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Leptin and Metabolic Syndrome in Obese Pediatric Population: A Cross-sectional Study

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Abstract

Background/Objectives: Childhood obesity represents the most relevant nutritional disorder in our environment. This study examines the prevalence of metabolic syndrome in an obese pediatric population and its relation to serum Leptin concentrations.

Subjects/Methods: A cross-sectional clinical and metabolic study was accomplished in a group of 106 obese children (47 males and 59 females). Patients were classified in prepubertal group (Tanner stage I) and pubertal group (Tanner stages II–V).

Results: Prevalence of insulin resistance (HOMA), hypertriglyceridemia, low high-density lipoprotein (HDL) and arterial hypertension (HTA) was 38.7, 45.3, 28.3 and 33.8% respectively. Metabolic syndrome prevalence (30.2%) was significantly higher in the pubertal group (38%) in relation to the prepubertal group (23.2%). There was a positive correlation between leptin and BMI (r=0.529), leptin and HOMA indexes (r=0,562) and Leptin and triglycerides (r=0,314). In addition, there was a positive correlation between HOMA indexes and triglycerides (r=0,596).

Conclusions: Clinical and metabolic disorders associated to obesity and related to the so-called metabolic syndrome are already present in pediatric population. Leptin could play an important role in the etiopathogenesis of the metabolic syndrome.

Keywords: Leptin; Metabolic syndrome; Childhood obesity; Insulin resistance; Puberty; Triglycerides; Blood pressure

Introduction

Childhood obesity represents the most relevant nutritional disorder in our environment [1,2]. It usually initiates at early stages in life, when child feeding depends –almost exclusively- on feeding habits and preferences in a family setting; it is subsequently exacerbated (by the time of school attendance and/or adolescence), probably in relation to the adoption of unhealthy feeding habits and lifestyle [3,4].

Additional studies –except for uncommon situations such as endocrine, genetic or metabolic pathologies, which justify excess body weight-, are used for the diagnosis and/or early detection of metabolic complications and, particularly, the metabolic syndrome. This syndrome is characterized by a cluster of symptoms associated to obesity, such as insulin resistance, arterial hypertension and dyslipidemia, and its interest lies in the high predictive value for cardiovascular disease and type 2 diabetes in adulthood, especially when it is already present in school children and/or adolescents [5-9]. Even when the International Diabetes Federation (IDF) [10] refers to the inability for diagnosis in school age, epidemiological data allow suspecting that metabolic syndrome or its components are already present at early stages [11-14].

Leptin is an adipocytokine that, in addition to multiple neuroendocrine functions, has a role in the regulation of energy balance, as well as in carbohydrate and lipid metabolism and arterial pressure regulation. In this way, many authors have suggested that leptin might be involved in the etiopathogenesis of metabolic syndrome [15-17].

The aim of this work is to determine the prevalence of metabolic syndrome and its relation to serum leptin concentrations in a group of obese pediatric population.

Methods

Patients: A clinical assessment and metabolic study was accomplished in all patients diagnosed with obesity who attended follow-up consultation within the year 2014. Clinical evaluation was conducted in one of the three offices of the Pediatric Endocrinology Unit of the Navarra Hospital Complex. Pubertal stage was determined in each patient according to Tanner's criteria, and patients were classified in two different groups: prepubertal group (Tanner stage I) and pubertal group (Tanner stages II–V).

All those patients with personal history of endocrine disease, malformation syndromes or iatrogenic obesity (drug treatments) were excluded.

The metabolic syndrome was defined by modified Cook's criteria [18] as the manifestation of at least three of the following features: low HDL-cholesterol (<40 mg/dl), hypertriglyceridemia (TG>110 mg/dl), obesity, arterial hypertension and insulin resistance.

