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Intima media thickness in childhood obesity
Relations to inflammatory marker, glucose metabolism, and blood pressure

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Abstract

Obesity in childhood is discussed to be associated with hypertension, dyslipidemia, impaired glucose metabolism, and chronic inflammation. It has not yet been studied in obese children which of these cardiovascular risk factors are related to intima media thickness (IMT), a noninvasive marker for early atherosclerotic changes. We collected the clinical data (age, sex, pubertal stage, percentage of body fat, SD score of body mass index [SDS-BMI]) and measured systolic blood pressure [SBP] and diastolic blood pressure [DBP], triglycerides [TGs], high- and low-density lipoprotein cholesterol, glucose, insulin, and high-sensitivity C-reactive protein [hsCRP]) in 96 obese children (median age, 11 years). The control group was composed of 25 nonobese children of the same age, sex, and pubertal stage. We determined the carotid IMT of all the patients by B-mode ultrasound with a 14-MHz linear transducer. Obese children demonstrated a significantly ($P < .001$) thicker intima media (median, 0.6 mm) as compared with the control group (median IMT, 0.4 mm). IMT was significantly correlated to the SDS-BMI ($r = 0.38$, $P < .001$), percentage of body fat ($r = 0.39$, $P < .001$), SBP ($r = 0.39$, $P < .001$) and DBP ($r = 0.29$, $P = .002$), glucose ($r = 0.30$, $P = .001$), and hsCRP levels ($r = 0.29$, $P = .002$). In stepwise backward multiple linear regression analysis, IMT correlated significantly to BMI ($r^2 = 0.05$, $P = .044$), SBP ($r^2 = 0.15$, $P = .013$), glucose ($r^2 = 0.05$, $P = .028$), and hsCRP ($r^2 = 0.07$, $P = .005$). Because IMT is increased in obese children, vascular changes in obesity seem to occur already in childhood. These changes are related to the cardiovascular risk factors of obesity, especially hypertension, chronic inflammation, and impaired glucose metabolism.

1. Introduction

Obesity in childhood is an increasing phenomenon [1]. Childhood obesity has a wide range of serious complications and increases the risk of early illness and death in later life. As in adulthood, obesity in childhood contributes to an increased prevalence of cardiovascular risk factors, such as hypertension, dyslipidemia, and impaired glucose metabolism [1-4]. It is discussed that the exposure to these cardiovascular risk factors in early life may induce changes in the arteries contributing to the development of atherosclerosis in adulthood [5]. Recently, further markers of atherosclerosis have been found, such as the inflammation factor high-sensitivity C-reactive protein (hsCRP) [6-9]. hsCRP has been shown to be a predictor of cardiovascular events in both healthy subjects and patients with coronary disease in prospective studies [10-13].

The measurement of the intima media thickness (IMT) of the common carotid artery (CCA) is an acknowledged noninvasive marker for early atherosclerotic changes and is a feasible, reliable, valid, and cost-effective method [5,14-17]. Increased IMT of the CCA is reported to be predictive and is related to the severity and extent of coronary artery disease and strokes in adults [18,19]. Studies in adults revealed associations among IMT, cardiovascular risk factors, such as hypertension and dyslipidemia, and obesity [18,20,21]. Studies in children showed significantly

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increased IMT in patients with familial hypercholesterolemia [22,23], in children with type 1 diabetes [24], and in children with hypertension [25]. In obese children, an increased IMT was reported in 4 studies [26-29], whereas the study of Tounian et al [30] reported no statistically significant difference in the carotid IMT between severely obese children and lean control subjects.

It is unclear if obesity per se or the occurrence of obesity with cardiovascular risk factors determines IMT. Therefore, we studied the IMT in obese and normal-weight children and for the first time analyzed the relationships among blood pressure, serum lipids, glucose metabolism, chronic inflammation markers such as hsCRP, and IMT in one study sample of obese children to determine which of these cardiovascular risk factors are related to IMT.

