Metabolic Cardiovascular Syndrome in Obese Prepubertal Children: The Role of High Fasting Insulin Levels

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The aim of this study was to detect the presence and degree of impairment of cardiovascular disease (CVD) risk factors, grouped as metabolic cardiovascular syndrome (MCS), in obese prepubertal children. We also assessed the influence of high fasting insulin levels in this pathological status. A cross-sectional study was performed on obese children based on fasting blood samples. Subjects were 61 obese children (aged 6 to 9 years) and an equal number of non-obese children paired by age and sex. The obese children presented the following characteristics in comparison to the non-obese group: significantly high levels of insulin (8.2 ± 0.52 *v* 6.12 ± 0.34 μU/mL), triglycerides (TG) (0.79 ± 0.04 *v* 0.60 ± 0.02 mmol/L), uric acid (0.24 ± 0.005 *v* 0.21 ± 0.004 mmol/L), systolic (SBP) (94.59 ± 1.06 *v* 88.85 ± 1.2 mm Hg) and diastolic (56.49 ± 1.07 *v* 52.21 ± 1.06 mm Hg) blood pressure (DBP), and low levels of high-density lipoprotein cholesterol (HDL-C) (1.30 ± 0.04 *v* 1.46 ± 0.03 mmol/L), and nonesterified fatty acids (0.407 ± 0.02 *v* 0.505 ± 0.02 mmol/L). The hyperinsulinemic obese children showed the same types of differences when compared with the normoinsulinemic group. In the obese group, having adjusted for age, waist/hip ratio (WHR), body mass index (BMI), and sex hormone-binding globulin (SHBG), insulin was an independent prediction factor for triglycerides (*P* = .0004), apolipoprotein A-I (Apo-AI) (*P* = .005), and alanine aminotransferase (ALT) (*P* = .029). BMI was an independent prediction factor for HDL-C (*P* = .001) and triglycerides (*P* = .027). However, insulin was an independent prediction factor in the control group for triglycerides (*P* = .0002) and SBP (*P* = .012), just as BMI was for HDL-C (*P* = .011) and uric acid (*P* = .041). We conclude that the cluster of CVD risk factors associated with MCS and intra-abdominal fat is present in obese prepubertal children. This situation seems to depend, to a large extent, on the insulin basal level. The apparent association between BMI and MCS is due to the correlation between BMI and insulin, and to the fact that insulin associates with MCS. Within the obese group, hyperinsulinemic children present the greatest impairment in the parameters considered to be constituents of MCS.

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OBESITY IS ONE of the most frequent problems in Western civilization. It is associated with high morbidity rates and has recently been included within the major modifiable cardiovascular risk factors.[1] Adults with obesity, mainly of the abdominal kind, present a greater risk of coronary arterial disease, with an increase of the disorders related to metabolic cardiovascular syndrome (MCS).[2-4] Hyperinsulinemia and/or insulin resistance participates, either directly or indirectly, in the development of this group of disorders known as MCS or insulin resistance syndrome (IRS).[5,6] High insulin levels precede the development of dyslipemia and hypertension.[7,8]

Peripheral insulin resistance is one of the first disorders present in obese subjects, characterized by an increase in the secretion of insulin and a defect in hepatic glucose release inhibition by insulin.[9,10] High insulin levels were described in obese children when compared with non-obese children, particularly from 6 years upwards.[11] It has recently been described that only 14.4% of obese pubertal children (mean age, 13 years) were free of any risk factor for MCS, in contrast to 79.1% of non-obese children.[12]

The obesity that appears from 5 years upwards increases the risk of remaining obese in adolescence, with the subsequent effect of the obese adolescent becoming an obese adult.[13,14] However, the obesity that appears at this age allows for an analysis of the effect of the drop in insulin sensibility, independently to sexual hormones. Some alterations associated with IRS and intra-abdominal fat deposits have not been sufficiently studied in prepubertal children.

