Original Article

Elevation of Serum C-Reactive Protein Levels Is Associated with Obesity in Boys

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This study aimed to reveal the relationships among C-reactive protein (CRP), obesity, blood pressure (BP), and serum lipids in children. Eighty-six obese and 58 non-obese boys aged an average of 11.2 years were examined. Serum CRP levels were measured by high sensitivity latex turbidimetric immunoassay and subjects with CRP levels below 0.3 mg/dl were adopted. Comparisons of serum CRP levels, BP, and serum lipids levels between age-matched obese and non-obese groups were performed. A comparison of serum CRP levels among the percentage of relative weight quartiles and the relationships among percentage of relative weight, BP, and serum lipids in CRP quartiles were analyzed. The relationships between CRP and other parameters were analyzed by simple and stepwise multiple regressions. Obese children had significantly higher high-sensitivity CRP (hs-CRP) levels than their non-obese counterparts. The mean hs-CRP level was 5.5-fold higher in the top quartile of the percentage of relative weight than in the bottom quartile. In the top quartile of CRP, the percentage of relative weight, systolic BP, diastolic BP, pulse pressure, and low density/high density lipoprotein-cholesterol (LDL-C/HDL-C) were significantly higher than in the bottom quartile. The percentage of relative weight, BP, LDL-C, and apolipoprotein B (ApoB) showed positive correlations and HDL-C showed a negative correlation with log CRP by simple regression. Stepwise multiple regression analysis indicated that only the percentage of relative weight was strongly related to CRP. In conclusion, this study revealed a significant relationship between CRP and obesity in children. Obese children tended to have high CRP levels, BP elevation, and slight dyslipidemia. These results support the findings that CRP is one of the useful indices of childhood obesity that would affect the progression to future atherosclerotic disease. We consider that a strategy of preventing obesity from childhood would contribute to a drop in the future incidence of metabolic syndromes. (*Hypertens Res* 2003; 26: 541–546)

Key Words: C-reactive protein, children, obesity, serum lipids, blood pressure

Introduction

Approximately 30 million Japanese adults have hypertension (HT), and 13 million Japanese adults have type 2 diabetes mellitus (DM). HT and type 2 DM are the major risk factors for atherosclerosis (AS), and the clustering of these factors increases the risk of coronary events (1). This is a serious public health problem necessitating urgent protective and therapeutic strategies in adult subjects. In addition, the frequency of obesity in children has increased from 5% to more

than 10% over the last two decades (2) and this also constitutes a serious public health problem. It is well known that obesity is often associated with metabolic syndromes such as HT, DM, and dyslipidemia. Thus the prevalence of obesity-related metabolic syndromes can be expected to increase in the near future (3, 4). Clearly, a strategy for preventing obesity will also be needed in children.

Recently, many markers of AS have been found, and these are expected to serve as useful indices of prevention and early intervention of coronary events. C-reactive protein (CRP), one of these markers, has been used as an acute phase reac-

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tant and a marker of systemic inflammation. In particular, CRP values as measured by a high-sensitivity assay (hs-CRP) have been recognized as a very useful and sensitive predictor of the future risk of myocardial infarction (MI) and stroke in the past several years (5, 6). It is well known that CRP levels in adult subjects elevate with aging, excess of body mass index (BMI), smoking, and progression of HT (7, 8). It has been proven that weight loss and the improvement of insulin resistance lead to decreases of CRP levels and event risk (9–11).

However, there have been very few reports concerning hs-CRP in children, and the clinical significance of hs-CRP as a marker of inflammation in children remains uncertain. In some longitudinal studies, HT and obesity have been tracked since childhood (12, 13). During this process, if chronic inflammation already exists in children, this inflammation would affect CRP levels. For the purpose of preventing AS from childhood, it is important to clarify the association between metabolic syndromes and elevation of CRP in children.

To confirm the existence of obesity-induced inflammation and to clarify the influence of such inflammation on serum lipids and blood pressure (BP) levels, we investigated the relationship among CRP, obesity, BP, and serum lipids in schoolboys.

