

Serum Leptin Level among School Children with Atopic Dermatitis

Saad Ahmed Mohamed¹, Tarek Alsayad², Ahmad El-Askary³ and Hany Abo Alwafa⁴

¹Department of Pediatrics, Al-Azhar University, New Damietta, Egypt

²Department of Pediatrics, Al-Azhar University, Cairo, Egypt

³Department of Medical Biochemistry, Al-Azhar University, New Damietta, Egypt

⁴Department of Dermatology, Al-Azhar University, New Damietta, Egypt

*Corresponding author: Mohamed SA, Department of Pediatrics, Al-Azhar University, New Damietta, Egypt, Tel: 00201002201602; E-mail: saad_dawody@yahoo.com

Received date: July 12, 2017; Accepted date: July 28, 2017; Published date: August 07, 2017

Copyright: © 2017 Mohamed SA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin condition. The pathogenesis of AD is still not fully understood. The association between obesity and AD suggests a potential role for adipocytes hormones, mainly leptin, which had variable immunological functions.

Objective: The aim of the present study was to assess serum leptin concentrations in children with AD and to evaluate the relationship between serum leptin levels and various demographic and clinical parameters.

Material and Methods: A case control study included 90 school age children (54 cases and 36 controls) conducted at Al-Azhar University Hospital (New Damietta), from January 2016 to April 2017. The diagnosis of AD was based on ISAAC questionnaire. Enrolled children completed scoring of severity of AD (SCORAD), blood tests for total IgE, eosinophil counts. Serum leptin was measured by ELIZA.

Results: There was no significant difference between cases and controls as regard age, sex and BMI. Serum leptin was significantly ($P=0.015$) higher among patients than healthy control. This difference was apparent between both boys ($P=0.043$) and girls ($P=0.026$). In addition, serum leptin was significantly higher among atopic girls ($P=0.017$) than boys. Regarding type of AD, there was no significant difference between patients with intrinsic AD and patients with extrinsic AD considering variable clinical parameters. Serum leptin was higher among intrinsic AD patients but it was not significant ($P=0.062$). Correlation analysis revealed significant negative correlation between leptin and total IgE ($P=0.004$). Also, non-significant negative correlation between serum leptin level and SCORAD value ($P=0.062$).

Conclusion: There was significant association between serum leptin levels and atopic dermatitis, which was apparent among both atopic boys and girls. However, serum leptin was significantly higher among atopic girls than boys. Thus, leptin might play a role in the pathogenesis of AD. The tendency of leptin to increase among girls and with intrinsic AD suggests complex pathological mechanisms.

Keywords: Leptin; Obesity; Allergy; Atopic dermatitis; School children; Immunity; Eczema

Introduction

Atopic dermatitis (AD), also recognized as eczema, is a condition characterized by chronic relapsing skin inflammation that is often associated with other allergic conditions, such as asthma, rhinitis, and food allergy [1-3]. In recent years, there is evident increase in the worldwide prevalence of AD. Furthermore, figures from the developing world indicate that the prevalence is increasing, approaches that of wealthier countries where AD affects over 20% of children [4,5].

The pathogenesis of atopic dermatitis is not fully understood; the immune response observed during the course of AD is characterized by a biphasic inflammation. A Th2- based immune response (IL-4, IL-13, TSLP and eosinophils) is predominant in the initial and acute phase of AD, while in chronic AD skin lesions, a Th1/Th0 dominance has been described [6,7]. It has been suggested that a barrier

disruption may initiate a "type 2 immune response" characterized by interleukins production including (IL)-4 and IL-13 [8,9]. A cascade of inflammation occurs upon exposure to allergens resulting in dendritic cell maturation and differentiation and eventually a type 2 T-helper lymphocyte (Th2)-mediated inflammation [10].

Leptin is one of the most important hormones secreted by adipose tissue [11]. It circulates primarily at levels proportional to the amount of adipose tissue, signaling long-term energy storage, and secondarily at levels modified by acute changes in caloric intake. Altogether, leptin appears to generally regulate energy homeostasis, decreasing energy intake and increasing energy expenditure [12].

In addition to its role in metabolism, leptin has numerous proinflammatory effects on the immune system, including proliferation and activation of circulating monocytes [13] and CD41 and CD81 T cells, polarization of T cells toward a TH1 response, [14] development and activation of natural killer cells [15], promotion of neutrophil chemotaxis, and upregulation of numerous cytokines, including TNF- α , IL-6,12 IFN- γ , and IL-2 [16].

