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Leptin and Atopic Dermatitis in Korean Elementary School Children

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ABSTRACT

The prevalence of atopic dermatitis (AD) and obesity have been increasing considerably in Korean school-children. AD is a chronic pruritic recurrent inflammatory skin disorder. Leptin is secreted by adipocytes which has been suggested to be immunologically active; however, their role in AD has not been well understood yet.

A total of 227 subjects out of 2,109 elementary school children were defined as having AD based on the ISAAC questionnaire survey. Ninety subjects with AD, aged between 6 and 12 years, completed scoring of severity of AD (SCORAD), skin prick testing, blood tests for total IgE, eosinophil counts, eosinophil cationic protein (ECP) and lipid profiles. Serum leptin levels were also measured. A subject with atopic AD was defined as an AD patient showing at least 1 positive reaction to allergens in skin prick testing.

There were no significant differences in age, body mass index, percentage of breast milk feeding, mode of delivery, prevalence of atopy, and lipid profiles between atopic AD and non-atopic AD subjects. The serum leptin levels (log mean±SD) were significantly higher in non-atopic AD group than in the atopic AD group (0.86±0.57 ng/mL vs 0.53±0.72 ng/mL, p=0.045). Subjects with mild-to-moderate AD showed significantly higher serum leptin levels than those with severe AD (0.77±0.67 ng/mL vs 0.33±0.69 ng/mL, p=0.028). There was a marginal inverse correlation between the SCORAD index and the serum leptin concentration in total AD subjects (r=-0.216, p=0.053).

The serum leptin levels were significantly higher in non-atopic AD subjects or mild-to-moderate AD subjects. Leptin did not seem to be associated with IgE-mediated inflammation in AD. Obesity-associated high leptin differed between non-atopic AD and atopic AD subjects.

Keywords: Atopic dermatitis; Child; Leptin; Obesity

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INTRODUCTION

Atopic dermatitis (AD) is one of the most common allergic diseases in childhood which is characterized by

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chronic, relapsing, pruritic skin inflammation. The prevalence of AD increased from 11.3% in 2000 to as high as 17.9% in 2010 among elementary school-children in South Korea.[1] However, the reasons for such an increase have not been well understood yet. Moreover, the prevalence of obesity has more than doubled in Korean school-children.[2]

Obesity is found to provoke pro-inflammatory responses; thus, it is considered to be associated with inflammatory allergic diseases such as AD, in both children and adults.[3,4] Hyperlipidemia plays a pro-inflammatory role and is a possible mechanism linking obesity and allergic diseases. A few studies have demonstrated an association between dyslipidemia and AD in children.[5,6] However, to date, studies exploring the relationship between obesity-related leptin and AD have not yet been well established.

Adipocytes have been thought to be immunologically active, although their role in allergic diseases is unclear. They produce various pro-inflammatory adipokines, including leptin. Leptin is involved in the regulation of food intake and body weight, and has been considered to have pleiotropic effects on hematopoiesis, angiogenesis, lymphoid organ homeostasis, and immune modulatory function as well. Previous investigators have shown that leptin promotes T-lymphocyte deviation toward Th1 phenotype.[7-9]

A previous report has indicated an association between obesity and AD.[3] A previous animal study has also demonstrated that leptin plays a role between these 2 chronic inflammatory diseases.[10] In this study, we aimed to assess serum leptin concentrations in children with AD and to evaluate the relationship between serum leptin levels and clinical manifestations of AD.

MATERIALS AND METHODS

Study Population

A cross-sectional study was carried out as a part of the 'Allergy Control Program of the Ministry of Environment, South Korea', in school-children with AD. Students from 5 elementary schools in Gyeonggi-do, South Korea were invited to participate in this study. From October 2012 to March 2013, a total of 2,109 elementary school children were enrolled in the study after written informed consent were obtained from their parents. Based on the results of the 12-month prevalence of AD symptoms, estimated by the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, 227 children with current AD were screened. Of these, 137 who did not complete blood tests were excluded. Therefore, a total of 90 children were finally enrolled in this study. The study protocol was approved by the Public Institutional Review Board (PIRB 12-039-02).

ISAAC Questionnaire

Parental questioning by means of the standardized ISAAC questionnaire was performed. Information on AD and lifestyle variables were collected. The diagnosis of AD was established when parents gave positive answer to the following question: 'Has your child had an itchy skin rash, which has been coming and going for at least 6 months in the past 12 months?'

