

Letter to the Editor

Ghrelin and leptin: A link between obesity and allergy?

To the Editor:

Recent epidemiologic studies have demonstrated that the prevalence of asthma and obesity are both increasing concomitantly, suggesting that these factors may be causally related.¹ Asthma and obesity are both important current public health problems; however, the precise mechanisms of any association between them have not yet been established. Many hypotheses have been proposed regarding this possible link. One possibility is that obesity and allergy share common risk factors such as sedentary lifestyle and dietary factors. A second possibility is that obesity can have a significant effect on normal lung physiology by reducing chest wall compliance.² As a third possibility, accumulating evidence has implicated systemic changes in immune function in the development of obesity; several obesity-related hormones and cytokines may lead to airway hyperresponsiveness.²⁻⁴ Serum IgE levels seem to be a reliable predictor for future development of allergic disorders, including asthma,⁵ and allergic responses are markedly enhanced when IgE levels are high.⁶ In this study, we examined the relationship between obesity and serum IgE levels and then attempted to elucidate a possible link between obesity and allergy mediated by the immunomodulative effects of 2 representative appetite-regulating peptides, leptin^{4,7} and ghrelin,⁸ based on clinical findings.

Ninety-eight children were enrolled in this study. Forty-nine children (21 females and 28 males with a mean age of 9.9 years) participated in health education classes for obese children; these subjects had a body mass index (BMI) greater than 25 or percent body fat values greater than 35% (TBF-1310 BIA Systems; Tanita Corp, Tokyo, Japan). The 49 remaining children (27 females and 22 males with a mean age of 9.7 years) who were referred to our outpatient clinic for routine health check-ups and who had BMI values less than 22 were examined as nonobese controls. Children with more than 2 wheezing episodes in the previous 12 months or worse than moderate atopic dermatitis were considered to have a positive allergy history. These children had neither underlying illnesses, other than allergic disorders and obesity, nor a history of receiving systemic corticosteroids within the 3 months before enrollment. Clinical characteristics of participants are shown in Table I. Blood specimens were obtained after an overnight fast and immediately transferred to chilled polypropylene tubes containing EDTA-2Na (1 mg/mL) and centrifuged at 4°C. Plasma leptin levels were measured by a commercially available ELISA kit (R&D Systems, Minneapolis, Minn) according to the manufacturer's instructions. Plasma ghrelin levels were measured by double antibody radioimmunoassay system as previously described.⁹ The Pearson correlation coefficient was calculated between the log of IgE concentrations and the levels of plasma ghrelin and leptin. Informed consent

TABLE I. Clinical characteristics of study subjects (n = 98)*

	Obese children	Nonobese children	P
Number of subjects (female/male)	49 (21/28)	49 (27/22)	.23
Age (y), mean $\pm$ SD	9.9 $\pm$ 2.6	9.7 $\pm$ 2.7	.71
BMI (kg/m ²), mean $\pm$ SD	26.3 $\pm$ 3.4	18.2 $\pm$ 2.9	<.0001
Percent body fat (%), mean $\pm$ SD	34.7 $\pm$ 7.3	19.7 $\pm$ 3.3	<.0001
Number of subjects having a history of allergic disorder (female/male)	16 (5/11)	15 (5/10)	.83

*Age, BMI, and percent body fat are summarized as the means $\pm$ SDs. For mean comparisons, we used the unpaired 2-tailed Student *t* test. χ^2 Test for independence was used to compare sex and number of subjects having a positive allergic history between 2 groups. Differences were considered statistically significant at *P* values < .05.

was obtained from both the children and their parents. This study was approved by the Ethical Committee of Kurume University.

There were no significant differences between the 2 groups in age, sex, or prevalence of allergic disorders (Table I). Obese children had significantly higher log serum IgE levels (2.33 ± 0.77 U/mL) than nonobese children (1.86 ± 0.82 U/mL; *P* < .01). Furthermore, IgE levels were higher in obese children regardless of allergic state. No significant differences between the 2 groups were observed in the number of peripheral eosinophils, an indicator of allergic inflammation and present prevalence of allergic disorders. We confirmed the significant correlation between the levels of plasma ghrelin and leptin levels and BMI (*n* = 65; *P* < .01; *r* = -0.35; and *n* = 98; *P* < .001; *r* = 0.71, respectively). Interestingly, we also discovered a significant inverse correlation between plasma ghrelin levels and IgE levels (*n* = 65; *P* < .001; *r* = -0.51) in all subjects. In contrast, plasma leptin levels did not correlate with IgE levels. When subjects with allergy alone were examined, however, leptin levels correlated positively with IgE levels (*n* = 30; *P* < .001; *r* = 0.48; Fig 1).

