

# ALLERJİK HASTALIKLARI OLAN HASTALARDA OBEZİTE, C-REAKTİF PROTEİN (CRP) VE SERUM TOTAL IGE ARASINDAKİ İLİŞKİNİN DERİ PRİCK TESTİ SONUÇLARI İLE İLİŞKİSİ

## Association Between Obesity, C-Reactive Protein and Serum Total IgE with Skin Prick Test Results in Patients with Allergic Diseases Economic Situation

Yavuz Selim İNTEPE<sup>1</sup>(0000-0002-5697-5291), Eylem YILDIRIM<sup>2</sup>(0000-0003-3998-2139),  
Emine ÇÖLGEÇEN<sup>3</sup>(0000-0001-9651-6068), Zeliha KAPUSUZ GENCER<sup>4</sup>(0000-0003-4707-5862),  
Bülent ÇİFTÇİ<sup>1</sup>(0000-0003-2703-3817)

### ÖZET

**Amaç:** Alerjik hastalığı olan hastalarda cilt prick test sonuçları ile serum total IgE, C-reaktif protein, vücut kitle indeksi arasındaki ilişkiyi değerlendirmek.

**Metod:** Bu çalışma Ekim 2011 ile Eylül 2018 tarihleri arasında üniversite hastanesinde yapıldı. Astım, alerjik rinit, kronik ürtiker ve atopik dermatit tanısı ile başvuran göğüs hastalıkları kliniğindeki 433 hastaya deri prik testi (DPT) uygulandı. Ayrıca hastaların serum total IgE, C-reaktif protein (CRP) düzeyleri ve vücut kitle indeksi ölçümleri (BMI) değerlendirildi.

**Bulgular:** Çalışma grubu 433 hastadan oluşmaktadır, 189'u (% 43,6) erkek, 244'ü (% 56,4) kadındı. Tanıya göre 177 (% 40,9) hastada astım, 108 (% 24,9) hastada alerjik rinit, 82 (% 18,9) hastada atopik dermatit ve 66'sında (% 15,2) kronik ürtiker vardı. SPT 285 (% 65,8) hastada pozitif, 148 (% 34,2) hastada negatif bulundu. En sık görülen alerjenler % 23,2, ev tozu % 19,2, vahşi çimenlerde % 14,8 ağaç karışımıydı. DPT pozitif grupta total IgE, CRP ve BMI değerleri istatistiksel olarak daha yüksekti (p=0.001). Obez hastalarda istatistiksel olarak anlamlı pozitif deri prik sonuçları vardı (p = 0.036). Ayrıca pozitif total IgE ve CRP grupları pozitif DPT grubunda anlamlı olarak daha yüksekti (p =0.001 ve p = 0.008). Total IgE düzeyleri ile DPT arasında orta düzeyde ve anlamlı pozitif korelasyon vardı (r = 0.463, p=0.001). Ayrıca CRP seviyeleri (r = 0.128, p = 0.008) ve obezite (r = 0.101, p = 0.036) düşük seviyede ve DPT ile anlamlı pozitif korelasyon gösterdi. DPT için sadece total IgE istatistiksel olarak anlamlı risk faktörü idi. Pozitif total IgE düzeyi, pozitif SPT olasılığını 8.11 kat artırır.

**Sonuç:** Bu çalışma, yüksek total IgE, CRP ve obezite düzeylerinin, pozitif deri prik testi olasılığının artmasıyla atopi ile ilişkiye sahip olabileceğini göstermektedir. Pozitif total IgE düzeyi, deri prik test pozitifliği için güçlü bir prediktör olabilir.

**Anahtar kelimeler:** *Atopi; C-Reaktif Protein; Deri prik Testi; Obezite; Total IgE*

### ABSTRACT

**Aim:** To evaluate relationship between skin prick test results and serum total IgE, C-reactive protein, body mass index in patients with allergic diseases.

