

Obesity Can Contribute to Severe Persistent Allergic Rhinitis in Children through Leptin and Interleukin-1 β

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Keywords

Allergic rhinitis · Obesity · Interleukin-1 β · Leptin · BMI

Abstract

Background: Obesity/overweight is associated with a higher risk of allergic rhinitis (AR) in children. **Objective:** This study aimed at exploring the mechanisms by which obesity affects the severity of AR through leptin and interleukin (IL)-1 β were investigated. **Methods:** In all, 210 subjects with AR and 82 subjects without AR were included in this study. The levels of leptin and inflammatory biomarkers were measured in the serum to investigate the correlation with the severity of AR. Additionally, we analyzed whether changes in BMI regulate the severity of AR through serial follow-up of obese children. **Results:** IL-1 β , which is a biomarker of active inflammation in AR, was significantly higher in individuals with AR than in those without and higher in subjects in the obesity group than in those in the normal weight group. A regression analysis showed that the leptin level was associated with increased IL-1 β expression in children with AR. In the multivariate analysis, only parental AR (9.2-fold increase in risk), elevated leptin (11.3-fold increase in risk), and high expression of IL-1 β (5.8-fold increase in risk) emerged as significant risk factors of moderate to severe persistent allergic

rhinitis. We also found that children with an increase or decrease in BMI showed changes in IL-1 β and AR symptoms, which these changes were dependent on leptin and BMI.

Conclusions: These results suggest that obesity is an important risk factor for the exacerbation of symptoms and leptin can exacerbate inflammation as well as severe and persistent symptoms through IL-1 β in AR. © 2021 S. Karger AG, Basel

Introduction

Allergic rhinitis (AR) is one of the most common diseases worldwide and usually persists throughout life. The prevalence of self-reported AR is estimated to be approximately 2–25% in children. AR is frequently associated with asthma, and compared with other medical conditions, AR might not appear to be serious because it is not associated with severe morbidity or mortality. However, AR reduces the quality of life of many patients due to impairments in sleep quality and cognitive function as well as its association with irritability and fatigue. AR is also associated with decreased school and work performance,

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especially during the peak pollen season [1–3]. In addition, uncontrolled moderate to severe AR affects asthma control [4, 5], and AR itself is a risk factor for uncontrolled asthma in children [6].

Obesity and atopic diseases such as asthma and AR are major public health problems worldwide. Multiple epidemiological studies have shown an association between obesity and asthma or AR in children and adults. Studies of overweight or obesity and AR have predominantly included children and have yielded conflicting results [7, 8]. Obesity in children significantly increases the risk for newly diagnosed asthma, and even though a high proportion of subjects with asthma also experience AR, a meta-analysis of observational studies suggests that obesity/overweight (according to BMI) may be associated with a higher risk of AR in children [9, 10]. While some studies have reported that neither overweight nor obesity was associated with symptoms that are suggestive of AR in children, several others have shown a negative (inverse) association in school-aged children [11–13]. Additionally, a recent study suggested that obesity exacerbated inflammation and contributed to disease severity in AR and that leptin was involved in enhanced TH inflammation as well as in the accumulation and activation of inflammatory cells in obese children with AR [9].

To date, no studies have evaluated inflammatory targets in the treatment of pediatric obesity. In a previous study, we found that an excessive release of biologically active interleukin (IL)-1 β may promote inflammation in children with severe persistent allergic rhinitis (PAR). Based on these results, the mechanisms by which obesity affects the severity of AR with respect to the levels of leptin and IL-1 β were investigated. Additionally, through serial follow-up of obese children, we analyzed whether changes in BMI regulate the severity of AR.