Our results indicate that a subset of obese children exhibiting high IgE levels were associated with a preallergic state.¹ This result may partially explain the association of obesity with an increased susceptibility to future allergic disorders, including asthma. Of the metabolic factors that affect the immune system, we paid special attention to the recently discovered appetite-modulating hormones ghrelin and leptin, because the proinflammatory effects of leptin might be relevant to asthma in both the human and murine models.^{4,7} Both hormones have some immunomodulatory effects and counteract each other with regard to the production of proinflammatory cytokines such as TNF- α and IL-1 β on human lymphocytes *in vitro*.¹⁰ The strong inverse correlation between plasma ghrelin and serum IgE levels suggests that ghrelin may inhibit IgE production in a direct or indirect manner. In

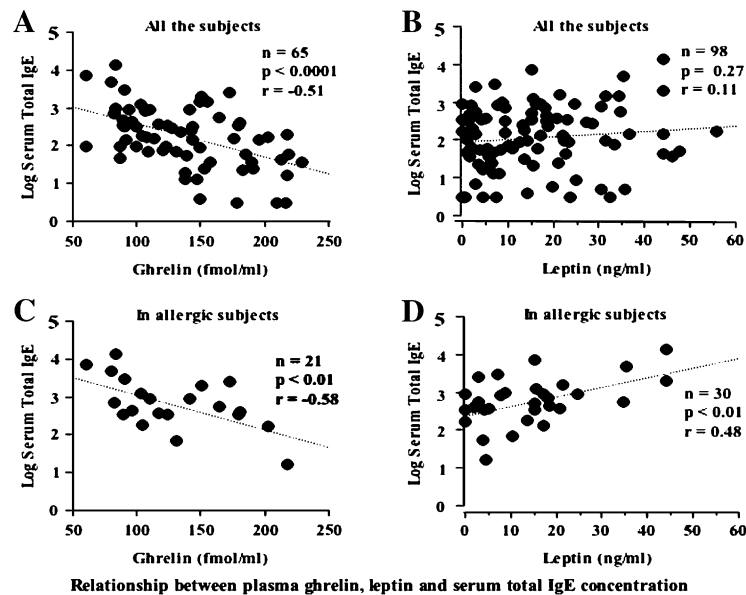


FIG 1. A significant inverse correlation was observed between ghrelin and IgE levels in all the subjects (A) and subjects with allergy (C), whereas leptin showed a significant positive correlation with IgE only in children with a positive allergic history (B, D).

splenic murine T lymphocytes, mRNA levels of the T_H2 cytokines IL-4 and IL-10, which both increase IgE synthesis, are suppressed by ghrelin.¹¹ In conjunction with our results, this study supports our hypothesis of a link between obesity and IgE levels. For leptin, we could only observe a significant correlation in subjects with allergy, which is consistent with previous reported findings.⁷ Our results reveal the possibility that these hormones may link obesity and allergic disorders. Further studies will be needed to clarify the immunoregulatory effects of ghrelin and leptin on IgE production.

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REFERENCES

- Hancox RJ, Milne BJ, Poulton R, Taylor DR, Greene JM, McLachlan CR, et al. Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med* 2005;171:440-5.
- Shore SA, Fredberg JJ. Obesity, smooth muscle, and airway hyper-responsiveness. *J Allergy Clin Immunol* 2005;115:925-7.
- Sood A. Does obesity weigh heavily on the health of human airway? *J Allergy Clin Immunol* 2005;115:921-4.
- Shore SA, Schwartzman IN, Mellema MA, Flynt L, Imirich A, Johnston RA. Effect of leptin on allergic airway responses in mice. *J Allergy Clin Immunol* 2005;115:103-9.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133-8.
- Kawakami T, Galli SJ. Regulation of mast-cell and basophil function and survival by IgE. *Nat Rev Immunol* 2002;2:773-86.
- Guler N, Kircerleri E, Ones U, Tamay Z, Salmayenli N, Darendeliler F. Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol* 2004;114:254-9.
- Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999;402:656-60.
- Hosoda H, Kojima M, Matsuo H, Kangawa K. Ghrelin and des-acyl ghrelin: two major form of rat ghrelin peptide in gastrointestinal tissue. *Biochem Biophys Res Commun* 2000;279:909-13.
- Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, et al. Ghrelin inhibits leptin- and activation induced proinflammatory cytokine expression by human monocytes and T cells. *J Clin Invest* 2004;114:57-66.
- Xia Q, Pang W, Pan H, Zheng Y, Kang JS, Zhu SG. Effects of ghrelin on the proliferation and secretion of splenic T lymphocytes in mice. *Regul Pept* 2004;122:173-8.

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