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Leptin Levels, Basal Metabolic Rates, and Insulin Resistance in Obese Pubertal Children

Níveis de leptina, taxa metabólica basal e resistência insulínica em crianças obesas púberes

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Abstract

Introduction Obesity in children and adolescents is considered a serious public health problem. The consequences of overweight can last for life. It is extremely important to have formulas to calculate the basal metabolic rate (BMR) that are truly reliable in relation to the individual caloric expenditure.

Objectives To investigate the association of serum levels of leptin, lipid profile, and insulin resistance (insuline resistance by Homeostatic Model Assessment [HOMA] index) with the body mass index (BMI) z-score of pubertal obese children. In addition, to compare the basal metabolic rate (BMR) evaluation carried out using bioimpedance (BIA) with the Food and Agricultural Organization/World Health Organization (FAO/WHO) equation.

Methods Cross-sectional study including 37 pubertal obese children (aged 7 to 12 years old) seen for the first time in the outpatient care unit specialized in child obesity between June 2013 and April 2014. The participants were assessed regarding anthropometric data, body composition (fat mass) by BIA 310 bioimpedance analyzer (Biodynamic Body Composition Analyser, model 310 - Biodynamics Corporation, Seattle, EUA), and blood pressure. Blood samples were collected to measure glucose, insulin, lipid profile, triglycerides, and leptin. The stage of sexual maturity was determined by self-assessment according to the Tanner scale.

Results Higher leptin levels were found in the severe obesity group ($p = 0.007$) and, as expected, higher BMI ($p < 0.001$), and fat mass ($p = 0.029$). The groups did not differ in relation to insulin, insulin resistance (HOMA-IR), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and blood pressure. The BMR measured by bioimpedance was lower as compared to the measure by the FAO/WHO equation ($p < 0.001$).

Keywords
- basal metabolism
- child
- insulin resistance
- leptin
- obesity

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Conclusions These results suggest that severely obese children may present leptin resistance in this early stage of life, (since this hormone is higher in these children). It is suggested that health professionals prioritize the calculation of BMR by bioimpedance, since the FAO/WHO equation seems to overestimate the caloric values.

Resumo

Introdução A obesidade em crianças e adolescentes é considerada um grave problema de saúde pública. As consequências do excesso de peso podem durar a vida toda. É extremamente importante ter fórmulas para calcular a taxa metabólica basal (TMB) que sejam realmente confiáveis em relação ao gasto calórico individual.
Objetivos Investigar a associação dos níveis séricos de leptina, perfil lipídico e resistência à insulina (índice insuline resistance by Homeostatic Model Assessment [HOMA]) com o escore z do índice de massa corporal (IMC) de crianças obesas púberes. Além disso, comparar a avaliação da taxa metabólica basal (TMB) realizada usando a bioimpedância (BIA) com a equação Food and Agricultural Organization/Organização Mundial de Saúde (FAO/OMS).
Métodos Estudo transversal, incluindo 37 crianças obesas pubertárias (de 7 a 12 anos) atendidas pela primeira vez no ambulatório especializado em obesidade infantil entre junho de 2013 e abril de 2014. Os participantes foram avaliados quanto aos dados antropométricos, composição corporal (massa gorda) pelo BIA 310 bioimpedance analyzer (Biodynamic Body Composition Analyser, model 310 - Biodynamics Corporation, Seattle, EUA) e pressão arterial. Amostras de sangue foram coletadas para medir glicose, insulina, perfil lipídico, triglicerídeos e leptina. O estágio da maturidade sexual foi determinado pela autoavaliação de acordo com a escala de Tanner.
Resultados Níveis mais elevados de leptina foram encontrados no grupo obesidade grave ($p = 0{,}007$) e, como esperado, maior IMC ($p < 0{,}001$) e massa gorda ($p = 0{,}029$). Os grupos não diferiram em relação à insulina, resistência à insulina (HOMA-IR), triglicerídeos (TG), colesterol total (CT), colesterol de lipoproteína de baixa densidade (LDL-c), colesterol de lipoproteína de alta densidade (HDL-c) e pressão arterial. A TMB medida pela bioimpedância foi menor quando comparada à medida pela equação FAO/OMS ($p < 0{,}001$).
Conclusões Esses resultados sugerem que crianças gravemente obesas podem apresentar resistência à leptina nesta fase inicial da vida (uma vez que esse hormônio é mais alto nessas crianças). Sugere-se que os profissionais de saúde priorizem o cálculo da TMB por BIA, uma vez que a equação FAO/OMS parece superestimar os valores calóricos.