The prevalence of atopic dermatitis and obesity has been increasing considerably all over the world. Leptin is secreted by adipocytes, and have been suggested to be immunologically active [17]. Therefore, we conducted this study to evaluate the extent of contribution of leptin to the occurrence and severity of atopic dermatitis, which might assists in the development of new targeting therapies that reduce the burden of the disease.

The role of leptin in the pathogenesis of AD has not been well understood yet. Thus, the aim of this work is to assess serum leptin concentrations in children with AD and to evaluate the relationship between serum leptin levels and various demographic and clinical parameters.

Materials and Methods

A case control study included 90 school age children (54 cases and 36 controls) recruited from Pediatrics and dermatology outpatient clinics of Al-Azhar University Hospital (New Damietta), during the period from January 2016 to April 2017. The diagnosis of AD was based on the presence of AD symptoms, estimated by the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [18]. Parental questioning by means of a standardized questionnaire based on the ISAAC was performed.

The severity of AD was assessed according to the Severity scoring of atopic dermatitis (SCORAD) index [19]. The studied subjects were divided according to the severity of the disease into: mild-to-moderate AD subjects (SCORAD < 40); and severe AD subjects (SCORAD ≥40).

Exclusion criteria included immune disorders, infection, or endocrine disease

The study was approved by the local ethical committee. Written informed consent was obtained from parents.

The following data were collected: age, gender, age of onset of the disease, family history of AD and the presence of other allergic conditions (asthma, eye allergies and food allergy) in the child. Body mass index (BMI) was calculated by dividing the weight in kg by the square height in meters.

Laboratory methods

Blood samples were withdrawn from all patients and controls under complete aseptic conditions tubes. All specimens were centrifuged at 4000 rpm within 2 hour of collection and serum stored at -20°C until analysis. After preparation of serum, Blood samples were centrifuged and aliquoted, and frozen at -80°C until analysis.

A complete blood picture by using a Coulter counter (T660; Beckman Coulter, Brea, CA) with differential count was done accurate detection of eosinophilic count.

Total serum IgE levels were measured by using IgE Accubind enzyme-linked immunosorbent assay (Monobind, Inc., Lake Forest, CA) according to the manufacturer's instructions. This procedure has a sensitivity of 1 IU/mL. Intrinsic (non-atopic) AD was defined by low total serum IgE levels (≤150 kU/L), and extrinsic (atopic) AD was defined by high total serum IgE levels (>150 kU/L) [20].

Serum leptin was measured with (ELIZA) method using DRG (DRG Instruments GmbH, Marburg, Germany) kits.

Statistical analysis

Data were analyzed using the SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as the mean ± standard deviation (SD). For comparisons of data, the Student's t test or Mann-Whitney test were used to compare between two variables. Qualitative data were presented as relative frequency and percent distribution. For comparison between groups, Chi square test was used. Pearson correlation coefficient was performed to correlate different variables. For all tests, significance was considered if P <0.05.

Results

General characters of cases and controls are shown in Table 1. There was no significant difference as regard age, sex, BMI and BMI percentiles. A significant difference (P=0.015) was observed in the mean levels of serum leptin between patients and healthy children in spite of a similar BMI in both groups. This significant difference was also apparent between both boys (P=0.043) and girls (P=0.026). Table 2 demonstrates clinical and laboratory characteristics of atopic boys and girls. No significant sex difference was detected as regard all variables; however, serum leptin levels was significantly higher among atopic girls (P=0.017). Regarding type of AD, there was no significant difference between patients with intrinsic AD and patients with extrinsic AD considering variable clinical parameters.

Serum leptin was higher among intrinsic AD patients but it was not significant (P=0.062) as shown in Table 3. Correlation analysis revealed significant negative correlation between leptin and total IgE (P=0.004). Also, non-significant negative correlation between serum leptin level and SCORAD value (P=0.062) as in Table 4 and Figure 1.

