AJMHR
Asian Journal of Medical and Health Research
Journal home page: www.ajmhr.com

Correlation between Tuberculin responses and Atopy

Dasdemir Ilkhan Gulay[1]*, Celikhisar Hakan[2]
1.Okmeydanı Trainning and Research Hospital, Chest Diseases Clinic, Kaptan Pasa Mahallesi, Darulaceze Cad. No:25, 34384 Okmeydanı /Sisli/Istanbul-Turkey
2.Izmir Metropolitan Municipality Hospital, Chest Diseases Clinic Gaziler Caddesi No:315, 35110 Yenisehir- Izmir-Turkey

ABSTRACT

The prevalence of atopic diseases in developed countries has increased in recent years. The reasons for this increase are not clear. It is assumed that the decrease in infections and immunization programs may have contributed to the increase in the prevalence of atopic diseases. The aim of the present study was to examine whether there is a correlation between atopy and exposure to tuberculosis in addition to the factors that affect the correlations if any. A total of 93 cases followed up with "atopic asthma" diagnosis were included to the study as the atopy group and 111 healthy individuals were included as the control group. All cases were evaluated for atopic symptoms (skin, nasal and ocular complaints), allergy tests, eosinophilia and total IgE level, respiratory function test, PPD Test. It was observed when all cases were evaluated that the atopic symptoms (skin, nasal and ocular complaints), allergy tests, eosinophilia and total IgE levels were higher at a statistically significant level in comparison with those of the control group ($p<0.05$). PPD positivity ratios in the atopy and control groups were determined respectively as (35.4 %, 78.4 %), mean PPD values as (8.12±6.05 mm, 14.59±6.58 mm) and PPD response levels as (≤10mm, ≥11mm) and the difference between the 2 groups was observed to be statistically significant ($p<0.05$). In conclusion, it was considered that there is an inverse correlation between atopy and tuberculosis exposure and that subclinical exposure to tuberculosis reduces atopy development.

Keywords: Atopic diseases, BCG vaccine, Mycobacterium tuberculosis, tuberculin responses.

gdasdemir1111@gmail.com

Received 12 April 2020, Accepted 29 April 202-

Please cite this article as: Gulay DI *et al.*, Correlation between Tuberculin responses and Atopy. Asian Journal of Medical and Health Research 2020.

INTRODUCTION

Even though significant advancements have recently been made in the treatment of allergic diseases, the prevalence of asthma and atopy continues to increase reaching about 30 % in developed countries (1, 2). The reasons for this are not known for certain, however various environmental factors such as air pollution, smoking, diet and changes in conditions of life are held responsible (3,4). On the other hand, decrease in infectious diseases attracts attention due to the ongoing vaccination programs as well as the hygienic areas of life resulting from increasing life standards (3). It was considered when all these are taken into consideration that the increase in atopy may be related with the decrease in infectious diseases. This issue has attracted further attention when a converse relationship was obtained between atopy and viral infections and tuberculin skin test sensitivity as a result of the studies carried out (3,5,6). It was reported in later studies that gender differences may have an impact on this relationship (7).

T helper (Th) lymphocytes are central regulators in allergic inflammation and are classified into subgroups based on the cytokines they produce. Th1 cells secrete interferon to inhibit immunoglobulin E (IgE) production in B cells, while Th2 cells stimulate IgE production. Th2 activity is dominant in atopic individuals (8,9). Some of the cytokines produced by Th2 cells such as IL-4, IL-10 and IL-13 suppress the microbisidial activity of macrophages and Th1 cell mediated immunity. Any circumstance with an impact on the immune system may shift the balance to one side due to the aforementioned interaction. E.g.; BCG (BacillusCalmette-Guerin) vaccine as a potent stimulant of cellular immunity induces IFN-gama resulting in Th1 type immune response (10). It is also asserted that exposure to mycobacterium tuberculosis will suppress Th2 origin cytokines in a similar manner (6). However, studies on this subject have put forth contradictory results. Shedding light on this interaction between infections and atopy may lead to new options in treatment by mimicking its effects.

The aim of the present study was to examine whether there is a relationship between atopy and tuberculin exposure and to put forth whether gender difference has an impact on this relationship if any.

MATERIALS AND METHOD

The study was carried out with patients followed up with atopic asthma diagnosis who applied to the thoracic diseases polyclinic of our hospital during the dates of October 2018 and January 2020 who were accepted after signing the written consent form. Cases who have not received corticosteroid and antihistaminic treatment, who have not been subject to immunotherapy for at least four years and who have no contraindications for PPD (Purified Protein Derivative) test were included in the study. Patients in asthma attack and with

infection findings along with those with immunologic diseases and those who have not given consent to take part in the study were excluded.

