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# Behavior of adipokines after a year follow-up in the Obesity Outpatient Clinic for Children and Adolescents

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**Abstract**

***Objective:*** **demonstrate adipokines progression, along 12 months, in obese children and adolescents who attend the Obesity Outpatient Clinic for Children and Adolescents of the HCPA.**

***Methods:*** **children and adolescents in medical treatment for obesity were followed for 12 months, assessing anthropometry, blood pressure, waist circumference, lipid profile, fasting blood sugar and insulin, inter leukine-6, tumor necrosis factor alpha, and adiponectin in two points in time: at inclusion and after 12 months follow-up in the Obesity Outpatient Clinic for Children and Adolescents.**

***Results:*** **27 children and adolescents were assessed with median age of 10.3 years. The mean BMI z-scores lowered during this period ($p < 0.01$), HDL-c increased in the period ($p = 0.025$). The medians of adipokines did not vary during the period: IL-6 ($p = 0.470$), TNF-$\alpha$ ($p = 0.753$) and adiponectin ($p = 0.943$). There was no correlation of IL-6 and TNF-$\alpha$ with central and global obesity along the 12-months follow-up. Adiponectin increased in 45% of the sample, the increase being more pronounced in females.**

***Conclusion:*** **children and adolescents in medical treatment for obesity, after one-year follow-up, did not improve their adiponectin profile.**

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Key words: *Children. Obesity. Adolescents. Adiponectin. Inflammation.*

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## COMPORTAMIENTO DE LAS ADIPOCINAS DESPUÉS DE UN AÑO DE SEGUIMIENTO EN EL AMBULATORIO DE OBESIDAD DE LA NIÑEZ Y LA ADOLESCENCIA

**Resumen**

***Objetivo:*** **demostrar la evolución de las adipocinas a lo largo de 12 meses en niños obesos usuarios del Ambulatorio de Obesidad Infantojuvenil.**

***Metodología:*** **se hizo el seguimiento de niños y adolescentes en tratamiento clínico para obesidad a lo largo de 12 meses. Se los evaluó en lo tocante a antropometría, presión arterial, circunferencia de cintura, perfil lipídico, glicemia e insulina en ayuno, interleucina 6, factor de necrosis tumoral alfa y adiponectina en dos instancias: inclusión y después de 12 meses de seguimiento en el Ambulatorio de Obesidad Infantojuvenil.**

***Resultados:*** **se evaluaron 27 niños y adolescentes con una media de edad de 10,3 años. Los valores promedio de la puntuación-z del IMC bajaron en el período ($p < 0,01$), el HDL-c aumentó sus niveles en este período ($p = 0,025$). Las medianas de las adipocinas no variaron a lo largo del período: IL-6 ($p = 0,470$), TNF- $\alpha$ ($p = 0,753$) y adiponectina ($p = 0,943$). No hubo correlación entre la IL-6 y el TNF-$\alpha$ con obesidad central y global a lo largo de los 12 meses de seguimiento. El 45% de la muestra aumentó sus valores de adiponectina, siendo mayor este aumento en el sexo femenino.**

***Conclusión:*** **los niños y adolescentes en tratamiento clínico para obesidad tras un año de seguimiento no mejoraron su perfil de adipocinas.**

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Palabras clave: *Niños. Obesidad. Adolescentes. Adipocinas. Inflamación.*

## Introduction

Obesity in children and adolescents is considered a severe public health problem in both developed and developing countries with increased prevalence, especially in urban areas[1,2], and in children[3,4]. In adolescence, in developed countries, 110 million youngsters have excess weight[1], associated to cardiovascular risk factor including abdominal fat deposition, insulin resistance (IR), dyslipidemia and hypertension[5,6].

We currently believe that obesity is a mainly inflammatory process, which contributes to IR[7] and early risk of developing cardiovascular diseases (CVD)[8]. Recent studies suggest an association between the development of CVD and a low-grade chronic inflammatory state in those subjects[9].