Materials and Methods

Study Subjects

Subjects included children who were enrolled in the Elementary School Students Cohort (2016–2018) for the identification of environmental factors of allergies at the Environmental Health Center of Ulsan University Hospital (Ulsan, Korea). The study participants were recruited from 4 elementary schools in Ulsan. Parental informed consent was obtained before enrollment. This study was approved by the institutional Ethics Review Committee of Ulsan University Hospital (approval number 2009-09-061-011). In all, 292 subjects (6–10 years of age) were recruited (AR group, 210 children; control group, 82 children) for the nested case-control study. At the time of enrollment, the subjects were given a detailed questionnaire, and laboratory tests were performed. All the

students responded to the questionnaire and underwent routine medical checkups, including a skin prick test and a blood test to determine total immunoglobulin E (IgE) levels and eosinophil counts. The questionnaires used in this study consisted of the International Society of Asthma and Allergy of Children survey questions [14] in addition to questions regarding the patients' socioeconomic status and any hazardous environmental factors they may have encountered. The parents or legal guardians of all participants provided written informed consent. We assembled a cohort of patients diagnosed with AR to perform a nested case-control study. We identified all children who were diagnosed with AR based on clinical symptoms and objective tests, such as the IgE-mediated skin prick test.

Anthropometric Measurements

Body weight and height were measured when each subject was lightly clothed and barefooted to calculate the BMI in kilograms per square meter. Overweight was defined as a BMI greater than the local age- and gender-specific 95th percentile, while obesity was defined as a BMI greater than the 95th percentile (or 30 kg/m², whichever was smaller); the remaining subjects were considered to be of normal weight. These percentile standards were previously established by a Korean population survey [15].

Diagnosis of AR

We used the clinical definition of AR for diagnosis, namely, the symptoms of AR, such as rhinorrhea, nasal obstruction, nasal itching, and sneezing, which are reversible either spontaneously or with treatment, and objective tests of IgE-mediated allergy, such as the skin prick test. The skin prick test was performed during a routine medical examination to measure the patient's response to 18 allergens, which were compared with positive and negative controls. Positive reactions to each allergen were defined as a wheal diameter at least 3 mm greater than that of the negative control.

Measurement and Analysis of Serum Leptin and Inflammasome Levels

The levels of eosinophils and IgE in the blood were examined. To determine the expression of leptin and inflammatory biomarkers in children (obese children, normal children, obese children with AR, and nonobese children with AR), the levels of several biomarkers were measured in the serum. The levels of leptin (an obesity), caspase-1, and IL-1 β (which represents inflammasome activation) were measured by ELISA. The details of each of the ELISA kits used in the study are as follows: leptin (DLP00) and caspase-1/interleukin-1 β -converting enzyme (DLB50). The kits were obtained from R&D Systems (Minneapolis, MN, USA).

Statistical Analysis

The independent *t* test and the χ^2 test were used to analyze baseline differences. Univariate and multivariate analyses were performed to determine the possible relationships between the variables and the development of severe AR. Multiple logistic regression analyses were performed using variables that were found to be significant ($p < 0.05$) in the univariate analysis and those reported to be associated with the development of severe AR. A *p* value of <0.05 was considered statistically significant in all analyses. Analyses of the receiver operating characteristic [16] curve and the differences in the area under curves [17] were used to estimate the diagnostic accuracy of each test.

Table 1. Demographic characteristics of AR children and normal controls as obesity defined based on BMI calculation

	AR (N = 210)			Control (N = 82)		
	Normal (n = 87)	Obesity (n = 123)	Total	Normal (n = 67)	Obesity (n = 15)	Total
Sex, male, %	43 (49.4)	70 (56.7)	113 (53.8)	30 (44.8)	9 (60)	39 (47.5)
Age, year	7.80	7.41	7.57	7.69	7.87	7.72
Obesity (BMI), kg/m ²	16.39	23.17	20.37	15.08	22.68	16.47
Total IgE, IU/mL	372.58	461.47	412.21			
Eosinophil, %	4.20	3.83	4.05			
Leptin, pg/mL	1,928.03	5,627.31	4,094.75	1,743.52	6,414.59	2,597.99
Caspase-1, pg/mL	39.03	43.67	41.74	39.50	41.90	39.94
IL-1 β , pg/mL	11.07	15.08	13.42	0.13	0.69	0.23

AR, allergic rhinitis; IgE, immunoglobulin E; IL, interleukin.

