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Changes in body mass index are associated with changes in inflammatory and endothelial dysfunction biomarkers in obese prepubertal children after 9 months of body mass index SD score loss

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Abstract

The metabolic syndrome is associated with insulin resistance, a systemic low-grade inflammatory state, and endothelial dysfunction. These disorders may arise at a very early age in obese children. The aim of this study was to confirm changes in endothelial dysfunction and inflammatory biomarkers in obese prepubertal children and to evaluate the effect of body mass index (BMI) modification on these biomarkers. Biomarkers for inflammation, endothelial dysfunction, and insulin resistance were measured in obese children (47) and healthy controls (47). Baseline pretreatment levels of insulin (P = .019), homeostasis model assessment of insulin resistance (P = .004), soluble intercellular adhesion molecule (sICAM) (P = .003), and C-reactive protein (CRP) (P < .001) were significantly higher in obese children than in controls. After 9 months of treatment, obese children with lowered BMI SD score (SDS-BMI) displayed a significant decrease in insulin (P = .011), homeostasis model assessment of insulin resistance (P = .012), CRP (P = .006), and interleukin-6 (IL-6) (P = .045) levels compared with obese children with stable SDS-BMI; they also displayed a nonsignificant drop in sICAM levels. Similarly, obese children with lowered SDS-BMI displayed a decrease in CRP (P = .005) and IL-6 (P = .065) compared with baseline levels before treatment. In the total obese group, changes in SDS-BMI correlated positively with changes in CRP (P = .035), IL-6 (P = .027), and sICAM-1 (P = .038) levels. Only SDS-BMI was an independent predictive factor for CRP (P = .031), IL-6 (P = .027), and sICAM-1 (P = .033). Prepubertal obese children displayed alterations indicative of endothelial dysfunction, insulin resistance, and inflammatory state. Lowering of the SDS-BMI after 9 months of treatment was associated with an improvement in these variables compared with those in obese children with stable SDS-BMI status.

1. Introduction

The last few years have seen an alarming increase in the prevalence of childhood obesity [1]. Obesity is a major risk factor for coronary heart disease and can induce several other major risk factors [2,3]. It is frequently associated with various metabolic disorders grouped under the heading of *metabolic syndrome* (MS) [4-6].

The MS is associated with high risk for diabetes and atherosclerotic cardiovascular disease (CVD) [7,8]. It has also been established that a number of metabolic disorders associated with obesity in adults arise at a very early age in obese children. There is evidence that obesity in childhood is predictive for adult CVD [9].

Metabolic syndrome is associated with insulin resistance, a systemic low-grade inflammatory state, and high plasma C-reactive protein (CRP) [10,11]. C-reactive protein is a prototypical marker of inflammation and has been shown in several prospective studies to predict cardiovascular events [12,13]. Subclinical inflammation could be a unifying factor because it is a precursor of CVD, is associated with insulin resistance, and precedes development of type 2 diabetes mellitus [14,15]. A proinflammatory state is detectable in obese children, which is

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accompanied by impaired vascular endothelial function and early changes in artery structure [16].

Atherosclerosis is an inflammatory disease that begins with dysfunction of the vascular endothelium [17,18]. Endothelial dysfunction can be detected by measurement of elevated plasma levels of cellular adhesion molecules. Obesity and insulin resistance are associated with higher levels of circulating endothelial dysfunction biomarkers such as soluble intercellular adhesion molecule–1 (sICAM-1) [19,20]. An early activation of vascular endothelial cells and platelets is reported in obese children [21,22].

The sICAM-1 plays an important role in the initiation of the inflammatory process [23,24] and is a biochemical marker associated with atherosclerotic progression and with other inflammatory disease processes [25].

Insulin resistance and a range of metabolic disorders grouped under the label *metabolic syndrome* are reported in obese children [26,27]; a number of authors—including the present team—have detected systemic low-grade inflammation [28-30], alterations indicative of endothelial dysfunction [24,31], and findings consistent with inappropriate fibrinolysis [32] in these children.

Lowering of the body mass index (BMI) has been associated with improvement in the variables associated with this syndrome. It has been shown that obese adults have high CRP levels that can be reduced by weight loss [33]. Fewer data are available regarding the effect of a lowered BMI on inflammatory and endothelial dysfunction biomarkers, particularly in obese prepubertal children.

