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Increased Carotid Intima-media Thickness and Associations with Cardiovascular Risk Factors in Obese and Overweight Children and Adolescents

R. Schiel[1], W. Beltschikow[1], S. Radón[1], G. Kramer[1], T. Perenthaler[1], G. Stein[2]

[1]Medigreif Group, Inselklinik Heringsdorf GmbH, Department of Diabetes and Metabolic Diseases, Seeheilbad Heringsdorf, and [2]University of Jena Medical School, Department of Internal Medicine, Jena, Germany

Abstract

Obejective: Overweight and obesity in children and adolescents contribute to the development of overweight and obesity in adulthood and subsequent cardiovascular disease. It was the aim of the trial to assess vascular status and associations with cardiovascular risk factors.

Patients and Methods: Eighty-one overweight or obese children and adolescents (age 13.6 ± 2.7 years, 62% females) hospitalised for weight reduction were consecutively recruited. In all subjects carotid intima-media thickness (IMT), body-mass index (BMI), body composition, serum lipid and blood glucose concentrations, CRP, TSH, uric acid and blood pressure values were measured.

Results: Mean IMT was 0.48 ± 0.09 mm. Twenty-nine subjects (36%) had an IMT <0.45 mm, 32 (40%) an IMT ≥0.45≤0.50 mm, and 20 (24%) an IMT >0.50 mm. Comparing children with low carotid IMT (<0.45 mm, n = 29 [36%]) with those with higher values (≥0.45 mm, n = 52 [64%]), there were significant differences: Those with higher IMT had higher weight (73.5 ± 17.6 vs 91.1 ± 24.0 kg, p = 0.001), higher BMI (28.6 ± 4.4 vs 32.7 ± 5.5 kg/m², p = 0.001) and BMI-SDS (2.23 ± 0.57 vs 2.61 ± 0,50, p = 0.002), higher fatmass (26.3 ± 9.5 vs 37.1 ± 15.2 kg, p = 0.001) and a higher percentage of fat in relation to total body weight (35.2 ± 5.5 vs 39.5 ± 7.8 %, p = 0.010), as well as higher systolic (117.7 ± 6.9 vs 124.6 ± 10.6 mmHg, p = 0.004) and diastolic blood pressure values (64.4 ± 5.5 vs 68.6 ± 6.7 mmHg, p = 0.008), and higher serum uric acid concentrations (385.6 ± 91.7 vs 439.9 ± 100.5 µmol/l, p = 0.023). There was a correlation between IMT and height (r = 0.237, p = 0.033), weight (r = 0.442, p<0.001), BMI (r = 0.482, p<0.001), BMI-SDS (r = 0.449, p<0.001), fatmass (r = 0.482, p <0.001), percentage of fat (r = 0.412, p<0.001), TSH (r = 0.238, p = 0.037), uric acid (r = 0.238, p = 0.040) as well as systolic (r = 0.359, p = 0.001) and diastolic blood pressure values (r = 0.359, p = 0.001) measured spontaneously and systolic blood pressure values registered during 24 h monitoring (r = 0.344, p = 0.004). Performing multivariate analysis, an association between IMT and BMI was found (R-square = 0.263, β = 0.525, p<0.001).

Conclusions: In overweight and obese children and adolescents there is a significant association between carotid IMT and weight, BMI, BMI-SDS, blood pressure, as well as various other metabolic parameters. Based on these and other epidemiological data, demonstrating the continuing and significant increase in incidence of overweight and obesity in childhood and adolescence, comprehensive strategies for the long-term prevention and the treatment of risk factors should be emphasized with an early start in childhood.