Table 2. Multiple linear regression between leptin and inflammatory markers

Variables	Standardized coefficient (95% CI)	Adjusted R ²	p value
Total IgE	-0.129 (-5,124 to 0.716)	0.012	0.063
Eosinophil	0.038 (-1.424 to 4.181)	-0.003	0.585
Caspase-1	0.331 (-1.566 to 5.361)	0.105	<0.001
IL-1 β	0.644 (-0.631 to 4.402)	0.411	<0.001

CI, confidence interval; IgE, immunoglobulin E.

Results

Characteristics of Subjects and Comparison of the AR and Control Groups

Table 1 summarizes the characteristics of 210 subjects with AR and 82 without AR who were included in this study. No significant differences were found in gender or age between the AR and control groups. Both the AR and control groups were subdivided into the normal weight and obesity subgroups. As expected, the BMI was significantly correlated with the obesity indicator leptin. Of the subjects with AR, 87 were of normal weight and had an average BMI of 16.39 kg/m², while 123 were obese and had an average BMI of 23.17 kg/m². In the AR group, no significant differences were observed in the level of IgE, eosinophil count in the blood, or level of caspase-1 between the normal weight and obesity groups. However, the level of IL-1 β , which is a biomarker of active inflammation, was significantly higher in obese subjects than in subjects with a normal weight ($p < 0.001$). Additionally, the IL-1 β level

in subjects with AR was significantly higher than that in subjects without AR ($p < 0.001$). In obese individuals, the leptin level was significantly higher in both the AR and control groups ($p < 0.001$ and $p = 0.010$, respectively).

Relationship between Obesity Indicators and Inflammatory Biomarkers

A regression analysis showed that the leptin level was associated with increased caspase-1 and IL-1 β expression in children with AR (Table 2, $p < 0.001$). However, the leptin level was not correlated with the IgE level or eosinophil count. In the non-AR group, the serum leptin level was not positively associated with caspase-1 and IL-1 β expression (data not shown). These results suggest that leptin can induce active inflammation in AR through IL-1 β activation.

Independent Risk Factors for the Development of Moderate to Severe PAR

We selected 210 children who had experienced AR within the last year and in whom the severity and dura-

Table 3. Univariate analysis to determine factors related to the severity of AR

Variables	Group 1 (N = 104)	Group 2 (N = 106)	p value
No obesity	56	48	<0.001
Obesity	31	75	
AR alone	70	30	0.005
Comorbidity of asthma	94	10	
AR alone	81	23	0.014
Comorbidity of atopy	67	39	
No paternal Hx of AR	86	18	<0.001
Paternal Hx of AR	62	44	
No maternal Hx of AR	85	19	<0.001
Maternal Hx of AR	48	58	
No siblings' Hx of AR	80	24	0.005
Siblings' Hx of AR	62	44	
BMI (≤ 20.60 kg/m ²)	65	39	<0.001
BMI (> 20.60 kg/m ²)	38	68	
Leptin ($\leq 2,661.60$ pg/mL)	70	34	<0.001
Leptin ($> 2,661.60$ pg/mL)	34	72	
IgE (≤ 342.20 IU/mL)	60	44	0.006
IgE (> 342.20 IU/mL)	40	66	
Eosinophil ($\leq 3.55\%$)	60	46	0.040
Eosinophil ($> 3.55\%$)	46	60	
IL-1 β (≤ 7.35 pg/mL)	65	39	<0.001
IL-1 β (> 7.35 pg/mL)	39	67	

Group 1: children with intermittent AR or mild PAR; group 2: children with moderate to severe PAR. AR, allergic rhinitis; PAR, persistent allergic rhinitis; Hx, history; IgE, immunoglobulin E; IL, interleukin.

tion of symptoms could be classified according to the allergic rhinitis and its impact on asthma classification. We classified the patients into 2 groups, as follows, based on the severity of the condition: group 1 (intermittent AR [IAR] or mild PAR) and group 2 (moderate to severe PAR). In all, 104 patients were in group 1 (mild IAR and PAR), and 106 patients were in group 2 (severe PAR). A significant difference was observed in BMI (18.91 vs. 21.79 kg/m², $p < 0.001$), the leptin level (2817.64 vs. 5,348.78 pg/mL, $p < 0.001$), IgE level (224.64 vs. 388.79 IU/mL, $p = 0.005$), percentage of eosinophils (3.51 vs. 4.45%, $p = 0.006$), and IL-1 β level (11.45 vs. 15.34 pg/mL, $p < 0.001$), but no difference was found in the caspase-1 level.

