

Total and low-density lipoprotein Cholesterol Levels are Associated with Atopy in Schoolchildren

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Analysis of general childhood population data showed that there was a significant positive association between total and low-density lipoprotein cholesterol levels and atopy, independent of obesity or sex, which suggest a relationship between hyperlipidemia and greater allergic sensitization among schoolchildren. (*J Pediatr* 2010; ■: ■-■)

A recent increase in the prevalence of allergy has potentially been explained by changes in environmental factors, including dietary intake of fatty acids. In this context, several studies have evaluated the possible association between serum lipid levels and allergy.¹⁻⁹ However, the results have been inconsistent; some data showed positive associations,^{2-4,6,8,9} and others showed negative associations.^{1,5,7} There are very few data on this topic in children. The purpose of this study was to further examine this issue by evaluating the association between serum lipid levels and allergic sensitization in a general childhood population.

Methods

In 2008, blood sampling for serum fasting lipid levels (triglycerides [TG], total cholesterol [TCHO], and high-density lipoprotein cholesterol [HDL-C]) (Kyowa Medex Co, Ltd, Tokyo, Japan), total IgE, and IgE specific to house dust mite and three pollen allergens (ImmunoCAP, Phadia, Uppsala, Sweden), as well as measurement of body weight and height, were performed on all 11-year-old children at every primary school in Ohmi-Hachiman City, Shiga Prefecture, Japan. Of the 654 11-year-old children who attended primary school, 618 (94.5%) underwent blood tests. A questionnaire regarding allergic diseases was distributed to the parents of the students who underwent blood tests. The details of the questionnaire, as well as the definition of each allergic disease based on the questionnaire, have been described previously.¹⁰ The study was approved by the Ethics Committee of Kyoto University Graduate School of Medicine. Pollen allergens used for allergy testing were (1) Japanese cedar (cedar), the most prevalent evergreen tree and the most frequent cause of pollen allergy in Japan; (2) Japanese cypress (cypress),

another evergreen tree in Japan, whose pollen has cross allergenicity to that of cedar; and (3) orchard grass (OG), the most frequent cause of grass pollen allergy in Japan.

The 25th, 50th, and 75th percentiles of TG, HDL-C, TCHO, and low-density lipoprotein cholesterol (LDL-C), which was calculated by the Friedewald equation ($LDL-C = TCHO - HDL-C - TG/5$), were determined. For each lipid variable, participants were divided into four groups by quartile. For each lipid variable, the rate of high IgE, defined as 1000 IU/mL or more, and the rate of a positive test for each allergen, defined as allergen-specific IgE of 0.7 or more, as well as the prevalence of any allergic disease, bronchial asthma, atopic dermatitis, allergic rhinitis or conjunctivitis, were compared among the groups.

For statistical analysis, multivariate logistic regression models with the first quartile group of lipid levels as reference were developed, and the linear trends across quartiles of lipid levels were assessed. On multivariate analysis, sex, body mass index, birth order, gestational age, birth weight, and family history of allergy were chosen as confounding factors. A *P* value of <.05 was considered statistically significant, and *P* < .1 was considered a tendency. STATA/IC 10.0 Software (STATA Corporation, College Station, Texas) was used for all of the analyses.

Results

The sex ratio (male:female) was 1:1. The average ($\pm$ SD range) of IgE (log value) was 138 (7 to 955). The positivity rates for mite, cedar, OG, and cypress were 46.6%, 40.3%, 35.1%, and 28.5%, respectively. The averages $\pm$ SD of TCHO, TG, HDL-C, LDL-C were 175 ± 25 , 52 ± 24 , 65 ± 13 , 99 ± 23 mg/dL, respectively. The prevalence of participants with higher TCHO

HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
OG	Orchard grass
TCHO	Total cholesterol
TG	Triglycerides

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(≥ 200 mg/dL), higher LDL-C (≥ 130 mg/dL), higher TG (≥ 150 mg/dL), and lower HDL-C (≤ 40 mg/dL) was 15.7%, 8.7%, 1.3%, and 1.8%, respectively. The prevalence of bronchial asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis was 5.0%, 6.8%, 26.7%, and 23.9%, respectively. There was a significant positive relationship between the TCHO level and the rate of high IgE ($P = .04$) and cedar-positive ($P = .005$) participants. Moreover, there was a tendency for a positive relationship between the TCHO level and the prevalence of OG-positive ($P = .08$), cypress-positive ($P = .06$), and any allergen-positive ($P = .05$) participants (Table I). There was also a significant positive relationship between the LDL-C level and the rate of mite-positive ($P = .01$), cedar-positive ($P = .001$), cypress-positive ($P = .03$), and any allergen-positive ($P = .003$) participants. Furthermore, there was a tendency for a positive relationship between the LDL-C level and the prevalence of high IgE ($P = .09$) and OG ($P = .09$)-positive participants (Table II). No such association was observed for either the TG or HDL-C level (data not shown), and no association was observed between the levels of these lipids and the prevalence of allergic diseases (data not shown).