All cases were subject to a detailed assessment for atopy. Regarding the symptom assessment of the cases for atopy; it was examined whether there is at least one of the ocular complaints of watering, burning, itching in the eyes; nasal complaints of sneezing, nasal discharge or congestion which are observed frequently in cases other than cases of influenza and symptoms of swelling, itching, reddening of the skin in addition to questioning whether the patients are allergic to a certain medication or food. History of atopy in the family was examined. Prick test was applied on all participants against a total of 16 allergens such as pine, house dust, fruit, tree, grass, cat, dog, sheep wool. Test results were read 15 minutes later and ≥3 mm induration against any one of the antigens used was considered as "positive".

With regard to laboratory tests, total IgE level ≥150 IÜ/ml and eosinophilia count ≥ 4 % in peripheral smear was accepted as "positive." The presence of 2 or more from having at least one atopic symptom, skin test positivity, high total IgE and eosinophilia presence was considered as "atopy criteria". A total of 93 asthma patients between the ages of 18-59 with atopy based on the aforementioned criteria made up the atopy group. While the control group was comprised of 111 volunteering individuals in the same age group with no complaints and atopy based on the examinations.

It was questioned during the assessment of the cases with regard to tuberculosis whether they previously had tuberculosis or not, whether there is tuberculin story in the family in addition to BCG vaccination. Clinical, physical examination and chest radiography along with active pulmonary tuberculosis were excluded. Tuberculin skin test was applied on the forearms of all patients and induration diameter was evaluated in "mm" after 72 hours with ≥10 mm accepted as "positive".

Statistical Analyses

Statistical analyses were performed using SPSS version 21.0 (SPSS Inc. Chicago, IL, USA). All data were presented as mean ± standard deviation (SD) for continuous variables and as frequencies (%) for categorical variables. Group averages were compared with one-way analysis of variance (Oneway, Anova) and Tukey test (t-test). The differences between the rates are "Q-Square and Fisher exact test". $p < 0.05$ value was considered significant.

RESULTS AND DISCUSSION

It was observed when the groups were compared with regard to age and gender that the mean age of the atopy group comprised of 69 women (74,2 %) and 24 men (25,8 %) was 32.78 ±

10.23 (18-59); while the mean age of the control group comprised of 75 women (67.6 %) and 36 men (32.4 %) was 35.21 ± 10.18 (17-58).

It was determined that there are no statistically significant differences between the groups with regard to age and gender and that the groups are comparable with each other (p>0.05). It was observed when the 2 groups were compared with regard to atopic symptoms that; skin symptoms were 52.3 % in the atopy group and 15.1 % in the control group; nasal symptoms were 91.1 % in the atopy group and 47.3 % in the control group; ocular symptoms were 73 % in the atopy group and 28.6 % in the control group with a statistically significant difference for all 3 parameters (p<0.05) (Table 1).

Table 1: **Distribution of the cases with regard to atopic symptoms, eosinophilia and total IgE level**

	Atopic symptoms						**eosinophilia**		**Total IgE**	
	eye		*nasal*		*skin*					
	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	<150	>150
Atopy	66	27	84	9	48	45	42	51	30	63
(n:93)n (%)	(73.0)	(27.0)	(91.1)	(8.9)	(52.3)	(47.7)	(45.2)	(54.8)	(32.3)	(67.7)
Control (n:111)	33	78	54	57	18	93	12	99	111	0
n (%)	(28.6)	(71.4)	(47.3)	(52.7)	(15.1)	(84.9)	(10.8)	(89.2)	(100)	(0)
p	<0.05		<0.05		<0.05		<0.05		<0.05	

Medication allergy, food allergy and atopy anamnesis in the family were observed respectively as 16.1 %, 6.5 % and 12.9 % in the atopy group and as 7.9 %, 5.2 % and 7.9 % in the control group. A statistically significant difference could not be observed between the groups with regard to all 3 parameters (p>0.05).

Positive reaction against at least one allergen was determined in 57 cases (61.2 %) in the atopy group as a result of allergy tests. While reaction against one allergen was observed in 6 cases (5.4 %) in the control group. The difference between the groups was observed to be statistically significant (p<0.05).

Eosinophilia and total IgE level was observed higher in the atopy group at a statistically significant level in comparison with the control group (p<0.05) (Table 1).

When evaluated with regard to tuberculosis, a tuberculin story was determined neither in the history of the cases nor of their families in both the atopy and the control groups. Active or inactive tuberculosis was not determined as a result of physical examination, chest radiography and phlegm examination.

With regard to vaccination with BCG, vaccination rate was observed as 90.4 % in the atopy group and as 89.2 % in the control group with no statistically significant difference (p>0.05).