Methods

Subjects

This study examined 169 (109 obese and 60 non-obese) boys with a mean age of 11.2 years, all of whom received regular medical examinations in conjunction with the “The Prevention of Cardio- and Cerebrovascular Diseases in Childhood” program in September 2001. The Department of Pediatrics of the Niigata University School of Medicine and the School Health Division of the local governments in Niigata Prefecture undertake this program every year. No subjects had DM, endocrinological disorders, hereditary diseases or systemic inflammatory diseases. All were nonsmokers without any regular medication. All of the obese subjects were simply obese, with fasting blood glucose levels below 110 mg/dl, and an HbA1c of below 5.6%. Each of body height, body weight, percentage of relative weight, systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), serum CRP, total cholesterol (T-C), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), apolipoprotein (Apo) A1, ApoB, and ApoE were measured. Informed consent was obtained from the parents and guardians of all subjects. The Ethical Committee of the Niigata University Graduate School of Medicine and Dental Sciences approved this study.

Anthropometric Measurements

Body height and weight were measured by school nurses

with a portable standiometer and a digital scale to the nearest 1 mm and 0.1 kg, respectively. Percentage of relative weight was calculated based on the table published in 1990 by the Ministry of Education, Science and Culture of Japan. Both SBP and DBP were measured three times from the right arm with the subjects in a seated position using an automated recorder (Dinamap Model 8104; Critikon Inc., Tampa, USA). The third measurement of BP was used for analysis in this study. PP was calculated as SBP minus DBP.

Assays

Blood samples were obtained from the antecubital vein of the subjects in the morning and were centrifuged at 3,000 rpm for 10 min. The serum was frozen and stored at -20°C until analysis. T-C, HDL-C, LDL-C, ApoA1, ApoB, and ApoE were measured using an automatic analyzer. The LDL-C/HDL-C ratio was calculated as the atherogenic index. CRP values were measured by high sensitive latex turbidimetric immunoassay (Pure Auto S CRP Latex; Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan). The Pure Auto S CRP Latex utilized latex bearing an anti-CRP antibody, and one mouse monoclonal anti-CRP antibody was coupled to latexes having a diameter of 150 nm. The automated open system analyzer used was the CL-8000 (Shimadzu Corp., Kyoto, Japan). The sensitivity of this assay was 0.008 mg/dl. Intra-assay and interassay coefficients of variation were below 3% of 0.3 mg/dl, respectively. Because the 90th percentile of normal CRP distribution is 0.3 mg/dl (14), we adopted CRP values below 0.3 mg/dl to avoid the influence of acute infection.

Statistical Analysis

Data were expressed as the mean $\pm$ SD. First, CRP levels, BP, and lipids were compared between two age-matched groups, an obese (over 20% of relative weight) and a non-obese (below 20% of relative weight) groups, using the unpaired Student's *t*-test. Second, we divided the subjects into four groups according to the percentage of relative weight percentile. The mean values of CRP levels among the four groups were compared using nonparametric Kruskal-Wallis one-way analysis of variance (ANOVA). *Post hoc* comparisons between pairs of means were made using Wilcoxon's rank-sum test. We also divided the subjects into four groups according to CRP percentile, and comparisons of BP, PP, and serum lipids were analyzed with parametric one-way ANOVA. *Post hoc* comparisons between pairs of means were made using Scheffe's test. CRP values were logarithmically transformed before analyses of simple and stepwise multiple regressions. Percentage of relative weight, BP, and serum lipids were entered as independent variables, and log CRP was a dependent variable.

All statistical evaluations were made using StatView software (version 5.0; Abacus Concepts, Berkeley, USA) on a