The present study attempts to determine, in obese prepubertal children (aged 6 to 9 years, Tanner stage 1),[15] the degree of impairment of the cluster of cardiovascular disease (CVD) risk factors grouped as MCS, and to evaluate the influence of the fasting insulin level in this pathological process. We also examine the possibility of any significant differences between normo- and hyperinsulinemic obese children.

SUBJECTS AND METHODS

Subjects

A case-control study was performed with obese children of both sexes. To achieve an alpha error of 5% and a beta error of 0.10, the minimum required sample group was calculated at 60 children. The study was of 61 obese children (body mass index [BMI] > 90th percentile in growth curves for the study population[16]) and the same number of non-obese children paired by age and sex (aged 6 to 9 years) as the control group. All subjects were at Tanner stage 1.

Several schools in the area were informed of the study to be carried out, and the parents were asked permission for their children to participate. The 2 groups, both obese and non-obese, were formed with the children that agreed to participate in the study, and were classified according to their BMI. All parents submitted written consent, and the study was authorized by the ethical investigation committee of our hospital.

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In the obese group, a division was made between normoinsulinemic children and hyperinsulinemic children (basal insulin > the mean ± 2 SD of the control group, cutoff point 11.42 μU/mL). In the same way, another division was made in the obese group in terms of the different insulin level quartiles.

Children with diabetes (fasting glucose ≥ 7.0 mmol/L), impaired fasting glucose (fasting glucose ≥ 6.1 mmol/L and < 7.0 mmol/L),[17] hyperlipidemia (cholesterol total > percentile 95 for their age and sex in growth curves for the study population), hypertension (> percentile 95 for their age and sex in growth curves for the study population),[18] and secondary obesity (phenotype valuation and specific complementary exploration) were excluded from the study. Any child receiving pharmacological treatment was also excluded. All children had similar lifestyles with no significant physical training program.

Blood Sampling and Analysis

Venous extraction in the antecubital fossa was performed after 12 hours of fasting.

Glucose, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholinesterase (ChE), total cholesterol (TC), and triglycerides (TG) were determined using a random access analyzer (Axon, Bayer Diagnostics, Tarrytown, NY) with Bayer Diagnostics reactives.

High-density lipoprotein cholesterol (HDL-C) was determined after the precipitation of chylomicrons, very–low-density lipoproteins, and low-density lipoproteins, with phosphotungstic acid and magnesium ions. The concentration of low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.[19] Nonesterified fatty acids (NEFA) were quantified by a colorimetric enzyme assay (NEFA C ACS-ACOD Method, Woko Chemicals GmbH, Nissanstr, Germany).

Insulin was quantified by a microparticle immunoassay (IMx system Insulin, Abbott Laboratories, Chicago, IL) in an IMx automatic analyzer (Abbott Laboratories). Apolipoprotein A-I (Apo A-I), and apolipoprotein B (Apo B) were measured by nephelometry (N Antisera to Human Apolipoprotein A-I and Apolipoprotein B reagent, Behringwerke AG, Marburg, Germany) in a Dade Behring Analyzer II Nephelometer.

Sex hormone-binding globulin (SHBG) was quantified by an enzyme inmunoassay (Radim S.A., Liége, Beilgium) in a microtiter plate analyzer (Labotech, Chemila, Rome, Italy).

Anthropometric Measurements

Weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm. BMI was calculated as weight (kilograms)/height (meters)^2 and the ponderal index as weight (kilograms)/height (meters)^3. Waist circumference was measured at the level of the umbilicus, hip circumference at the level of the greater trochanters, and pubic symphysis to the nearest 0.1 cm.

Blood Pressure

Blood pressure was measured with a mercury sphygmomanometer (Pymah Corp, Sommerville, NJ) after 20 minutes of rest and in a supine position. Appropriate cuff sizes were used to allow for differences in arm circumference between children. One measure was taken on each of 3 days, and the mean was calculated.