2. Materials and methods

We collected the clinical data (age, sex, degree of overweight) and the cardiovascular risk factors of 96 nonsyndromally obese and 25 nonobese healthy white children in a prospective study. 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.

Obesity was defined according to the body mass index (BMI) 97th percentile using the definition of the International Task Force of Obesity in Childhood and population-specific data [31,32]. The weight status was recorded as BMI. Because the BMI is not normally distributed in childhood, we used the least mean square method of Cole et al [32], which normalizes the BMI skewed distribution and expresses BMI as an SD score (SDS-BMI) by the formula SDS-BMI = $\mathrm{BMI}/M(t)^{L(t)-1}/(L(t) \times S(t)$. The M and S curves correspond to the median and coefficient of variation in BMI for German children at each age and sex, whereas the L curve allows for the substantial age-dependent skewness in the distribution of BMI [31,32].

Percentage of body fat was calculated based on a skinfold thickness equation using the following formulas [33]: boys, body fat % = 0.783 × (skinfold thickness subscapularis + triceps in millimeters) + 1.6; girls, body fat % = 0.546 × (skinfold thickness subscapularis + triceps in millimeters) + 9.7. The triceps and subscapularis skinfold thickness were measured in duplicate and averaged. One investigator performed all the anthropometric measurements using a caliper.

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

The blood pressure was measured in the obese children by one investigator using a validated protocol [34]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice at the right arm after a 10-minute rest in the supine position using a calibrated sphygmomanometer and averaged. The cuff size, which was based on the length and circumference of the upper arm, was chosen to be as large as possible without having the elbow skin crease obstructing the stethoscope [34]. Hypertension was defined as blood pressure values above the 95th percentile for height, age, and sex [34].

Serum triglyceride (TG), low- and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively), and glucose and insulin concentrations were measured in the fasting state using commercially available test kits (LDL-C and HDL-C-Plus Roche Diagnostics, Mannheim, Germany; Vitros analyzer Ortho Clinical Diagnostics, Neckargemuend, Germany; MEIA, Abbott, Wiesbaden, Germany). The children and their parents had been carefully instructed to fast over a period of at least 14 hours. Intra- and interassay variations for the serum concentrations of these variables were less than 5%. Cutoff points above the 95th percentile of healthy children were used to define dyslipidemia and impaired fasting glucose according to international recommendations [35,36]. These cutoff points were 130 mg/dL (3.4 mmol/L) for LDL-C, 35 mg/dL (0.9 mmol/L) for HDL-C, 150 mg/dL (1.7 mmol/L) for TG, and 100 mg/dL (5.4 mmol/L) for glucose concentrations. hsCRP 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 inter- and intra-assay coefficients of variation were 3.8%.

Table 1
Clinical characteristics of obese and nonobese children

	Obese	Lean	*P*
n	96	25	
Age (y)	11 (9-13)	11 (9-13)	.556[a]
Sex	46% male	44% male	.858[b]
Pubertal stage	41% pubertal	48% pubertal	.528[b]
weight (kg)	64.5 (52.4-83.7)	43.0 (37.9-53.0)	<.001[a]
BMI (kg)	27.2 (24.5-29.7)	19.1 (18.3-20.5)	<.001[a]
SDS-BMI	2.3 (2.0-2.6)	0.7 (0.4-0.9)	<.001[a]
Percentage of body fat (%)	47 (40-52)	32 (27-38)	<.001[a]
LDL-C (mg/dL)	105 (90-131)	99 (92-111)	.133[a]
HDL-C (mg/dL)	46 (38-51)	49 (42-62)	.024[a]
TGs (mg/dL)	101 (69-145)	89 (56-151)	.303[c]
SBP (mm Hg)	120 (111-131)	109 (99-111)	<.001[c]
DBP (mm Hg)	61 (58-79)	54 (51-60)	<.001[c]
Glucose (mg/dL)	88 (83-93)	87 (84-90)	.149[a]
Insulin (mU/L)	17 (11-24)	9 (6-13)	<.001[c]
hsCRP (mg/L)	1.8 (1.0-3.3)	0.2 (0.0-0.34)	<.001[c]
IMT (mm)	0.6 (0.5-0.7)	0.4 (0.4-0.5)	<.001[c]

Data are presented as median and interquartile range.
[a] Student *t* test.
[b] χ^2 Test.
[c] Mann-Whitney *U* test.