Table 1. Clinical Characteristics of Subjects

	Non-obese (n = 58)	Obese (n = 86)	All subjects (n = 144)
Age (year)	11.3 ± 0.63	11.2 ± 1.65	11.2 ± 1.30
Height (cm)	138.1 ± 7.7***	147.4 ± 10.6	143.7 ± 10.6
Weight (kg)	31.6 ± 6.4***	60.8 ± 14.4	49.0 ± 18.6
Percent of relative weight (%)	- 4.3 ± 10.0***	+ 52.2 ± 12.0	+ 29.4 ± 30.0
SBP (mmHg)	100.2 ± 8.9***	117.2 ± 12.0	110.3 ± 13.7
DBP (mmHg)	51.7 ± 7.1***	58.6 ± 8.3	55.8 ± 8.5
PP (mmHg)	48.5 ± 8.3***	58.6 ± 11.4	54.5 ± 11.4
T-C (mg/dl)	180.5 ± 30.7	185.7 ± 32.3	183.6 ± 31.7
HDL-C (mg/dl)	67.5 ± 13.2***	56.8 ± 11.9	61.1 ± 13.5
LDL-C (mg/dl)	99.7 ± 23.2**	116.3 ± 28.0	109.6 ± 27.4
ApoA1 (mg/dl)	143.7 ± 17.4*	136.1 ± 15.7	139.2 ± 16.8
ApoB (mg/dl)	73.1 ± 13.7**	83.1 ± 18.7	79.1 ± 17.5
ApoE (mg/dl)	3.8 ± 0.84**	4.4 ± 1.0	4.1 ± 0.98
LDL-C/HDL-C	1.52 ± 0.39***	2.13 ± 0.60	1.9 ± 0.63
hs-CRP (mg/dl)	0.033 ± 0.037***	0.120 ± 0.067	0.085 ± 0.071

Data are mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; T-C, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoE, apolipoprotein E; hs-CRP, high sensitivity C-reactive protein; NS, not statistically significant. * $p < 0.01$, ** $p < 0.001$, and *** $p < 0.0001$ vs. obese subjects' value using unpaired *t*-test.

Fig. 1. Mean values of hs-CRP levels among the percentage of relative weight quartiles. The percent of relative weight quartile cut points are < - 4.4% (group 1), - 4.5 to 42.7% (group 2), 42.8 to 52.4% (group 3), > 52.4% (group 4) and numbers of each group are 36 boys, respectively. Data were analyzed by Kruskal-Wallis one-way ANOVA by ranks and *p* value among the four groups was below 0.05. * $p < 0.05$, ** $p < 0.0001$ post hoc comparisons between pairs of means using Wilcoxon's rank-sum test.

personal computer. For all analyses, probability (*p*) values below 0.05 were considered to indicate statistical significance.

Results

The baseline clinical characteristics of all subjects are shown in Table 1. One hundred and forty-four children were included in this study. Two non-obese and 23 obese children were excluded because their hs-CRP levels were over 0.3 mg/dl. Obese children, when compared with their non-obese counterparts, had significantly higher hs-CRP levels (0.120 ± 0.067 vs. 0.033 ± 0.037 mg/dl, $p < 0.0001$) and significantly higher SBP, DBP, and PP. Obese children also had significantly lower HDL-C and ApoA1, and significantly higher LDL-C, ApoB, ApoE, and LDL-C/HDL-C than non-obese children.

Figure 1 shows the hs-CRP levels among the percentage of relative weight quartiles. The mean hs-CRP levels were as follows: for group 1 (mean percentage of relative weight: - 10.8%) the level was 0.024 mg/dl; for group 2 (+ 18.9%) it was 0.067 mg/dl; for group 3 (+ 46.9%) it was 0.115 mg/dl; and for group 4 (+ 62.5%) it was 0.133 mg/dl. In the lowest percentage of relative weight group, the hs-CRP level was significantly lower than that of the other groups. The hs-CRP value was 5.5-fold higher in the top quartile compared with the bottom.

Table 2 shows the relationships of anthropometric measurements, BP, and serum lipids among CRP quartiles. There was no significant difference in age among the four groups. In the top quartile, height, weight, percentage of relative weight, SBP, DBP, PP, and LDL-C/HDL-C were significantly higher than those of the bottom quartile. HDL-C was significantly lower in the top quartile than in the bottom quar-

Table 2. Characteristics of the Subjects among CRP Groups (n = 144)