**Material and methods:** This study was conducted in university hospital between October 2011 and September 2018. Skin Prick test (SPT) was applied to 433 patients in chest diseases clinic who were referred with diagnosis of asthma, allergic rhinitis, chronic urticaria and atopic dermatitis. Also patients' serum total IgE, C-reactive protein (CRP) levels and body mass index (BMI) measurements were evaluated.

**Results:** The study group were consisted of 433 patients, 189 (43.6%) male, and 244 (56.4%) female. According to the diagnosis, 177 (40.9%) patients had asthma, 108 (24.9%) had allergic rhinitis, 82(18.9%) had atopic dermatitis and 66 (15.2%) had chronic urticaria. SPT was positive in 285 (65.8%) patients while negative in 148(34.2%). Most frequently seen allergens were the mixture of trees 23.2%, home dust 19.2%, savage grass 14.8%. Total IgE, CRP, and BMI values were statistically higher in SPT positive group (p=0.001). Obese patients had statistically significant positive skin prick results (p=0.036). Also, positive total IgE and CRP groups were significantly higher in positive SPT group (p =0.001 and p=0.008). There was a moderate level and significant positive correlation between total IgE levels and SPT (r=0.463, p=0.001). Also CRP levels (r= 0.128, p=0.008) and obesity (r=0.101, p=0.036) had a low level and significant positive correlation with SPT. Only total IgE was the statistically significant risk factor for the SPT. Positive total IgE level increases the probability of positive SPT by 8.11 times.

**Conclusion:** This study suggests that elevated levels of total IgE, CRP and obesity may have relationship with atopy by increased likelihood of positive skin prick test. Positive Total IgE level can be a strong predictor for skin prick test positivity.

**Key Words:** *Atopy; C-Reactive Protein; Obesity; Skin prick Test; Total IgE*

<sup>1</sup>Yozgat Bozok Üniversitesi, Göğüs Hastalıkları AD., Yozgat, Türkiye

<sup>2</sup>Sağlık Bilimleri Üniversitesi, Suat Seren Göğüs Hastalıkları Eğitim ve Araştırma Hastanesi, İzmir, Türkiye Göğüs Hastalıkları Kliniği, İzmir, Türkiye

<sup>3</sup>Yozgat Bozok Üniversitesi, Cilt Hastalıkları AD., Yozgat, Türkiye

<sup>4</sup>Doç. Dr., İstinye Üniversitesi, Tıp Fakültesi, Kulak Burun Boğaz Hastalıkları AD., İstanbul, Türkiye.

Yavuz Selim İNTEPE, Doç. Dr.  
Eylem YILDIRIM, Uzm. Dr.  
Emine ÇÖLGEÇEN, Doç. Dr.  
Zeliha KAPUSUZ GENCER, Doç. Dr.  
Bülent ÇİFTÇİ, Prof. Dr.

### İletişim:

Yavuz Selim İNTEPE, Associate Prof. Dr.  
Department of Chest Diseases, Faculty of Medicine, Bozok University, Yozgat, Turkey.

Tel: +90 354 212 70 50

e-mail:

dryavuz76@yahoo.com

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## INTRODUCTION

World Health Organization (WHO) refers to obesity as the global epidemic due to increased prevalence which is more than double between 1980 and 2014 worldwide. It is reported that about 13% (over 600 million) of the world's adult population (11% of men and 15% of women) were obese in 2014. Obesity is characterized by excessive deposition of subcutaneous and visceral adipose tissue which act as an endocrine organ by secretion more than 100 bioactive peptides so-called adipokines. These adipokines are thought to be responsible for impaired immune tolerance which could be the possible association between allergic diseases and obesity. There are huge amount of studies showing interaction between parallel rise of prevalence for obesity and allergic diseases (1,2).

C-reactive protein (CRP), a classic acute phase reactant, is a member of the pentraxin family of plasma proteins synthesized by hepatocytes. Its production is stimulated by interleukin (IL)-6, IL-1  $\beta$ , tumor necrosis factor-  $\alpha$  (3,4). CRP is increased in systemic inflammation associated with infection, cardiovascular diseases, autoimmune diseases. There are various studies showing either positive or negative association between CRP and asthma, atopy and bronchial hyperresponsiveness (5-7).