Clinical assessment: The assessment of weight and height was accomplished in underwear and barefoot. Weight was measured using an Año-Sayol scale, with a reading interval 0-120 kg and precision 100 g, and height was measured using a Holtain wall stadiometer ranging 60-210 cm, and precision 0.1 cm. Body mass index (BMI) was calculated according to the corresponding formula: weight (kg)/height^2 (m). Values of Z-score for BMI were calculated using a Nutrition application (Aplicación Nutricional) program from the Spanish Society of pediatric Gastroenterology, Hepatology and Nutrition (available at http://www.

gastroinf.es/nutritional/). The inclusion criterion was BMI (Z-score) values exceeding +2,0 (97 percentile) by age and sex according to growing charts from Ferrández et al. (Centro Andrea Prader, Zaragoza 2002) [19].

Blood pressure (BP) was measured in the right arm with the patient in the supine position using Visomat comfort 20/40 (Roche Diagnostics Inc.) digital blood pressure monitor, recording the lowest of three measurements. Arterial hypertension (HTA) was considered when systolic and/or diastolic pressure was equal to or higher than 95th percentile by age, sex and height from the American reference charts (National high blood pressure Program in Children and Adolescents) [20].

The institutionalized program for Child Care in the Community of Navarre (Comunidad Foral de Navarra, Spain) includes periodic health examinations at ages 1, 2, 3, 4, 6, 8, 10 and 12 years. The anthropometric measurements (weight and height) are recorded in the corresponding clinical history. This record has allowed the registration of the age of onset for obesity and the time of evolution at the moment of the examination.

Metabolic study: Plasma concentrations for glucose, insulin, triglycerides, total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and leptin were measured under basal fasting conditions using standardized methodologies.

In order to determine insulin resistance, the HOMA (*homeostasis model assessment*) indexes were calculated from fasting glucose and insulin concentrations (glucose levels in mmol × insulin in μUml/L/22.5). Insulin resistance was considered when HOMA value was equal to or higher than 3.8 [21].

Statistical analysis

Results are displayed as percentages (%) and means (M) with corresponding standard deviations (SD). Statistical analysis (descriptive statistics, student's T and Chi square test, Pearson's correlation) was done using the Statistical Packages for the Social Sciences version 20.0 (Chicago, Illinois, USA). Statistical significance was assumed when p value was lower than 0.05.

Results

The sample of patients consisted of 106 patients (47 males and 59 females). The prepubertal group included 56 patients (22 males and 34 females) and the pubertal group included 50 patients (25 males and 25 females).

Table 1 lists and compares the clinical features in both groups according to pubertal stage and sex. Within the pubertal group, the average values for age of onset, age at examination, years of evolution and systolic blood pressure were significantly higher (p<0.05); within the prepubertal group, BMI values (Z-score) at examination were higher (p<0.05). There were no statistically significant differences among the average values of diastolic blood pressure between the different groups. The average BMI values (Z-score) in pubertal group were significantly higher (p<0.05) in males. Finally, within pubertal group, the average values for age of onset (obesity) were significantly lower (p<0.05) in females.

Table 2 displays and compares the average values for the results of blood tests among the different groups according to pubertal stage and sex. Within the pubertal group, average values for insulin were significantly higher (p<0.05) with respect to the prepubertal group. The average values for HDL-C within pubertal group were significantly higher (p<0.05) in females, and the average values for HOMA and leptin within the pubertal group were significantly higher (p<0.05) in males.

There was a significant positive correlation (p<0.05) between leptin plasma levels and BMI values (r=0.529) (Figure 1). In addition, there was a significant positive correlation between leptin plasma levels and HOMA indexes (r=0.562) (Figure 2). There was also a significant positive correlation (p<0.05) between HOMA indexes and plasma concentrations of triglycerides (r=0.596) (Figure 3), as well as with age at examination (r=0,207). And there was also a significant positive correlation (p<0.05) between leptin plasma levels and plasma concentrations of triglycerides (r=0.314) (Figure 4).

