REGULAR ARTICLE

Association of serum hs-CRP and lipids with obesity in school children in a 12-month follow-up study in Japan

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Abstract

Objectives To investigate the association of serum lipids and high-sensitivity C-reactive protein (hs-CRP) with obesity in school children and to explore whether hs-CRP levels could be used to predict the presence or absence of obesity 12 months later.

Methods The subjects were school children (6–11 years old) in Japan. Blood sampling and physical measurements were performed in school (2001); low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and hs-CRP levels were measured. Data from children who could be followed 12 months later were analyzed. Subjects weighing 20 % or more over his/her standard weight were regarded as obese, and the association of obesity with serum parameters was analyzed.

Results Data from 612 subjects were analyzed (follow-up rate, 75.4 %). The mean of each serum parameter was significantly higher (inverse for HDL-C; lower) in obese than that in non-obese children. Logistic regression analysis for obesity at baseline showed that the odds ratio (OR) of hs-CRP was the highest [OR, 2.15; 95 % confidence interval (CI), 1.65–2.78 for an interquartile rage (IQR) increase]; the association with triglycerides and LDL-C/HDL-C was significant. At the 12-month follow-up, the OR of high hs-CRP remained the highest of all serum parameters (2.09; 95 % CI, 1.63–2.69 for an IQR increase).

Conclusions High levels of triglycerides, LDL-C/HDL-C, and hs-CRP increased the risk of obesity in school children. Hs-CRP is considered to be a better predictor of obesity 12 months later than is LDL-C/HDL-C.

Keywords Follow-up · Hs-CRP · Low-grade-inflammation · Obesity · School children

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Introduction

Serum high-sensitivity C-reactive protein (hs-CRP) has attracted recent attention as a sensitive marker of cardiovascular diseases [1, 2]. Hs-CRP serves as a marker of low-grade inflammation in the development of cardiovascular disease and diabetes [3–5] and predicts vascular risk in healthy women [6]. Elevated serum hs-CRP is associated with obesity and abnormal lipid metabolism in adults. This association has also been confirmed in children [7–13], although the number of reports is fewer than those in adults. Overweight or obese adolescents with dyslipidemia have shown an increased risk of high carotid intima-media thickness in adulthood compared with those without these risk factors [14]. Excess visceral fat induces vascular- and

atherosclerosis-related diseases. CRP is produced in the liver, macrophages, and adipose tissues. Further, serum hs-CRP concentrations were found to inversely correlate with the concentrations of adiponectin, a protein that enhances insulin sensitivity and prevents atherosclerosis [15, 16]. Decreased levels of adiponectin and elevated levels of hs-CRP in adulthood appear to be related to the difference in physique between childhood and adulthood [17]. Therefore, the physique of children should be assessed in combination with parameters associated with atherosclerosis.

Only a few studies have investigated the association of serum parameters, including hs-CRP, with physique in children, and most studies were cross-sectional [7, 9]. Furthermore, many studies on children have included only those receiving medical care [8, 12, 18], whereas similar studies on adults have included both patients and healthy subjects. Secondary sex characteristics begin to appear in children of primary school age. The rate of change in total body fat during growth and sexual maturation differs between boys and girls. Few studies in children compare serum hs-CRP [8] and TG [9] concentrations between the sexes. In Japan, measurement of serum lipids and hs-CRP levels is not included in school health checkups, and it is difficult to obtain informed consent for blood sampling from school children and their parents. Thus, few serological surveys have been performed in healthy children. We performed serological tests in public primary school children in 2001 and 2002 [19] and evaluated the relationship between the test results and physique.

The objective of this study was to investigate the association of serum lipids and hs-CRP with obesity in school children and to explore whether hs-CRP levels could be used to predict the presence or absence of obesity 12 months later.

Materials and methods

Subjects, data collection, and laboratory measurements

Our cohort included 1072 children (grades 1–5; ages 6–11 years) attending 3 primary schools in the urban regions of Chiba Prefecture, Japan (October and November, 2001). Blood sampling and the measurement of height and weight were performed at school in the same morning. They had eaten breakfast as usual on that day. The same examination was performed 12 months later, and the children available for follow-up were included in the data analysis. Children with signs of acute inflammation, such as cold or fever, were excluded from the present study. The collected blood samples were analyzed by latex-enhanced immuno-nephelometric assays using a BN II analyzer (Dade Behring, Marburg, Germany). The minimum detection level of CRP was 0.02 mg/dL [2].