Atopy is an individual and/or familial propensity, usually starts in childhood or adolescence, to become sensitized and produce immunoglobulin(Ig) E antibodies in response to ordinary exposures to allergens, usually proteins. It is shown by increased serum IgE levels or positive skin prick test. Atopy has a role in the pathogenesis of asthma, allergic rhinitis, atopic dermatitis and chronic urticaria (8). Specific B lymphocytes produce IgE following the exposure of allergens in type 1 hypersensitivity reaction. Total IgE level is increased in allergic diseases and discriminatory tool between atopic and non-atopic persons (9). There are various studies investing effects of high body mass index or CRP on asthma and other allergic diseases. Although elevated levels of total IgE is a diagnostic tool in atopy, its sensitivity and specificity remains undetermined (10-12). In the literature, there is no research combining obesity, CRP and total IgE in

atopics. The aim of this study was to evaluate whether obesity, CRP and total IgE level consistent with skin prick test results in allergic patients.

## MATERIAL AND METHODS

The study was conducted in state university hospital between October 2011 and September 2018. Patients who had allergic symptoms and diagnosed as asthma, allergic rhinitis, chronic urticaria, and atopic dermatitis in chest diseases, ear nose throat and dermatology clinics were referred to allergy department for skin prick test.

The diagnosis of asthma was based upon the global initiative for asthma guideline, characterized by episodic attacks of dyspnea, wheezing, cough and compatible changes in FEV1 after inhalation of short acting  $\beta$ 2 agonist. Immunologically mediated hypersensitivity symptoms from nose like sneezing, itching, discharge was defined as allergic rhinitis. Recurrent hives lasting more than 6 weeks mediated by IgE was accepted as chronic urticaria. Atopic dermatitis is an allergic condition of pruritic, exfoliative skin lesions (8).

Patients who had infectious diseases including parasitics, malignancies including multiple myelom, hepatic or renal pathologies, auto-immune disorders, have regular use of oral or systemic corticosteroid, antihistaminic, anti-depressant drugs were excluded from the study.

Skin Prick test was applied with 10 allergens (Allergopharma-Germany) by prick test lancets (Stallerpoint) on the volar surface of the forearm. Histamine dihydrochloride, 1 mg / mL, and saline were used for positive and negative control. Informed written consent was obtained from all patients who accepted the skin prick test. A wheal diameter  $\geq$ 3 mm was accepted as positive response after 20 minutes of application. Tree mixture, home dust, savage grass, dog epithelial, fur mixture, cat epithelial, hazelnut, fungus mould, cockroach and strawberry were applied allergens. Atopy was present with at least one positive response. Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults which are defined as

the weight in kilograms divided by the square of the height in meters (kg/m<sup>2</sup>). Obesity is accepted as a BMI>30 kg/m<sup>2</sup>.

Total IgE, CRP and White blood cell count (WBC) were measured by venous blood (10 mL) obtained in the morning. Blood samples were allowed to clot at room temperature and the serum was separated by centrifugation at 1,200×g for 10 minutes and stored at -80°C. Total IgE and CRP levels were measured by turbidimetric methods using Archem diagnostics industry company products (Turkey) via Abbot Architect (USA) device. Total IgE level above 200 IU/ML and CRP above 6 mg/L were accepted positive result. Ethical approval for the study was received from the clinical research ethics committee of the local university (Decision number: 2017-KAEK-189\_2019.09.11\_13).