Key words: Body mass-index, diabetes mellitus, myocardial infarction, stroke, arterial hypertension

Introduction

Overweight and obesity in children and adolescents is reported to be rising dramatically [6, 7, 8, 12, 23]. Some studies have shown that children and adolescents with weight-for-height at the top of normal range are more likely to become overweight and obese adults [20, 30]; others have reported higher morbidity and mortality rates [5, 13, 18]. However, although associations between overweight, obesity, morbidity and also mortality with dyslipidaemia, elevated fasting plasma insulin levels, impaired glucose tolerance, arterial hypertension and increased carotid intima media-thickness (IMT) have long been suggested [19], the long-term role of possible risk factors is not entirely clear [20]. These risk factors also increasingly appear to be associated with vascular endothelial dysfunction, oxidative stress and low-grade inflammation, early key events in atherogenesis and markers of arterial damage that precede plaque formation [9, 10]. Atherosclerosis is a complex multifactorial disease beginning (as is increasingly clear particularly in the presence of risk factors) in youth [21, 29].

The present study aimed to assess vascular status (IMT) and to analyze associations with cardiovascular risk factors and surrogate markers (blood pressure, lipid status, C-reactive protein [CRP], fasting blood glucose [FBG] and blood glucose levels following an oral glucose tolerance test [OGTT]) in overweight and obese children and adolescents.

Patients and Methods

Eighty-one overweight or obese children and adolescents hospitalised for weight reduction were consecu-

tively recruited from the Department of Diabetes and Metabolic Diseases of the Inselklinik Heringsdorf, Seeheilbad Heringsdorf, Germany over a period of five months (01.12.2005-30.04.2006). The inclusion criteria for participation in the trial were: age 6-16 years, no personal history of diabetes mellitus or impaired fasting glucose, hypercholesterolaemia, or arterial hypertension, absence of any pharmacological therapy, and no history of cardiovascular disease. Obesity was defined as a body-mass index (BMI) >95th percentile of the reference values as stated by the National Guidelines [2]. Initially all patients participated in a structured treatment and teaching programme (STTP) according to the National guidelines [2] over a period of 36.2 ± 8.1 days .

The following examinations were performed:

1. Measurements of height and body weight were assessed with the patients wearing light clothing and without shoes. BMI and BMI-SDS were calculated according to the formulae „BMI = kg/m²“ and „BMI-SDS = ([BMI/$M_{(t)}$]$L_{(t)}$-1)/($L_{(t)}$*$S_{(t)}$)“ ($M_{(t)}$, $L_{(t)}$ and $S_{(t)}$ are pre-defined parameters depending on $age_{(t)}$ and sex [2]).
2. Quantitaive B-mode ultrasound (Toshiba®, Type SSA – 350 A „Corevision PRO“, 8 MHz, Linear Sonde Type PLF – 805 St, Toshiba“ Medical Systems, Neuss, Germany) measurements of carotid intima-media thickness (IMT) were done by a physician (T.P.) performing 5 measurements on each side and calculating the mean.
3. Blood pressure in the sitting position was measured after the patients had rested for 10 min by using a standard sphygmomanometer according to the World Health Organization (WHO) recommendations [11]. To define normal and elevated ranges of blood pressure values, percentile charts taken from the pooled data of studies on blood pressure conducted in six north-west European countries (a total of 28,043 children) were used [4]. Moreover, in all patients 24-h-monitoring was performed (Premo Trend, Zimmer Elektromedizin, Neu-Ulm, Germany).
4. Body composition analyses were done using a Body Composition Analyzer (BC 418MA, TANITA® Europe GmbH, Sindelfingen, Germany, variation coefficient: 1.88%).
5. Laboratory parameters
   Following a 12 h overnight fasting period, venous blood samples were taken and analysed for the following parameters:
   a) TSH, chemiluminescence-assay
   b) Lipids: total Cholesterol, LDL-Cholesterol and triglyzerides, enzymatically
   c) Uric acid, enzymatically
   d) C-reactive protein (CRP), turbidimetry
   e) Fasting blood glucose (FBG), enzymatically
   f) Oral glucose tolerance test with 75 g glucose [1].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 13.0). All continuous data are presented as mean ± standard deviation (SD) or, in the case of no normal distribution, as median and range. Dichotomous data were presented as number (n) or in percent (%). Univariate, unadjusted analyses between overweight/obese and control subjects were performed with the independent samples t-test, chi-square test, Fisher's exact test for frequencies at or below 5 and the Wilcoxon's rank sum test. Pearson's correlation coefficient was calculated and multivariate analysis was used to evaluate the presence of associated variables in the relationship between various parameters. Significance was defined at the 0.05 level.