Table 3 presents the results of the univariate analysis of factors, including the BMI and leptin level, and their relationship with the presence of moderate to severe PAR. The analysis revealed a significant difference in obesity indicators (BMI and leptin) and inflammatory biomarkers (IgE, eosinophil count, and IL-1 β), which can be con-

tributing factors to severe or PAR. We also attempted to determine whether BMI, leptin, IgE, eosinophils percent, and IL-1 β expression could be used as diagnostic biomarkers in patients with moderate to severe PAR that was classified according to the cutoff value using receiver operating characteristic curves. In the univariate analysis, obesity, asthma, atopy, history of parental AR, history of asthma in a sibling, BMI (> 20.60 kg/m²), leptin ($> 2,661.60$ pg/mL), IgE (> 142.20 IU/mL), percentage of eosinophils ($> 3.55\%$), and the IL-1 β level (≥ 7.35 pg/mL) were associated with the development of moderate to severe PAR ($p < 0.001$, 0.005, 0.014, < 0.001 , 0.005, < 0.001 , < 0.001 , 0.006, 0.040, and < 0.001 , respectively). After the multivariate analysis, only parental AR (9.2-fold increase in risk), elevated leptin (11.3-fold increase in risk), and high expression of IL-1 β (5.8-fold increase in risk) emerged as significant risk factors for moderate to severe PAR (Table 4).

Changes in Inflammatory Markers with Increased BMI

Additionally, through serial follow-up, we investigated whether changes in obesity (BMI) can affect the severity of AR and the inflammation level. Fifteen obese children with AR whose BMI increased were followed up. We also found that, with one exception, children with an increase in BMI also exhibited increases in IL-1 β and leptin, the levels of which were dependent on the BMI. Of the children whose BMI had increased, 13 with severe AR showed no change in their symptoms, while 2 with mild AR showed exacerbation of their symptoms and progression to severe AR according to their BMI increase. The BMI was decreased in 17 obese children with AR. Sixteen children exhibited a decrease in IL-1 β and leptin levels as their BMI decreased, and one case showed no change. In addition, among 17 children, 11 initially had severe AR and 6 had mild AR. Six children of the BMI decrease group showed symptomatic improvement severe to mild AR with a decrease in IL-1 β and leptin levels, while the others exhibited no changes in their symptoms. Taken together, these results suggest that obesity is an important risk factor for the exacerbation of symptoms and the activation of inflammation in AR, and that only regulation of obesity can improve severe AR.

Discussion and Conclusions

The prevalence of obesity has increased significantly in the last few decades worldwide, and the excess fat present in obese individuals results in hypertrophic white adipose

Table 4. Multivariate analysis to determine factors related to the severity of the PAR

	B	SE	OR	<i>p</i> value	95% CI
Obesity	0.307	0.646	0.226	0.634	0.383–4.819
Comorbidity of asthma	0.974	0.525	3.443	0.064	0.947–7.408
Comorbidity of atopy	0.629	0.407	2.388	0.122	0.845–4.167
Maternal AR	1.658	0.402	17.006	<0.001	2.387–11.547
Paternal AR	1.640	0.539	9.244	0.004	1.791–14.829
Siblings' AR	0.134	0.406	0.109	0.742	0.516–2.532
BMI (>20.60 kg/m ²)	−0.007	0.684	0.000	0.992	0.260–3.793
Leptin (>2,661.60 pg/mL)	1.447	0.431	11.275	0.004	1.826–9.887
IgE (>342.20 IU/mL)	0.776	0.407	3.640	0.056	0.979–4.821
Eosinophil (>3.55%)	0.143	0.381	0.141	0.707	0.547–2.435
IL-1 β (>7.35 pg/mL)	0.944	0.396	5.674	0.007	1.182–5.587