Statistical Analysis

Statistical assessment was conducted using Microstat (Ecosoft, Inc, Indianapolis, IN) or GraphPAD InStat (GraphPAD Software, San Diego, CA). The abnormal values (outliers) were excluded using Reed's method.[20] Results were expressed as the mean ± SEM and with a 95% confidence interval (95% CI). The distribution of each variable was tested for departure from Gaussian distribution and the equality of variances was controlled by Snedecor's F test. The mean values of the groups were compared using Student's unpaired t test or one-way analysis of variance (ANOVA). Statistical significance was set at $P < .05$.

Correlation between variables was evaluated using Pearson's correlation coefficient and regression analysis. Multivariant regression analysis was performed using the Stepwise method. It is important for the statistical procedure to include a check for regression. The distribution of residuals must be verified as normal, and their variance as constant. In this study, the normality of residuals was checked using the chi-square test, and a graphic analysis of residuals was performed to provide information on the constancy of variance. Diagnostic measures were used for the detection of problematic observations: an observation was considered an outlier if its residual was greater than 3 Sy.x (standard error of estimate). For each variable, potential confounding factors ($.05 < P < .2$) were evaluated by an analysis of raw and adjusted regression coefficients. In the correlation analysis, when a variable had to be eliminated, the total results of that patient were removed.

RESULTS

Table 1 shows the anthropometric data of both groups. The median age was 7.7 years (obese) and 7.8 years (control), with a range of 6 to 9 years.

Nonsignificant differences were found in ALT levels ($P = .073$) between obese and non-obese children (Table 1). However, these levels were significantly higher in hyperinsulinemic obese children than in the normoinsulinemic group (mean [95% CI], 23.06 U/L [19.63 to 26.5] *v* 18.93 U/L [17.6 to 20.3]) (Table 2).

Mean values (obese *v* control) of TG (0.79 mmol/L [95% CI, 0.71 to 0.87] *v* 0.60 mmol/L [0.56 to 0.64]), TC/HDL-C index (3.48 [3.39 to 3.78] *v* 3.1 [2.97 to 3.23]) and LDL-C/HDL-C index (2.21 [2.11 to 2.47] *v* 1.86 [1.78 to 2.03]) were significantly higher in the obese children. On the other hand, the mean values of HDL-C (1.30 mmol/L [1.24 to 1.38] *v* 1.46 mmol/L [1.40 to 1.54]) and NEFA (0.407 mmol/L [0.372 to 0.443] *v*

Table 1. Descriptive Statistics and Selected Biochemical Parameters of the Study Groups

	Mean ± SEM		
	Control	Obese	*P* Value
n	61	61	
Male/female	22/39	22/39	
Age (yr)	7.74 ± 0.11	7.69 ± 0.12	>.20
Weight (kg)	27.28 ± 0.63	37.67 ± 0.80	<.001
Height (cm)	127.21 ± 1.02	129.39 ± 0.85	.103
BMI (kg/m^2)	16.73 ± 0.18	22.35 ± 0.27	<.001
WHR	0.836 ± 0.005	0.845 ± 0.006	>.20
SBP (mm Hg)	88.85 ± 1.2	94.59 ± 1.06	<.001
DBP (mm Hg)	52.21 ± 1.06	56.49 ± 1.07	.005
Uric acid (mmol/L)	0.21 ± 0.004	0.24 ± 0.005	<.001
ALT (U/L)	18.31 ± 0.68	20.08 ± 0.71	.073
AST (U/L)	29.57 ± 0.90	27.23 ± 0.42	.020
ChE (U/L)	10800.4 ± 212.2	11541.8 ± 226.9	.019

Abbreviations: BMI, body mass index; WHR, waist/hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChE, cholinesterase.