**Statistical Analysis**

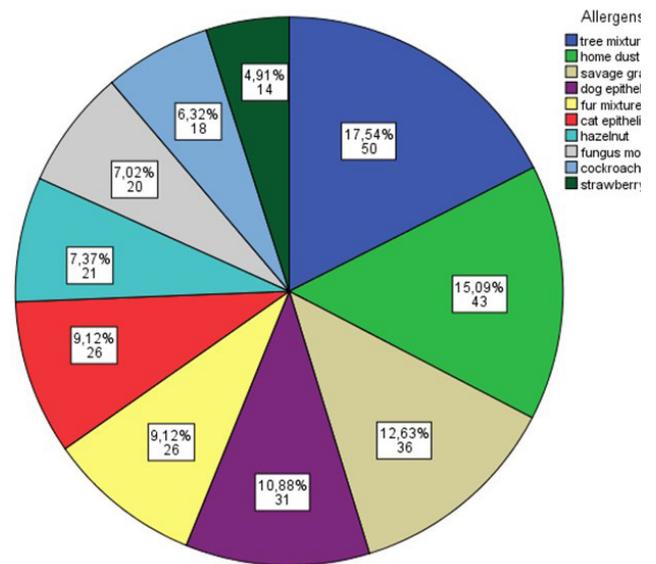
Statistical analyses were performed using the SPSS software version 20. The numerical variables were investigated using visual (histograms, probability plots, skewness/kurtosis) and analytical methods (Kolmogorov-simirnov/ Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables. Since the age of years, package/years of smoking, ESR, WBC, CRP, Total IgE and BMI values were normally distributed; the student's t-test was used to compare these parameters between SPT positive and negative groups. Also, these variables were compared among the diseases groups by using one-way ANOVA test. The chi-square test was used to compare variables expressed as a ratio such as a gender, CRP levels, obesity, Total IgE levels and the smoke status between SPT groups. These ordinal variables were compared between diseases by using Kruskal-Wallis test. Mann-Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. The Spearman test was used to calculate correlation coefficients and their significance while investigating the associations between gender, CRP levels, obesity, Total IgE levels, smoke status and SPT groups. The logistic regression analysis was used to identify independent predictors

of SPT result. The Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A p-value of less than 0.05 was considered to show a statistically significant result.

**RESULTS**

The study group was consisted of 433 patients, 189 (43.6%) male, and 244 (56.4%) female. Mean age and BMI of all patients were 28,44±6.98 (18-44) years and 27,23±4.03 (18,20-33,73) kg/m<sup>2</sup>. The average smoking history was 4,83±5.34 (0-20) package per years. Mean biochemical parameters of all patients were 7,11±1.53 (3,70-9,92) k/uL for WBC, 184,22±89,52 (20-395) IU/ml for total IgE, 6,36±2.87 (1-14) mm/hour for ESR and 6,26±1,49 (3,10-9,83) mg/L for CRP.

Two hundred and twenty-two (50.8%) patients were nonsmokers while 144 (33.3%) were smokers and 69 (15.9%) were exsmokers. According to the diagnosis, 177 (40.9%) patients had asthma, 108 (24.9%) had allergic rhinitis, 82 (18.9%) had atopic dermatitis and 66 (15.2%) had chronic urticaria. Skin prick test (SPT) was positive in 285 (65.8%) patients while negative in 148 (34.2%) patients. The most common allergens detected in the SPT positive group were tree mixture (17.54 %), home dust (15.09%) and savage grass (12.63%) (Figure 1).



**Figure 1:** Percentage of Allergens

Obesity was present in 188 (43.4%) patients while 245 (56.6%) were non-obese. Total IgE levels were positive in 235 (54.3%) and negative in 198 (45.7%) patients. CRP levels were positive in 243 (56.1%) patients while were negative in 190 (43.9%) patients. Patients were homogeneous for age and gender between SPT

groups. Total IgE, CRP, and BMI values were statistically higher in SPT positive group ( $p=0.001$ ) (Table 1). Obese patients had statistically significant positive skin prick results ( $p=0.036$ ). Also, positive total IgE and CRP groups were significantly higher in positive SPT group ( $p=0.001$  and  $p=0.008$ ) (Table 2).