Severity of AD (SCORAD)

The severity of AD was assessed according to the SCORAD index.[11] The enrolled subjects were divided into 2 groups according to the severity of the disease: Group 1, mild-to-moderate AD subjects (SCORAD < 40); and Group 2, severe AD subjects (SCORAD ≥40).

Measurement of Lipid Profiles and Leptin

Serum levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol were measured by a biochemistry analyzer. Serum leptin concentration was measured using a commercially available ELISA kit (R&D Systems, Inc., Minneapolis, MN, USA). The lower detection limit of leptin in this assay was 0.078 ng/mL.

Serum Total IgE and Blood Eosinophil Markers

Serum total IgE levels were measured using a Coat-A-Count Total IgE IRMA (Diagnostic Products Co, Los Angeles, CA, USA) according to the manufacturer's instructions. The number of peripheral blood eosinophils was counted in blood samples containing EDTA using an automated hematology analyzer (Coulter Counter STKS, Beckman Coulter, Fullerton, CA, USA). Serum eosinophil cationic protein (ECP) levels were measured using a commercially available fluoroimmunoassay kit (Pharmacia ECP UniCAP System FEIA, Pharmacia Diagnostics, Uppsala, Sweden) which had a detection limit of less than 2.0 μg/L. Blood sample collection, serum preparation, and serum ECP measurement were

performed according to the manufacturer's instructions.

Skin Prick Testing

Skin prick testing was performed using 13 common aeroallergens: house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), animal danders (cat epithelium and dog epithelium), pollens (mugwort, ryegrass, ragweed, hazel, alder, and oak), molds (*Aspergillus fumigates* and *Alternaria alternata*), and cockroach (*Blatella germanica*). The allergens were supplied by Allergopharma (Reinbek, Germany). A mean wheal diameter larger than 3 mm in the absence of any reaction to the negative control was considered a positive reaction. Atopy was defined as the presence of at least one positive reaction to these allergens. An atopic AD subject was defined as an AD patient with at least one positive reaction to these allergens.

Statistical Analysis

Data are presented as mean±SD. The values for serum total IgE, serum ECP, blood eosinophil count and leptin were log transformed before statistical analysis and expressed as log mean±SD. The variables or frequencies were compared between the groups, using Student's *t*-test or chi-square tests. Correlations between variables were calculated using Pearson's correlation test. All statistical analysis was performed using SPSS software (version 17; SPSS Inc, Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

RESULTS

The comparison of clinical characteristics, lipid profiles, and leptin levels between the boys and girls are shown in Table 1. There were no significant differences in age, BMI, the SCORAD index, and percentages of breast-milk feeding, or vaginal delivery between the boys and girls. The serum total IgE level (log mean±SD) were higher in the boys than that in the girls (5.59±1.65 IU/mL vs 4.94±1.58 IU/mL, p=0.060), without statistical significance. Neither blood eosinophil percentage nor serum ECP levels were different between the 2 groups. The mean±SD levels of total cholesterol, triglyceride, and LDL/HDL-cholesterol were not different. The leptin levels (log mean±SD) was significantly higher in the girls than in the boys (0.89±0.55 ng/mL vs 0.42±0.73 ng/mL, p=0.002).

When comparing clinical characteristics between atopic AD subjects (n=59) and non-atopic AD subjects (n=31), there were no significant differences in most variables except serum total IgE, ECP levels, and blood eosinophil percentages between the 2 groups (Table 2).

Table 1. The clinical characteristics and lipid profiles of the study subjects.

Parameters	Boys (n=43)	Girls (n=47)
Age (years)	10.1±1.6	9.5±1.7
Body mass index (kg/m^2)	19.1±3.0	17.6±2.4
Breast milk feeding (%)	29 (67)	35 (74)
SCORAD	29.5±17.5	25.0±11.0
Atopy (%)	30 (70)	29 (62)
log Total IgE (IU/mL)	5.59±1.65	4.94±1.58
log Blood eosinophil (%)	1.49±0.78	1.23±0.68
log ECP	3.66±0.97	3.35±0.94
Total cholesterol (mg/dL)	162.0±28.2	169.9±27.1
Triglyceride (mg/dL)	82.3±41.2	100.6±52.7
LDL-cholesterol (mg/dL)	100.6±20.2	107.9±22.5
HDL-cholesterol (mg/dL)	52.9±12.2	50.9±9.1
log Adiponectin (μg/mL)	1.11±0.77	1.52±0.71
log Leptin (ng/mL)*	0.42±0.73	0.89±0.55

Data was presented as mean±SD. Abbreviations: SCORAD, scoring atopic dermatitis; ECP, eosinophil cationic protein. *p<0.05

Table 2. Comparison of clinical characteristics and lipid profiles between atopic AD and non-atopic AD groups.