0.505 mmol/L [0.462 to 0.548]) were significantly lower in the obese children (Table 3). Within the obese group (Table 2), the hyperinsulinemic children showed significant increases of TG (1.04 mmol/L [0.82 to 1.25) *v* 0.69 mmol/L [0.62 to 0.76]) and significant decreases of Apo A-I (54.25 μmol/L [50.98 to 57.42] *v* 58.66 μmol/L [56.50 to 60.82]) with regard to normoinsulinemics. HDL-C values were also lower and close to significance in the hyperinsulinemic group.

As for carbohydrate metabolism, no significant differences were found in glucose concentration (Table 3), but insulin levels were significantly higher in the obese group than in the control group: 8.2 μU/mL (95% CI, 7.19 to 9.21) against 6.12 μU/mL (5.46 to 6.79). Similar differences were found in hyperinsulinemic obese subjects with regard to normoinsulinemics (Table 2), with the insulin/glucose index also registering as significantly higher. In the group of non-obese children, only 3 were hyperinsulinemic.

Systolic blood pressure (SBP) values (obese *v* control) of 94.59 mm Hg (95% CI, 92.52 to 96.66) versus 88.85 mm Hg (86.5 to 91.2) and diastolic blood pressure (DBP) values of 56.49 mm Hg (95% CI, 54.39 to 58.59) versus 52.21 mm Hg (50.15 to 54.28) were significantly higher in the obese children group (Table 1).

Obese children presented uric acid concentrations (Table 1) that were significantly higher than those of the control group: 0.24 mmol/L (95% CI, 0.23 to 0.25) against 0.21 mmol/L (0.21 to 0.22). Furthermore, in the obese group, uric acid correlated positively with waist/hip ratio (WHR) ($r = 0.393$; $P = .018$), but not with BMI or insulin.

The multiple regression analysis for the obese group variables is summarized in Table 4. In the obese group, using stepwise multiple regression analysis, insulin and BMI have additive effects on TG levels, which explains a TG variance of 20% and 9%, respectively. BMI also explains an HDL-C variance of 23%.

The ponderal index (weight/height^3) showed the same relations as BMI, and was an independent prediction factor for HDL-C ($P = .008$) and TG ($P = .004$), adjusting for insulin, age, WHR, and SHBG. The WHR was not an independent prediction factor for the variables analyzed.

In the control group, insulin was an independent prediction factor for TG ($P = .0002$) and SBP ($P = .012$), and BMI was an independent prediction factor for HDL-C ($P = .011$) and uric acid ($P = .041$).

The means of the variables considered of interest in the group of obese children, grouped for the insulin quartiles, are shown in Table 5.

Table 2. Descriptive Statistic and Selected Biochemical Parameters of the Obese Group

	Mean ± SEM		
	Normoinsulinemic Obese	Hyperinsulinemic Obese	*P* Value
n	44	17	
Male/female	16/28	6/11	>.20
Age (yr)	7.62 ± 0.14	7.88 ± 0.24	>.20
Glucose (mmol/L)	4.69 ± 0.06	4.88 ± 0.09	.094
Insulin (μU/mL)	6.33 ± 0.36	13.03 ± 0.79	<.001
Insulin/glucose ratio	1.36 ± 0.004	2.66 ± 0.008	<.001
BMI (kg/m^2)	21.88 ± 0.33	23.54 ± 0.31	.005
WHR	0.837 ± 0.007	0.867 ± 0.01	.023
TG (mmol/L)	0.69 ± 0.03	1.04 ± 0.23	.022
HDL-C (mmol/L)	1.34 ± 0.04	1.21 ± 0.05	.074
Apo A-I (μmol/L)	58.66 ± 1.10	54.25 ± 1.49	.031
ALT (U/L)	18.93 ± 0.69	23.06 ± 1.62	.007
ChE (U/L)	11244 ± 252	12311 ± 447	.034
SBP (mm Hg)	93.64 ± 1.34	97.06 ± 1.42	.148
DBP (mm Hg)	55.73 ± 1.24	58.47 ± 2.12	>.20
NEFA (mmol/L)	0.406 ± 0.02	0.411 ± 0.03	>.20

Abbreviations: BMI, body mass index; WHR, waist/hip ratio; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; Apo A-I, apolipoprotein A-I; ALT, alanine aminotransferase; ChE, cholinesterase; SBP, systolic blood pressure; DBP, diastolic blood pressure; NEFA, nonesterified fatty acids.