Variable		Patients (n=54)	Control (n=36)	P value
Age (years)		9.66 ± 1.67	9.11 ± 1.8	0.17
Sex	Boys	29 (54%)	20 (55%)	0.86
	Girls	25 (46%)	16 (45%)	
BMI (Kg/m ²)	Boys	18.95 ± 2.62	17.96 ± 2.61	0.26
	Girls	19.62 ± 3.43	19.33 ± 2.84	0.9
	Total	19.26 ± 3	18.57 ± 2.77	0.12
BMI percentile	Boys	64.31 ± 18.84	53.5 ± 23.68	0.089
	Girls	62.4 ± 25.17	64.7 ± 22.1	0.86
	Total	63.43 ± 21.8	58.47 ± 23.35	0.14
Eosinophilic count		502.46 ± 170.8	101.7 ± 64.28	<0.001*
IgE (IU/ml)		194.7 ± 78.11	22.19 ± 9.54	<0.001*
Leptin (ng/ml)	Boys	6.3 (3.9-8.75)	5.32 (3.4-6.22)	0.043*
	Girls	8.8 (5.8-10.7)	7.1 (4.35-7.95)	0.026*
	Total	7.31 ± 2.98	5.62 ± 2.33	0.005*
*Significant				

Table 1: comparison of clinical and laboratory characteristics between cases and controls.

	Boys (n=29)	Girls (n=25)	P
Age (years)	9.48 ± 1.62	9.86 ± 1.73	0.338
Duration of disease (years)	6.17 ± 1.89	5.4 ± 1.97	0.15
BMI percentile	64.3 ± 18.8	62.4 ± 25.2	0.95
Family history	13 (45%)	10 (40%)	0.72
Other allergies			
Asthma	11 (38%)	12 (48%)	0.45
Rhino- conjunctivitis	5 (17%)	5 (20%)	0.79
Food allergy	4 (14%)	5 (20%)	0.72
SCORAD	31.97 ± 14.79	28.76 ± 18.67	0.29
Disease severity			
Mild to moderate	20 (69%)	18 (72%)	0.81
Severe	9 (31%)	7 (28%)	
Type of AD			
Intrinsic (non-atopic)	7 (24%)	7 (28%)	0.74
Extrinsic (atopic)	22 (76%)	18 (72%)	
Eosinophilic count	509 ± 172	494 ± 172	0.716
IgE (IU/ml)	213 ± 74	174 ± 79	0.142
Leptin (ng/ml)	6.33 ± 2.47	8.43 ± 3.18	0.017*
*Significant			

Table 2: comparison of clinical and laboratory characteristics in relation to patients' gender.

	Intrinsic (non-atopic, n=14)	Extrinsic (atopic; n=40)	P
Age (years)	9.75 ± 1.69	9.62 ± 1.68	0.757
Duration of disease (years)	5.54 ± 1.8	5.91 ± 2	0.486
BMI percentile	59.64 ± 26.19	64.75 ± 20.25	0.634
SCORAD	26.36 ± 16.18	31.93 ± 16.73	0.319
Disease severity			
Mild to moderate	11 (78%)	27 (68%)	0.51
Severe	3 (22%)	13 (32%)	
Leptin (ng/ml)	8.81 ± 3.15	6.77 ± 2.8	0.062
*Significant			

Table 3: comparison of clinical and laboratory characteristics in relation to type of atopic dermatitis.

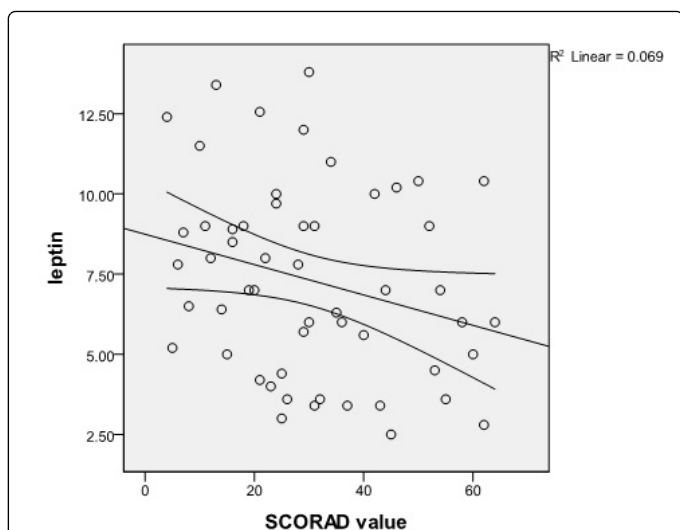


Figure 1: Correlation between SCORAD value and serum Leptin.

Parameter	SCORAD		Leptin	
	r	P	r	P
Age	-0.129	0.35	-0.03	0.83
BMI	-0.142	0.305	0.318	0.019*
BMI percentile	-0.048	0.72	0.229	0.096
Diseases duration	-0.087	0.53	-0.26	0.054
Eosinophilic count	0.093	0.503	-0.22	0.104
IgE	0.126	0.362	-0.389	0.004*
Leptin	-0.264	0.054		
*Significant				

Table 4: Correlation between SCORAD value and serum leptin with clinical parameters.