Results

The characteristics of the patients examined are shown in Table 1.

Mean IMT was 0.48 ± 0.09 mm. A total of 29 children and adolescents (36%) had an IMT <0.45

Table 1. Characteristics of 81 children and adolescents with overweight and obsity.

Parameter	**Mean ± SD***
Number (n)	81
Age (years)	13.6 ± 2.7
Females (n [%])	50 (62%)
Height (cm)	164 ± 12
Weight at onset (kg)	84.8 ± 23.4
BMI at onset (kg/m2)	31.2 ± 5.5
BMI-SDS at onset	2.47 ± 0.55
Weight at the end of STTP (kg)	77.8 ± 21.2
BMI at the end of STTP (kg/m2)	28.6 ± 4.9
BMI-SDS at the end of STTP	2.13 ± 0.59
Weight reduction during STTP (kg)	-7.0 ± 3.3
Systolic blood pressure (sponteous) (mmHg)	119.1 ± 12.1
Body composition analyses	
Fatmass at onset (kg)	33.2 ± 14.3
Percentage of fat in total body mass at onset(%)	38.0 ± 7.3
Fatmass at the end of STTP (kg)	27.5 ± 11.6
Percentage of fat in total body mass at the end of STTP (kg)	34.3 ± 6.6
Reduction in fatmass (kg)	5.7 ± 3.9
Reduction in fat percentage (%)	3.7 ± 2.6
Blood pressure	
Diastolic blood pressure (spontaneous) (mmHg)	73.7 ± 10.1
Systolic blood pressure during 24-h-monitoring (mmHg)	121.9 ± 9.9
Diastolic blood pressure during 24-h-monitoring (mmHg)	66.9 ± 6.6

*Mean ± SD (standard deviation), or, if the parameters showed no normal distribution, median (range), frequencies (n [%]), STTP = structured treatment and teaching programme.

Table 2. Comparison of children and adolescents with low (<0.45 mm) and higher (≥0.45 mm) carotid intima-media thickness (IMT).

Parameter	IMT <0.45 mm (low)	IMT ≥0.45 mm (higher)	p-value
Number (n [%])	29 (36%)	52 (64%)	/
Age (years)	13.1 ± 2.6	13.9 ± 2.7	0.190
Height (cm)	160 ± 12	166 ± 12	0.035
Weight at onset (kg)	73.5 ± 17.6	91.1 ± 24.0	0.001
BMI at onset (kg/m^2)	28.6 ± 4.4	32.7 ± 5.5	0.001
BMI-SDS at onset	2.23 ± 0.57	2.61 ± 0.50	0.002
Fatmass at onset (kg)	26.3 ± 9.5	37.1 ± 15.2	0.001
Percentage of fat in total body weight at onset (%)	35.2 ± 5.5	39.5 ± 7.8	0.010
Fasting blood glucose (mmol/l)	4.10 ± 0.58	4.31 ± 0.56	0.117
Blood glucose 2 h following OGTT (mmol/l)	5.79 ± 1.73	5.47 ± 0.80	0.272
TSH (µIU/ml)	2.23 ± 0.69	2.56 ± 0.80	0.070
CRP (mg/dl)	0.58 ± 0.18	0.91 ± 1.15	0.134
Uric acid (µmol/l)	385.6 ± 91.7	439.9 ± 100.5	0.023
Total cholesterol (mmol/l)	4.20 ± 0.73	4.22 ± 0.97	0.921
LDL (mmol/l)	2.54 ± 0.65	2.30 ± 0.89	0.205
Triglyzerides (mmol/l)	0.87 ± 0.47	1.08 ± 0.84	0.321
Systolic blood pressure (spontaneous) (mmHg)	114.1 ± 10.5	121.8 ± 12.2	0.006
Diastolic blood pressure (spontaneous) (mmHg)	69.5 ± 8.8	76.1 ± 10.1	0.004
Systolic blood pressure (24 h monitoring (mmHg)	117.7 ± 6.9	124.6 ± 10.6	0.004
Diastolic blood pressure (24 h monitoring) (mmHg)	64.4 ± 5.5	68.6 ± 6.7	0.008