The aim of this study was to confirm changes in endothelial dysfunction and inflammatory biomarkers in obese prepubertal children and to evaluate the effect of BMI SD score (SDS-BMI) modification on these biomarkers.

2. Material and methods

2.1. Subjects

2.1.1. Cross-sectional study

A case-control study was carried out in obese children of both sexes. One group comprised 47 obese children (BMI over percentile 95 in growth curves for the study population [34]), and the other (control group) comprised 47 nonobese children paired by age and sex (percentile <85) (aged 6-9 years). For calculating SDS-BMI, we used growth curves for our population [34]. The study included only prepubertal children (Tanner stage 1). Anthropometric parameters, glucose, insulin, homeostasis model assessment for insulin resistance (HOMA-IR), CRP, interleukin-6 (IL-6), and sICAM were studied.

Several schools in the area were informed of the study to be carried out, and parents were asked permission for their children to participate. The 2 groups, both obese and nonobese, were formed with the children who agreed to participate in the study and were classified according to their BMI.

Children with diabetes (fasting glucose ≥7.0 mmol/L) or impaired fasting glucose (fasting glucose ≥6.1 mmol/L and <7.0 mmol/L) were excluded from both the test group and the control group. Children with secondary or endogenous obesity were also excluded (children with dysmorphic phenotypes [Prader-Willi syndrome, Alström syndrome...] or hormonal impairments [by measurement of thyroid-stimulating hormone, free thyroxine, cortisol...] were excluded); bone growth was checked where appropriate. None of the subjects were receiving regular drug treatment. All parents gave their written consent, and the study was authorized by the hospital ethical research committee. Follow-up of nonobese children (longitudinal study) was not authorized.

2.1.2. Longitudinal study

Changes in anthropometric parameters, glucose, insulin, HOMA-IR, CRP, IL-6, and sICAM were monitored in the obese group. All obese children were offered the chance to take part in the 9-month obesity intervention program. This program consists of behavioral components, physical exercise, and nutrition education both for the individual and for his or her family, according to recommendations of the Nutrition Committee of the Spanish Association of Pediatrics [35]. The main aim of obesity treatment is to achieve an ideal weight for a given height, at the same time ensuring the required supply of nutrients to avoid interfering with growth; it is essential to achieve full compliance by the child and his or her family with the principles of obesity prevention and treatment. Dietary intervention is based on the principle of matching energy and nutrient input to the child's real needs by means of a 2-level strategy: error correction and active dietary intervention. Moderate obesity requires nutritional intervention, with a low-calorie diet calculated on the basis of age rather than weight and aimed at maintaining body weight while not impairing growth, thus achieving a decrease in BMI. Severe or refractory obesity may require restriction of the diet to 25% to 30% of the diet recommended for a healthy age- and sex-matched child. Obese subjects should engage in moderate to intense physical activity for 60 min/d at least 5 d/wk. Daily movement should also be increased as part of an improved physical activity schedule: walking, climbing stairs, housework, avoidance of lifts...

All variables were measured at baseline, and after both 3 and 9 months of treatment in the obese group. Changes in the variables tested were calculated after 3 months (baseline − 3 months) and 9 months of treatment (baseline − 9 months). A *considerable drop* in SDS-BMI was defined as decrease in SDS-BMI of 0.5 or more. Previous studies have reported an improvement of insulin sensitivity and cardiovascular risk factors in obese children only if the SDS-BMI decreased by at least 0.5 [36,37]. Children *without SDS-BMI change* were defined by a change in SDS-BMI of less than 0.05.

2.2. Blood sampling and analysis and anthropometric measurements

Blood samples were collected after 12 hours of fasting from a vein in the antecubital fossa, without venous

occlusion. All collections were made between 8:00 and 9:00 AM. The samples were separated into aliquots and frozen immediately at −45°C until analysis.

The following were measured in all children: sICAM protein, CRP, IL-6, glucose, and insulin.

Glucose concentrations were measured using a random access analyzer (Axon; Bayer Diagnostics, Tarrytown, NY) with reagents from Bayer Diagnostics. The HOMA-IR was used to detect the degree of insulin resistance. Resistance was assessed from fasting glucose and insulin concentrations using the following formula: resistance (HOMA-IR) = [insulin (in microunits per milliliter) × glucose (in millimoles per liter)]/22.5.

Insulin was quantified using an Access 2 Immunoassay System (Beckman Coulter, Fullerton, CA). C-reactive protein was measured by nephelometry (N High Sensitivity CRP reagent; Behringwerke, Marburg, Germany) in a Dade Behring Analyzer II Nephelometer (Marburg, Germany).

Antigenic immunoassay methods were used for the quantification of IL-6 (Quantikine Human IL-6; RD Systems, Wiesbaden-Nordenstadt, Germany), and sICAM-1 was measured by enzyme-linked immunosorbent assay (IBL Immuno-Biological Laboratories, Hamburg, Germany) using a microtiter plate analyzer (PersonalLAB; Pharmacia Diagnostics, Barcelona, Spain).

Weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm. Body mass index was calculated as weight (in kilograms)/height (in meters)^2.

2.3. Statistical analysis

Statistical assessment was performed using Microstat (Ecosoft, Indianapolis, IN) or GraphPAD InStat software (GraphPAD Software, San Diego, CA). Abnormal values (outliers) were excluded [38]. Results were expressed as mean ± SEM, with a 95% confidence interval (CI). The distribution of each variable was tested for departure from Gaussian distribution, and variance equality was controlled by the Snedecor F test. The mean values of the groups were compared using Student *t* test for paired observations as well as that for unpaired observations. Statistical significance was set at P less than .05.

In this longitudinal study, correlations between changes in variables were evaluated using Pearson correlation coefficient and regression analysis. Multivariate regression analysis was performed using the stepwise method. For each variable, potential confounding factors ($.05 < P < .2$) were evaluated by an analysis of raw and adjusted regression coefficients.

3. Results

3.1. Cross-sectional study

Clinical, anthropometric, and biochemical parameters were measured in the obese and control groups at baseline, that is, before treatment in the obese group.

Descriptive study group statistics and selected biochemical parameters of control and obese groups were compared at the start of the study (Table 1). Age range was 6 to 9 years.

The mean values for glucose, insulin, and HOMA-IR were significantly higher in the obese group than in the control group (Table 1).

Mean sICAM-1 levels were significantly higher in obese children at 281.29 ng/mL (95% CI, 263.48-299.11) compared with 249.7 ng/mL in the control group (95% CI, 237.83-261.66) (Table 1).

Mean CRP concentrations were significantly higher in obese children at 2.34 mg/L (95% CI, 1.78-2.91) compared with 0.92 mg/L in the control group (95% CI, 0.483-1.341). Interleukin-6 levels were higher in the obese group, but the difference was not statistically significant (Table 1).

3.2. Longitudinal study

Changes with respect to baseline values in the obese group were analyzed after 3 and 9 months of treatment. All except one of the children displaying a drop in SDS-BMI of at least 0.5 at 9 months also displayed lower values at 3 months. Moreover, an analysis was made of any differences between those obese children with substantial SDS-BMI loss (decrease in SDS-BMI of ≥0.5) vs obese children with stable SDS-BMI status.

The 2 subgroups of obese children displayed similar values at baseline and before treatment, with no age- or sex-related differences. There were no significant baseline differences in weight (P = .442), height (P = .611), BMI (P = .560), or SDS-BMI (P = .977).

After 3 months, 53.2% of obese children displayed a decrease of SDS-BMI; after 9 months, 51.1% of obese children displayed that decrease. However, the mean drop in SDS-BMI was greater at 9 months (1.02) than at 3 months (0.82).

Within the obese group, tests were performed to determine the extent to which changes in SDS-BMI were associated with changes in the variables studied.

Table 1
Descriptive study group statistics and selected biochemical parameters

	Nonobese children	Obese children	P
	n = 47	n = 47	
Male/female	19/28	19/28	
Age (y)	7.87 ± 0.13	8.00 ± 0.15	.530
Weight (kg)	27.34 ± 0.68	41.16 ± 0.89	<.001
Height (cm)	127.42 ± 1.03	131.98 ± 0.99	.002
BMI (kg/m^2)	16.88 ± 0.19	23.55 ± 0.33	<.001
SDS-BMI	0.06 ± 0.001	3.38 ± 0.17	<.001
Waist-hip ratio	0.846 ± 0.007	0.862 ± 0.008	.136
Glucose (mg/dL)	86.72 ± 0.78	91.15 ± 1.14	.002
Insulin (μU/mL)	5.40 ± 0.34	6.68 ± 0.41	.019
HOMA-IR	1.177 ± 0.057	1.519 ± 0.103	.004
sICAM-1 (ng/mL)	249.7 ± 5.34	281.29 ± 9.09	.003
CRP (mg/L)	0.92 ± 0.22	2.34 ± 0.29	<.001
IL-6 (pg/mL)	1.58 ± 0.19	1.89 ± 0.18	.251

Values are means ± SEM.

3.3. Results after 3 months of treatment (obese group)

After 3 months, no difference was found between obese children with substantial SDS-BMI loss (mean decrease in SDS-BMI, 0.82; 95% CI, −0.98 to −0.66) and obese children with stable SDS-BMI status. No differences were recorded with respect to baseline values. Nor was any correlation detected between changes in SDS-BMI and changes in biomarkers for inflammation or endothelial dysfunction.

3.4. Results after 9 months of treatment (obese group)

The 24 obese children who had achieved a substantial SDS-BMI loss decreased their SDS-BMI on average by 1.02 (95% CV, −1.22 to −0.82). The 23 obese children with stable SDS-BMI status changed their SDS-BMI on average by 0.03 (95% CV, −0.11 to 0.18).

After 9 months, children with lowered SDS-BMI displayed a significant decrease (obese children with decreased SDS-BMI vs obese children with stable SDS-BMI status) in insulin (95% CI, 5.18-6.81 vs 6.46-9.48), HOMA-IR (95% CI, 1.160-1.551 vs 1.494-2.128), CRP (95% CI, 0.735-1.732 vs 1.75-3.48), and IL-6 (95% CV, 0.83-1.57 vs 1.33-2.15) levels compared with obese children with stable SDS-BMI status (Table 2). Levels of sICAM-1 also fell in children with lowered SDS-BMI, though not significantly (Table 2).

The 24 children displaying SDS-BMI loss also displayed a significant drop in CRP values with respect to baseline levels, together with a drop in IL-6 values that almost attained statistical significance. A decrease—albeit non-significant—was also recorded in insulin, HOMA-IR, and sICAM values (Table 3).

In the 23 children showing no SDS-BMI loss, no significant change was recorded in CRP, IL-6, insulin, HOMA-IR, or sICAM values with respect to baseline (Table 4).

Table 2
Values after 9 months of treatment

	Obese children (SDS-BMI decrease)	Obese children (SDS-BMI stable)	*P*
	n = 24	n = 23	
Male/female	10/14	9/14	
Age (y)	8.81 ± 0.22	8.95 ± 0.21	.648
Weight (kg)	40.80 ± 1.35	46.32 ± 1.59	.011
Height (cm)	136.08 ± 1.30	137.71 ± 1.63	.436
BMI (kg/m^2)	21.95 ± 0.48	24.32 ± 0.54	.002
SDS-BMI	2.37 ± 0.24	3.39 ± 0.25	.005
Glucose (mg/dL)	91.21 ± 1.35	90.78 ± 1.47	.830
Insulin (μU/mL)	5.99 ± 0.39	8.06 ± 0.68	.011
HOMA-IR	1.355 ± 0.09	1.811 ± 0.15	.012
sICAM-1 (ng/mL)	266.96 ± 11.22	283.97 ± 10.46	.274
CRP (mg/L)	1.23 ± 0.24	2.62 ± 0.42	.006
IL-6 (pg/mL)	1.20 ± 0.18	1.74 ± 0.19	.045

Comparison of obese children with substantial SDS-BMI loss (decrease in SDS-BMI of ≥0.5) and obese children with stable SDS-BMI status. Values are means ± SEM.

Table 3
Changes in weight status (BMI, SDS-BMI), glucose, insulin, HOMA-IR, sICAM, CRP, and IL-6 concentrations over a period of 9 months in 24 obese children with substantial SDS-BMI loss (decrease in SDS-BMI of ≥0.5)

	At baseline	9 mo later	*P*
Weight (kg)	40.48 ± 1.13	40.80 ± 1.35	.409
Height (cm)	131.48 ± 1.23	136.08 ± 1.30	<.001
BMI (kg/m^2)	23.36 ± 0.44	21.95 ± 0.48	<.001
SDS-BMI	3.39 ± 0.25	2.37 ± 0.24	<.001
Glucose (mg/dL)	90.88 ± 1.68	91.21 ± 1.35	.854
Insulin (μU/mL)	6.51 ± 0.64	5.99 ± 0.39	.503
HOMA-IR	1.474 ± 0.16	1.355 ± 0.10	.530
sICAM-1 (ng/mL)	283.06 ± 12.07	266.96 ± 11.22	.187
CRP (mg/L)	2.21 ± 0.39	1.23 ± 0.24	.005
IL-6 (pg/mL)	1.74 ± 0.24	1.20 ± 0.18	.065

Values are means ± SEM.

Single linear correlation in the total obese group (obese children with SDS-BMI loss and obese children with stable SDS-BMI status together) showed a positive correlation between SDS-BMI changes and changes in CRP, IL-6, and sICAM-1 (Fig. 1).

After 9 months of treatment, a significant correlation was noted between changes in insulin levels and changes in CRP values (r = 0.323, P = .027); a comparable, although nonsignificant, correlation was noted with IL-6 (r = 0.253, P = .086) and sICAM levels (r = 0.229, P = .155). Similar findings were recorded for the correlation between changes in HOMA-IR levels and CRP (r = 0.325, P = .03), IL-6 (r = 0.258, P = .097), and sICAM values (r = 0.231, P = .141).

Using multivariate regression analysis, only SDS-BMI proved to be an independent predictive factor for CRP (P = .031), IL-6 (P = .027), and sICAM-1(P = .033).

4. Discussion

Obesity is a chronic pathology with high morbidity-mortality rates, frequently associated with various metabolic disorders grouped under the heading of MS [4-6].

Table 4
Changes in weight status (BMI, SDS-BMI), glucose, insulin, HOMA-IR, sICAM, CRP, and IL-6 concentrations over a period of 9 months in 23 obese children with stable SDS-BMI status

	At baseline	9 mo later	*P*
Weight (kg)	41.87 ± 1.40	46.32 ± 1.59	<.001
Height (cm)	132.50 ± 1.58	137.71 ± 1.63	<.001
BMI (kg/m^2)	23.75 ± 0.50	24.32 ± 0.54	.132
SDS-BMI	3.38 ± 0.24	3.39 ± 0.25	.801
Glucose (mg/dL)	91.43 ± 1.55	90.78 ± 1.47	.725
Insulin (μU/mL)	6.85 ± 0.55	8.06 ± 0.68	.137
HOMA-IR	1.565 ± 0.14	1.811 ± 0.15	.202
sICAM-1 (ng/mL)	279.46 ± 13.92	283.97 ± 10.46	.808
CRP (mg/L)	2.49 ± 0.43	2.62 ± 0.42	.692
IL-6 (pg/mL)	1.77 ± 0.29	1.74 ± 0.20	.375

Values are means ± SEM.

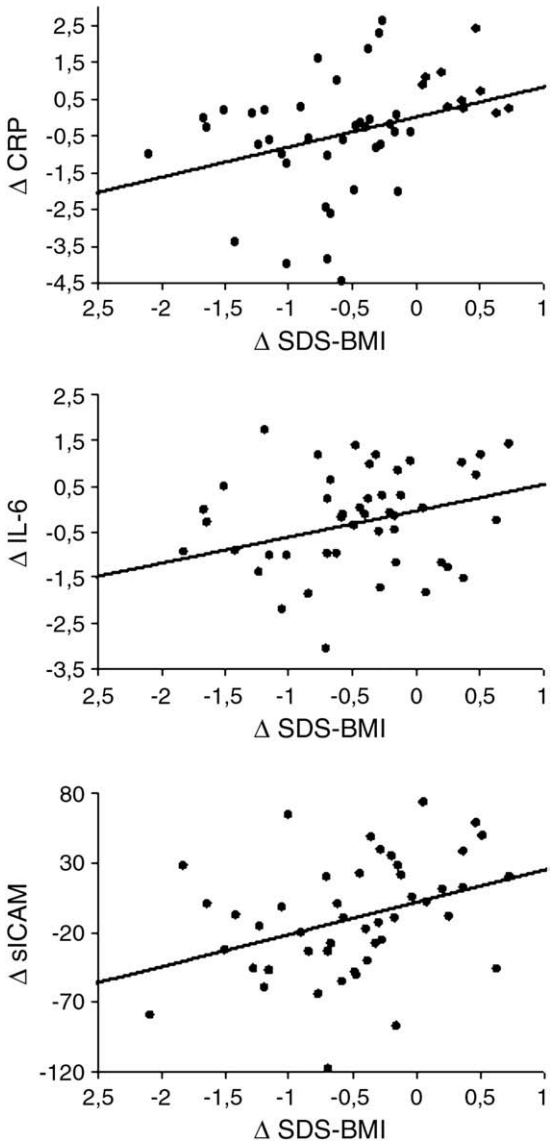

Fig. 1. Serum Δ CRP ($r = 0.312$, $P = .035$), Δ IL-6 ($r = 0.322$, $P = .027$), and Δ sICAM ($r = 0.301$, $P = .038$) concentrations as a function of Δ SDS-BMI. Changes (Δ) in CRP, IL-6, and sICAM levels are expressed as values after 9 months of treatment minus baseline values.

The last few years have seen a progressive increase in childhood obesity. It has been found that a large number of metabolic disorders associated with obesity in the adult arise at a very early age—even before puberty—in obese children.

Insulin resistance and a range of metabolic disorders grouped under the label *metabolic syndrome* are reported in obese children [26,27]; a number of authors—including the present team—have detected systemic low-grade inflammation, alterations indicative of endothelial dysfunction [23,28-31], and findings consistent with inappropriate fibrinolysis [32] in these children.

This study of obese prepubertal children showed an increase in biomarkers for insulin resistance, inflammation, and endothelial dysfunction compared with age- and sex-matched nonobese children. Baseline examination of age- and sex-matched obese and nonobese children showed that obese children were significantly taller. This was to be expected because obese children display normal or accelerated bone growth and are generally tall for their age, except where obesity is secondary to endogenous disorders—such subjects being excluded from the present study.

After 9 months of treatment, an improvement in these variables was found to correlate positively with lowered SDS-BMI.

The onset of the MS in prepubertal children may hasten the development of diabetes and CVD.

Atherosclerosis is an inflammatory disease that begins with dysfunction of the vascular endothelium [17,18]. Endothelial dysfunction consists of enhanced and maintained endothelial activation reflected by elevated plasma concentrations of soluble endothelial adhesion molecules. Elevated levels of this molecule are indicative of endothelial dysfunction and imply enhanced leukocyte adhesion to the endothelium [39], a physiopathologically decisive stage in atherogenesis. Vascular endothelial dysfunction is considered to be the earliest stage in the atherogenic process [40,41]

In adults, obesity and insulin resistance are associated with higher levels of circulating endothelial dysfunction biomarkers such as sICAM-1 [19,20].

Obesity in children is associated with increased circulating levels of soluble markers of vascular endothelial cell and platelet activation [21]. Overweight children and adolescents with normal glucose tolerance exhibit increased plasma markers of endothelial dysfunction and subclinical inflammation in association with obesity and insulin resistance [31]. Previous studies in obese prepubertal children recorded elevated sICAM-1 levels [22], which were significantly associated with BMI levels and variables indicative of both systemic low-grade inflammation (CRP) and proinflammatory cytokines (IL-6). C-reactive protein, IL-6, and ICAM-1 are molecular markers associated with atherosclerosis and its progression [42].

Obese children in the present study displayed higher baseline sICAM-1 levels than controls. After 9 months of treatment, sICAM-1 levels were lower in obese children with a considerable drop in SDS-BMI compared with obese children with stable SDS-BMI status. As Table 2 shows, this decrease in BMI was largely due to a drop in weight because height was similar in the 2 groups.

In obese children with SDS-BMI loss, sICAM values also decreased with respect to baseline levels, although differences were not significant in either case. This decline in BMI was obviously due to an increase in height over the 9 months of treatment.

However, a significant correlation was recorded between changes in SDS-BMI and changes in sICAM levels. A longer follow-up period may be required for differences in this variable to become statistically significant. Indeed, after 3 months of treatment, sICAM-1 values were actually higher in children who had lost SDS-BMI and there was no

correlation with BMI, whereas values after 9 months of treatment were lower in children with SDS-BMI loss and a correlation was recorded between SDS-BMI changes and changes in sICAM-1 levels. Results showed that the mean decrease in SDS-BMI was greater after 9 months than after 3 months. In adults, after 6 months of treatment leading to a 5% to 7% drop in weight, improved macrovascular endothelial function and a significant reduction in sICAM have been reported [43]. Further research is required to evaluate the full effects of decreased BMI in children.

Elevated concentrations of CRP and IL-6 have been shown to predict the development of type 2 diabetes mellitus. The elevated CRP concentrations in obese subjects might be explained by the expression of the cytokine IL-6 in adipose tissue [44] and its release into the circulation [45]. Interleukin-6 is a proinflammatory cytokine that stimulates the production of CRP in the liver [46]. C-reactive protein is a prototypical marker of inflammation that has been shown in several prospective studies to predict cardiovascular events [12,13]. Weight loss is related to reduction of inflammation [47]. Thus, measurement of CRP provides clinically important prognostic information regarding the MS in adults [48].

Adiposity is the major determinant of CRP levels in children [49]. Increased CRP [50] and a proinflammatory state [16] have been detected in obese children. In earlier studies of prepubertal obese children, the present authors found low-grade systemic inflammation and a decrease in anti-inflammatory and antiatherogenic (adiponectin) factors [28] correlating with a range of variables involved in the MS. Inflammation and adipocytokines may play a key role in the etiopathogeny of the MS.

In the present study, in very young obese children, after 9 months of treatment, a significant decrease was recorded in CRP values (a decrease not found after 3 months) in obese children with SDS-BMI loss compared with those with stable SDS-BMI. In obese children with SDS-BMI loss, CRP values also declined with respect to baseline pretreatment levels. Similar results have been reported for a group of obese children older than those studied here in a study addressing obese children at various stages of sexual development after a 1-year follow-up [51]. A significant correlation was also noted between changes in SDS-BMI and changes in biomarkers for insulin resistance, although only BMI proved to be an independent predictive factor for CRP. Interleukin-6 levels also decreased in obese children with lowered SDS-BMI, and a significant correlation was found between changes in SDS-BMI and changes in insulin and IR-HOMA values. Only SDS-BMI changes proved to be an independent predictive factor for changes in IL-6. As in the case of sICAM, changes were appreciable after 9 months of treatment, coinciding with the greatest drop in SDS-BMI. Similar findings are reported in adults, where an improvement in endothelial dysfunction parameters as a result of weight loss is accompanied by a decrease in proinflammatory cytokine levels [52]. These results are of particular interest because these biomarkers (CRP, IL-6, and ICAM) are reportedly associated with atherosclerosis and its progression [42]. Endothelial dysfunction and inflammation thus appear to be related to obesity from a very early age.

It should be noted that this decrease in SDS-BMI was due in large measure to increased height, as is to be expected in children; weight remained stable over the 9 months of treatment. This, indeed, is the aim of treatment at this age.

To summarize, changes similar to those reported in obese adults arise at a very early age in obese children, who display elevated levels of biomarkers for insulin resistance, inflammation, and endothelial dysfunction compared with age- and sex-matched nonobese children. Moreover, a lowered SDS-BMI after 9 months of treatment is associated with an improvement in these biomarkers compared with obese children with stable SDS-BMI status. No substantial changes were noted here after 3 months of treatment, but changes were apparent after 9 months. These results highlight the need for early treatment of childhood obesity to avoid the hazards associated with prolonged exposure to cardiovascular risk factors.

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