Research Paper

Carotid Intima-media thickness in childhood and adolescent obesity relations to abdominal obesity, high triglyceride level and insulin resistance

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Abstract

Aim: To investigate risk factors which impact on common carotid artery intima media thickness (IMT).

Methods: A total of 86 obese children and adolescents and 22 healthy children and adolescents with normal weight were enrolled. Moreover, 23 of 86 obese children and adolescents were diagnosed with metabolic syndrome (MetS). The clinical, biochemical data and the IMT of the common carotid artery were measured in all subjects.

Results: Obese and obese with MetS subjects demonstrated a significantly ($p < 0.01$) thicker intima media (0.69mm, 0.66mm) as compared to the control group (0.38mm), but there was no significant difference of IMT between obese and MetS group. IMT was correlated to body weight, body mass index, waist circumference, waist to hip ratio, systolic blood pressure, diastolic blood pressure, fasting insulin, homoeostasis model assessment-insulin resistance, triglyceride, high-density lipoprotein- cholesterol, low-density lipoprotein-cholesterol, alanine aminotransferase, aspartate aminotransferase and fatty liver. Waist circumference, waist to hip ratio, triglyceride and homoeostasis model assessment-insulin resistance were independent determinants of mean IMT level.

Conclusion: Obesity especially abdominal obesity, high TG and insulin resistance may be the main risk predictors of increased IMT.

Key words: obesity, metabolic syndrome, intima-media thickness, children, adolescents

Introduction

The rapidly increasing prevalence of obesity among children is one of the most challenging problems. The prevalence of the metabolic syndrome (MetS) in children is increasing exponentially because of global increase in obesity. As indicated in previous studies [1,2,3], children and adolescents with risk factors such as obesity, dyslipidemia, elevated blood pressure and impaired glucose metabolism are at increased risk of developing atherosclerosis in adulthood. It has been found that obesity results in the early onset of adulthood chronic disease such as cardio-cerebrovascular disease. Recent researches [4,5,6] have revealed that adiposity-associated inflammatory factors such as C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor (TNF)-α may play a role in promoting adverse vascular outcomes.

The intima media thickness (IMT) of the common carotid artery (CCA) is a well-known marker of subclinical atherosclerosis and is a noninvasive, feasible, reliable and inexpensive method for detecting development of subclinical atherosclerosis. Studies in adults have revealed that IMT was related to cardiovascular risk factors and could predict the possibility of future cardio-cerebrovascular disease [7,8]. Increase

IMT was also reported in children with obesity, familial hypercholesterolemia and nonalcoholic fatty liver disease (NAFLD) compared with control children.

There has been no statistical data about the association between IMT and the components of MetS since new definition for children and adolescent MetS was published by International Diabetes Federation (IDF). This study aimed to verify the relationships among obesity, dyslipidemia, elevated blood pressure, impaired glucose metabolism, chronic inflammation, fatty liver and IMT to explore as to which of these factors are related to IMT.

Subjects and Methods

Subjects

A total of 86 obese Chinese children were enrolled from July 2008 to March 2009. The obese group was defined as obese children without MetS, which included 46 boys and 17 girls with a mean age of 10.5 ± 1.6 years (range 7.4 to 13.3 years). The MetS group was defined as obese children with MetS, which included 18 boys and 5 girls with a mean age of 10.9 ± 1.6 years (range 7.6 to 14.2 years). Children with other chronic disease (endocrine disease, hereditary disease, or systemic inflammation) or those taking any medications were excluded. The control group consisted of 22 healthy non-obese children, which included 16 boys and 6 girls with a mean age of 11.1 ± 2.1 years (ranging from 7.6 to 14.8 years).

Consent was obtained from the parents and the Ethical Committee of the Children's Hospital of Zhejiang University School of Medicine.