This study was approved by the Ethics Committee of Chiba University Graduate School of Medicine in 2001. After approval by the Board of Education of the city and the school principals, the study was explained to the children (orally) and their parents (written). Written informed consent was obtained from the parents.

Evaluation of physical and serum parameters

The standard weight (SW) of each child was estimated as per the gender, age, and height based on the methods reported by the Ministry of Education, Culture, Sports, Science and Technology, Japan [20, 21]. The percent over the standard weight (POW) was calculated for each child as follows: POW $(\%) = [(\text{measured body weight} - \text{SW})/\text{SW}] \times 100$ and the children were classified as obese (POW ≥ 20 %) or non-obese (POW < 20 %) [20].

Serum parameters measured included total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and hs-CRP. As an atherosclerosis index, LDL-C/HDL-C was calculated [22–24].

Statistical analysis

Data regarding physical parameters and serum levels of lipids and hs-CRP were analyzed blind to the identity of the subjects. The percentage of obese children was estimated at baseline and after 12 months in relation to gender. Changes in these percentages were analyzed using the McNemar test. Moreover, physical and serum parameters at baseline and the means and percentages of obesity were compared between follow-up and non-follow-up subjects. Differences by sex (boys versus girls) and physique (obese versus non-obese at baseline) in the 5 serum parameters (LDL-C, HDL-C, LDL-C/HDL-C, TG, and hs-CRP) at baseline were analyzed. TG and hs-CRP data were analyzed after logarithmic transformation because these distributed approximately log normally. Simple regression analysis of physical and serum parameters at baseline, including log-transformed hs-CRP (log CRP) and log-transformed TG (log TG), were calculated using Pearson's correlation coefficient.

Finally, the association between obesity at baseline or after 12 months (object variable) and baseline levels of 3 serum parameters (log CRP, log TG, and LDL-C/HDL-C), sex, and age (explanatory variables) were determined using logistic regression models; the odds ratios per each interquartile range (IQR) for the serum parameters and that per 1-year for age were estimated.

Statistical analyses were performed using IBM SPSS Statistics 22.0 for Windows (IBM Corp. Armonk, NY, USA). Significance levels were set at 5 % for all tests.

Results

Blood samples were analyzed at baseline from 403 boys and 405 girls in 2001 (total, 808; consent rate, 75.4 %) and after 12 months from 299 boys and 313 girls (total, 612; follow-up rate, 75.7 %).

Obesity at baseline and after 12 months

The percentages of obese children among follow-up subjects by sex and age are shown in Table 1. At baseline, the percentage of obese boys was 12.7 %, which was significantly higher than that of girls (7.3 %). The percentages of obese boys 8–10 years of age were particularly high (above 15 %), with a maximum of 17.5 % (8-year-old boys).

After 12 months, the percentages of obese children were similar to those at baseline. However, the sex difference decreased and became non-significant. The percentages of obese boys were lower or the same as those at baseline for all ages.

Baseline characteristics of 808 study subjects at baseline are shown in Table 2. The differences in mean age and serum parameters between subjects who did and did not participate in the follow-up were not significant. However, the percentage of obese children was significantly lower among those who participated in the follow-up than those who did not. There was no difference in serum levels of hs-CRP between the 2 groups.

Data regarding obesity in follow-up subjects at baseline and after 12 months are shown in Table 3. Fifty of the 61 obese children at baseline were also obese after 12 months; of these children, 33 were boys. Eleven of the 551 children who were non-obese at baseline became obese after 12 months; of these, 9 were girls. The percentages of obese children did not markedly change between baseline and after 12 months either in boys or girls.

Association of baseline serum levels of lipids and hs-CRP with obesity

The means of serum lipids and hs-CRP levels at baseline are shown in Table 4 (boys and girls) and Table 5 (obese and non-obese at baseline). HDL-C and TG levels were higher in boys than girls, but the differences were not significant. Moreover, mean levels of hs-CRP, TG and LDL-C were significantly higher and of HDL-C was significantly lower in obese than non-obese children.

Simple regression analysis of the physical and 4 serum parameters at baseline are shown in Table 6. POW was found to have a strong positive correlation with weight, a weak positive correlation with each serum parameter (log CRP, LDL-C, and log TG), and a weak inverse correlation with HDL-C. The correlation coefficient for log CRP was higher than that of LDL-C and log TG.