Palavras-chave
- metabolismo basal
- criança
- resistência à insulina
- leptina
- obesidade

Introduction

Obesity in children and adolescents is considered a serious public health problem, since the consequences of excess weight can last for life.[1] The trend of overweight and obesity (1975 to 2016), estimated as 31.5 million children aged 5 to 9 years old, is of a growing increase in mean body mass index (BMI). However, in many high-income countries, BMI values have reached a plateau (although the level is high), while in low- and middle-income countries it continues to increase.[1]

In Brazil, the prevalence of overweight and obesity is around 12 and 30%, respectively, in the years 2008–2009 in children aged between 0 and 5 years old.[2]

Child obesity can affect several systems of the body and cause serious consequences such as high blood pressure (HBP), dyslipidemia, insulin resistance (IR), abnormal levels of plasma glucose, liver diseases, and psychosocial complications.[3]

Insulin exerts influence on leptin levels. It is produced in the adipocytes; it acts leading to the inhibition of feeding behavior. Serum levels of leptin are proportional to the amount of adipose tissue in the body.[4,5] A systematic review demonstrated a positive correlation between leptin levels and BMI; as leptin levels decrease, BMI levels also fall.[6] Postpubertal Hispanic girls with normal BMI and high body fat content (assessed via Dual-energy X-ray absorptiometry [DEXA]) have insulin and leptin resistance, as compared with girls with adequate BMI and fat.[7] Obese adolescents have high circulating levels of leptin and insulin in the plasma (although they do not present insulin resistance).[8] It is still unclear whether overweight children have high levels of leptin and insulin at puberty, which may be an important biochemical marker to aid in the process of screening for the risk of early metabolic alterations.

Dyslipidemia, acanthosis nigricans (ACN), and HBP, usually associated with IR, are often found in obese children. However, it is not known whether the level of obesity influences the

onset and worsening of these variables. The objective of the present study is to correlate the serum levels of leptin, the biochemical profile, and the IR with the BMI z-score of pubertal obese children and adolescents, besides evaluating the levels of basal metabolic rate (BMR) determined by the bioimpedance device (BIA),as compared with the calculation recommended by the Food and Agricultural Organization/World Health Organization (FAO/WHO) equation.

Subjects and Methods

Participants

A cross-sectional study performed at the outpatient care unit for Child and Adolescent Obesity (AmO, in the Portuguese acronym) of the Hospital de Clínicas de Porto Alegre (HCPA, in the Portuguese acronym), between June 2013 and April 2014. All pubertal children and adolescents, Tanner stages II and III (referred), aged 7 to 12 years old who were seen for the first time with the diagnosis of obesity (BMI z-score $\geq +2$) were included. The total number of eligible subjects was 41. The exclusion criteria were the use of continuous medication ($n = 0$), neurological disease ($n = 0$), general refusal to participate ($n = 1$), and refusal at the time of blood collection ($n = 3$). A total of 37 subjects who met the inclusion and exclusion criteria were included.

Nutritional Evaluation

Body weight was measured using a Filizola electronic scale (Filizola, Rio de Janeiro, RJ, Brazil) with an accuracy of 0.1 kg. Height was measured with an accuracy of 0.5 cm using a Sanny stadiometer (Sanny, São Bernardo do Campo, SP, Brazil) fixed to the wall, according to the standards of the World Health Organization (WHO).[9]