Discussion

Atopic dermatitis is one of the most common chronic inflammatory skin diseases [21]. It usually begins in childhood, has a significant impact on patients' quality of life, and results in considerable healthcare costs [8]. Available treatment for AD, especially moderate to severe cases, are generally lacking efficacy and had many side effects [22]. However, over the last decade, considerable advances in the understanding of the pathogenesis of atopic dermatitis have paved the way for a number of new treatments [23]. Most notable are the drugs that target the Th2-polarized immune system, which is thought to play a key role in many of the signs and symptoms characteristic of this disease [24-27].

Because leptin had variable effects related to immune functions, it was necessary to investigate its role among a sample of school children with atopic dermatitis.

In the present study, serum leptin was significantly elevated among cases than healthy controls. Previous studies involved healthy controls are very scarce and yielded conflicting results. Early report by Kimata [28] has demonstrated that serum leptin levels were significantly elevated in patients with IgE-associated atopic eczema/dermatitis syndrome (AEDS), and the elevation was further augmented in patients with IgE-associated AEDS with fatty liver. In contrast, Nagel et al. [29] found no statistically significant associations were found between high leptin levels and lifetime prevalence of eczema and symptoms of atopic dermatitis; however, in their study, prevalence of atopic dermatitis were somewhat increased in children with high leptin levels.

The link between leptin and allergic diseases was suggested because of the frequent association between these diseases and obesity. Three studies, including a UK cohort study and a substantial worldwide series of cross-sectional surveys based on the ISAAC Phase Three data set, found an association with obesity, while no association was detected in a number of other cross-sectional studies [30-35]. It remains unclear whether the positive associations seen are causal, for instance due to inflammation mediated by adipokines such as leptin, or related to dietary factors, which could facilitate AD through oxidative stress pathways are related to increased obesity and AD [4].

It had been suggested that the adipose tissue in obese individuals leads to a systemic inflammatory state producing changes in the serum levels of cytokines, chemokines, and adipokines. Among adipokines, serum leptin is a proinflammatory that affects both innate and adaptive immune responses and serum adiponectin has important anti-inflammatory effects in obesity. Adipokines have been reported to be associated with allergic diseases such as asthma, AD, and allergic rhinitis [36,37]. In asthma, increased airway hyperresponsiveness induced by high leptin levels and low adiponectin levels is considered one of the mechanisms of association between obesity and asthma [38].

Serum leptin was significantly elevated among both boys and girls with AD; however, it was significantly higher among atopic girls than atopic boys. These results are consistent with the study of Korean elementary school children by Seo et al. [39]. Thus, the role of leptin in the contribution of atopic dermatitis does not seem to have sex-specific distribution.

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. Similar results obtained by Seo, et al. [39]. In contrast, Han et al. [40] couldn't find such association.

Although the distinction between intrinsic and extrinsic AD based on the presence ("extrinsic") or absence ("intrinsic") of increased IgE and atopic disease is widely used, it remains controversial [41]. Thus, the presence of significant negative correlation between leptin and total IgE is suggestive of the potential link among non-IgE AD and leptin-induced inflammation.

In contrast to the negative correlation between leptin and IgE among patients with AD in our study, early reports have found positive correlations between serum leptin levels and immunoglobulin (Ig) E levels, particularly among asthmatic boys [42,43].

Recent studies demonstrated that obese asthmatic children had greater Th1 polarization than non-obese children [44,45]. Since chronic AD is higher in Th1 inflammatory disorder, no association

between leptin and atopic sensitization recommends that the underlying biological pathway may entail non-IgE-mediated inflammatory mechanisms [46].

The study has some limitations. There was not enough number of obese children to reach statistical significance; so, we did not introduce appropriate data regarding the relation between obesity-related AD and leptin. 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 our study revealed that high levels of leptin in AD may contribute to the pathogenesis of non-IgE mediated allergic inflammation, but may not be related to obesity. Additional studies should be carried out to clarify the mechanisms of association between leptin, obesity, and AD in children.

In summary, leptin might have a role in the pathogenesis of AD, especially intrinsic type, through complex pathological mechanisms.