	Group 1 (n = 36)	Group 2 (n = 36)	Group 3 (n = 36)	Group 4 (n = 36)	ANOVA p
Age (year)	11.3 ± 0.5	11.4 ± 1.3	11.1 ± 1.7	11.0 ± 1.5	NS
Height (cm)	137.0 ± 7.5 ^{*,†,‡}	145.1 ± 11.0	145.8 ± 11.1	146.8 ± 9.7	< 0.05
Weight (kg)	30.2 ± 5.6 ^{*,†,‡}	50.5 ± 19.6	56.3 ± 15.6	59.2 ± 15.1	< 0.05
Percent of relative weight (%)	- 6.27 ± 8.1 ^{*,†,‡}	+ 29.5 ± 30.4 ^{†,‡}	+ 44.6 ± 19.3	+ 49.8 ± 18.3	< 0.05
SBP (mmHg)	98.3 ± 7.8 ^{*,†,‡}	111.4 ± 13.6	116.8 ± 13.2	114.9 ± 11.4	< 0.05
DBP (mmHg)	50.7 ± 7.1 ^{*,†,‡}	57.6 ± 9.5	57.6 ± 8.2	57.4 ± 7.3	< 0.05
PP (mmHg)	47.6 ± 8.3 ^{†,‡}	53.9 ± 10.9	59.1 ± 11.2	57.5 ± 11.6	< 0.05
T-C (mg/dl)	177.9 ± 24.9	185.1 ± 33.9	190.3 ± 39.5	181.2 ± 26.1	NS
HDL-C (mg/dl)	68.4 ± 12.8 ^{†,‡}	62.4 ± 13.6	59.0 ± 13.1	54.8 ± 11.0	< 0.05
LDL-C (mg/dl)	96.2 ± 18.1 [†]	110.2 ± 28.1	119.1 ± 34.8	113.1 ± 21.3	< 0.05
ApoA1 (mg/dl)	144.5 ± 17.4	140.0 ± 14.4	137.4 ± 16.9	134.8 ± 17.4	NS
ApoB (mg/dl)	71.2 ± 11.9 [†]	78.9 ± 15.9	84.4 ± 23.3	81.7 ± 14.9	< 0.05
ApoE (mg/dl)	3.7 ± 0.8	4.2 ± 0.9	4.3 ± 1.1	4.3 ± 1.0	NS
LDL-C/HDL-C	1.4 ± 0.4 ^{*,†,‡}	1.8 ± 0.6	2.1 ± 0.7	2.2 ± 0.6	< 0.05

Data are mean ± SD. Subjects are divided into four groups according to CRP percentiles. CRP quartile cut points are < 0.025 mg/dl (group 1), 0.025 to 0.067 mg/dl (group 2), 0.07 to 0.123 mg/dl (group 3), > 0.123 mg/dl (group 4). CRP, C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; T-C, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoE, apolipoprotein E. * $p < 0.05$ vs. group 2, † $p < 0.05$ vs. group 3, and ‡ $p < 0.05$ vs. group 4 using Scheffe's *post hoc* test.

Table 3. Simple Regression Analysis between log CRP and Other Parameters

	r	p
Height (cm)	0.309	< 0.001
Weight (kg)	0.584	< 0.0001
Percent of relative weight (%)	0.730	< 0.0001
SBP (mmHg)	0.492	< 0.0001
DBP (mmHg)	0.280	< 0.001
PP (mmHg)	0.383	< 0.0001
TC (mg/dl)		NS
LDL-C (mg/dl)	0.273	< 0.001
HDL-C (mg/dl)	- 0.343	< 0.0001
ApoA1 (mg/dl)		NS
ApoB (mg/dl)	0.260	< 0.01
ApoE (mg/dl)	0.246	< 0.01
LDL-C/HDL-C	0.428	< 0.0001

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoE, apolipoprotein E; NS, not statistically significant.

tile.

The relationships among log CRP, BP, and serum lipids by simple regression are shown in Table 3. The percentage of relative weight, SBP, DBP, and PP all showed positive correlations with log CRP. LDL-C, LDL-C/HDL-C, ApoB, and ApoE showed positive correlations with log CRP. HDL-C showed a negative correlation with log CRP. Only the per-

centage of relative weight was strongly related to log CRP; however, neither BP nor serum lipids was considered to be an independent factor in the stepwise multiple regression (data not shown).

Discussion

After Ridker *et al.* (15) described the association between risk of MI and hs-CRP in adult subjects, several large-scale prospective studies revealed the usefulness of measuring hs-CRP levels as a predictor of future MI (5, 16–18). These studies demonstrated that obesity, HT, DM, and smoking were directly correlated to increased hs-CRP levels, and that hs-CRP has prognostic utility in patients with acute coronary syndrome and is a strong independent predictor of future coronary events in apparently healthy subjects.

The results of the present study provided evidence that CRP elevation in children is associated with obesity. This is especially significant because, while there have been many reports concerning CRP in adults, there have been only a few in children (using the search system of PubMed from 1997 to 2002), and even fewer regarding the relation between hs-CRP and obesity in children.

