity Check Index (QUICKI): [1/(log fasting insulin (μU/mL) + log fasting glucose (mg/dL)] (Katz et al., 2000). Homeostasis Model Assessment- Adiponectin (HOMA-AD) was calculated from fasting blood glucose, insulin and adiponectin: [fasting glucose (mg/dl) x fasting insulin (μU/L)/Adiponectin (μg/mL)] (Matsuhisa et al., 2007). The cutoff of HOMA-IR adopted for adolescents *was* 3.16 (Keskin et al., 2005) and insulin was 15.0 (SBP, 2012).

Visceral and subcutaneous adiposity measurements. Measurements of visceral and subcutaneous adiposities were performed by abdominal ultrasonography. The procedures were performed by the same physician, who evaluated the participants (Ribeiro-Filho et al., 2003).

Statistical analysis. Statistical analysis was performed using SPSS software version 20 and the significance level was set at $p < 0.05$. The Gaussian distribution of variables was verified with Kolmogorov–Smirnov test. Variables with normal distribution were expressed as mean ± standard deviation and by Z-score. General Linear Model (GLM) Univariate test were performed to compare descriptive data among tertiles of adiponectin values.

The current study used a structural equation modeling (SEM) approach to examine correlates of adiponectin after controlling for HOMA-IR, HOMA-adiponectin, triglycerides, LDL-c, HDL-c and adiponectin/leptin ratio (Fig. 3). Standardized parameter was used for informal comparisons of parameters throughout the model that corresponded to effect-size estimates (Hoyle, 1995). Also, the better model was indicated by: the Comparative Fit Index (CFI) is equal to the discrepancy function adjusted for sample size, and Root Mean Square Error of Approximation (Hu and Bentler, 1999). Thus, one of three models were explored and better fit was chosen: [$\chi 2$ (df = 15) = −84.17; CFI = 1.00; RMSEA = 0.00]; all $p < 0.005$.

3. Results

3.1. Descriptive analyses

In this cross-sectional study, a total of 220 obese adolescents were evaluated. The total sample was composed of 44, 1% (n = 97) males and 55,9% (n = 123) females. The studied population was grouped by tertiles of adiponectin concentration: low (≤4.85 μg/mL), medium (>4.85 e ≤ 9.63 μg/mL) and high (>9.63 μg/mL).

Comparison between adiponectin tertiles of the metabolic and inflammatory profile of Brazilian adolescents with obesity: