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High-sensitive C-reactive protein, tumor necrosis factor α, and cardiovascular risk factors before and after weight loss in obese children

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Abstract

To confirm the existence of obesity-induced inflammation and to clarify the association between such inflammation and other cardiovascular risk factors, we investigated the relationships between high-sensitive C-reactive protein (hsCRP), tumor necrosis factor α (TNF-α), obesity, blood pressure, lipids, and insulin resistance in a long-term follow-up of obese children. We compared the serum concentrations of hsCRP, TNF-α, high-density lipoprotein cholesterol, and triglycerides as well as blood pressure and the insulin resistance index (homeostasis model assessment [HOMA]) of 14 nonobese and 31 obese children. Furthermore, we studied the changes in these parameters in 16 obese children who lost weight and in 15 obese children without weight change over a 1-year period. In the obese children, blood pressure (P = .003), HOMA (P = .034), and triglyceride (P = .011), TNF-α (P = .015), and hsCRP (P < .001) levels were significantly higher, whereas high-density lipoprotein cholesterol concentrations were significantly (P = .015) lower compared with the nonobese children. Weight loss was associated with a significant decrease in hsCRP (P = .008) and triglyceride (P = .048) levels, HOMA (P < .001), and blood pressure (P = .019), whereas there were no significant changes in the children with stable weight status. The changes in hsCRP and TNF-α levels over the 1-year period were not significantly correlated to the changes in lipids, blood pressure, and HOMA. Obese children demonstrated significantly higher levels of hsCRP and TNF-α compared with nonobese children. The chronic inflammation markers TNF-α and hsCRP were independent of lipids, blood pressure, and insulin resistance index. Weight loss was associated with the significant decrease of hsCRP and triglyceride levels, and blood pressure.

1. Introduction

Cardiovascular morbidity and mortality of obesity is associated with cardiovascular risk factors such as dyslipidemia (hypertriglyceridemia and low high-density lipoprotein cholesterol [HDL-C]), hypertension, and impaired glucose metabolism (metabolic syndrome), leading to atherosclerosis [1,2]. These clinical features already occur in childhood obesity [3-5]. Recently, further markers of atherosclerosis have been found, such as the inflammation factors high-sensitive C-reactive protein (CRP) (hsCRP) and tumor necrosis factor α (TNF-α) [6-9]. High-sensitive CRP has been shown to be a predictor of cardiovascular events in both healthy subjects and patients with coronary disease in prospective studies [10-13].

Studies in adults have reported independent associations of serum hsCRP and TNF-α concentrations with the body mass index (BMI) [9-11,14]. It has been proven that, in adulthood, weight loss leads to a decrease of serum hsCRP concentrations and event risks [13-18], whereas studies concerning serum TNF-α concentrations in weight loss are controversial. Some studies reported decreasing TNF-α concentrations [19-23], whereas others described stable TNF-α concentrations in weight loss [17,24,25].

However, there are very few reports concerning hsCRP and TNF-α concentrations in obese children and their relationship to the BMI and cardiovascular risk factors [6,26,27]. Because adverse patterns of atherosclerosis itself begin in childhood [28], studies of population and

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individual differences in the early onset and progression through childhood of possible initiating risk factors are important. The advantage of examining the inflammatory markers in children is that there is no potential confusion with coronary disease or active tobacco smoking [10,29].

Long-term studies are required to determine whether in some individuals, associations between inflammatory markers and obesity reflect long-term deviation of the risk factors or whether in other individuals, they reflect short-term fluctuation. There are no long-term studies in obese children concerning the relationships between serum hsCRP and TNF-α, insulin resistance, cardiovascular risk factors, and change in weight status. To confirm the existence of obesity-induced inflammation and to clarify the association between such inflammation and other cardiovascular risk factors, we investigated the relationship between hsCRP, TNF-α, obesity, blood pressure, lipids, and insulin resistance in a long-term follow-up of obese children.

2. Methods

We studied 14 nonobese healthy and 16 obese children who lost a substantial amount of their overweight, as well as 15 obese children without weight change over a 1-year period (see Table 1). None of the subjects had diabetes mellitus, endocrinologic disorders, hereditary diseases, or systemic inflammatory diseases. All were nonsmokers without any regular medication. Subjects with intercurrent infections and/or febrile subjects were rescheduled and examined at a time when they were not ill to control for artificially elevated hsCRP levels. No child underwent changes in his/her pubertal stage during the 1-year study period.