Discussion

In a general population of 11-year-old children, the serum TCHO and LDL-C levels were significantly positively associated with higher IgE levels and a higher rate of allergic sensitization. Because sex and body mass index were included as confounding factors, these associations were independent of sex or obesity.

There has been discussion regarding the possible mechanisms by which hyperlipidemia may be associated with allergic conditions, such as a general switch from a Th1 to a Th2 response in severe hypercholesterolemia,³ promotion of inflammation by hypercholesterolemia,⁴ shared common genetic factors, increased risk of high LDL-C and allergic sensitization by a high-fat diet, or increased risk of abnormalities in lipid profiles by allergic sensitization.⁶ All of these are based on animal research or are speculation, indicating the need for further research in this field.

Although the results have limitations because of the cross-sectional nature of the study, they may suggest that hyperlipidemia is a risk factor for greater allergic sensitization among schoolchildren. Socioeconomic status was unlikely to affect the results because it was quite homogeneous in the study

Table I. Associations between serum TCHO levels and allergy test results

	n	Range (mg/dL)	High IgE	Adjusted OR	95% CI	P value	P value for trend
Q1	151	<157	18 (11.9%)	reference	-	-	
Q2	156	≥ 157 , <174	25 (16.0%)	1.32	0.67-2.62	.42	
Q3	152	≥ 174 , <191	23 (15.1%)	1.28	0.64-2.56	.49	
Q4	159	≥ 191	34 (21.4%)	2.03	1.06-3.88	.03	$P = .04$
	n	Range (mg/dL)	Mite-positive	Adjusted OR	95% CI	P value	P value for trend
Q1	151	<157	60 (39.7%)	reference	-	-	
Q2	156	≥ 157 , <174	74 (47.4%)	1.38	0.86-2.23	.19	
Q3	152	≥ 174 , <191	73 (48.0%)	1.37	0.85-2.26	.2	
Q4	159	≥ 191	81 (50.9%)	1.52	0.94-2.46	.09	$P = .11$
	n	Range (mg/dL)	Cedar-positive	Adjusted OR	95% CI	P value	P value for trend
Q1	151	<157	49 (32.5%)	reference	-	-	
Q2	156	≥ 157 , <174	61 (39.1%)	1.23	0.75-2.02	.41	
Q3	152	≥ 174 , <191	65 (42.8%)	1.48	0.87-2.37	.15	
Q4	159	≥ 191	74 (46.5%)	2.00	1.22-3.27	.006	$P = .005$
	n	Range (mg/dL)	OG-positive	Adjusted OR	95% CI	P value	P value for trend
Q1	151	<157	44 (29.1%)	reference	-	-	
Q2	156	≥ 157 , <174	49 (37.8%)	1.50	0.91-2.48	.11	
Q3	152	≥ 174 , <191	55 (36.2%)	1.47	0.88-2.45	.14	
Q4	159	≥ 191	59 (37.1%)	1.60	0.97-2.64	.07	$P = .09$
	n	Range (mg/dL)	Cypress-positive	Adjusted OR	95% CI	P value	P value for trend
Q1	151	<157	34 (22.5%)	reference	-	-	
Q2	156	≥ 157 , <174	45 (28.8%)	1.36	0.79-2.34	.27	
Q3	152	≥ 174 , <191	49 (32.2%)	1.65	0.96-2.85	.07	
Q4	159	≥ 191	48 (31.0%)	1.63	0.95-2.80	.08	$P = .06$
	n	Range (mg/dL)	Any-positive	Adjusted OR	95% CI	P value	P value for trend
Q1	151	<157	82 (54.3%)	reference	-	-	
Q2	156	≥ 157 , <174	103 (66.0%)	1.63	1.00-2.66	.04	
Q3	152	≥ 174 , <191	96 (63.2%)	1.43	0.87-2.33	.16	
Q4	159	≥ 191	107 (69.0%)	1.76	1.07-2.88	.03	$P = .05$

OR, odds ratio; CI, confidence interval; Q1 to Q4, first to fourth quartiles group of TCHO levels; OG, orchard grass. Adjusted for sex, body mass index, birth order, gestational age, birth weight, and family history of allergy.