Diagnostic Criteria

Obesity was defined as body mass index (BMI) ≥95th percentile using the childhood date of Working Group on Obesity in China (WGOC) [9]. According to the IDF criteria for children and adolescents [10], MetS was identified if a subject had increased waist circumference (> 90th percentile) [11] and also had ≥ 2 of the following: 1) impaired fasting blood glucose (≥ 5.6 mmol/L), or Type 2 Diabetes Mellitus; 2) increased blood pressure (≥ 130 mmHg systolic and/or ≥ 85 mmHg diastolic); 3) elevated plasma triglycerides (≥ 1.7 mmol/L); 4) high plasma high-density lipoprotein cholesterol (< 1.03 mmol/L).

Clinical characteristics

The body weight was assessed using a calibrated standard balance beam, height was measured by a standard height bar, and BMI was calculated as body weight (kg) divided by square height (m^2). Waist circumference (WC) was measured at the midway be-

tween the lower rib and the iliac crest, hip circumference was measured at the widest part at the gluteal region. 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 an automated sphygmomanometer.

Biochemical measurements

Samples were drawn between 8 and 9 am after fasting for 10 hours. Triglycerides (TG), total cholesterol (TC) were measured by enzymatic and cholesterol oxidase method respectively, high plasma high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were both detected by the direct assay method, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were tested by enzyme-linked immunosorbent assay method. Fasting plasma glucose (FPG) was measured by glucose oxidase method; fasting plasma insulin (FINS) was measured by radioimmunity assay (Modula Analytics PP, Roche). Both intra-assay and inter-assay coefficient of variations were less than 2.1% and 4.4%, respectively. Plasma levels of IL-6 and TNF were measured by enzyme-linked immunosorbent assay method (Ju Ying bioscitech, Shenzhen, China), with both intra-assay and inter-assay coefficient of variations being less than 10%.

IMT measurement

IMT was measured by B-mode ultrasound using a 10-MHz linear transducer (Philips HD7). The subjects were examined supine with the neck extended and the probe in the antero-lateral position. All measurements of IMT were made in the longitudinal plane at the point of maximum thickness on the far wall of the common carotid artery along a 1 cm section of the artery proximal to the carotid bulb. The IMT was defined as the distance between the intimia-blood interface and the adventitia-media junction. After freezing the image, the measurements were made using electronic calipers. The maximal thicknesses of the intima-media width were measured to give three readings and the mean value was used for statistical purposes.

Statistical analysis

Statistical analysis was performed with SPSS 13.0. WHR, FBG, HOMA-IR, TNF were normalized by log-transformation. Statistically significant differences were tested for qualitative items by χ^2 test and for quantitative items by One-Way ANOVA. Thereafter, associations were examined by Pearson correlation analysis for continuous variables, and by Spearman correlation analysis for categorical variables. Finally,

multiple stepwise linear regression analysis was used to examine relationships between mean IMT and all other variables investigated. A p<0.05 was considered statistically significant.

Results

The characteristics of three groups

The obese and MetS group both demonstrated increased mean IMT, body weight, BMI, WC, WHR, SBP, FINS, HOMA-IR, lg (HOMA-IR), TG, LDL-C, ALT and AST levels, decreased HDL-C levels and higher prevalence of fatty liver (p < 0.05). Furthermore, the MetS group showed higher DBP compared with the control group. The children of MetS group had higher values of WC, SBP and TG, and lower HDL-C than these of obese group. There was no sta-tistical difference in the age and sex among three groups (p = 0.400, 0.672), as shown in table 1.

The relationship between IMT and all other variables investigated

In all subjects, mean IMT of CCA was significantly related to body weight, BMI, WC, lg (WHR), SBP, DBP, FINS, lg (HOMA-IR), TG, HDL-C, LDL-C, ALT, AST and fatty liver, as shown in table 2. IMT was not significantly related to age, sex, FBG, TC, IL-6 and lg (TNF).

Finally, the multiple stepwise linear regression analysis showed that WC, lg (WHR), TG, lg (HOMA-IR) were independent determinants of mean IMT level. All the other factors were excluded in the equations, as shown in table 3.