AR, allergic rhinitis; PAR, persistent allergic rhinitis; CI, confidence interval; IgE, immunoglobulin E; IL, interleukin; OR, odds ratio.

tissue with a consequent derangement in adipocyte metabolic activity. In some obese individuals, adipose tissue exhibits pro-inflammatory activity and has been associated with obesity-related comorbidities in both adults and children [18]. Specifically, leptin exhibits pro-inflammatory activity and interacts with elements of both the innate and adaptive immune system in the pathogenesis of obesity-related comorbidities.

A previous study demonstrated that IL-1 β was a strong risk factor for the development of moderate to severe PAR and other active allergic diseases, and therefore, it can serve as a biomarker for the exacerbation and activation of allergic diseases including AR [19]. The primary role of inflammasomes is to direct inflammation by controlling unregulated IL-1 β release; therefore, IL-1 β is an important marker of activation of allergic diseases and severity. Based on these findings, we focused on the relationships between leptin and IL-1 β and between leptin and the severity of AR in obese children. We found that a higher leptin level was significantly correlated with IL-1 β expression in children with AR. After the multivariate analysis, only parental AR (9.2-fold increase in risk), elevated leptin levels (11.3-fold increase in risk), and high expression of IL-1 β (5.8-fold increase in risk) emerged as significant risk factors of moderate to severe PAR. Leptin, which is released by adipocytes and other cells and was first described to regulate body weight, has other biologic functions in the processes of angiogenesis, hematopoiesis, and immune response. Previous data have provided evidence to show that leptin is involved in TH2/17-mediated inflammation and that the accumulation and activation of inflammatory cells in obese children with AR is

related to disease severity [20]. Moreover, the leptin concentration has been found to be correlated with the IL-1 β level in many diseases, including diabetes and allergies [21–23]; leptin also activates eosinophils to markedly induce the release of inflammatory cytokines, such as IL-1 β . Early-onset obesity in mice transiently activates pulmonary adipocytokine/insulin signaling and induces airway hyperreactivity through increased expression of IL-1 β , IL-23, and TNF- α , higher serum leptin levels, and reduced glucose tolerance [21]. Although it is known that childhood obesity is a risk factor for asthma and AR, the molecular mechanisms that link obesity and the severity of AR remain elusive. In this study, we found that obesity can be a risk factor of severe and persistent symptoms of AR and that the activation of symptoms can be induced by elevated leptin and IL-1 β levels. These results suggest that leptin can exacerbate inflammation as well as severe and persistent symptoms through IL-1 β in obese children with AR. We did not investigate the exact mechanism of overexpression of IL-1 β or leptin in the serum level association with exacerbation of AR symptoms in this study. Previous studies suggested that IL-1 β gene polymorphisms may constitute a risk factor for childhood atopic asthma or severity via influence on gene regulation leading to an altered protein serum level in atopic asthma or atopic dermatitis [24–27]. And although the serum leptin level is elevated by obesity, leptin and leptin receptor gene polymorphism is associated with higher serum leptin levels in asthma, and these 2 variables have a high predictive value for asthma risk [28, 29]. To date, there were no data about the genetic polymorphisms of inflammasomes including IL-1 β or leptin in AR. Further studies are re-

quired to clarify the potential gene-gene and/or gene-environment interactions between polymorphisms in the IL-1 β or leptin in terms of AR.

Additionally, we investigated whether certain changes in obesity can improve the severity of AR. During a serial follow-up of 2–3 years, children whose BMI decreased were selected, and the levels of leptin and IL-1 β expression as well as any changes in symptoms were investigated. In most of these children, leptin and IL-1 β had decreased as the BMI decreased. During follow-up, we found that in half of children whose BMI decreased, the leptin and IL-1 β levels showed an improvement in symptoms without a definite change in environment. Although obesity can be a risk factor of severe AR or uncontrolled asthma, it is unknown whether the regulation of obesity can improve severe AR in obese children. Our study suggests that only regulation of obesity can improve severe AR.