Table 3. Lipid Profile and Carbohydrate Metabolism in the Study Groups

	Mean ± SEM		*P* Value
	Control	Obese	
n	61	61	
Cholesterol (mmol/L)	4.46 ± 0.08	4.52 ± 0.08	>.20
Triglycerides (mmol/L)	0.60 ± 0.02	0.79 ± 0.04	<.001
Apo A-I (μmol/L)	57.34 ± 0.96	57.43 ± 0.93	>.20
Apo B (μmol/L)	1.24 ± 0.03	1.34 ± 0.04	.048
HDL-C (mmol/L)	1.46 ± 0.03	1.30 ± 0.04	.002
LDL-C (mmol/L)	2.71 ± 0.07	2.86 ± 0.08	.161
TC/HDL-C index	3.1 ± 0.07	3.48 ± 0.10	.002
LDL-C/HDL-C index	1.86 ± 0.06	2.21 ± 0.09	.001
NEFA (mmol/L)	0.505 ± 0.02	0.407 ± 0.02	<.001
Glucose (mmol/L)	4.77 ± 0.04	4.78 ± 0.04	>.20
Insulin (μU/mL)	6.12 ± 0.34	8.2 ± 0.51	<.001
Insulin/glucose ratio	1.28 ± 0.009	1.72 ± 0.006	<.001

Abbreviations: Apo A-I, apolipoprotein A-I; Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; NEFA, nonesterified fatty acids.

DISCUSSION

Dyslipemia, hypertension, diabetes and other metabolic disorders (increased uric acid and ALT) coexist in some patients.[5,21-23] These disorders have been related to obesity and to an increase in plasma levels of insulin.[24,25] Hyperinsulinemia and/or insulin resistance has been described as the key factor underlying the association of this group of metabolic disorders, known as metabolic cardiovascular syndrome or insulin resistance syndrome.[5]

Insulin resistance is one of the first alterations described in obese subjects.[10,11] Some metabolic alterations described in the IRS are present in most obese pubertal children and adolescents.[12,26] Disorders defined as MCS may therefore be present in infancy, particularly in hyperinsulinemic obese children.

In normal children, insulin resistance increases at puberty, and differs according to the Tanner stage, increasing significantly by Tanner 2 and remaining constant between Tanner 2 and 4.[27,28] In obese children, this increase in resistance to insulin can begin at a very early age. When studying some of the parameters related to insulin resistance, significantly high

Table 4. Multiple Regression Analyses for Variables of Interest in MCS

	Intercept	Slopes					R^2
		Age	WHR	BMI	SHBG	Insulin	
HDL-C	100.9	3.33‡	NS	−2.68*	NS	NS	0.3432
TG	29.61	−8.66‡	NS	3.96‡	NS	3.56*	0.3374
Apo A-I	129.1	7.03‡	NS	NS	NS	−2.04†	0.2893
Uric acid	2.375	NS	NS	NS	−0.02‡	NS	0.1867
ALT	3.761	NS	NS	NS	NS	0.47‡	0.1524

NOTE. None of the independent variables was significant for systolic blood pressure, diastolic blood pressure, or cholinesterase.

Abbreviations: NS, not significant; BMI, body mass index; WHR, waist/hip ratio; SHBG, sex hormone-binding globulin; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Apo A-I, apolipoprotein A-I.

*$P < 0.001$.

†$P < .01$.