Table 3 presents and compares the percentage values for the different clinical and metabolic parameters used as constituents of the metabolic syndrome in both groups. The percentage of patients who showed systolic blood pressure values higher than 95th percentile for the applied reference were significantly higher in the pubertal group (p<0.05). There were no statistically significant differences among both groups regarding the percentage of patients who present HOMA index values higher than 3.8, plasma triglycerides higher than 110 mg/dl, HDL-C values lower than 40 mg/dl and diastolic blood pressure values higher than 95th percentile for the applied reference charts. Within the pubertal group the metabolic syndrome prevalence (38%) was significantly higher (p<0.05) with respect to the prepubertal group (23.2%).

Discussion

The prevalence of metabolic syndrome within the whole sample was 30.2%, being significantly higher in the pubertal group (38%), in contrast to the prepubertal group (23.2%). The comparison of these results with those described by other authors reveals that the prevalence found is similar than references from Cook (28.7%) [18], Cruz (30%) [22], Weiss (38.7%) [23] Viner (30%) [24] and Ferranti (31.2%) [25] in obese UK or American children and adolescents, although slightly higher than references from Olza (16.8%) [13], Lopez-Capapé (18%) [26] and Tapia (18.6%) [27] in Spanish obese pediatric population. Nevertheless, the contrast of the rate of prevalence from different Studies has a relative value, since the criteria applied are different, and even different cut points for each component of MS are used [28].

The IDF considers fat distribution and, concretely, central or visceral obesity-which is defined by abdominal perimeter- as a "sine qua non" criterion for the diagnosis of metabolic syndrome due to its high predictive value for cardiovascular disease in adult life [29,30]. However, there is some controversy regarding the adequacy of its use as a main and/or necessary diagnostic criterion [31]; in fact, recent studies conducted in pediatric population have used both abdominal perimeter [18,22,27,32] and BMI [23,24,26,33] interchangeably. In this case, the inclusion criterion was BMI value (Z- score) higher than +2.0 (97th percentile) by age and sex according to the growing charts from Ferrández et al. (Centro Andrea Prader, Zaragoza) [19].

Insulin resistance, as several authors have highlighted [24,26] has been a very frequently noted metabolic disorder in the population studied. It is worth indicating that, when Reaven [34] described the syndrome X, he considered insulin resistance as the determining pathophysiological factor and, in fact, the WHO included it as main and necessary criterion in order to diagnose the metabolic syndrome [35]. However, the diagnosed criteria subsequently proposed by the

Clinical data	Prepubertal group	Pubertal group	Total
Age of onset (years)			
Males	3.50 ± 1.75	5.10 ± 3.22**	4.35 ± 2.73
Females	3.38 ± 1.36	7.89 ± 3.56**	5.29 ± 3.37
Total	3.43 ± 1.51*	6.50 ± 3.65*	4.88 ± 3.12
Age at examination (years)			
Males	8.78 ± 1.01	12.42 ± 1.43**	10.72 ± 2.21
Females	8.55 ± 1.26	13.22 ± 1.15**	10.53 ± 2.62
Total	8.64 ± 1.17*	12.82 ± 1.35*	10.61 ± 2.44
Evolution (years)			
Males	5.27 ± 1.49	7.95 ± 2.86	6.64 ± 2.64
Females	5.16 ± 1.85	6.65 ± 2.71	5.71 ± 2.23
Total	5.21 ± 1.71*	7.35 ± 2.84*	6.14 ± 2.49
BMI (Z-score)			
Males	4.05 ± 1.13	3.95 ± 1.31**	4.00 ± 1.21**
Females	3.55 ± 1.27	2.60 ± 0.50**	3.14 ± 1.11**
Total	3.74 ± 1.23*	3.27 ± 1.20*	3.52 ± 1.23
Systolic BP (mmHg)			
Males	113.68 ± 11.55	120.09 ± 14.74	116.88 ± 13.48
Females	108.78 ± 16.94	121.17 ± 16.10	113.96 ± 17.56
Total	110.77 ± 15.05*	120.64 ± 15.29*	115.26 ± 15.87
Diastolic BP (mmHg)			
Males	67.22 ± 11.45	70.81 ± 17.08	69.02 ± 14.49
Females	67.59 ± 11.85	70.04 ± 12.27	68.61 ± 11.98
Total	67.44 ± 11.58	70.42 ± 14.65	68.79 ± 13.08

(*) p<0.05 among age groups
(**) p<0.05 between sexes

Table 1: Average values (M ± SD) for the clinical features in both age groups according to sex.