**Table 1.** Biochemical Parameters

Parameters				
Age (years)	28.32±6.87	28.50±7.05	0.177(1.57-1.22)	0.802
Smoking (package/year)	4.41±5.23	5.06±5.39	0.651(1.71-0.41)	0.229
Total IgE (IU/ml)	110.62±69.68	222.44±73.41	111.820(126.19-97.45)	<0.001
ESR (mm/saat)	6.72±2.91	6.18±2.84	0.548(0.23-1.12)	0.060
CRP (mg/L)	5.76±1.10	6.52±1.60	0.76757(1.02-0.51)	<0.001
WBC (K/UL)	7.00±1.46	7.16±1.57	0.16152(0.47-0.14)	0.298
BMI (kg/m <sup>2</sup> )	25.83±4.41	27.96±3.61	2.13485(2.96-1.31)	<0.001

**Table 2:** Skin Prick Test

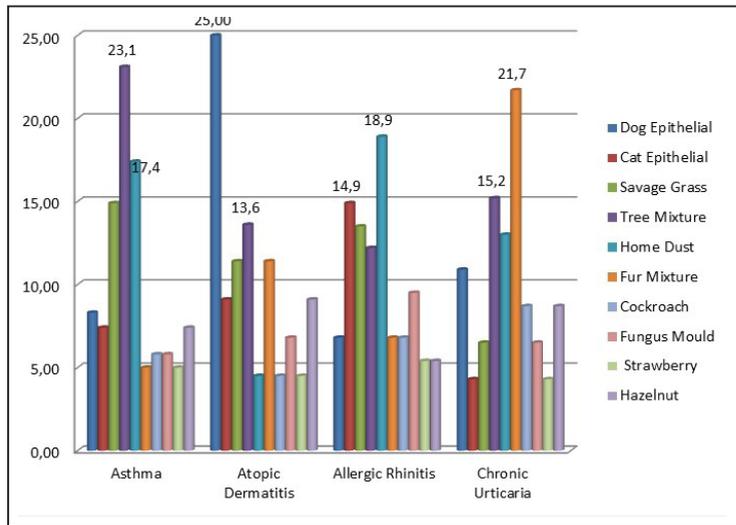
Parameters	SPT (-)	SPT (+)	p
Male	57 (38.5%)	132(46.3%)	0.120
Female	91(61.5%)	153 (53.7%)	
Nonsmoker	80 (54.1%)	140 (49.1%)	0.330
Smoker	68 (45.9%)	145(50.9%)	
NonObese	94 (63.5%)	151 (53%)	0.036
Obese	54 (36.5%)	134 (47%)	
Total IgE level (-)	115 (77.7%)	83(29.1%)	<0.001
Total IgE level (+)	33 (22.3%)	202(70.9%)	
CRP level (-)	78 (52.7%)	112(39.3%)	0.008
CRP level (+)	70(47.3%)	173(60.7%)	

**Table 3.** Relationship between diseases

Parameters	Asthma (n=177)	Atopic dermatitis (n=82)	Allergic rhinitis (n=108)	Chronic urticaria (n=66)	p
Age (years)	28.47±7.03	27.24±6.73	28.46±7.11	29.82±6.87	0.173
BMI (kg/m <sup>2</sup> )	27.06±3.92	27.12±4.01	27.13±4.35	28.00±3.82	0.416
Cigarette smoking (package/year)	4.59±5.57	4.02±5.15	5.25±5.57	5.82±4.37	0.160
Total IgE (IU/ml)	175.75±88.43	187.39±93.97	188.74±84.90	195.61±94.08	0.388
ESR(mm/saat)	6.14±2.84	6.55±2.86	6.53±2.89	6.47±2.97	0.595
CRP (mg/L)	6.20±1.50	6.07±1.42	6.34±1.40	6.53±1.66	0.249
WBC (K/UL)	6.97±1.56	7.10±1.51		7.43±1.53	0.216

**Table 4.** Risk factors predicting Skin Prick Test result

Gender(M/F)	0.72 (0.48-1.09)	0.118
Total IgE Positiveness	8.11(5.06-13.00)	<0.001
Obesity	1.34 (0.84-2.14)	0.215
CRP positiveness	1.14(0.72-1.80)	0.586
Smoke Status(Non/smoker)	1.08(0.68-1.70)	0.742