Adipose tissue is no longer considered an inert organ with mechanical or temperature regulation functions, but rather an endocrine organ, secreting many pro-inflammatory cytokines[10.11]. Tumor necrosis factor alpha (TNF- α), Interleukin- 6 (IL-6), and Plasminogen activator inhibitor factor (PAI-1) are examples of substances released by the adipose tissue, especially by the abdominal fat, which contribute to IR[12,13]. Leptin and adiponectin are the most abundant adipokines synthetized by the adipose tissue. They act in the metabolism of lipids and carbohydrates, regulating metabolic processes[14,15].

Literature has limited information on the relation of inflammatory process and obesity in children and adolescents[15]. The pathophysiologic mechanism of inflammation in obese children and adolescents is not entirely understood yet and there is no consensus in the pediatric literature on how it occurs[16-18].

In the last 10 years, some studies with this population have been demonstrating an association between the increase in ultra sensitive C-reactive protein (us-CRP) which is a marker for acute inflammation, but not with the markers of low-grade inflammation as interleukine-6 (IL-6) and the tumor necrosis factor alpha (TNF-α). It is important to consider those aspects, since due to deterioration in life style, the number of children and adolescents with IR is growing, what may trigger the inflammatory process[19,20]. In adults, this association is better demonstrated when one identifies the time exposed to excess weight as important determinant of the inflammatory process.

The objective of this study is to demonstrate the progression of adipokines and its association with central and global obesity, lipid profile, serum insulin, and Homeostasis Model Assessment (HOMA), in obese children and adolescents followed for 12 months in a reference ambulatory for the treatment of obesity in children and adolescents.

## Methods

A cohort study was conducted focused in the assessment of the presence of inflammation, studying adipokines and their behavior in a group of children and adolescents in medical treatment for obesity, along 12 months. Subjects were assessed in two time points: inclusion and after 12 months of follow-up in the Outpatient Ambulatory (AmO). This study followed the Regulatory Guidelines and Norms for Research in Human Beings (*Resolução 196/1996 do Conselho Nacional de Saúde*) and was approved by the Ethics in Research Committee of the Hospital de Clinicas de Porto Alegre (HCPA), protocol 10-0231.

Obese children and adolescents (BMI Z-score > +2) with ages ranging from 6 to 13 years from the metropolitan region of Porto Alegre were followed, accrued among the new patients referred to the AmO by other specialties of the HCPA and by the other health providers. All parents and/or mentors were informed of the study objectives, and consented signing the Free, Prior and Informed Consent (FPIC).

The study followed the health care routine of the AmO with monthly visits, where anthropometric evaluation, measurement of blood pressure, and laboratory tests were made in all participants. The blood pressure was measured with the subject seated, the cuff used was appropriated for the size of the arm according to the recommendations of the American Academy of Pediatrics[21]. Body weight was assessed in an electronic weight-scale, with the subjects wearing a sleeveless gown and barefooted, standing still in the center of the scale. The gown was then weighted and its weight subtracted. All participants had their height measured with a height-scale of 0.1 cm interval, standing, with parallel feet and heels, shoulders and buttocks touching the wall. The Body Mass Index (BMI) was calculated dividing the weight (in kg) by the square of the height (in $m^2$) to calculate the Z-score. To measure waist circumference an inelastic tape was used and the measure was taken in the mean point between the tenth rib and the superior iliac crest. When the measures were above the 90$^{th}$ percentile for age and gender, they were considered inadequate, as established by Freedman[22]. To assess bioimpedance, a Byodynamics® model 310 was used, following the recommendations for food and caffeine intake (4h), as well as water (8h), no exercise in the 4 hours before the exam, and no alcohol intake in the previous 24 hours. During the exam the limbs must not touch the body, and the leads must be fixed always on the same side, distant at least 5 cm from one another, the red-wire probe always in proximal position[23].

The routine laboratory tests ordered in the AmO: total cholesterol and fractions, triglycerides, fasting glucose, insulin (time 0), usCRP were done, processed in the Clinical Analysis Laboratory of the HCPA; blood was drawn after 12-hour fastening, following the protocols already established in the institution.

After signing the FPIC, blood was drawn and 5ml destined to measure IL-6, TNF-α and adiponectin. The blood was centrifuged at 4,000 rpm during 15 minutes at the Clinical Research Laboratory of the HCPA.