Table 7 shows the results of logistic regression analysis for obesity. The odds ratio of log CRP was 2.15 [95 % confidence interval (CI), 1.65–2.78] for IQR, which was the highest. The odds ratio of age was 1.25 (95 % CI, 1.04–1.52), and that of boys versus girls was 1.76 (95 % CI, 0.97–3.20).

Data analysis regarding obesity after 12 months revealed that neither gender nor age was significant. The odds ratios of all 3 serum parameters for obesity after 12 months decreased compared with those at baseline, but the odds ratio for hs-CRP (2.09; 95 % CI, 1.63–2.69, for an IQR range) was still the highest among them.

Discussion

Previous cross-sectional studies have reported that serum lipid and hs-CRP levels are higher in obese than those in non-obese children [7, 8, 10, 11]. While the subjects of these 4 studies were not school children, the results of our blood analysis and physical measurements in primary school children were the same. Our subjects were followed up at 12 months, allowing longitudinal analysis of obesity and lipid metabolism.

The height and body weight rise markedly in children during their primary school years (ages 6–12) [25–27]. Body mass index (BMI) also substantially changes with age during childhood [28]. The trend in BMI shifts from

Table 1 Obesity by sex and age among follow-up subjects (n = 612)

Age at baseline (years)	At baseline				p value	After 12 months		p value
	Boys		Girls			Boys	Girls	
	n	Obese (%)	n	Obese (%)		Obese (%)	Obese (%)	
6	27	1 (3.7)	26	1 (3.8)		1 (3.7)	1 (3.8)	
7	56	3 (5.4)	64	5 (7.8)		3 (5.4)	7 (10.9)	
8	57	10 (17.5)	60	5 (8.3)		9 (15.8)	5 (8.3)	
9	52	8 (15.4)	60	4 (6.7)		7 (13.5)	5 (8.3)	
10	61	10 (16.4)	60	3 (5.0)		10 (16.4)	5 (8.3)	
11	46	6 (13.0)	43	5 (11.6)		5 (10.9)	3 (7.0)	
Total	299	38 (12.7)	313	23 (7.3)	0.027	35 (11.7)	26 (8.3)	0.161

Obese, POW (percent over the standard weight) ≥ 20 %

p value, χ^2 test

Table 2 Baseline characteristics of follow-up subjects and non-follow-up subjects ($n = 808$)

At baseline	Follow-up ($n = 612$)		Non-follow-up ($n = 196$)		p value
	Mean	(95 % CI)	Mean	(95 % CI)	
Age (years)	8.65	(8.52–8.77)	8.77	(8.56–8.98)	0.639
Height (cm)	131.1	(130.3–131.9)	131.3	(129.9–132.8)	0.388
Weight (kg)	29.9	(29.2–30.5)	30.7	(29.4–32.0)	0.021
POW (%)	2.63	(1.45–3.81)	4.64	(2.10–7.17)	0.101
Obese (n, %) ($n = 99$)	61	(10.0 %)	38	(19.4 %)	<0.001*
LDL-C (mg/dL)	95.2	(93.4–97.0)	95.4	(92.4–98.3)	0.082
HDL-C (mg/dL)	67.6	(66.5–68.6)	66.8	(64.9–68.7)	0.145
LDL-C/HDL-C	1.47	(1.43–1.51)	1.49	(1.43–1.56)	0.099
TG[a] (mg/dL)	88.5	(85.2–92.0)	93.0	(86.2–100.4)	0.252
Hs-CRP[a] (mg/dL)	0.038	(0.035–0.041)	0.036	(0.032–0.040)	0.409

POW, percent over the standard weight; Obese, POW at baseline $\geq$ 20 %

p value, unpaired t test (* χ^2 test)

LDL-C low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *Hs-CRP* high-sensitivity C-reactive protein, *CI* confidence interval

[a] Geometric mean and p value analyzed by log-transformed mean

Table 3 Obesity presence and absence at baseline and after 12 months ($n = 612$)

At baseline	After 12 months				p value
	Obese		Non-obese		
	n	(%)	n	(%)	
Boys					
Obese	33	(86.8)	5	(13.2)	0.453
Non-obese	2	(0.8)	259	(99.2)	
Total	35	(11.7)	264	(88.3)	
Girls					
Obese	17	(73.9)	6	(26.1)	0.607
Non-obese	9	(3.1)	281	(96.9)	
Total	26	(8.3)	287	(91.7)	
Boys and girls					
Obese	50	(82.0)	11	(18.0)	1.000
Non-obese	11	(2.0)	540	(98.0)	
Total	61	(10.0)	551	(90.0)	