**Figure 2.** Allergens according to diseases

There was not statistically significant difference between diseases for age, BMI, smoking package/years and all biochemical parameters (Table 3). There were not statistically significant difference for gender ( $p=0.631$ ), SPT groups ( $p=0.083$ ), obesity groups ( $p=0.107$ ) and CRP positiveness ( $p=0.382$ ) while smoke status ( $p=0.001$ ) and total IgE positiveness ( $p=0.019$ ) had significant difference between diseases. These differences arise from chronic urticaria group (have much more smokers than other groups) for smoke status and atopic dermatitis group (have less positive results than other groups) for total IgE results. Tree mixture (28-23.1%) was the most common allergen seen in asthma while dog epithelial (11-25%) in atopic dermatitis, home dust (14-18.9%) in allergic rhinitis and fur mixture (10-21.7%) in chronic urticaria (Figure 2).

There was a moderate level and significant positive correlation between total IgE levels and SPT results

( $r=0.463$ ,  $p=0.001$ ). Also CRP values ( $r=0.128$ ,  $p=0.008$ ) and obesity ( $r=0.101$ ,  $p=0.036$ ) had a low level and significant positive correlation with SPT results. There was not a significant correlation between smoke status ( $r=0.047$ ,  $p=0.331$ ) and gender ( $r=-0.075$ ,  $p=0.121$ ) with SPT results. Only total IgE was the statistically significant risk factor for the SPT results. Positive total IgE level increases the probability of positive SPT by 8.11 times (Table 4). The sensitivity of total IgE was 70.8% and specificity was 77.7%. The positive predictive value was 85.9% and negative predictive value was 58.08%. Prevalence of SPT was 65.82%. Accuracy of the total IgE test was 73.9%.

## DISCUSSION

Tree mixture, home dust and savage grass were the most common allergens. Patients who were obese and had positive CRP and total IgE levels showed statistically increased positive SPT results. CRP values

and obesity had low level while total IgE values had a moderate level of significant positive correlation with SPT results. Smoking and gender had no effect on SPT results. Total IgE was the only significant risk factor for positive SPT result.

In the literature, there are studies which explore association between asthma and CRP. There is lack of study particularly exploring CRP and atopy on the basis of SPT. Our study showed positive correlation between CRP and atopy. Halvani compared the correlation between CRP level and sputum eosinophilia in asthmatic and control patients. Asthmatic patients were divided into two groups based on inhaled steroid usage, 30 user and 31 non-user patients. CRP levels were found significantly elevated in non-user and user group compared to control group (n=37). They reported no significant relation between CRP and atopy, sex, and age (3). Butland conducted the cohort study with 6490 British subjects who were born at 1958. They reported that CRP was positively associated with obesity and smoking. There was no correlation between asthma and CRP after adjustment for BMI and smoking (4). A multicenter study was conducted in Reykjavik, Uppsala and Tartu with 1289 participants. Blood samples were collected in order to study highly sensitive CRP (hs-CRP) whether it was related with bronchial responsiveness, asthma, and atopy. They found strong positivity between hs-CRP and obesity. There was not significant result between hs-CRP neither with atopy nor bronchial hyperresponsiveness. Also, non-allergic asthmatic patients had significantly higher hs-CRP levels compared to non-asthmatic patients (5). Another population based study including 259 adults was done to find out relationship between CRP and bronchial hyperresponsiveness. Increased CRP levels were significantly associated with bronchial hyperresponsiveness. Multivariate analyses after adjustment with asthma, CRP was still related with BHR (7). Kasayama et al. investigated CRP and asthma. They found that CRP level were significantly higher in 329 asthmatic patients than in 1684 non-asthmatics. By multivariate regression analysis, BMI, age and asthma were found independent risk factors for elevated CRP level. They also looked for treatment effect on CRP level. They started inhaled corticosteroids for 64