Weight and height measurements were collected with the participants using an apron and barefoot. The BMI was calculated using the software Anthro Plus (WHO, Geneva, Switzerland) to calculate the z-score.[10] The 37 participants were divided into 2 groups according to the degree of obesity. Group 1 ($n = 18$) presented a BMI z-score between $+2$ and $+3$, classified as obesity; group 2 ($n = 19$) included those with BMI z-score $> +3$, classified as severe obesity. Waist circumference (WC) was measured at the midpoint between the last fixed rib (tenth) and the upper border of the iliac crest.[11] The triceps skinfold was measured by pinching with the thumb and forefinger of the left hand the subcutaneous skin at the midpoint of the arm, between the olecranon and the acromion.[12]. The Subjects were examined for the presence of ACN, according to the protocol by Burke et al.[13] Blood pressure was measured with the participant sitting, using a cuff appropriate to the arm size (Missouri) (Aneroide Solidor® Sphygmomanometer, São Paulo, SP, Brazil), following recommendations by the American Academy of Pediatrics.[14] It was considered HBP when the values obtained were ≥ 90 of the percentile adjusted for age, gender, and height percentile.[15]

Biochemical Analysis

Blood samples were collected in the morning, around 8 AM, after night fasting, to determine fasting glucose, insulin, triglycerides (TG), total cholesterol (TC), and high-density lipoprotein (HDL-c) cholesterol. The analyses were performed at the HCPA laboratory, following protocols established by the institution. Low-density lipoprotein (LDL-c) was calculated by the Friedewald equation.[16] The remaining blood was distributed in specific tubes to obtain serum (leptin) and was centrifuged. Leptin levels were determined by enzyme-linked immunosorbent assay (ELISA), using the Human Leptin Elisa commercial kit (Life Sciences Int'l Inc., Plymouth Meeting, PA), following the instructions of the manufacturer.

The reference values used to classify the lipid profile were the ones by the Brazilian Society of Cardiology.[17] The value of fasting insulin was considered abnormal when $\geq$15mg/dL.[18] Insulin resistance (HOMA-IR) was determined by the formula: HOMA IR = (fasting insulin (mU mL)) x (fasting plasma glucose (mmol/L)/22.5); when HOMA IR was > 3.16, it was considered IR.[19]

Metabolic Rate Evaluation

The BIA Biodynamics model 310 (Biodynamic Body Composition Analyser, model 310 - Biodynamics Corporation, Seattle, EUA) was used to evaluate the BMR and percentage fat mass (%FM), and the evaluation was performed after night fasting and after the first morning void.[20] The BMR was also determined by the FAO/WHO equation.

Statistical Analyses

Statistical analyses were conducted using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA), with significance level set at 5%. The variables were described by mean and standard deviation (SD), or interquartile intervals and median, and percentages. The differences in means between the two groups of obese children were evaluated by the Student t-test or the Mann-Whitney test, and categorical variables by the Pearson chi-squared test and the Fisher exact test. The relationship between WC and BMI and the other quantitative variables were verified by the Pearson or Sperman correlation methods.

All parents or guardians signed the free and informed consent form with the consent of the children. The project was approved by the HCPA Internal Review Board, Rio Grande do Sul, Brazil, under the number 13–0129.

Results

A total of 37 pubertal children and adolescents, Tanner stages II and III, aged 7 to 12 years old, of which 18 (48.6%) were male, were evaluated. All had been obese for > 2 years, according to their parents.

The BMI z-score varied from 21.8 kg/m^2 to 43.2 kg/m^2, characterizing the presence of obesity throughout the group, according to the inclusion criteria. Acanthosis nigricans was found in 31 (83.8%) of the subjects, being mild in 16 (43.2%) and moderate in 14 (37.8%); only 1 (2.7%) had severe ACN.

Eighty-nine percent of the subjects had WC $>$ 90th percentile for gender and age. Of these, 32 patients (86.5%) had a

family history of obesity, and 24 (64.9%) of diabetes mellitus (DM).

Insulin resistance, as assessed by HOMA-IR, was the most commonly found metabolic abnormality; 27 (73.0%) patients presented HOMA-IR > 3.16. Of these, 17 (45.9%) had a family history of DM.

Waist circumference had a significant association with abnormal insulin levels ($p = 0.004$) and HOMA-IR ($p = 0.002$), with no association with undesirable lipid levels.