Table 2
Multiple backward linear regression analysis, with IMT (in millimeters) as the dependent variable and age, sex (0 = female, 1 = male), pubertal stage (0 = prepubertal, 1 = pubertal), degree of overweight (BMI), LDL-C and HDL-C, TGs, SBP and DBP, glucose, insulin, and hsCRP (r^2 = 0.32) as the independent variables in 96 obese children

	Coefficient	95% Confidence interval (+/−)	*P*	r^2
Constant	−0.024	−0.292-0.244	.854	
BMI (kg/m^2)	0.008	0.001-0.015	.044	0.05
SBP (mm Hg)	0.002	0.001-0.004	.013	0.15
Glucose (mg/dL)	0.004	0.001-0.007	.028	0.05
hsCRP (mg/L)	0.009	0.003-0.015	.005	0.07

We measured IMT by B-mode ultrasound using a 14-MHz linear transducer following a standardized protocol. The measurement was performed at the CCA near the bifurcation at the far wall. We measured 4 values on each side and took the maximum value for statistical purposes. The patients were examined in the supine position with the head turned slightly to the side. The same sonographer, who was blinded to the participants' cardiovascular risk factor status, performed all the examinations.

2.1. Statistical analysis

Statistical analysis was performed using Winstat for Excel (Fitch Software, Staufen, Germany). All continuous variables were tested for normal distribution by Kolmogorov-Smirnov test. A $P < .05$ was considered statistically significant. Statistically significant differences were tested for qualitative items by χ^2 test, and for normally distributed quantitative items by the student *t* test for unpaired observations. Not normally distributed variables were tested by Mann-Whitney *U* test for unpaired observations and multiple variables by Kruskal-Wallis test. Correlations were calculated by Pearson correlations. IMT (in millimeters), as the dependent variable, and age, sex, pubertal stage, degree of overweight (BMI), LDL-C and HDL-C, TGs, glucose, insulin, SBP and DBP, and hsCRP concentrations, as the independent variables, were analyzed in a stepwise backward multiple linear regression analysis using pubertal stage and sex as classified variables. The obese children were divided according to their IMT values to compare blood pressure, lipids, SDS-BMI, glucose, insulin, hsCRP, sex, and age. The local ethics committee of the University of Witten/Herdecke approved this study. Informed consent was obtained from all subjects and their parents.

3. Results

The obese children demonstrated a significantly increased IMT, lower HDL-C levels, higher insulin and hsCRP concentrations, and higher SBP and DBP as compared with the nonobese children (see Table 1). The obese children did not significantly differ from the normal-weight children in age, sex, and pubertal stage.

Forty-three (45%) of the obese children had hypertension, 22 (15%) hypertriglyceridemia, 25 (17%) increased LDL-C concentrations, 14 (10%) decreased serum HDL-C levels, and 8 (6%) of the obese children demonstrated impaired fasting glucose.

In the 96 obese children, IMT was significantly related to BMI ($r = 0.28$, $P = .003$), SDS-BMI ($r = 0.38$, $P < .001$), percentage of body fat ($r = 0.39$, $P < .001$), SBP ($r = 0.39$, $P < .001$) and DBP ($r = 0.29$, $P = .002$), glucose ($r = 0.30$, $P = .001$), and hsCRP levels ($r = 0.29$, $P = .002$), whereas IMT did not significantly correlate to age ($r = 0.0$, $P = .470$), insulin ($r = 0.13$, $P = .104$), HDL-C ($r = 0.06$, $P = .287$), LDL-C ($r = 0.07$, $P = .246$), and TG concentrations ($r = 0.02$, $P = .411$). In stepwise backward multiple linear regression analysis, IMT was significantly correlated to BMI, SBP, glucose, and hsCRP (see Table 2).