Conclusion

The present study suggested that leptin may have a significant role in the pathogenesis of atopic dermatitis away from the presence of obesity. The role of leptin was significant both among boys and girls. In addition, there was significant negative correlation between leptin and IgE level, which means that leptin is mainly involved in the development of intrinsic atopic dermatitis. These findings demonstrate the effects of an adipocyte hormone on the immune mechanisms of atopic dermatitis and propose that diverse pathological mechanisms are involved. Further large studies are needed including animal models to introduce new targeting therapies that reduce the burden of the disease.

References

1. Drucker AM (2017) Atopic dermatitis: Burden of illness, quality of life, and associated complications. *Allergy Asthma Proc* 38: 3-8.
2. Silverberg JI, Hanifin JM (2013) Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol* 132: 1132-1138.
3. Drucker AM, Li WQ, Lin L, Cho E, Li T, et al. (2016) Atopic dermatitis (eczema) in US female nurses: lifestyle risk factors and atopic comorbidities. *Br J Dermatol* 174: 1395-1397.
4. Flohr C, Mann J (2014) New insights into the epidemiology of childhood atopic dermatitis. *Allergy* 69: 3-16.
5. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, et al. (2012) Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. *PLoS One* 7: e39803.
6. Nutten S (2015) Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab* 66: 8-16.
7. Fiset PO, Leung DY, Hamid Q (2006) Immunopathology of atopic dermatitis. *J Allergy Clin Immunol* 118: 287-290.
8. Wang D, Beck LA (2016) Immunologic Targets in Atopic Dermatitis and Emerging Therapies: An Update. *Am J Clin Dermatol* 17: 425-443.
9. Hvid M, Vestergaard C, Kemp K, Christensen GB, Deleuran B, et al. (2011) IL-25 in atopic dermatitis: a possible link between inflammation and skin barrier dysfunction? *J Invest Dermatol* 131: 150-157.
10. Leung DY, Guttman-Yassky E (2014) Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol* 134: 769-779.
11. Matarese G, Procaccini C, Pucino V, Mantzoros C. Leptin (2015) *Leptin: Regulation and Clinical Applications*. Springer International Publishing Pp: 131-143.
12. Farr OM, Gavrieli A, Mantzoros CS (2015) Leptin applications in 2015: what have we learned about leptin and obesity? *Curr Opin Endocrinol Diabetes Obes* 22: 353-359.
13. Jitprasertwong P, Jaedicke KM, Nile CJ, Preshaw PM, Taylor JJ (2014) Leptin enhances the secretion of interleukin (IL)-18, but not IL-1 β , from human monocytes via activation of caspase-1. *Cytokine* 65: 222-230.
14. Silverberg JI, Kleiman E, Lev-Tov H, Silverberg NB, Durkin HG, et al. (2011) Association between obesity and atopic dermatitis in childhood: a case-control study. *J Allergy Clin Immunol* 127: 1180-1186e1.
15. Tian Z, Sun R, Wei H, Gao B (2002) Impaired natural killer (NK) cell activity in leptin receptor deficient mice: leptin as a critical regulator in NK cell development and activation. *Biochem Biophys Res Commun* 298: 297-302.
16. Naylor C, Petri WA (2016) Leptin regulation of immune responses. *Trends in molecular medicine* 22: 88-98.
17. Jeong KY, Lee J, Li C, Han T, Lee SB, et al. (2015) Juvenile obesity aggravates disease severity in a rat model of atopic dermatitis. *Allergy Asthma Immunol Res* 7: 69-75.
18. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, et al. (1995) International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 8: 483-491.
19. European Task Force on Atopic Dermatitis (1993) Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report. *Dermatology* 186: 23-31.
20. Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wuthrich B (2001) Epidemiology, clinical features, and immunology of the "Intrinsic" (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). *Allergy* 56: 841-849.
21. Bronkhorst E, Schellack N, Motswaledi MH (2016) Effects of childhood atopic eczema on the quality of life. *Curr Allergy Clin Immunol* 29: 18-22.
22. Simon D, Bieber T (2014) Systemic therapy for atopic dermatitis. *Allergy* 69: 46-55.
23. Elias PM, Steinhoff M. (2008) "Outside-to-inside" (and now back to "outside") pathogenic mechanisms in atopic dermatitis. *J Invest Dermatol* 128: 1067-1070.
24. Salimi M, Barlow JL, Saunders SP, Xue L, Gutowska-Owsiak D, et al. (2013) A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J Exp Med* 210: 2939-2950.
25. Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, et al. (2005) Anti-IL-5 recombinant monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy* 60: 693-696.
26. Oldhoff JM, Darsow U, Werfel T, Bihari IC, Katzer K, et al. (2006) No effect of anti-interleukin-5 therapy (mepolizumab) on the atopy patch test in atopic dermatitis patients. *Int Arch Allergy Immunol* 141: 290-294.
27. Thompson CA (2015) Mepolizumab approved as add-on long-term therapy for severe asthma. *Am J Health Syst Pharm* 72: 2125.
28. Kimata H (2002) Elevated serum leptin in AEDS. *Allergy* 57: 179.
29. Nagel G, Koenig W, Rapp K, Wabitsch M, Zoellner I, et al. (2009) Associations of adipokines with asthma, rhinoconjunctivitis, and eczema in German schoolchildren. *Pediatr Allergy Immunol* 20: 81-88.
30. Yao TC, Ou LS, Yeh KW, Lee WI, Chen LC, et al. (2011) Associations of age, gender, and BMI with prevalence of allergic diseases in children: PATCH study. *J Asthma* 48: 503-510.
31. Silverberg JI, Silverberg NB, Lee-Wong M (2012) Association between atopic dermatitis and obesity in adulthood. *Br J Dermatol* 166: 498-504.
32. Wang HY, Pizzichini MMM, Becker AB, Duncan JM, Ferguson AC, et al. (2010) Disparate geographic prevalences of asthma, allergic rhinoconjunctivitis and atopic eczema among adolescents in five Canadian cities. *Pediatr Allergy Immunol* 21: 867-877.
33. Murray CS, Canoy D, Buchan I, Woodcock A, Simpson A, et al. (2011) Body mass index in young children and allergic disease: gender differences in a longitudinal study. *Clin Exp Allergy* 41: 78-85.