**Table I**
*Comparison of adipokines and anthropometric and laboratory variables pre and post 12 months of medical treatment*

| *Variables** | *Inclusion* | *12m* | *p* |
|---|---|---|---|
| IL-6 (pg/ml) | <2 (<2 – 6.0) | <2 (<2 – 4.2) | 0.470 |
| *Adiponectin (ng/ml)* | 12800 (10800 – 16940) | 13940 (9620 – 16280) | 0.943 |
| *TNF-α (pg/ml)* | <3.9 (<3.9 – 19.3) | <3.9 (<3.9 – 15.6) | 0.753 |
| *HOMA* | 4.7 (3.1 – 6.4) | 4.1 (2.8 – 5.9) | 0.244 |
| *Insulin (mg/dl)* | 21.3 (14.8 – 25.9) | 18.3 (12.8 – 25.0) | 0.136 |
| ***HDL(mg/dl)*** | **37.7 ± 8.0** | **39.5 ± 7.7** | **0.025** |
| *TG (mg/dl)* | 81 (54 – 112) | 83 (49 – 120) | 0.773 |
| ***BMI-z score*** | **3.3 ± 0.8** | **2.9 ± 0.9** | **<0.001** |
| *Obesity* | 27 (100) | 22 (81.5) | 0.063 |
| *Large WC* | 17 (63.0) | 23 (85.2) | 0.109 |
| *% LM* | 70.7 ± 4.9 | 71.1 ± 3.2 | 0.651 |
| *% BF* | 31.8 ± 4.4 | 31.7 ± 4.8 | 0.897 |
| *Skin folds* | | | |
| *Tricipital (mm)* | 32.3 ± 6.1 | 30.1 ± 6.8 | 0.051 |
| *Subscapular (mm)* | 29.3 ± 9.2 | 30.1 ± 8.9 | 0.646 |
| *Sum (mm)* | 61.6 ± 13.6 | 60.2 ± 14.6 | 0.584 |

* described by n (%), mean ± standard deviation or median (percentiles 25 – 75), depending on the type of variable and data distribution
IL-6 – interleukine 6; TNF- α - tumor necrosis factor alpha ; HOMA - homeostatic model assessment; WC – waist circumference; LM – lean mass; BF – body fat

Serum was stored in that same place, in a freezer at -80C for further analysis.

IL-6, TNF-α and adiponectin were analyzed in the same laboratory, by a biologist, according to the recommendations by the manufacturer. The concentration of these markers was determined by ELISA (Enzyme-Linked Immunosorbent Assay), using commercial kits. The Human Adiponectin ELISA Kit (Invitrogen Corporation, Carlsbad, CA, USA) with standard deviation between 2 ng/ml and 64ng/ml was used to determine adiponectin. The Human IL-6 ELISA Ready-SET-Go! and Human TNF alpha ELISA Ready-SET-Go! Kits (eBioscience,San Diego, CA) were used for IL-6 and TNF-α, respectively. The sensitivity and deviation curve established for IL-6 were 2 pg/ml and 200 pg/ml, and for TNF-α 3.9 pg/ml to 500pg/ml. To quantify IL-6 the commercial essay IL-6 (RD Systens, Minneapolis, MN USA) was utilized.

## Statistical analysis

To evaluate the changes in usCRP, IL-6, TNF-α and adiponectin along the follow-up period, the *t test* was conducted, as the Wilcoxon's test, according to the sample distribution and symmetry. The association between usCRP and metabolic syndrome, as well as between IL-6, TNF-α, adiponectin and other variables, was tested by Spearman's correlation. Mann Whitney's test was used for the comparison of usCRP, IL-6, TNF-α and adiponectin variation between groups.

The significance level adopted was 5% and the statistical analyses were done using the software SPSS version 18.0.

## Results

Of the 30 children and adolescents electable for the study, 3 dropped out after the first evaluation. Therefore, 27 children and adolescents were followed, 14 girls and 13 boys, with median age 10.3 years (IQ: 6-13 years). The mean values of the BMI z-scores decreased along the 12 months ($p < 0.01$), according to the WHO criteria; high-density lipoprotein (HDL-c) increased in the same period ($p = 0.025$). The medians of the adipokines did not vary, along the period, as we may see in Table I.