Our study was a single-center study that focused on 7- to 12-year-old elementary school children. Our study also had some limitations. First, this study had geographic selection bias since the data from Ulsan, Korea, which is an industrial city, may not be generalizable to all children or adults. Second, a mechanistic study was not performed. However, we provided the results of a marker of severity and inflammation in AR during serial follow-up. Therefore, further prospective studies with larger sample sizes are needed to determine additional related variables. Since allergy is not a single disease but rather a collection of many allergic conditions, it is therefore not plausible that one marker would be useful in all these diseases. Thus, a more holistic approach using a combination of clinical history including obesity, clinical readouts, and environmental factors is needed for symptom control. Our study provides evidence that shows that leptin is in-

involved in IL-1 β -related inflammation and activation as well as in the exacerbation of symptoms in obese children with AR. However, the exact mechanism that underlies this effect requires further investigation both in vivo and in vitro studies with larger sample sizes. Future studies will help fully elucidate the potential roles of leptin and IL-1 β in AR treatment.

Statement of Ethics and Consent to Participate

This study was approved by the institutional Ethics Review Committee of Ulsan University Hospital (Approval number 2009-09-061-011). The parents or legal guardians of all participants provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.H. and J.L. designed the study. M.H., S.K., I.O., Y.K., and J.L. coordinated the overall undertaking of the study. M.H. and J.L. performed statistical analyses. M.H. and J.L. wrote the manuscript. All authors contributed to the revision. All authors read and approved the final manuscript.

References

- 1 Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic rhinitis and its impact on asthma (aria) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466–76.
- 2 Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (aria) 2008 update (in collaboration with the world health organization, ga(2)len and allergen). *Allergy*. 2008;63(Suppl 86):8–160.
- 3 Jauregui I, Davila I, Sastre J, Bartra J, del Cuvillo A, Ferrer M, et al. Validation of aria (allergic rhinitis and its impact on asthma) classification in a pediatric population: the pedi-
- 4 Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol*. 1992;90(2):250–6.
- 5 Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. *Cochrane Database Syst Rev*. 2003(4):Cd003570.
- 6 Xiang L, Zhao J, Zheng Y, Liu H, Hong J, Bao Y, et al. Uncontrolled asthma and its risk factors in chinese children: a cross-sectional observational study. *J Asthma*. 2016;53(7):699–706.
- 7 Mohan A, Grace J, Wang BR, Lugogo N. The effects of obesity in asthma. *Curr Allergy Asthma Rep*. 2019;19(10):49.
- 8 Ricketts HC, Cowan DC. Asthma, obesity and targeted interventions: an update. *Curr Opin Allergy Clin Immunol*. 2019;19(1):68–74.
- 9 Zhou J, Luo F, Han Y, Lou H, Tang X, Zhang L. Obesity/overweight and risk of allergic rhinitis: a meta-analysis of observational studies. *Allergy*. 2020;75(5):1272–75.
- 10 Han YY, Forno E, Gogna M, Celedón JC. Obesity and rhinitis in a nationwide study of children and adults in the United States. *J Allergy Clin Immunol*. 2016;137(5):1460–5.