‡$P < .05$.

levels of SBP and DBP, insulin, TG, and uric acid were found in obese prepubertal children with regard to non-obese children. There was also a significant decrease in HDL-C. Similar differences were found in obese hyperinsulinemic children when compared with the obese normoinsulinemic group. Some insulin resistance markers were found to have been altered.

It is known that insulin regulates lipid metabolism at several levels.[7,8,29,30] In comparison to the control group, the obese children in this study showed significantly high levels of TG and low levels of HDL-C. Insulin was an independent prediction factor for TG and Apo A-I, just as BMI was for HDL-C and TG. The obese hyperinsulinemic group showed similar differences with regard to the normoinsulinemic group, emphasizing the importance of insulin in regulating lipid metabolism.

The WHR is a useful index in obese adults to evaluate fat distribution. In our results, at this age, this index has little predictive value in metabolic disorders related to MCS. The degree of obesity (measured with BMI) and insulin levels appear to have more relevance. Also, in the control group the lipid profile is associated with insulin and BMI. This association between BMI and different MCS variables has been described in both black and white boys.[31,32] The correlation between central obesity and CVD risk factors, particularly in overweight children, is above that found in the present study with the WHR.[31,32] However, the children of the present study are of a lower age than those described in the above-mentioned works.

The level of insulin resistance depends on the type of tissue, making it impossible to extrapolarize disorders from one tissue to another.[33] Unlike obese adults described in other studies, the obese children included in this study had significantly lower basal levels of NEFA than the non-obese group, suggesting that adipose tissue in the obese group remains sensitive to the action of insulin. The insulin increase of these children could be expressed as a decrease of NEFA and an increase of lipogenesis. Nevertheless, when the group of obese children was separated into normo- and hyperinsulinemics, the latter (theoretically, those with a higher resistance to insulin) showed higher levels of NEFA (albeit without significant differences) and TG, corresponding to a situation of insulin resistance.

However, uric acid concentration has also been related to IR.[2,34] In young subjects (mean age, 18 years) a correlation has

Table 5. Mean Values (±SEM) of Selected Variables, According to Quartile of Fasting Insulin Concentration in the Obese Group

	Insulin Quartile				
	I	II	III	IV	ANOVA
Insulin (μmU/L)	3.75 ± 0.29	6.61 ± 0.17	9.23 ± 0.20	13.5 ± 0.82	
Glucose (mmol/L)	4.74 ± 0.07	4.61 ± 0.09	4.90 ± 0.08	4.86 ± 0.08	.058
Insulin/glucose ratio	0.79 ± 0.003	1.42 ± 0.002	1.88 ± 0.003	2.78 ± 0.008	<.001
BMI (kg/m^2)	21.9 ± 0.50	21.6 ± 0.54	22.62 ± 0.60	23.3 ± 0.43	.106
WHR	0.83 ± 0.01	0.83 ± 0.01	0.86 ± 0.01	0.87 ± 0.02	.075
HDL-C (mmol/L)	1.36 ± 0.07	1.40 ± 0.08	1.26 ± 0.06	1.19 ± 0.06	.129
TG (mmol/L)	0.66 ± 0.05	0.67 ± 0.05	0.77 ± 0.07	1.06 ± 0.11	<.001
Apo A-I (μmol/L)	59.19 ± 2.07	60.14 ± 1.61	57.70 ± 1.84	52.57 ± 1.27	.016
Uric acid (mmol/L)	0.24 ± 0.009	0.23 ± 0.01	0.24 ± 0.01	0.26 ± 0.01	.185
ALT (U/L)	16.9 ± 0.96	20.9 ± 1.39	19.4 ± 0.99	23.3 ± 1.78	.010
SBP (mm Hg)	91.2 ± 2.15	93.6 ± 2.18	98.1 ± 2.23	95.9 ± 1.51	.108
DBP (mm Hg)	54.4 ± 1.79	55.5 ± 1.90	57.4 ± 2.81	58.6 ± 1.88	>.20
NEFA (mmol/L)	0.40 ± 0.03	0.43 ± 0.04	0.36 ± 0.02	0.44 ± 0.04	>.20
SHBG (nmol/L)	54.7 ± 3.71	50.39 ± 3.40	45.64 ± 2.20	38.69 ± 2.35	.003

NOTE. 0, 25, 50, 75, 100th insulin percentile = 2.2, 5.1, 7.5, 10.7, 23.2 μU/mL.