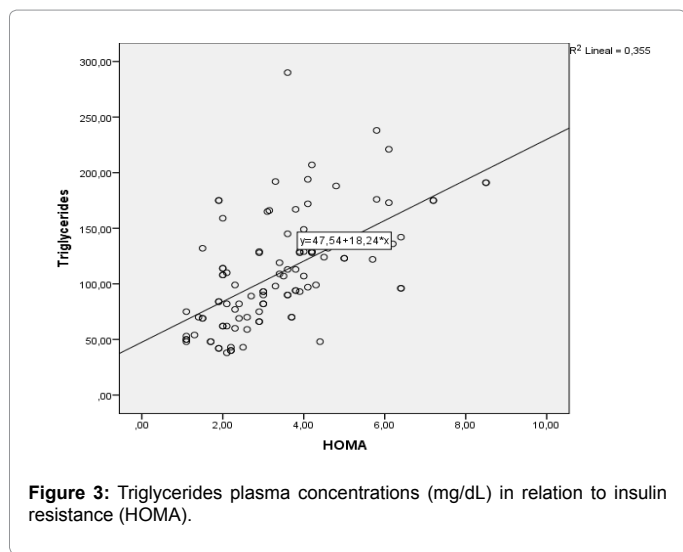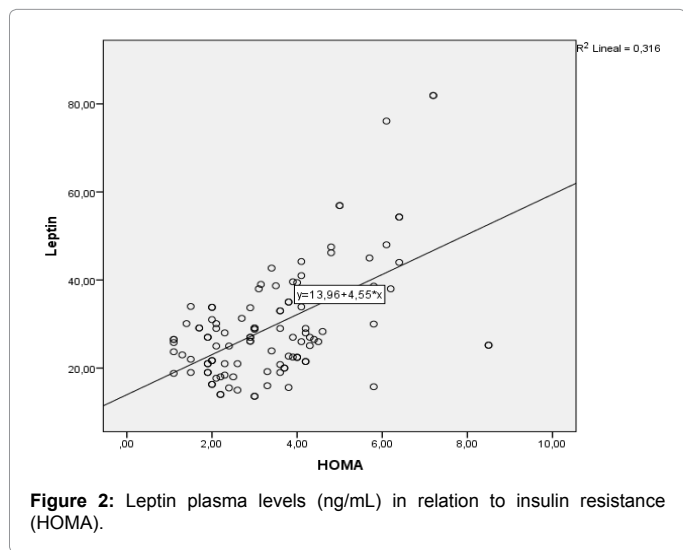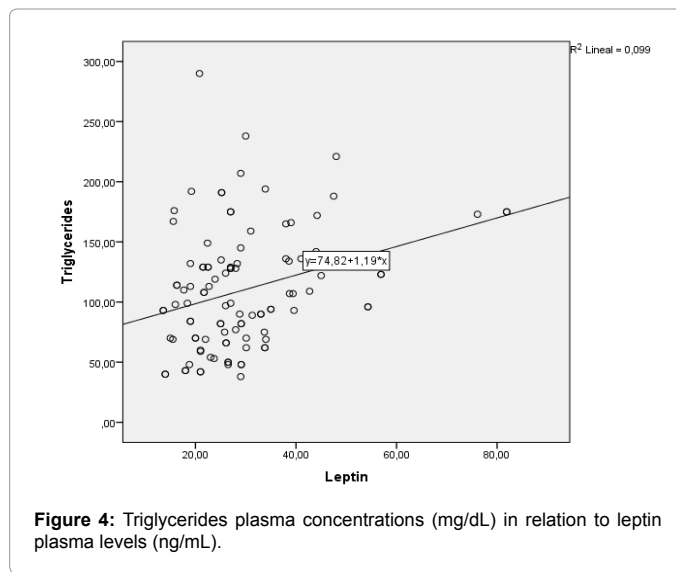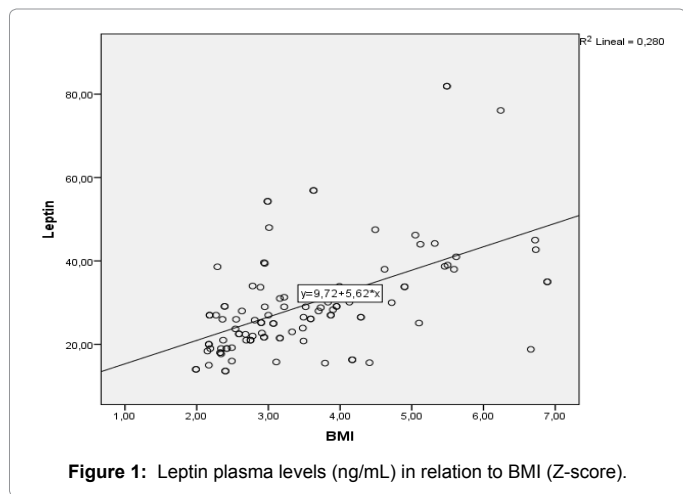| Biochemical data	Prepubertal group	Pubertal group	Total
Glucemia (mg/dl)			
Males	93.40 ± 10,58	92.92 ± 10,18	93.14 ± 10,39
Females	89.12 ± 7.55	90.16 ± 8.87	89.56 ± 8.08
Total	90.83 ± 9.17	91.54 ± 9.55	91.17 ± 9.31
Insulin (uU/ml)			
Males	17.48 ± 14.58	18.22 ± 10.49	17.86 ± 12.52
Females	13.58 ± 9.70	23.82 ± 15.58	17.57 ± 13.18
Total	15.14 ± 11.93*	20.89 ± 13.31*	17.70 ± 12,82
HOMA			
Males	3.50 ± 2.09	4.01 ± 1.64**	3.77 ± 1.86**
Females	3.17 ± 1.41	3.08 ± 1.25**	3.13 ± 1.34**
Total	3.30 ± 1.70	3.54 ± 1.52	3.42 ± 1.61
Cholesterol (mg/dl)			
Males	165.04 ± 27.34	152.72 ± 21.77	158.48 ± 25.05