Parameters	Atopic AD group (n=59)	Non-atopic AD group (n=31)
Age (years)	9.8±1.8	9.8±1.4
Body mass index (kg/m^2)	18.1±2.9	18.5±2.7
Breast milk feeding (%)	40(67.8)	24 (77.4)
SCORAD	26.9±15.1	27.7±13.7
log Total IgE (IU/mL)	5.75±1.47	4.31±1.54
log Blood eosinophil (%)	1.52±0.72	1.03±0.66
log ECP	3.77±0.79	2.99±1.06
Total cholesterol (mg/dL)	168.0±28.5	162.5±26.5
Triglyceride (mg/dL)	92.1±53.0	91.3±38.0
LDL-cholesterol (mg/dL)	107.0±22.2	99.5±19.9
HDL-cholesterol (mg/dL)	51.8±11.2	51.9±9.8
log Adiponectin (μg/mL)	1.39±0.80	1.27±0.65
log Leptin (ng/mL)*	0.53±0.72	0.86±0.57

Data are presented as mean ± SD. Abbreviations: SCORAD, scoring atopic dermatitis; ECP, eosinophil cationic protein. *$p < 0.05$

Table 3. Comparison of clinical characteristics and lipid profiles between mild-to-moderate AD and severe AD subjects.

Parameters	Mild-to-moderate AD group (n=73)	Severe AD group (n=17)
Age (years)	9.9±1.7	9.5±1.6
Body mass index (kg/m^2)	18.3±2.8	17.7±3.0
Breast milk feeding (%)	52 (71.2)	12 (70.6)
SCORAD	21.5±8.9	51.4±7.4
Atopy (%)	47 (64.4)	12 (70.6)
log Total IgE (IU/mL)	5.06±1.52	6.09±1.89
log Blood eosinophil (%)	1.26±0.73	1.76±0.61
log ECP	3.47±1.00	3.61±0.78
Total cholesterol (mg/dL)	167.5±28.0	160.0±26.7
Triglyceride (mg/dL)	89.9±47.9	100.3±49.9
LDL-cholesterol (mg/dL)	105.7±22.2	99.0±18.5
HDL-cholesterol (mg/dL)	52.5±10.0	48.9±13.2
log Adiponectin (μg/mL)	1.41±0.77	0.90±0.38
log Leptin (ng/mL)*	0.77±0.67	0.33±0.69

Data are presented as mean ± SD. Abbreviations: SCORAD, scoring atopic dermatitis; ECP, eosinophil cationic protein. *$p < 0.05$

The log mean±SD of serum leptin levels was significantly elevated in the non-atopic AD subjects compared to the atopic AD subjects (0.86±0.57 ng/mL vs 0.53±0.72 ng/mL, p=0.045).

We further analyzed clinical characteristics between the 2 groups according to clinical severity. The log mean ±SD of serum leptin level was higher in the mild-to-moderate AD group (0.77±0.67 ng/mL vs 0.33±0.69 ng/mL, p=0.028) (Table 3). Serum leptin levels showed a marginal inverse correlation with the SCORAD index (r=- 0.216, p=0.053) in total AD subjects (Table 4).

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Table 4. Correlations between SCORAD and clinical parameters in the study subjects

Parameters	r	*p*
Age	- 0.031	0.774
Body mass index	- 0.059	0.600
Breast milk feeding (duration)	0.031	0.806
Total IgE (IU/mL)	0.311	0.003
Blood eosinophil (%)	0.157	0.139
ECP	- 0.065	0.541
Total cholesterol (mg/dL)	- 0.057	0.593
Triglyceride (mg/dL)	0.131	0.219
LDL-cholesterol (mg/dL)	- 0.086	0.419
HDL-cholesterol (mg/dL)	- 0.064	0.549
Adiponectin (μg/mL)	- 0.122	0.438
Leptin (ng/mL)	- 0.216	0.053

Abbreviations: SCORAD, scoring atopic dermatitis; ECP, eosinophil cationic protein.

DISCUSSION

In this study, we demonstrated that leptin levels were elevated in children with non-atopic AD compared to those subjects with atopic AD and it is inversely correlated with the severity of AD. Serum lipid profiles did not show any differences according to the presence of atopy or the severity of AD.