Obese, POW (percent over the standard weight) $\geq$ 20 %, Non-obese: POW < 20 %

p value, McNemar test

decreasing to increasing (adiposity rebound) late in infancy and persists through the lower grades of primary school [28–30]. Therefore, differences in age as well as sex should be considered when evaluating the physique of children [31]. A 2013 survey in Japan found that 10.02 % and 8.69 % of boys and girls, respectively, aged 11 years were obese according to POW [32]. In our study, the percentage of obese boys was also higher than that of obese girls at both baseline and after 12 months. No significant change was noted in the percentage of obese children of either sex

at 12 months after baseline. Thus, we divided the children into obese and non-obese groups irrespective of gender.

Serum LDL-C, TG, and LDL-C/HDL-C have been used as risk indicators for arteriosclerosis. The serum hs-CRP level is increasingly used in healthy adults [33, 34] and children [7–11, 35] as a biochemical marker of vascular inflammation associated with atherosclerosis. Yoshida et al. reported a cross-sectional analysis of the association of serum hs-CRP and other serum parameters with physique in 568 Japanese children (7–10 years old). In

Table 4 Differences by sex in serum indicators at baseline ($n = 612$)

At baseline	Boys ($n = 299$)		Girls ($n = 313$)		p value
	Mean	(95 % CI)	Mean	(95 % CI)	
LDL-C (mg/dL)	93.5	(90.9–96.1)	96.7	(94.2–99.2)	0.082
HDL-C (mg/dL)	68.4	(66.9–69.9)	66.8	(65.4–68.3)	0.145
LDL-C/ HDL-C	1.44	(1.38–1.49)	1.50	(1.45–1.55)	0.099
TG[a] (mg/dL)	88.9	(83.9–94.2)	88.1	(83.6–92.8)	0.814
Hs-CRP[a] (mg/dL)	0.039	(0.035–0.044)	0.037	(0.033–0.041)	0.474

p value, unpaired t test

LDL-C low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *Hs-CRP* high-sensitivity C-reactive protein, *CI* confidence interval

[a] Geometric mean and p value analyzed by log-transformed mean

Table 5 Differences by physique in serum indicators at baseline ($n = 612$)

At baseline	Obese ($n = 61$)		Non-obese ($n = 551$)		p value
	Mean	(95 % CI)	Mean	(95 % CI)	
LDL-C (mg/dL)	106.2	(100.1–112.3)	93.9	(92.1–95.8)	<0.001
HDL-C (mg/dL)	61.7	(57.9–65.4)	68.2	(67.2–69.3)	<0.001
LDL-C/ HDL-C	1.82	(1.67–1.96)	1.43	(1.39–1.47)	<0.001
TG[a] (mg/dL)	119.7	(103.8–138.0)	85.6	(82.3–89.0)	<0.001
Hs-CRP[a] (mg/dL)	0.092	(0.068–0.126)	0.035	(0.032–0.037)	<0.001

Obese, POW (percent over the standard weight) at baseline ≥ 20 %, Non-obese, POW at baseline < 20 %

p value, unpaired t test

LDL-C low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *Hs-CRP* high-sensitivity C-reactive protein, *CI* confidence interval

[a] Geometric mean and p value analyzed by log-transformed mean

addition, no gender difference was noted in the mean TG, but the mean LDL-C, HDL-C, and hs-CRP levels were significantly higher in boys than those in girls [9]. Unlike the results of their study, we observed no gender difference in LDL-C, HDL-C, or hs-CRP. Thus, we analyzed serum parameters without division by gender.

We confirmed that the serum hs-CRP level was higher in obese than that in non-obese children, as reported in previous studies [7, 8, 11]. We also observed that the correlation between hs-CRP levels and obesity was the same as

that between indicators of lipid metabolism and obesity. The observation that both serum hs-CRP and leptin concentrations positively correlated with obesity has also been reported in girls aged 9–15 years in Greece [12]. Therefore, the high hs-CRP levels and abnormal serum lipids are confirmed in children of the same age.