Table 1 The characteristics of obese, MetS and control groups

	MetS group	Obese group	Control group	F/χ^2	P
Age(y)	10.9 ± 1.6	10.5 ± 1.6	11.1 ± 2.1	0.924	0.400
Sex(F/M)	18/5	46/17	16/6	0.425	0.672
Weight(kg)	70.15**	60.65**	31.86	96.045	<0.001
BMI(kg/m²)	29.63**	28.04**	17.32	182.510	<0.001
WC(cm)	94.22** #	88.83**	58.83	94.835	<0.001
WHR	0.96**	0.96**	0.76	46.027	<0.001
lg(WHR)	-0.02**	-0.02**	-0.12	40.424	<0.001
SBP(mmHg)	122.3** #	111.67**	103.32	15.079	<0.001
DBP(mmHg)	70.91**	67.06	63.14	6.994	0.002
FBG(mmol/L)	5.57	5.03	5.27	1.379	0.267
lg (FBG)	0.73	0.70	0.72	32.360	0.289
FINS(mmol/L)	29.36**	18.05**	5.62	32.237	<0.001
HOMA-IR	7.36**	4.20**	1.34	25.565	<0.001
lg (HOMA-IR)	0.72** #	0.50**	0.04	24.075	<0.001
TG(mmol/L)	2.53** ##	1.44**	0.95	27.587	<0.001
TC(mmol/L)	4.40	4.42	3.88	27.587	0.127
HDL-C(mmol/L)	0.94** ##	1.29**	1.54	37.089	<0.001
LDL-C(mmol/L)	2.94**	2.72**	2.05	9.566	<0.001
Fatty liver(%)	78.26**	58.73**	0.00	31.242	<0.001
ALT(mmol/L)	64.87**	61.17**	14.95	45.136	<0.001
AST(mmol/L)	39.83**	41.03**	24.41	50.953	0.001
IL-6(pg/ml)	5.06	4.32	4.26	1.982	0.143
TNF(pg/ml)	26.30	26.03	23.55	0.071	0.931
lg (TNF)	1.34	1.29	1.35	0.548	0.580
mean IMT(mm)	0.69**	0.66**	0.38	67.970	<0.001

BMI = body mass index; WC = waist circumference; WHR = waist to hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBG = fasting blood glucose; FINS = fasting insulin; HOMA-IR = homoeostasis model assessment- insulin resistance; TG = triglyceride; TC = total cholesterol; HDL-C = high-density lipoprotein- cholesterol; LDL-C = low-density lipoprotein-cholesterol; ALT = alanine aminotransfe-rase; AST = aspartate aminotransferase; lg = logarithmical transformation; Compared to control group, **P<0.01, *P<0.05; Compared to obese group, ##P<0.01, #P<0.05.

Table 2 Correlation between mean IMT and all other variables

Variable	Mean IMT	
	r	p
Age(y)	0.09	0.364
Sex	0.01	0.935
Weight(kg)	0.63	<0.001
BMI(kg/m²)	0.68	<0.001
WC(cm)	0.70	<0.001
lg (WHR)	0.64	<0.001
SBP(mmHg)	0.27	0.006
DBP(mmHg)	0.21	0.033
lg(FBG)	-0.01	0.944
FINS(mmol/L)	0.39	<0.001
lg (HOMA-IR)	0.58	<0.001
TG(mmol/L)	0.41	<0.001
TC(mmol/L)	0.17	0.080
HDL-C(mmol/L)	-0.41	<0.001
LDL-C(mmol/L)	0.28	0.004
Fatty liver	0.35	<0.001
ALT(mmol/L)	0.35	<0.001
AST(mmol/L)	0.30	0.002
IL-6(pg/ml)	0.17	0.082
lg (TNF)	0.03	0.780

BMI = body mass index; WC = waist circumference; WHR = waist to hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBG = fasting blood glucose; FINS = fasting insulin; HOMA-IR = homoeostasis model assessment- insulin resistance; TG = triglyceride; TC = total cholesterol; HDL-C = high-density lipoprotein- cholesterol; LDL-C = low-density lipoprotein-cholesterol; ALT = alanine aminotransferase; AST = aspartate aminotransferase; lg = logarithmical transformation.