Increasing IMT was significantly associated with increasing degree of overweight (SDS-BMI), SBP and DBP, and glucose and hsCRP concentrations, whereas age, TGs, and LDL-C and HDL-C concentrations did not significantly differ between children with different IMT (see Table 3).

Table 3
Comparison of the obese children according to their IMT values

	IMT 0.4 mm	IMT 0.5 mm	IMT 0.6 mm	IMT 0.7 mm	IMT 0.8 mm	*P*
n	10	24	31	22	9	
Age (y)	12 (9-14)	12 (9-13)	11 (9-13)	12 (9-13)	12 (7-13)	.586
Sex (% male)	70	33	38	50	67	.188
BMI (kg/m^2)	24.8 (21.8-29.6)	26.2 (23.7-28.9)	27.5 (24.5-29.6)	27.6 (25.6-31.3)	29.8 (26.9-33.4)	.093
SDS-BMI	2.0 (1.9-2.3)	2.1 (2.0-2.4)	2.4 (2.1-2.7)	2.5 (2.1-2.8)	2.6 (2.1-2.9)	.003
TGs (mg/dL)	83 (55-162)	98 (65-135)	108 (69-148)	107 (90-157)	77 (58-128)	.205
LDL-C (mg/dL)	96 (89-126)	110 (94-135)	106 (93-141)	106 (84-131)	98 (73-119)	.767
HDL-C (mg/dL)	43 (36-51)	48 (40-53)	45 (38-53)	44 (38-50)	50 (45-52)	.629
SBP (mm Hg)	111 (100-124)	111 (102-123)	119 (111-130)	124 (118-132)	132 (116-148)	.005
DBP (mm Hg)	60 (54-81)	62 (54-65)	60 (51-71)	66 (60-81)	81 (64-88)	.025
Hypertension (%)	20	25	45	64	78	.010
Glucose (mg/dL)	83 (81-87)	88 (83-91)	89 (85-95)	89 (85-95)	92 (85-98)	.029
Insulin (mU/L)	11 (6-21)	16 (11-23)	18 (14-33)	19 (12-26)	14 (11-21)	.210
hsCRP (mg/L)	0.8 (0.3-1.4)	1.5 (0.6-2.5)	1.6 (1.2-3.1)	2.7 (1.3-6.4)	3.3 (2.3-5.3)	<.001

Data are presented as median and interquartile range. Kruskal-Wallis test was used to compare all 5 groups according to IMT.

4. Discussion

This is the first study in obese children concerning the changes of IMT and its relationship to the cardiovascular risk factors hypertension, dyslipidemia, impaired glucose metabolism, and chronic inflammation. IMT in obese children was significantly increased as compared with nonobese children of similar age, sex, and pubertal stage in accordance with most other studies in childhood [26-29,37]. This emphasizes the early age at which arterial abnormalities can be demonstrated in obese children. The mechanisms leading obesity to increased IMT are unclear yet.

Obesity has been demonstrated to be associated with the cardiovascular risk factors hypertension, dyslipidemia, impaired glucose metabolism, and chronic inflammation not only in adults but also in children [1,2,38-40]. These clinical features are discussed to be responsible for the morbidity and mortality of obesity including atherogenic vascular changes [1]. In our study, the IMT of obese children was significantly related to SBP, glucose, and hsCRP, both in univariate and multiple linear regression analysis, suggesting a link between atherogenic changes and the cardiovascular risk factors hypertension, impaired glucose metabolism, and chronic inflammation.

The association between IMT and blood pressure in obese children is in concordance with the known association between coronary heart disease and hypertension in obese adults and with the findings in nonobese hypertensive adults and adolescents. Previous studies have shown that an increased IMT is related even to borderline hypertension in adult men [41]. IMT in the CCA was higher in hypertensive adolescents than in a healthy control group [42].