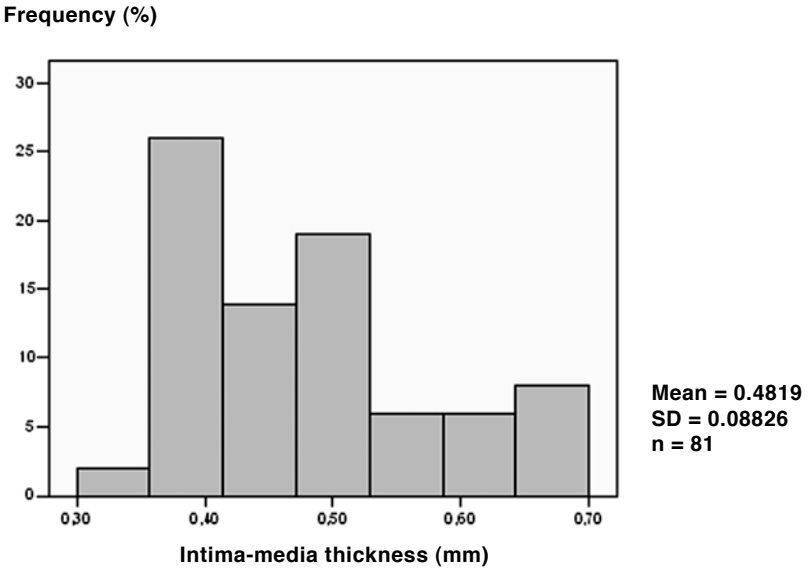

Fig. 1. Distribution of the results of IMT in 81 children and adolescents with overweight and obesity.

mm, 32 (40%) an IMT ≥0.45 ≤0.50 mm and 20 (24%) an IMT >0.50 mm (Fig. 1).

Comparing children and adolescents with low carotid IMT (<0.45 mm, n = 29 [36%]) and those with higher values (≥0.45 mm, n = 52 [64%]), there were multiple significant differences: Children and adolescents with higher IMT had at onset of the trial higher weight, higher BMI and BMI-SDS, higher fatmass and percentage of fat in relation to total body weight, as well as higher systolic and diastolic blood pressure values, and higher serum uric acid concentrations (Table 2).

Correlation Analyses

There was a correlation between carotid IMT and childrens' and adolescents' height (r = 0.237, p = 0.033), weight at onset of the trial (r = 0.442, p<0.001), BMI (r = 0.482, p<0.001) (Fig. 2), BMI-SDS (r = 0.449, p<0.001), fatmass (r = 0.482, p<0.001), percentage of