There was no correlation of the IL-6 and TNF-α with central and global obesity along the 12-months follow-up (Table II).

There was also no association in the correlation of the values of TNF-α with triglycerides ($r_s = 0.04$; $p = 0.984$) and serum insulin ($r_s = 0.178$; $p = 0.374$). On the other side, there was significant association between BMI and TNF-α ($r_s = 0.443$; $p = 0.023$) that might have happened because of one subject who increased the BMI in 2 kg/m$^2$ and increased a lot the TNF-alpha (in approximately 300pg/ml) (Fig. 1). Removing this person from the sample, the association would be borderline ($r_s = 0.349$; $p = 0.081$).

**Table II**
*Assessment of the variation (Δ) on IL-6 and Δ TNF-α in 12 months according to variables studied*

| *Variables** | *D IL-6 md (P25 – P75)* | *p* | *D TNF-a md (P25 – P75)* | *p* |
|---|---|---|---|---|
| Age - $r^s$ | 0.077 | 0.701 | -0.253 | 0.230 |
| Gender | | 0.943 | | 0.616 |
| Male | 0.0 (-0.47 to 2.35) | | 0.0 (-16.2 to 9.2) | |
| Female | 0.0 (0.0 to 1.82) | | 0.0 (0.0 to 0.14) | |
| Large WC at baseline | | 0.639 | | 0.863 |
| Yes | 0.0 (0.0 to 0.02) | | 0.0 (-11.0 to 0.27) | |
| No | 0.04 (-1.97 to 3.75) | | 0.0 (-4.51 to 4.35) | |
| Δ WC - $r^s$ | 0.058 | 0.775 | 0.257 | 0.196 |
| Baseline BMI-z | -0.039 | 0.845 | 0.024 | 0.905 |
| Δ BMI-z - $r^s$ | 0.349 | 0.081 | 0.443 | 0.023 |
| % baseline LM - $r^s$ | 0.216 | 0.279 | 0.047 | 0.815 |
| Δ % LM - $r^s$ | -0.146 | 0.467 | -0.475 | 0.012 |
| % initial BF - $r^s$ | -0.058 | 0.775 | 0.108 | 0.591 |
| Δ % BF - $r^s$ | 0.264 | 0.183 | 0.062 | 0.759 |
| Initial Tricipital folds - $r^s$ | 0.167 | 0.406 | 0.079 | 0.695 |
| Δ Tricipital folds - $r^s$ | 0.060 | 0.765 | 0.186 | 0.353 |
| Initial subscapular folds - $r^s$ | 0.180 | 0.369 | 0.186 | 0.353 |
| Δ Subscapular folds - $r^s$ | 0.116 | 0.563 | -0.090 | 0.657 |
| Sum initial folds - $r^s$ | 0.155 | 0.440 | 0.145 | 0.471 |
| Δ sum folds - $r^s$ | 0.143 | 0.478 | 0.041 | 0.839 |

In the evaluation of the behavior of adiponectin along the 12 months, the values increased in 45% of the sample. The evaluation of the behavior of the median (p25-75) between gender, demonstrated that the girls (md=-650(-1,935 to 2,765) had higher increase as compared to the boys (md=-1,940 (-4,360 to 5,190), although this was not statistically significant (p = 0.583). Those subjects who had large waist circumference in the beginning were the ones who increased the least this adipokine: large waist circumference at baseline md= -1,940 (-3,990 a 3,220) vs. WC not elevated at baseline md = -330 ( -1,230 to 3,370); p = 0.414.

There was also no correlation between adiponectin and waist circumference values ($r_s$ =0.118; p = 0.559), HDLc ($r_s$ =0.347; p = 0.082), TG ($r_s$ =-0.018; p = 0.92), serum insulin ($r_s$ =-0.078; p = 0.698) and HOMA ($r_s$ =-0.131; p = 0.514), age-adjusted.