The serum level of leptin was significantly associated with %FM (r = 0.525), insulin values (r = 0.326), and BMI z-score (r = 0.458), but there was no significant association with HOMA-IR (r = 0.318).

The BMR of the pubertal obese children assessed by BIA (1,311.4 ± 304.1 cal) was lower than the BMR obtained by the FAO/WHO prediction equation (1985) (1,736.6 ± 261.2 cal); this difference was statistically significant ($p < 0.001$). The averages of the anthropometric and metabolic data, as well as of body composition for the two groups are depicted in ►**Table 1**.Weight, BMI, and leptin differed significantly between groups, as well as %FM and BMR, according to the FAO/WHO equation. (1985).

As depicted on ►**Table 2**, pubertal children and adolescents in the present study, regardless of the degree of obesity, presented high levels of insulin (70.3%), HOMA-IR > 3.16 (73.0%), low HDL-c levels (67.6%), and WC > p90 (89.2%). Regarding the variables analyzed, there was no significant difference between the groups.

Discussion

The objective was to study a relationship between metabolic changes, serum levels of leptin, and BMR in overweight pubertal children and adolescents. A total of 73% of the subjects presented hyperinsulinism. Hyperinsulinism is the main risk factor for the occurrence of DM, HBP, and dyslipidemia.[21,22] Acanthosis nigricans, which is a clinical manifestation of hyperinsulinism, was found in 84% of the subjects studied, of whom 70% had elevated insulin and only 8.1% had abnormal levels of plasma glucose. Only 5.4% of the participants had elevated insulin with no ACN. This data corroborates an aspect widely studied, that pubertal obese children have IR, although not presenting yet abnormal glucose levels. Therefore, if we are to wait for plasma glucose to be elevated, many tissue changes may have already occurred due to the presence of IR.[23] The group with severe obesity was the only group with subjects that presented plasma glucose levels higher than desirable (15.8%). Lavrador et al performed with 80 obese postpubertal adolescents, IR was found in 37.5% of the subjects, the cutoff levels of HOMA-IR being ≥ 3.43.[22] Zambon et al studied 70 subjects between 2 and 19 years old and found ACN in 58%, normal values of fasting plasma glucose, and 15% with increased insulin levels.[24] These results differ from ours, since we found more ACN and IR, perhaps influenced by the different pubertal stages of the sample. At puberty, insulin sensitivity decreases, causing a

Table 1 Anthropometric, biochemical, and body composition variables, according to the degree of obesity or severe obesity in pubertal children and adolescents

Variables	BMIz between 2 and 3 ($n = 18$)	BMIz above 3 ($n = 19$)	*p-value*
Age (years old)	9.72 ± 1.48	9.74 ± 1.48	0.976
Weight (Kg)	58.21 ± 15.43	68.62 ± 14.60	0.042*
Height (m)	1.45 ± 0.13	1.46 ± 0.09	0.781
BMI (Kg/m^2)	27.10 ± 2.84	31.87 ± 4.20	< 0.001*
TSF (cm)	27.11 ± 4.30	29.6 3 ± 6.32	0.219
WC (cm)	87.60 ± 9.76	92.32 ± 13.19	0.250
Glucose (mg/dl)	89.83 ± 5.43	93.10 ± 11.21	0.278
Insulin (uUI/ml)	19.7 (1.0–65.5)	20.32 (10.18–100.92)	0.288
HOMA-IR	4.177 (0.208–5.20)	4.61 (2.26–28.40)	0.316
TC (mg/dl)	150.89 ± 27.78	151.42 ± 26.63	0.953
HDL-c (mg/dl)	39.28 ± 9.95	43.32 ± 9.79	0.222
LDL-c (mg/dl)	94.78 ± 20.66	89.50 ± 24.79	0.487
TG (mg/dl)	84.11 ± 27.54	93 ± 50.14	0.512
Leptin (ng/ml)	11.58 ± 5.61	18.33 ± 8.45	0.007*
SBP (mmHg)	115.56 ± 9.83	117.00 ± 16.94	0.695
DBP (mmHg)	70.00 ± 9.39	68.68 ± 8.95	0.665
(%) Fat mass	32.95 (16.2–38.1)	35.90 (18.8–42.20)	0.029*

Abbreviations: BIA, bioimpedance; BMI, body mass index; BMIz, BMI z-score; BMR, basal metabolic rate; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein; HOMA, Homeostasis model assessment; LDL-c, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; TSF, tricipital skinfold; SBP, systolic blood pressure; WC, waist circumference.
*$p < 0.05$.