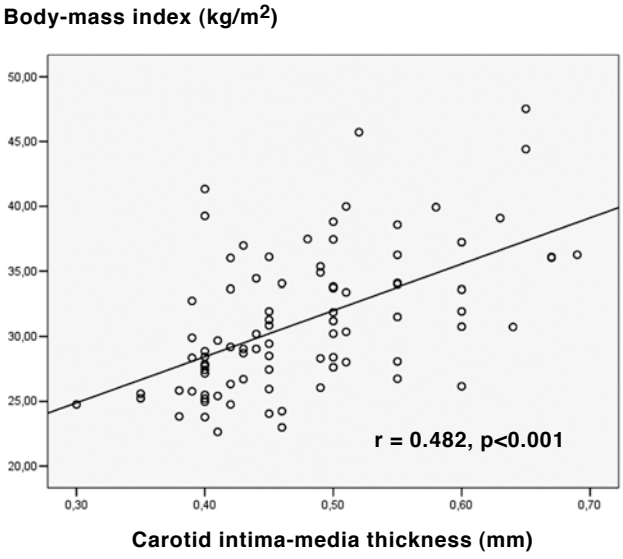

Fig. 2. Correlation analysis: Correlation between BMI at onset of the trial and carotid intima-media thickness in 81 children and adolescents with overweight and obesity.

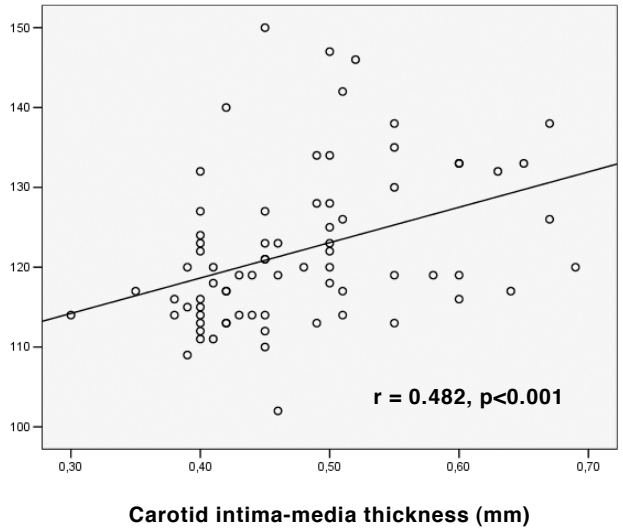

Fig. 3. Correlation analysis: Correlation between systolic blood pressure measured during 24 h monitoring and carotid intima-media thickness in 81 children and adolescents with overweight and obesity.

fat in relation to the total body weight ($r = 0.412$, $p<0.001$), serum TSH ($r = 0.238$, $p = 0.037$), serum uric acid ($r = 0.238$, $p = 0.040$) as well as systolic ($r = 0.359$, $p = 0.001$) and diastolic blood pressure values ($r = 0.359$, $p = 0.001$) measured spontaneously and systolic blood pressure values registered during 24 h monitoring ($r = 0.344$, $p = 0.004$) (Fig. 3).

Multivariate Analysis

Performing multivariate analysis an association between carotid IMT and BMI at onset of the trial was found (R-square = 0.263, $\beta = 0.525$, $p<0.001$). All other parameters included in the model revealed no significant associations (age, sex, height, weight, BMI-SDS, body composition at onset and after participation in the STTP, BMI after participation in the STTP, systolic and diastolic blood pressure measured spontaneously and during 24 h monitoring, FBG, blood glucose 2 after OGTT, TSH, CRP, total cholesterol, LDL, triglyzerides, uric acid).

Discussion

In overweight and obese children and adolescents the present trial documented a significant association between carotid IMT and weight, BMI, BMI-SDS, blood pressure as well as various metabolic parameters. Not only did the children and adolescents with higher IMT have significanty higher values in body weight and BMI, blood pressure and uric acid, but they also showed a tendency towards higher levels of CRP, FBG and triglyzerides. The increased IMT accompanied by further cardiovascular risk factors in overweight and obese children and adolescents and the correlation of risk factors with weight and BMI strongly suggests that overweight and obesity represent powerful determinants of early manifestations of atherosclerosis which affects structural and mechanical properties of major vessels. In various trials, it has been shown that atherosclerosis is a multifactorial process which is accelerated by metabolic disorders, high blood pressure and low-grade inflammation. It seems that lipid disorders and elevated levels of blood glucose, glycated proteins, advanced glycation end-products (AGE), elevated concentrations of proinflammatory cytokines, acute phase proteins, and enhanced activation of proinflammatory signalling are key players in the development of vascular disorders [16, 25, 26]. Additionally, in overweight and obese subjects there is often an accumulation of macrophages in the adipose tissue. The macrophage accumulation in adipose tissue has been positively correlated with adipozyte size and contributes to a further expression of proinflammatory mediators, such as TNF-α, IL-6 and inducible nitric oxide synthase [27, 28, 32]. It appears that the co-existence of various risk factors and an underlying chronic inflammatory process may well explain an increased mortality risk and risk for cardiovascular events in overweight and obese subjects.