- 11 Szentpetery SS, Gruziova O, Forno E, Han YY, Bergström A, Kull I, et al. Combined effects of multiple risk factors on asthma in school-aged children. *Respir Med*. 2017;133:16–21.
- 12 Sybilski AJ, Raciborski F, Lipiec A, Tomaszewska A, Lusawa A, Furmańczyk K, et al. Obesity: a risk factor for asthma, but not for atopic dermatitis, allergic rhinitis and sensitization. *Public Health Nutr*. 2015;18(3):530–6.
- 13 Weinmayr G, Forastiere F, Büchele G, Jaensch A, Strachan DP, Nagel G. Overweight/obesity and respiratory and allergic disease in children: international study of asthma and allergies in childhood (ISAAC) phase two. *PLoS One*. 2014;9(12):e113996.
- 14 Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995; 8(3):483–91.
- 15 Kim JH, Yun S, Hwang SS, Shim JO, Chae HW, Lee YJ, et al. The 2017 Korean national growth charts for children and adolescents: development, improvement, and prospects. *Korean J Pediatr*. 2018;61(5):135–49.
- 16 Dai C, Yao X, Gordon EM, Barochia A, Cuen-to RA, Kaler M, et al. A ccl24-dependent pathway augments eosinophilic airway inflammation in house dust mite-challenged cd163(-/-) mice. *Mucosal Immunol*. 2016;9(3):702–17.
- 17 Madouri F, Guillou N, Fauconnier L, Marchiol T, Rouxel N, Chenuet P, et al. Caspase-1 activation by nlrp3 inflammasome dampens il-33-dependent house dust mite-induced allergic lung inflammation. *J Mol Cell Biol*. 2015;7(4):351–65.
- 18 Umano GR, Pistone C, Tondina E, Moiraghi A, Lauretta D, Miraglia Del Giudice E, et al. Pediatric obesity and the immune system. *Front Pediatr*. 2019;7:487.
- 19 Adamko DJ, Khamis MM, Steacy LM, Regush S, Bryce R, Ellis AK. Severity of allergic rhinitis assessed by urine metabolomic profiling: proof of concept. *J Allergy Clin Immunol*. 2018 Aug;142(2):687–9.e6.
- 20 Liu W, Zeng Q, Zhou L, Luo R, Dong H. Association of leptin with disease severity and inflammation indicators in Chinese obese children with allergic rhinitis. *Pediatr Allergy Immunol*. 2018;29(2):186–93.
- 21 Dinger K, Kasper P, Hucklenbruch-Rother E, Vohlen C, Jobst E, Janoschek R, et al. Early-onset obesity dysregulates pulmonary adipocytokine/insulin signaling and induces asthma-like disease in mice. *Sci Rep*. 2016;6: 24168.
- 22 Liu Y, Zheng J, Zhang HP, Zhang X, Wang L, Wood L, et al. Obesity-associated metabolic signatures correlate to clinical and inflammatory profiles of asthma: a pilot study. *Allergy Asthma Immunol Res*. 2018;10(6):628–47.
- 23 Wong CK, Cheung PF, Lam CW. Leptin-mediated cytokine release and migration of eosinophils: implications for immunopathophysiology of allergic inflammation. *Eur J Immunol*. 2007;37(8):2337–48.
- 24 Behniafard N, Gharagozlou M, Sotoudeh S, Farhadi E, Khaledi M, Moghaddam ZG, et al. Association of single nucleotide polymorphisms of interleukin-1 family with atopic dermatitis. *Allergol Immunopathol*. 2014; 42(3):212–5.
- 25 He Y, Peng S, Xiong W, Xu Y, Liu J. Association between polymorphism of interleukin-1 beta and interleukin-1 receptor antagonist gene and asthma risk: a meta-analysis. *ScientificWorldJournal*. 2015;2015:685684.
- 26 Padrón-Morales J, Sanz C, Dávila I, Muñoz-Bellido F, Lorente F, Isidoro-García M. Polymorphisms of the il12b, il1b, and tnfa genes and susceptibility to asthma. *J Investig Allergol Clin Immunol*. 2013;23(7):487–94.
- 27 Sobkowiak P, Wojsyk-Banaszak I, Kowalewska M, Wasilewska E, Langwiński W, Kycler Z, et al. Interleukin 1β polymorphism and serum level are associated with pediatric asthma. *Pediatr Pulmonol*. 2017;52(12):1565–71.
- 28 Mukherjee N, Lockett GA, Merid SK, Melén E, Pershagen G, Holloway JW, et al. DNA methylation and genetic polymorphisms of the leptin gene interact to influence lung function outcomes and asthma at 18 years of age. *Int J Mol Epidemiol Genet*. 2016;7(1):1–17.
- 29 Szczepankiewicz D, Sobkowiak P, Narożna B, Wojsyk-Banaszak I, Bręborowicz A, Szczepankiewicz A. Leptin gene polymorphism affects leptin level in childhood asthma. *World J Pediatr*. 2018;14(6):601–6.