Table 2 Frequency of the variables related to the body mass z-score of pubertal children and adolescents

Variables	Total ($n = 37$)		BMI z-score from 2 to ≤ 3 ($n = 18$)		BMI z-score > 3 ($n = 19$)		
	n	%	*n*	%	*n*+	%+	*p-value*
Plasma glucose ≥ 100 mg/dl	3	8.1	0	0	3	15.8	0.230
Insulin ≥ 15 mg/dl	26	70.3	12	66.7	14	73.7	0.728
HOMA-IR > 3.16	27	73	12	66.7	15	78.9	0.476
TG ≥ 100 mg/dl	10	27	5	27.8	5	26.3	1
HDL-c ≤ 45 mg/dl	25	67.6	13	72.2	12	63.2	0.728
TC > 150 mg/dl	19	51.4	10	55.6	9	47.4	0.746
LDL-c ≥ 100 mg/dl	13	35.1	8	44.4	5	26.3	0.313
SBP $\geq$ p95	11	29.7	4	22.2	7	36.8	0.476
DBP $\geq$ p95	2	5.4	1	5.6	1	5.3	1
WC $>$ p90	33	89.18	15	45.5	18	54.5	0.340
ACN	31	83.78	14	77.7	17	89.4	0.405

Abbreviations: % +, percentage of patients with exams above normal values, *p-value* < 0.05; ACN, acanthosis nigricans; DB, diastolic blood pressure; HDL-c, high-density lipoprotein; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-c, low-density lipoprotein; *n* +, number of patients with exams above normal values, *p-value* <0.05; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

compensatory increase in insulin secretion.[25] It should be emphasized that in the presence of ACN, found in the physical examination, we should always consider the presence of IR. In our study, 23 (60.5%) subjects had ACN, large WC, high insulin and/or HOMA-IR; however, 84 had ACN.

Waist circumference had a significant association with abnormal insulin levels; however, there was no association with undesirable lipid levels. Increased WC is a sign of increased visceral fat, which is the most pathogenic and associated with metabolic syndrome. The diagnosis of metabolic syndrome can only be considered if the WC is $>$ p90. In our study, 89% of the children and adolescents presented WC $>$ p90. The accumulation of abdominal fat has an important relation between IR and lipid changes in the overweight pediatric age group.[26] A similar result was found in the study by Buff et al, in which abdominal obesity was present in 88.1% of subjects.[27]

Values higher than desirable for TC, LDL-c and TG were seen in 19 (51.4%), 13 (35.1%), and 10 (27.0%) of the subjects studied, respectively. High-density lipoprotein cholesterol levels below the desirable levels were found in 25 (67.6%) subjects. Dyslipidemia had no significant association with the age of the participants. These abnormal variables are risk factors, which when associated with obesity, in the long term, may lead to the development of cardiovascular disease. Atherosclerotic changes begin in the coronary arteries already during childhood.[21]

In our study with pubertal obese children and adolescents, the groups did not present significant differences regarding changes in TC, HDL-c, TG, LDL-c, IR, insulin, glucose, ACN, and blood pressure levels. However, Lavrador et al, in their study of obese postpubertal adolescents between 14 and 19 years old, identified that the higher the degree of obesity, the greater the frequency of the changes evaluated, with significant differences for fasting plasma glucose, IR, TG, HDL-c, and blood pressure.[22]

The low levels of HDL-c were the main lipid abnormality found in the two studied groups. This result deserves attention because HDL-c is an anti-atherogenic fraction, protective against atherosclerosis.[28] In the study by Koglin et al, it was found that after 4 months of diet intervention in obese children and adolescents, there was a reduction in TC and LDL-c levels, and an increase in HDL-c.[29]