Our study revealed that boys with high CRP levels and a high percentage of relative weight had high LDL-C and ApoB levels, and low HDL-C levels. High LDL-C levels and low HDL-C levels are traditional risk factors for AS, and ApoB is strongly associated with LDL-C and triglyceride. LDL-C/HDL-C is known as the atherogenic index and expresses impaired lipid metabolism. Our report indicates that obesity has significant relationships to CRP and lipid metab-

olism also in children.

On the other hand, our results revealed that boys with high CRP levels and a high percentage of relative weight had high SBP, DBP, and PP. The clustering of risk factors such as obesity and metabolic syndrome increases the risk of BP elevation (19). SBP and DBP are known to be significantly associated with inflammatory biomarkers and adipocytokines such as interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), leptin, and insulin (20). Jarvisalo *et al.* (21) reported on the relationship among CRP levels, ICAM-1, and endothelial dysfunction in children. Their results led to the hypothesis that an inflammatory reaction may contribute to BP elevation. In addition, several studies have shown that elevations in SBP, DBP, and PP are predictive of an increased risk of a cardiovascular event. The reason that HT increases the risk of AS *via* proinflammatory effects may be that high BP and PP may impair endothelin-dependent relaxation by generating reactive oxygen species and elevated oscillatory shear stress (22). This hypothesis led to another, *i.e.*, that BP elevation may contribute to an inflammatory reaction.

In the present study, it remains unclear whether the observed relation between obesity and CRP levels was directly due to metabolic abnormalities, or was a manifestation of excess adipose tissue. However, obesity has been independently associated with all cardiovascular risk factors, and IL-6, the primary stimulant of the *de novo* hepatic synthesis of CRP, is secreted by activated macrophages and adipose tissue (23). It has also been suggested that CRP levels reflect the amount and activity of tumor necrosis factor- α , which is implicated in the process of AS plaque formation (24). We speculate that CRP elevations do not indicate the amount of fat directly, but rather reflect an increasing risk of chronic inflammation which progresses to AS. It is therefore clear that careful management of obesity is important from childhood. More longitudinal studies of CRP and childhood obesity will be needed.

As regards CRP levels, the concentrations of CRP in healthy subjects are tightly regulated; except for the response to acute-phase stimuli, values cluster within the range of 0.01–0.3 mg/dl, and seasonal variations in CRP levels have been attributed to seasonal variations in minor respiratory infection (25). In the cases of CRP levels above 0.3 mg/dl, CRP evaluation may be of limited clinical utility and we must consider the possibility of acute infection. None of the subjects in this study were overtly febrile, but we adopted subjects with hs-CRP levels below 0.3 mg/dl in order to avoid infection and excluded 2 non-obese and 23 obese children because of their high hs-CRP values (> 0.3 mg/dl). However, this exclusion ratio of obese children was significantly higher than that of non-obese children using Fisher's exact probability method ($p < 0.001$), and this discrepancy is one of the facts supporting the idea that CRP level elevation in obese children is not necessarily due to acute infection.

Which cytokines mainly regulate CRP synthesis from

adipocytes or from early atherosclerotic lesions remains unclear, but our result that obese children had high CRP levels revealed an important finding that occult inflammation can already exist in childhood. Even in adult subjects whose chronic inflammation would have a long-term effect, however, statin therapy, independent of lipid levels and diet therapy, would be more effective to reduce CRP levels and cardiovascular events. Therefore, we speculated that the inflammation is not yet severe and is reversible in children. The management to reduce risk factors for AS is important in adults, but these strategies do not completely prevent AS. The combined evaluation of hs-CRP and other parameters is a better therapeutic aid, and careful management of lifestyle from childhood may contribute to the prevention and progression of metabolic syndromes in the future.

In conclusion, the results of the present study provided evidence of the significant relationship between CRP and obesity in children. Obese children have high CRP levels, BP elevation, and slight dyslipidemia. High-sensitivity CRP may be a useful marker of obesity in children and a predictor of future metabolic syndromes. In recent years, approximately 10% of Japanese children have come to be obese, and obesity-related metabolic disorders will increase in the near future; for this reason, the prevention of metabolic syndromes from childhood is necessary. A strategy for reducing obesity in children may therefore contribute to primary prevention of metabolic syndromes in the future.

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