34. Vlaski E, Stavric K, Isjanovska R, Seckova L, Kimovska M (2006) Overweight hypothesis in asthma and eczema in young adolescents. *Allergol Immunopathol (Madr)* 34: 199-205.
35. del Rio-Navarro BE, Velazquez-Monroy O, Sanchez-Castillo CP, Lara-Esqueda A, Berber A, et al. (2004) The High Prevalence of Overweight and Obesity in Mexican Children. *Obes Res* 12: 215-223.
36. Hersoug LG, Linneberg A (2007) The Link Between The Epidemics of Obesity and Allergic Diseases: Does Obesity Induce Decreased Immune Tolerance?. *Allergy* 62: 1205-1213.
37. Yuksel H, Sogut A, Yilmaz O, Onur E, Dinc G (2012) Role of Adipokines and Hormones of Obesity in Childhood Asthma. *Allergy Asthma Immunol Res* 4: 98-103.
38. Shore SA, Terry RD, Flynt L, Xu A, Hug C (2006) Adiponectin Attenuates Allergen-Induced Airway Inflammation and Hyper Responsiveness In Mice. *J Allergy Clin Immunol* 118: 389-395.
39. Seo S, Yoon WS, Cho Y, Park SH, Choung JT, et al. (2016) Leptin and Atopic Dermatitis in Korean Elementary School Children. *Iran J Allergy Asthma Immunol* 15: 138-144.
40. Han B, Wu WH, Bae JM, Son SJ, Lee JH, et al. (2016) Serum leptin and adiponectin levels in atopic dermatitis (AD) and their relation to disease severity. *J Am Acad Dermatol* 75: 629-631.
41. Karimkhani C, Silverberg JI, Dellavalle RP (2015) Defining intrinsic vs. extrinsic atopic dermatitis. *Dermatol Online J*.
42. Guler N, Kirerleri E, Ones U, Tamay Z, Salmayenli N, et al. (2004) Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol* 114: 254-259.
43. Matsuda K, Nishi Y, Okamatsu Y, Kojima M, Matsuishi T (2006) Ghrelin and leptin: a link between obesity and allergy? *J Allergy Clin Immunol* 117: 705-706.
44. Baumann S, Lorentz A (2013) Obesity-a promoter of allergy? *Int Arch Allergy Immunol* 162: 205-213.
45. Rastogi D, Canfield SM, Andrade A, Isasi CR, Hall CB, et al. (2012) Obesity-associated asthma in children: a distinct entity. *Chest* 141: 895-905.
46. Kusunoki T, Morimoto M, Nishikomori R, Heike T, Ito M, et al. (2008) Obesity and the prevalence of allergic diseases in school children. *Pediatr Allergy Immunol* 19: 527-534.