This study provides further documentation of the early presence of cardiovascular risk factors in a cohort of overweight and obese children and adolescents. Although in most of these young subjects the levels of the parameters and extent of cardiovascular risk factors were not be defined as pathological resulting in specific treatments (i.e. antihypertensive treatment in patients with arterial hypertension or lipid lowering drugs in patients with dyslipidaemia), these factors must be considered as significantly higher or, at a minimum, as showing a tendency.

These data agree with conclusions reached by other trials: In an earlier study performed with similar methods, it was shown that overweight and obese children and adolescents, comparable with the present group in both, had more than 5 mmHg higher systolic and dias-

tolic blood pressure values compared to normal-weight controls [24]. The study, published by Meyer et al. [17], also demonstrated in 67 children and adolescents with a mean age of about 15 years and a mean IMT of 0.48 mm, which was very comparable to the mean IMT in our group, a noticeable cardiovascular risk profile. Compared to the lean subjects, the obese children and adolescents had an impaired flow-mediated vasodilatation, higher FBG values, lipid abnormalities and also low-degree inflammation. In a further study published in 2004 by Iannuzzi et al. [14], although using different methods for measuring higher IMT-values than us and the Meyer et al. investigation [17], higher systolic and diastolic blood pressure values, higher concentrations of fasting triglyzerides, blood glucose and insulin and a higher CRP-level in obese children (aged about 10 years) in comparison to normal weight controls were also found. Similarly to our results, all the trials [14, 15, 17, 22, 24, 31] have clearly demonstrated a high cardiovascular risk profile in overweight and obese children and adolescents compared with lean subjects. From this data, it must be strongly assumed that such alterations may be indicators of early, preclinical atherosclerosis. Based on an epidemiological design, but not proven by intervention trials, these studies provide some evidence that obesity in childhood and adolescence may lead to multiple comorbidities, elevated blood pressure values, dyslipidaemia, reduced insulin sensitivity and alterations of major and most likely minor blood vessels, with the result of an increased incidence of myocardial infarction, stroke and other vascular complications in adulthood. Overweight and obesity in children and adolescents should no longer be regarded as variations of normality, but as a disease with an extremely high risk for future development of atherosclerosis and cardiovascular complications [3]. Awareness of these complex associations, underlined by other solid epidemiological data which demonstrate the dramatic and continuing increase of overweight and obesity in childhood and adolescence occurring during the last two decades, points to the urgent and immediate need for early intervention [6, 7, 8, 12, 23]. Moreover, large trials have shown that overweight and obesity in childhood and adolescents can lead to increased risk of overweight and obesity in adulthood [20, 30]. Based on these important data, as long as no results derived from well-designed intervention studies yet exist, weight reduction and risk-factor control should be emphasized. Comprehensive strategies for the long-term prevention of risk factors and development of atherosclerosis and its sequelae should begin early in childhood.

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Address for correspondence:
Priv.-Doz. Dr. med. Ralf Schiel
Head and Medical Director
Medigreif Group, Inselklinik Heringsdorf GmbH
Department of Diabetes and Metabolic Diseases
Setheweg 11
17424 Seeheilbad Heringsdorf
Germany
Phone: +49-38378/780500
Fax: +49-38378/780555
E-mail: inselklinik.schiel@medigreif.de