## Discussion

In this study we evaluated the behavior of adipokines along 12 months, in children and adolescents in medical treatment for obesity. Although the literature does not have as yet cut-off points to determine "abnormal" and "normal" values in children and adolescents, there are, nevertheless, values suggested for adiponectin (3 to 30 $\mu$g/ml) and TNF-α (< 8 ng/ml) for the adult population[24].

This study demonstrated that obesity, although considered a mild inflammation, in this group did not modify adipokines. Lira *et al*[25] followed 54 obese adolescents in the Interdisciplinary Program in Obesity for 12 months. Of those, 18 who lost around 5% of their BMI were selected for the assessment of adipokines. After one year, there was significant difference in the insulin values (p = 0.001), HOMA (p = 0.002) and adiponectin (p = 0.001), and the values of IL-6 were borderline (p = 0.06). In our group, although the BMI z-score decreased, only 5 children modified their nutritional status from obesity to overweight.

The key to understand the mechanism of the inflammatory state in obesity is directly related to the presence of abdominal fat and, as a consequence, IR[26]. In our group of patients, in spite of HOMA values corresponding to IR, there was no correlation to adipokines. Another relevant aspect to be considered is that our sample included children and adolescents with median

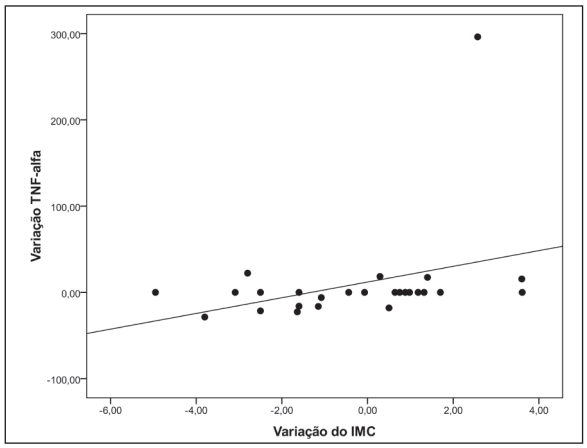


*Fig. 1.—TNF-alpha and BMI variation in obese children and adolescents in medical treatment, along 12-months follow-up.*

age of 10.3 years, while in other studies that found statistic difference between adipokines and HOMA, the mean ages were closer to 14 years (Garanty-Bogacka *et al,* 2011); 15 years (Lira *et al*, 2012); 16.4 years (Kim *et al*, 2012) and between 12 and 16 years (Cordero *et al*, 2012). Maybe the younger age and the consequent shorter time exposed to obesity explain the non-association between adipokines and IR.

Our obesity outpatient clinic (AmO) works with change in life style based on goals agreed in the appointments relative to feeding habits and physical exercise, followed monthly. Other studies with dietetic intervention, diet and physical exercise prescription and weekly follow-up, have demonstrated significant changes in weight loss as well as in improving adipokines[25,27], during a period similar to the one studied in our sample. Obesity is a chronic disease, difficult to manage, with many patients abandoning treatment, demanding that the patient remains motivated and conscious[30,31]. A closer follow-up may possibly contribute in the process as well. Our ambulatory focuses in slow, gradual changes, by means of short, feasible goals, not drastic ones, but that will remain through adult life.

In the last decade, the large influence of the Internet, social networks, and television, as well as urban violence that prevent children from practicing recreational outdoor activities, have increased sedentary activities and decreased energetic expenditures, increasing the risk for early development of obese-associated cardiovascular diseases[32,33].

Our study has some limitations. The age of the children and adolescents, the duration of follow-up for the verification of adipokines, the absence of a control group, and the sample size seem to have contributed to the non-significant results. Even though the results have no statistical power, we must underscore the clinical relevance of these findings, because of the development of those inflammatory components so early on in this population.

## Conclusion

In our findings, children and adolescents in medical treatment for obesity, after one year of follow-up, did not improve their adipokines profile. There was also no association between these cytokines and waist circumference, HOMA or lipid profile. We may therefore speculate that the time exposed to obesity, the follow-up time, and the absence of a control group, might have precluded the finding of mild inflammation. No doubt new studies with prospective methodology, longer follow-up, and a control group will be useful to elucidate this issue in our setting.

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