Abbreviations: BMI, body mass index; WHR, waist/hip ratio; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Apo A-I, apolipoprotein A-I; ALT, alanine aminotransferase; SBP, systolic blood pressure; DBP, diastolic blood pressure; NEFA, nonesterified fatty acids; SHBG, sex hormone-binding globulin.

been described between BMI and WHR on the one hand, and uric acid levels on the other.[2] For some investigators, these anthropometric measures are predictors of uric acid concentration, rather than fasting insulin.[35] The present study's group of obese children had significantly higher levels of uric acid than the non-obese group.

The intra-abdominal fat deposit in obese adults has been described as a predictor of diabetes, arterial disease, hypertension, and dyslipemia.[36-38] ALT levels are useful as a screening test for hepatic fat,[39,40] with increased levels detected in obese children.[24] Hyperinsulinemia contributes largely to liver fat development, apparently more than anthropometric data, glycemia, or lipids.[41] Our results coincide with this affirmation: no significant differences were found in the ALT levels between the obese and non-obese groups ($P = .073$). However, significant increases were found in the obese hyperinsulinemic group when compared with obese normoinsulinemics. Insulin was the only independent prediction factor for ALT levels.

Various studies have shown hyperinsulinemia/insulin resistance in an important percentage of patients with arterial hypertension.[42-44] The obese children included in the present study show significant increases in SBP and DBP with regard to the non-obese group. No significant differences were found between the normo- and hyperinsulinemic obese groups. Insulin was not an independent prediction factor for blood pressure in the obese group. Nevertheless, a sharply progressive tendency was observed in SBP and DBP, according to insulin level (Table 5). Insulin was an independent prediction factor for SBP in the control group. It is interesting to assess the foreseeable changes in insulin concentration in these children with the development of puberty and its relation to blood pressure levels. Other factors associated with adipose tissue, such as leptin and tumor necrosis factor-α, cannot be ruled out as having an effect on blood pressure.

For this age range, no differences were found between the BMI and ponderal index, in terms of the correlation with MCS.

According to the fasting insulin level quartile in the obese group (Table 5), the majority of parameters related to MCS present an evident tendency that coincides with the alterations described in adults. In this regard, SHBG, a parameter considered a marker for insulin resistance,[45,46] showed significant differences according to the value of basal insulin (Table 5). A strong relation has been described in this group of children between insulin and SHBG.[47] Our data support the role of insulin in the regulation of serum SHBG levels.

Furthermore, in this group of obese children, hemostatic alterations have been described that are considered to be risk factors for the development of atherothrombotic disorders (plasmatic increase of plasminogen activator inhibitor-1 [PAI-1], tissue-plasminogen activator [t-PA], and fibrinogen) .[48] A high plasmatic concentration of PAI-1 has been correlated significantly with IRS in adults,[49] and is now considered to form part of this syndrome.[50]

In conclusion, the clustering of CVD risk factors known as MCS is altered in obese children before puberty, particularly in the hyperinsulinemic group. Basal insulin would be a good marker for insulin resistance in obese children aged 6 to 9 years. The apparent association between BMI and MCS is due to the association between BMI and insulin, and that insulin correlates with MCS. New studies are needed to clarify this matter. The knowledge of subgroups with greater cardiovascular risk within a group of obese children would facilitate the application of preventive actions in a more efficient way.

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