asthmatic patients who were previously not treated with inhaled and/or oral corticosteroids. After 3 months, patients' plasma CRP levels were significantly reduced by 32% as their respiratory function improved (12). Fujita investigated hs-CRP levels at 109 asthmatic patients during attack and remission periods. They found that hs-CRP were higher during attack and non-attack periods compared to control group. They also further examined attack and non-attack periods for identical 31 patients. HS-CRP was significantly higher during attack period (13). Serum protein profiling is performed by analyzing proteomic signatures in a group of common allergic skin disorders. CRP was found to be upregulated in all 3 diseases compared to healthy controls. They also studied IgE and found significant upregulation in atopic dermatitis alone in contrast to psoriasis and contact dermatitis (14). A recent study was conducted in german adolescents in order to search relationship between hs-CRP and allergic diseases. The study was designed as a longitudinal and comprise 1955 cases who were followed up from 15 years age. Allergic diseases were asthma, eczema, allergic rhinitis, food sensitization, aeroallergen sensitization, and any sensitization. Investigators report no association between hs-CRP and allergic endpoints (15). CRP levels were studied in 178 asthmatic patients and 50 healthy controls. CRP was higher in asthmatic group than control. Besides, exacerbation was also made significant effect on CRP level as compared to stable and control groups In addition, BMI was statistically higher in asthma group (16).

Total IgE and atopy relation had been shown in many studies. Increased IgE level is a key feature of atopy. It is widely used as screening tool. Type 2 helper cells have a crucial role in the inflammation of asthma by the production of IgE. As compatible with literature, we found that Total IgE was the most important predictor for positive SPT. Chang et al. analyzed the level of total and specific IgE in 3721 patients with allergic diseases. They found increased total IgE levels in 2419 cases and specific IgE in 1215 patients. Coherence rate between these two parameters was 60.4% (9). A study from Poland queried whether total and specific IgE could take place of skin prick test in atopic dermatitis. The

study consisted of 286 atopic dermatitis patients while asthma and allergic rhinitis were also evaluated. They found no statistically difference between SPT and IgE concentrations. There was a consistency between SPT and total IgE levels (17). A recent study was conducted in Turkey with 443 children at ages of 2-18 years. Children were divided into three groups as asthma (n=179), allergic rhinitis (n=171) and control (n=93). Total IgE levels were statistically higher in asthmatic children in contrast to other 2 groups. Although total IgE levels were higher in allergic rhinitis group compared to control group, there was no significant difference between them (18). A cross-sectional study was run on 142 refractory asthmatic patients in order to find an alignment with total IgE level and eosinophil count. Researchers found statistically significant correlation between total IgE and eosinophil count while 110 (77.5%) had elevated levels for both markers. Furthermore, these 110 patients were subdivided according to increased levels for total IgE and eosinophil count. Most severe refractory asthmatic patients had the highest levels for these biomarkers (19).

Genetic factors, environmental circumstances, gender, age and increased body mass index are risk factors for allergic diseases. In recent years, there are various studies showing link between obesity and atopy. Pro-inflammatory cytokines and reactive proteins are found higher in obese people which cause decreased immune tolerance. Berisha et al. investigated relationship between obesity and allergic diseases at 139 patients on the basis of gender and total IgE. They found that 55.6% females and 50% males in allergic diseases were overweighted in contrast to non-atopics. The highest BMI in females were found in asthma while in asthma and rhinitis for males. Also, both gender had the highest BMI in urticaria/eczema group. With regard to total IgE levels, they found significant differences between allergic diseases and control group for both gender (10). A cross-sectional study involving 1997 participants, was conducted in Canada in order to assess obesity and atopy interaction. Of all cases, 33.3% patients were obese who had one or more positive skin tests. Their results showed significant relationship between atopy and obesity (11).

The major strength of this study is that atopic patients had been approved by SPT. Also four types of allergic diseases were evaluated. Finally, number of cases included were high and there were no missing data for blood and physical parameters. In case of limitations, this was not a prospective design. In addition, specific IgE and high sensitive CRP could not be studied.

In conclusion, total IgE is not key factor for diagnosis of atopic diseases however it can be clue for positive SPT. Also it can be combined with CRP and BMI value before performing SPT in order to detect presence of allergic diseases.

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