Females	160.84 ± 27.18	157.32 ± 22.62	159.32 ± 25.17
Total	162.52 ± 27.07	155.02 ± 22.10	158.95 ± 25.00
LDL-C (mg/dl)			
Males	93.50 ± 27.51	87.86 ± 21.26	90.62 ± 24.40
Females	94.06 ± 27.58	87.50 ± 20.64	91.25 ± 24.85
Total	93.83 ± 27.29	87.68 ± 20.72	90.97 ± 24.53
HDL-C (mg/dl)			
Males	51.90 ± 11.31	43.30 ± 8.57**	47.51 ± 10,80
Females	49.48 ± 12,37	50.08 ± 9.93**	49.73 ± 11,32
Total	48.73 ± 9.76	47.25 ± 9.01	48.75 ± 11,09
Triglycerides(mg/dl)			
Males	115.95 ± 65.88	126.36 ± 45.59	121.48 ± 55.62
Females	98.08 ± 42.87	104.32 ± 42.08	100.72 ± 42.29
Total	105.10 ± 53.27	115.34 ± 44.83	109.93 ± 49.50
Leptin (ng/ml)			
Males	30.14 ± 11.75	34.38 ± 17.01**	32.39 ± 14.78**
Females	29.11 ± 12.43	24.66 ± 8.72**	27.22 ± 11.15**
Total	29.51 ± 12.07	29.52 ± 14.25	29.51 ± 13.08