Height was measured to the nearest centimeter using a rigid stadiometer. Weight was measured undressed to the nearest 0.1 kg using a calibrated balance scale. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. Obesity was defined according to the BMI 97th percentile reaching BMI values of 30 kg/m^2 at 18 years of age using population-specific data [30]. Because BMI is not normally distributed, we use the LMS method for calculating BMI SD score (SDS-BMI) [30,31]. The M and S curves correspond to the median and coefficient of variation BMI for German children at each age and sex, whereas the L curve allows for the substantial age-dependent variation in the distribution of the BMI. The assumption behind the LMS method is that, after Box-Cox power transformation, the data at each age are normally distributed [31].

Table 1
Age, weight status (BMI, SDS-BMI), pubertal stage, insulin resistance (HOMA), blood pressure, and serum insulin, glucose, lipids, hsCRP, and TNF-α concentrations in obese and nonobese children

	Obese children	Nonobese children	*P*
No.	31	14	
Age (y)	11 (9-13)	11 (10-13)	.179
Weight (kg)	62.3 (47.6-73.2)	44.5 (38.7-55.6)	.026
BMI (kg/m^2)	26.4 (24.5-28.7)	20.4 (18.3-23.2)	<.001
SDS-BMI	2.21 (2.09-2.75)	0.81 (0.48-1.16)	<.001
Sex	52% males	50% males	.922
Pubertal stage	57% prepubertal	61% prepubertal	.558
Insulin (mU/L)	17 (11-22)	9 (6-11)	<.001
Glucose (mg/dL)	89 (83-92)	82 (78-87)	.026
HOMA	3.7 (2.4-4.7)	2.7 (1.8-3.2)	.034
HDL-C (mg/dL)	46 (40-53)	55 (41-70)	.015
Triglyceride (mg/dL)	98 (61-148)	71 (62-78)	.011
SBP (mm Hg)	115 (110-122)	99 (96-109)	<.001
DBP (mm Hg)	58 (52-71)	51 (47-59)	.003
TNF-α (pg/mL)	7.8 (6.2-9.8)	6.9 (5.1-7.8)	.015
hsCRP (mg/L)	2.00 (0.50-3.06)	0.27 (0.00-0.42)	<.001

Data are presented as median and interquartile range or percentage.

Substantial weight loss was defined by a decrease in SDS-BMI of 0.5 or more because in previous studies, we demonstrated the improvement of insulin sensitivity and cardiovascular risk factors in German obese children only if the SDS-BMI decreased by at least 0.5 over a 1-year period [32,33]. Children without weight change were defined by a change in SDS-BMI of less than 0.05 over the 1-year period.

The pubertal developmental stage was determined according to Marshall and Tanner and categorized into 2 groups (prepubertal: boys with pubic hair and gonadal stage I, and girls with pubic hair stage and breast stage I; and pubertal: boys with pubic hair and/or gonadal stage ≥II, and girls with pubic hair stage and/or breast stage ≥II).

The following variables were measured in serum during fasting state in all children: insulin, glucose, hsCRP, TNF-α, triglyceride, and HDL-C concentrations. The children and their parents had been carefully instructed to fast over a period of at least 14 hours. High-density lipoprotein cholesterol concentrations were measured by an enzymatic test (HDL-C-Plus; Roche Diagnostics, Mannheim, Germany), and triglyceride concentrations, by a colorimetric assay using a Vitros analyzer (Ortho Clinical Diagnostics, Neckargemuend, Germany). Insulin concentrations were measured by microparticle-enhanced immunometric assay (MEIA, Abbott, Wiesbaden, Germany). Glucose levels were determined by colorimetric test using a Vitros analyzer (Ortho Clinical Diagnostics). Intra-assay and interassay coefficients of variation were <5% in all methods. Homeostasis model assessment (HOMA) [34] was used to detect the degree of insulin sensitivity in glucose metabolism. The sensitivity can be assessed from the fasting glucose and insulin concentrations by the formula: HOMA = (insulin [mU/L] × glucose [mmol/L]) / 22.5. High-sensitive CRP concentrations were measured by means of a particle-enhanced immunonephelometric assay using a BN II analyzer (Dade Behring, Marburg, Germany). The sensitivity of this assay was 0.18 mg/L. The interassay and intra-assay coefficients of variation were 3.8% (mean, 1.1 mg/L; n = 20) and 3.9% (mean, 1.3 mg/L; n = 20), respectively. Tumor necrosis factor α concentrations were determined by an immunometric assay using