Table II. Associations between serum LDL-C level and allergy test results

	n	Range (mg/dL)	High IgE	Adjusted OR	95% CI	P value	P value for trend
Q1	155	<83.7	17 (11.0%)	reference	-	-	
Q2	150	≥83.7, <97.8	28 (18.7%)	1.76	0.89-3.49	.11	
Q3	158	≥97.8, <113.8	25 (15.8%)	1.64	0.83-3.24	.15	
Q4	155	≥113.8	30 (19.4%)	1.92	0.97-3.79	.06	P = .09
	n	Range (mg/dL)	Mite-positive	Adjusted OR	95% CI	P value	P value for trend
Q1	155	<83.7	58 (37.4%)	reference	-	-	
Q2	150	≥83.7, <97.8	67 (44.7%)	1.17	0.72-1.90	.52	
Q3	158	≥97.8, <113.8	78 (49.4%)	1.52	0.95-2.45	.08	
Q4	155	≥113.8	85 (54.8%)	1.87	1.15-3.05	.01	P = .01
	n	Range (mg/dL)	Cedar-positive	Adjusted OR	95% CI	P value	P value for trend
Q1	155	<83.7	52 (33.5%)	reference	-	-	
Q2	150	≥83.7, <97.8	53 (35.3%)	0.89	0.54-1.47	.65	
Q3	158	≥97.8, <113.8	69 (43.7%)	1.47	0.91-2.38	.12	
Q4	155	≥113.8	75 (48.4%)	2.03	1.23-3.33	.005	P = .001
	n	Range (mg/dL)	OG-positive	Adjusted OR	95% CI	P value	P value for trend
Q1	155	<83.7	49 (31.6%)	reference	-	-	
Q2	150	≥83.7, <97.8	48 (32.0%)	0.95	0.57-1.58	.84	
Q3	158	≥97.8, <113.8	63 (49.9%)	1.56	0.96-2.54	.07	
Q4	155	≥113.8	57 (36.8%)	1.33	0.81-2.20	.27	P = .09
	n	Range (mg/dL)	Cypress-positive	Adjusted OR	95%CI	P value	P value for trend
Q1	155	<83.7	38 (24.5%)	reference	-	-	
Q2	150	≥83.7, <97.8	39 (26.0%)	0.92	0.53-1.60	.76	
Q3	158	≥97.8, <113.8	50 (31.6%)	1.41	0.84-2.38	.2	
Q4	155	≥113.8	49 (31.6%)	1.61	0.94-2.74	.08	P = .03
	n	Range (mg/dL)	Any-positive	Adjusted OR	95% CI	P value	P value for trend
Q1	155	<83.7	85 (54.8%)	reference	-	-	
Q2	150	≥83.7, <97.8	88 (58.7%)	0.95	0.58-1.54	.83	
Q3	158	≥97.8, <113.8	105 (66.4%)	1.58	0.97-2.58	.07	
Q4	155	≥113.8	110 (71.0%)	1.91	1.15-3.18	.01	P = .003

OR, odds ratio; CI, confidence interval; Q1 to Q4, first to fourth quartiles group of low-density lipoprotein-C levels; OG, orchard grass. Adjusted for sex, body mass index, birth order, gestational age, birth weight, and family history of allergy.

population. Early intervention against hyperlipidemia for children through diet and exercise may be useful for the prevention of the occurrence and/or aggravation of future allergic conditions. This deserves further investigation by a prospective, longitudinal study. ■

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References

- Schäfer T, Ruhdorfer S, Weigl L, Wessner D, Heinrich J, Döring A, et al. Intake of unsaturated fatty acids and HDL cholesterol levels are associated with manifestations of atopy in adults. *Clin Exp Allergy* 2003;33:1360-7.
- McKeever TM, Lewis SA, Smit H, Burney P, Britton J, Cassano PA. Serum nutrient markers and skin prick testing using data from the third national health and nutrition examination survey. *J Allergy Clin Immunol* 2004;114:1398-402.
- Robertson AKL, Zhou X, Strandvik B, Hansson GK. Severe hypercholesterolaemia leads to strong Th2 responses to an exogenous antigen. *Scand J Immunol* 2004;59:285-93.
- Al-Shawwa B, Al-Hunt N, Titus G, Abu-Hasan M. Hypercholesterolemia is a potential risk factor for asthma. *J Asthma* 2006;43:231-3.
- Pesonen M, Ranki A, Siimes MA, Kallio MJT. Serum cholesterol level in infancy is inversely associated with subsequent allergy in children and adolescents: a 20-year follow-up study. *Clin Exp Allergy* 2007;38:178-84.
- Ouyang F, Kumar R, Pongracic J, Story RE, Liu X, Wang B, et al. Adiposity, serum lipid levels, and allergic sensitization in Chinese men and women. *J Allergy Clin Immunol* 2009;123:940-8.
- Fessler MB, Massing MW, Spruell B, Jaramillo R, Draper DW, Madenspacher JH, et al. Novel relationship of serum cholesterol with asthma and wheeze in the United States. *J Allergy Clin Immunol* 2009;124:967-74.
- Nagel G, Weiland SK, Rapp K, Link B, Zoellner I, Koenig W. Association of apolipoproteins with symptoms of asthma and atopy among schoolchildren. *Int Arch Allergy Immunol* 2009;149:259-66.
- Fessler MB, Jaramillo R, Crockett PW, Zeldin DC. Relationship of serum cholesterol levels to atopy in the US population. *Allergy* 2010;65:859-64.
- Kusunoki T, Morimoto T, Nishikomori R, Heike T, Ito M, Hosoi S, et al. Obesity and the prevalence of allergic diseases in schoolchildren. *Pediatr Allergy Immunol* 2008;19:527-34.