(*) p<0.05 among age groups
(**) p<0.05 between sexes

Table 2: Average values (M ± SD) for metabolic study in both age groups according to sex.

National Cholesterol Education Programs Adult Treatment Program III [36] as well as by the IDF [9] opted for a "lipid centric" theory, with special focus on dyslipidemia and/or fat distribution.

Even though several criteria have been used to evaluate peripheral insulin sensitivity and/or alterations in glucose metabolism (fasting glucose, glycemia after an oral glucose tolerance test, fasting insulin

Figure 1: Leptin plasma levels (ng/mL) in relation to BMI (Z-score).

Figure 2: Leptin plasma levels (ng/mL) in relation to insulin resistance (HOMA).

Figure 3: Triglycerides plasma concentrations (mg/dL) in relation to insulin resistance (HOMA).

Figure 4: Triglycerides plasma concentrations (mg/dL) in relation to leptin plasma levels (ng/mL).

Diagnostic criteria	Prepubertal group n (%)	Pubertal group n (%)	Total n (%)
HOMA >3,8	21 (37.5%)	20 (40.0%)	41 (38.7%)
TG>110 mg/dl	23 (41.1%)	25 (50.0%)	48 (45.3%)
HDL-C<40 mg/dl	13 (23.6%)	17 (36.2%)	30 (28.3%)
SBP>p95(*)	14 (25.9%)	21 (46.7%)	35 (33.8%)
DBP>p95	9 (16.7%)	7 (15.6%)	16 (15.1%)

(*) $p<0.05$ among age groups

Table 3: Prevalence of the different diagnostic criteria of metabolic syndrome in both groups

(hyperinsulinemia with euglycemia). In this case, despite the application of a quite restrictive cut point [21], insulin resistance was already detected in thirty nine per cent of the patients included in the study. In addition, the existing correlation between the HOMA indexes and the age of the patients at the moment of examination suggests that the onset of this metabolic comorbidity associated to obesity is related to hormonal changes concomitant with puberty rather than to the evolution time of obesity.

The situation of insulin resistance usually involves a disturbance in

levels, etc.), the use of a mathematical model called *homeostasis model assessment* (HOMA) as a criterion for insulin resistance has been widely contrasted as an early disorder in glucose homeostasis

lipid profile by stimulating lipolysis and, therefore, an increase in plasma exchange of fatty acids that, at the same time, stimulates the hepatic triglyceride synthesis. This explains its correlation with the HOMA index of the patients. In addition, the concentration of low density lipoproteins is usually in normal range while the concentration of high density lipoproteins is usually low, being this considered as a side effect of hypertriglyceridemia [37-39]. Dyslipidaemia observed in patients with insulin resistance corresponded with the situation expected in this metabolic condition. Furthermore, hyperinsulinemia causes water and sodium retention and activates the sympathetic nervous system, contributing to the development of hypertension.

Leptin participates directly in the regulation of energy homeostasis through an anorectic effect and the increase of thermogenesis. Plasma concentrations reflect the reserve of organic fat and are considered as a predictive factor for insulin resistance [40]. This would explain, on one hand, the existing correlation between plasma concentrations and BMI, and, on the other hand, the correlation with the HOMA index in the patients included in this work. In addition, Leptin stimulates lipolysis in adipocytes and, consequently, contributes to dyslipidaemia (there was a correlation with Leptin plasma levels and triglycerides); it also stimulates angiogenesis and/or endothelial dysfunction and would explain, to a great extent, the development of hypertension, which is frequently associated to obesity [15].

As a conclusion, we remark the finding of clinical and metabolic disorders associated to obesity and related to the so-called metabolic syndrome, which, to a great extent, are already present in pediatric population. In the same way, leptin serum levels could play an important role in the etiopathogenesis of metabolic syndrome and/or comorbidities that are associated to obesity.

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