A previous epidemiologic study has shown that prolonged obesity in early childhood is a risk factor for AD.[12] Another large number of birth cohort from the UK has also revealed that being overweight in early age, significantly increases the risk for persistent eczema.[13] However, an ultimate causal relationship between obesity and AD has not yet been well identified. Leptin, an adipokine of the obesity gene, is mainly produced by the adipose tissue, upregulated in obesity, and associated with allergic immune regulation due to its pro-inflammatory properties. Obesity and AD seem to be linked to each other, and leptin has been implicated in the regulation of allergic immune responses.[14]

Previous studies evaluating leptin in AD are inconclusive. Kimata[5] has demonstrated that significantly elevated leptin levels in children with atopic eczema/dermatitis syndrome (AEDS) and fatty acid dysregulation may be involved in the pathogenesis of AEDS. In his study, elevated leptin levels seemed to facilitate development of fatty liver disease, but were not directly related to AD. In contrast, studies in children with AD[15] and adults with AD[16] have shown that leptin levels were not different from those of controls. Nagel et al.[17] also found no significant associations between high leptin levels and AD symptoms in German school-children. Moreover, in their study, serum leptin levels were inversely associated with the prevalence of eczema. However, it should be noted that their study did not differentiate between the IgE-mediated and non-IgE mediated types of AD. Considering the fact that leptin enhances non-atopic Th1 immune response, it is necessary to differentiate between the 2 phenotypes according to the presence of atopic status.

Dyslipidemia plays a pro-inflammatory role and is thought to be a possible mechanism underlying promotion of inflammation by hypercholesterolemia, switch to Th2 response in severe hypercholesterolemia,[18] and a link between obesity and allergic diseases. Due to the small number of children with hyperlipidemia in this study, we did not find any significant relationship between dyslipidemia and AD. In this study, we found higher leptin levels in non-atopic AD subjects than in atopic AD subjects. The association between obesity and allergic diseases is inconclusive but it tends to be stronger in non-atopic AD subjects than in atopic AD subjects.

A Canadian large population national survey[19] demonstrated an association between obesity and asthma, which was stronger in non-atopic asthmatics than in atopic asthmatics. Thus, it is assumed that an association between obesity and allergic diseases is independent of atopic status. Absence of association between serum leptin and atopic sensitization, which has also been observed in previous studies with European children, suggests that the biologic pathway of leptin to develop AD may involve non-IgE mediated mechanisms.[20] Various studies have proposed that high leptin levels in obese subjects modulate the Th1/Th2 balance toward the Th1 phenotype, supporting the concept that non-IgE mediated responses are involved in the pathogenesis of obesity-related AD.[3,9]

In contrast to higher leptin levels in non-atopic AD subjects in our study, Guler *et al.*[7] found higher leptin levels in atopic asthmatic children than in non-atopic asthmatic children. They showed a positive correlation between serum leptin and IgE levels and suggested that leptin may play a role in atopic asthma. However, they could not find any association between leptin levels and skin test reactivity. A recent study[10] of obese AD rats

with higher serum levels of leptin and IgE has proposed that a decrease in immunological tolerance caused by an increase in serum leptin due to obesity is related to the development of AD.

According to a recent pediatric study, obese asthmatics showed greater Th1 polarization than non-obese asthmatics.[3,21] Since chronic AD is higher in Th1 inflammatory disorder, no association between leptin and atopic sensitization suggests that the underlying biological pathway may involve non-IgE-mediated inflammatory mechanisms.[22]

This study has some limitations. First, the number of obese children was too small to reach statistical significance; thus, we did not provide relevant data regarding obesity-related leptin induced AD. Second, our cross-sectional study design was not able to provide information about obesity in early childhood. It has been demonstrated that prolonged obesity in early childhood is associated with the increased odds of AD and the severity of AD. The results of this study indicated that altered leptin levels in AD may play a causative role in non-IgE mediated allergic inflammation, but may not be related to obesity. Further studies should be performed to elucidate the mechanisms of association among obesity, leptin, and AD in children.

Although the relationship among obesity, leptin, and AD could not be adequately addressed in this study, elevated leptin levels in non-atopic AD subjects implied that leptin may play a role in AD skin inflammation. In conclusion, serum leptin levels were higher in children with non-atopic AD and showed a modest inverse correlation with the severity of AD. These findings suggest that obesity-associated leptin levels may differ between non-atopic AD and atopic AD subjects.

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