In our study, HBP was found in 13 (35.1%) subjects, the group with severe obesity showing a higher frequency of abnormal systolic blood pressure (SBP).[15] The group of adolescentes with the higher degree of obesity presented a higher percentage of arterial hypertension (26,9 Vs 9,2) compared to the group with lower levels of obesity.[22]

We found a significant difference ($p < 0.001$) between the BMRs evaluated by different methods, and the BMR according to the FAO/WHO equation.[30] overestimated the BMR when compared with that determined by the BIA. Other studies have shown overestimation of BMR by prediction equations in obese children.[31] Schneider et al found results similar to ours. They analyzed overweight boys aged 12 to 17 years old comparing the BMR measured by indirect calorimetry with the BMR values estimated by prediction equations, and concluded that the prediction equations are not adequate and in most cases may overestimate the energy requirements.[32] The BMRs evaluated by the equations were $\sim$ 22% higher in the obesity group and 25% higher in the severe obesity group. It is therefore suggested to prioritize the use of BMR as determined by the BIA.

The severe obesity group presented higher mean values, but no significant difference on glucose, insulin, HOMA, TC, HDL-c, TG, leptin, HBP, BMR-BIA, BMR-FAO/WHO, and %FM. In this group, the BMR was higher, which can be explained by

the increase in lean mass caused by the need for the displacement of a larger body mass displacement. There was a strong association between BMI and BMR ($r = 0.737$ and $p < 0.001$). In the study by Butte et al, with 836 children aged 5 to 19 years old, energy expenditure was higher in overweight children and much of this difference was attributed to size and body composition.[33]

Jeffery et al studied 307 healthy children between 5 and 14 years old and noted that the level of leptin had a strong correlation with %FM in both genders, as well as moderate correlation with IR, regardless of the percentage of body fat. Leptin levels in children and adolescents aged 7 to 12 years old ranged from 2.8 to 5.3 ng/mL in females and from 4.6 to 9.8 ng/mL in males.[34] In our study with pubertal obese children and adolescents, leptin correlated positively with the BMI z-score, BMI, %FM, and insulin. Leptin levels in females ranged from 3.3 ng/mL to 30.4 ng/mL, and in males from 4.3 ng/mL to 26.8 ng/mL.

In our study, we found that subjects with severe obesity had higher levels of leptin as compared with obese subjects. As leptin acts on food control inhibiting it,[4,5] we can infer that leptin resistance is being established in these subjects.

The BMI z-score had a significant correlation with leptin levels in our study, as well as in Madeira et al.[28] Stylianou et al, in their study comparing 20 obese adolescents with IR, found 20 obese adolescents without IR, and 15 nonobese adolescents, and that the values of BMI, %FM, insulin, and HOMA-IR were positively correlated with serum leptin levels. And that leptin levels were significantly high in the obese subjects as compared with controls.[35]

The changes found in HDL-c, TC, and insulin levels in the studied group pose an alert regarding the need to assess them in obese children. In addition, the high prevalence of ACN, marker of IR, reinforces the importance of physical examination.

The results of our study with pubertal children and adolescents divided into two groups according to the degree of obesity did not show significant differences in relation to abnormal glucose, lipids, and blood pressure, demonstrating that obese children and adolescents do not necessarily present deterioration of these indicators when the BMI z-score rises.

Therefore, we noted that the BMR calculated by BIA seems to be the most adequate as compared with the FAO/WHO equation, not overestimating the calories. We conclude that obese children do not necessarily present deterioration of biochemical indicators when the BMI z-score rises. However, severe obesity seems to lead to leptin resistance at this stage of life. This is a period of high vulnerability and plasticity, therefore it becomes a crucial moment for intervention by health professionals aiming to treat these children and adolescents so that they do not get to adulthood obese.

Author Contributions

Conterato E. V. and Mello, E. D. contributed with the conception and design of the study. EC organized the database. EC performed the statistical analysis. EC, Machado T. D., Mello, E. D. and Nogueira-de-Almeida C. A. wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Conflict of Interests

The authors have no conflict of interests to declare.

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