Impaired fasting glucose is regarded as a cardiovascular risk factor in adults [36,43,44]. Accordingly, fasting glucose levels were significantly related to IMT in our study. Increased glucose levels seems to be more important for atherogenic changes than hyperinsulinemia, as demonstrated by the facts that glucose, but not insulin, was significantly related to IMT in both univariate and multiple regression analysis.

hsCRP as a chronic inflammation marker was significantly related to IMT in our study in concordance with studies in obese adults [29,45]. Chronic inflammation plays a role in the progression and initiation of atherothrombotic disease [46]. CRP induces complement activation, enhances infiltrations of monocytes, and stimulates tissue factor production, thus enhancing the risk of thrombosis and the generation of atherosclerotic lesions [13,47-49].

In contrast to studies in adolescents with familial hypercholesterolemia and familial hypertriglyceridemia demonstrating that cholesterol and TG concentrations were predictive of carotid IMT [18,23,50], lipids were not significantly related to IMT in our study. Probably, the effects of blood pressure, impaired fasting glucose, and hsCRP have covered the effect of lipids on IMT, suggesting that in obese children, blood pressure, impaired glucose metabolism, and chronic inflammation have a greater impact on IMT than lipids. On the other hand, TGs and LDL-C did not significantly differ between obese and nonobese children in our study, and HDL-C was only very moderately decreased in our obese children as compared with nonobese children. These facts may explain the missing association between IMT and lipids because TGs and LDL-C, respectively, are much higher in familial hypertriglyceridemia and familial hypercholesterolemia as compared with the lipid levels of our obese children. In a previous study concerning a small study sample size and not regarding the effect of chronic inflammation and disturbed glucose metabolism on IMT, we demonstrated a significant relationship between TGs and IMT in obese children [37].

Because the cardiovascular risk factors chronic inflammation, impaired glucose metabolism, and elevated blood pressure seem to be associated already with atherogenic changes in obese children, a therapeutic strategy is urgently necessary to improve these risk factors, especially in clustering of these factors. In previous studies, we demonstrated that substantial weight loss in obese children led to a decrease in hsCRP [40] and blood pressure [51] and to an improvement of glucose metabolism [52]. Furthermore, weight loss in obese children is associated with decreasing IMT [53].

Many studies have used the mean value of the measurements of IMT for statistical purposes. The strongest association among the different measurements of IMT between coronary risk factors in otherwise healthy individuals is reached by applying the maximum and not the mean value of IMT [54]. This confirms the findings that atherosclerosis is not equally distributed in all the blood vessels, but that the extent of the thickening of the arterial wall differs in the various regions. We performed analyses with both values, maximum and mean value of IMT, but decided to use the maximum value because of the narrow correlation to cardiovascular risk factors.

This study has a few potential limitations. First, BMI percentiles were used to classify overweight. Although BMI is a good measure for overweight, one needs to be aware of its limitations as an indirect measurement of adiposity. Second, the cross-sectional study design does not prove causality. However, obesity, hypertension, disturbed glucose metabolism, and increased hsCRP are unlikely to be consequences of increased IMT. Third, the IMT in children is probably also influenced by other factors not examined in this study. Regarding the genetic aspect, a twin study showed that within a normal population, carotid IMT is under a familial and not under a genetic influence [55,56]. Finally, although previous reports presume that IMT is related to an initial atherosclerotic process, an increased IMT was also discussed to reflect a nonatherosclerotic adaptive response to changes in shear stress and tensile stress. Nevertheless, most authors assume that the measurement of the IMT is predictive and related to arterial changes,

being responsible for cardiovascular damages as well as for peripheral arterial atherosclerosis [18,20,25,54,57].

In summary, obese children demonstrated a significantly increased IMT as compared with a normal-weight control group, and the IMT was significantly related not only to the degree of overweight, but also to blood pressure, glucose, and hsCRP. Therefore, intima media thickening seems to start already in childhood obesity in relation to the presence of the cardiovascular risk factors hypertension, impaired glucose metabolism, and chronic inflammation.

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