Table 3 Multiple stepwise linear regression analysis, with mean IMT of CCA as the dependent variable and all other variables investigated as the independent variable in all subjects

	Regression Coefficient	Standardized Coefficient	95% Confidence interval	*P*
WC(cm)	0.003	0.292	0.001~0.005	0.009
lg(WHR)	0.666	0.221	0.077~1.255	0.027
TG(mmol/L)	0.038	0.222	0.014~0.062	0.002
lg(HOMA-IR)	0.257	0.662	0.149~0.366	<0.001

WC = waist circumference; WHR = waist to hip ratio; TG = triglyceride; HOMA-IR = homoeostasis model assessment- insulin resistance; lg = logarithmical transformation.

Discussion

IMT is a well-known marker of subclinical atherosclerosis and it also can indicate future cardio-cerebrovascular disease [8,12,13]. Recent reports indicate that the presence of obesity in childhood is associated with increased adult IMT [2,3]. In our study we measured the IMT in obese and nonobese subjects. We found that IMT in obese children and adolescents was significantly increased as compared with non obese children of similar age and sex, which was in accordance with other studies [14,15,16]. This tendency was further intensified in the presence of MetS. IMT was closely associated with obesity especially abdominal obesity in childhood and adolescence as confirmed by our correlation analysis and regression analysis.

Obesity has been demonstrated to be associated with cardiovascular risk factors, such as hypertension, dyslipidemia, impaired glucose metabolism and chronic inflammation not only in adults but also in children and adolescents. In our study, IMT was significantly related to lg (HOMA-IR) and TG in both bivariate correlation and multiple stepwise linear regression analysis, suggesting a link between IMT, insulin resistance and dyslipidemia.

Insulin resistance is a common phenomenon and plays an important role in the cardio-cerebrovascular disease in obese population [17,18]. In our study, the obese and MetS group both demonstrated increased fasting insulin than control group rather than fasting blood glucose. Meanwhile, fasting insulin and HOMA-IR levels were significantly related to IMT, however, fasting blood glucose was not related. This information demonstrates that an increased insulin levels seem to be an earlier predictor for atherogenic changes than hyperglycemia, and concur with data published by Atabek et al [19]. Insulin not only di-

rectly stimulates the expression of vascular cell adhesion molecule [20], but disrupts the balance between the production of NO and ET-1 leading to endothelial dysfunction [21]. Our regression analysis showed that lg (HOMA-IR) was an independent determinant of mean IMT level, which indicates that insulin resistance was involved in the basic pathological changes associated of obesity [22], and was closely related to cardio-cerebrovascular disease.

Dyslipidemia, especially low HDL-C and high LDL-C, or a high TG is related to cardio-cerebrovascular disease [23,24]. These risk factors association with IMT was also shown in our study. According to Pearson correlation analysis, HDL-C, LDL-C and TG were all related to IMT. Therefore, dyslipidemia and cardio-cerebrovascular disease were inseparable. In addition, prevalence of nonalcoholic fatty liver in obese subjects with and without MetS was 78.26%, 58.73% respectively. In contrast, non obese children and adolescents had no fatty liver disease. The correlation between the fatty liver and IMT was significant. It was shown that nonalcoholic fatty liver disease (NAFLD) patients had an increase IMT compared with control subjects in children, just as many other studies have reported [25,26,27].

Deficiencies still exist in our study. First, our sample size was not large enough, especially the number of MetS group. The levels of SBP, DBP, IL-6 and TNF were not statistically related to IMT as other research [4,5,28,29,30]. However, the trend of increase was noted. This bias might due to the small sample size. Second, we used the standard of WC in Beijing rather than Zhe Jiang province, which might influence samples selection. Finally, the IMT may also probably be influenced by other risk factors which have not been tested in our study.

In conclusion, atherosclerosis begins in obese children and adolescents, and this tendency is intensified in the presence of MetS. Obesity especially abdominal obesity, high TG level and insulin resistance are strong predictors of increased IMT.

Acknowledgments

Conflict of Interest

The authors have declared that no conflict of interest exists.

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