We found that the mean weight and the percentage of children with obesity were lower among those who participated in the follow-up than those who did not. A higher percentage of obese than non-obese children did not participate in the follow-up examination 12 months after baseline; therefore, follow-up of obese children was insufficient. However, there were no significant differences in POW, age, or serum parameters between these 2 groups. Thus, we considered that follow-up and non-follow-up children were similar with respect to these parameters.

The presence of low-grade chronic inflammation can be evaluated by analyzing the course of serum hs-CRP levels. At the same time point, the odds ratio of log CRP for obesity was higher than that of LDL-C/HDL-C and log TG. In addition, after 12 months, the odds ratio of log CRP for obesity was the highest of all serum parameters. Abnormal serum lipids and low-grade inflammation were observed at baseline in our obese school children, and this progression of abnormal metabolism greatly concerned us. In school children, in Quebec, aged 9, 14, and 16 years, an increased CRP concentration was found to be independently associated with the worsening of the lipid profile (high TG and low HDL-C concentrations) [36]. Low-grade inflammation of the vascular tunica intima was present in obese school children at baseline, suggesting that metabolic abnormalities in obese children are more detectable based on hs-CRP than those on serum lipids.

In the present study, we observed that indicators of lipid metabolism and hs-CRP levels in school children were significantly associated with obesity at baseline and after 12 months of blood sampling. These data establish that in children, hs-CRP is a better predictor of obesity 12 months later than is LDL-C/HDL-C, which has been widely used as a predictor of cardiovascular disease in all populations [22–24].

Our study has several limitations. First, TG levels are influenced by food intake before the test [37]. We collected blood samples without fasting. TG was included in the parameters because >2 h had passed from breakfast time, as estimated from the start time of school, but the possibility of an influence by breakfast remains. Logistic regression analysis excluding TG from explanatory variables was performed, but similar results were obtained. Second, while the consent rate was high (75.4 %), not all children could be followed up 12 months after the baseline measurements, and the percentage of obese children was

Table 6 Simple regression analysis of physical and serum parameters at baseline ($n = 612$)

	POW	Height	Weight	Log CRP	LDL-C	HDL-C	Log TG
POW	1	0.07	0.61	0.31	0.20	−0.23	0.25
Height		1	0.82	−0.07	−0.05	−0.001	0.06
Weight			1	0.12	0.09	−0.14	0.20
Log CRP				1	0.06	−0.23	0.004
LDL-C					1	−0.06	0.10
HDL-C						1	−0.36
Log TG							1

Simple regression analysis, Pearson's correlation coefficient, *POW* percent over the standard weight, *Log CRP* logarithm of high-sensitivity C-reactive protein, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Log TG* logarithm of triglycerides

Table 7 Logistic regression analysis of obesity at baseline and after 12 months ($n = 612$)

Explanatory variable	Obesity at baseline (obese/non-obese)		Obesity after 12 months (obese/non-obese)	
	Odds ratio (95 % CI)	p*	Odds ratio (95 % CI)	p*
Log CRP (mg/dL)	2.15 (1.65–2.78)[a]	<0.001	2.09 (1.63–2.69)[a]	<0.001
Log TG (mg/dL)	2.09 (1.39–3.15)[a]	<0.001	1.86 (1.25–2.77)[a]	0.002
LDL-C/HDL-C	1.50 (1.11–2.02)[a]	0.008	1.40 (1.04–1.88)[a]	0.028
Sex (boy/girl)	1.76 (0.97–3.20)	0.065	1.36 (0.76–2.43)	0.298
Age (years)	1.25 (1.04–1.52)[b]	0.021	1.18 (0.98–1.42)[b]	0.081

Obese, POW (percent over the standard weight) ≥ 20 %; Non-obese, POW < 20 %

Log CRP logarithm of high-sensitivity C-reactive protein, *Log TG* logarithm of triglycerides, *LDL-C/HDL-C* low-density lipoprotein cholesterol/high-density lipoprotein cholesterol, *CI* confidence interval

* Logistic regression analysis

[a] Per each interquartile range at baseline

[b] Per 1-year

higher among non-follow-up than follow-up participants. Moreover, data was only collected at 12 months after the baseline date. To investigate the feasibility of using hs-CRP to predict obesity in children, prolonged follow-up will be necessary.

In conclusion, high levels of TG, LDL-C/HDL-C, and hs-CRP increased the risk of obesity in school children. Hs-CRP was a better predictor of obesity 12 months later than was LDL-C/HDL-C.

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