While the PPD positivity ratio as a result of the tuberculin test applied on all cases was 35.4 % for the atopy group, it was determined as 78.4 for the control group. The difference was

observed to be statistically significant (p<0.05) (Table 2).

Table 2: Distribution of the atopy and control group according to the PPD test

	Positive		**Negative**	
	n	%	n	%
Atopy (n:93)	33	35.4	60	64.6
Control (n:111)	87	78.4	24	21.6
p	0.003		0.002	

Of all PPD positive cases, 27.5 % were in the atopy group and 72.5 % were in the control group. The difference was observed to be statistically significant (p:0.002).

It was observed when both groups were compared with regard to PPD measurement that the mean PPD response in the atopy group was 8.13 ± 6.06 mm (0-22mm) while that of the control group was determined as 14.58 ± 6.57 mm (0- 25mm). The difference was statistically significant (p:0.004). It was determined when the cases were examined with regard to PPD reaction level that ≤10mm (maximum 5-10mm) cases were in majority in the atopy group, while ≥11mm (maximum >15mm) cases were in majority in the control group (p:0.004). Table 3 presents this finding.

Table 3: Distribution of the cases according to PPD response level

	PPD response							
	<5mm		5-10 mm		11-15 mm		>15 mm	
	n	%	n	%	n	%	n	%
Atopy	27	29.1	45	48.3	9	9.7	12	12.9
Control	12	10.8	12	10.8	30	27	57	51.3

It was observed when the variation according to gender was examined for the relationship between atopy and PPD response that for women; PPD positivity ratio in the atopic group (30.4 %) was observed to be lower at a statistically significant level in comparison with the control group (80 %) (p:0.003). However, a complete assessment could not be carried out for men due to the low number of cases but still positive response ratio (50 %) was observed to be lower in the atopic group in comparison with the control group (75 %) but the difference was not statistically significant (p:0.5) (Table 4).

Table 4: PPD response in atopy and control groups for women and men

	Men				**Women**			
PPD response	Atopy		Control		Atopy		Control	
	n	%	n	%	n	%	n	%
Atopy	12	50	27	75	21	30.4	60	80
Control	12	50	9	25	48	69.9	15	50

It was observed when the tuberculin response level was evaluated that mean PPD was 7.56 ± 5.58mm for women in the atopy group, while it was 14.52 ± 6.64mm in the control group with a statistically significant difference between the two (p:0.03). While it was determined

as 9.75 ± 7.44mm for men in the atopy group and as 14.75 ± 6.75mm in the control group with no statistically significant difference between the two (p:0.13).

It was determined when the PPD response level was examined for women cases that it was 5-10mm in the atopy group and that >15mm reaction made up the majority in the control group with a statistically significant difference between the two (p:0.002) (Table 5).

Table 5: PPD response level in women cases

	PPD response							
	<5mm		5-10 mm		11-15 mm		>15 mm	
	n	%	n	%	n	%	n	%
Atopy	18	26	39	56.5	9	13	6	4.3
Control	9	12	6	8	24	32	36	48

DISCUSSION

Atopic symptoms (skin, nasal and ocular complaints), allergy tests, eosinophilia and total IgE level were observed to be higher at a statistically significant level in the atopic asthma group in our study in comparison with the control group. It was observed when the correlation between atopy and exposure to tuberculosis was examined that the control group makes up a significant portion of all “PPD positive” cases. PPD positivity ratio of the atopy group, mean PPD values and PPD response level was determined to be lower at a statistically significant level in comparison with the control group. The results of the study group lead us to think that subclinical exposure to tuberculosis reduces the prevalence of atopy (atopic asthma) development. Similarly, results of subgroup analysis according to gender put forth that the PPD response in atopic cases was lower at a statistically significant level for women in comparison with the control group while a statistically significant relationship could not be observed for men.

Any circumstance with an impact on the immune system may shift the T-helper lymphocyte balance in a certain direction. Some infectious diseases that stimulate Th1 type immune response may suppress Th2 type immunity thus preventing the development of atopic diseases (10,11,12). It is put forth that exposure to M. Tbc suppresses Th2 based cytokines (13). BCG vaccine which is a potent stimulant of cell mediated immunity induces IFN oscillation thereby resulting in Th1 type immune response (14). Upper respiratory tract infections in early periods of life were observed to be protective against the onset of allergic asthma in later stages of life. There is a similar relationship between tuberculosis infection and asthma. Tuberculosis infection shifts the immune response in the protective direction thereby acting as a protection against the development of asthma.

Shirakawa et al. were the first to determine in Japan that the prevalence of atopic diseases is lower in PPD (+) children in comparison with the negative cases thus reporting a converse

relationship between subclinical exposure to tuberculosis and atopy. Moreover, they observed that the Th2 based cytokines (IL-4, IL- 10 and IL-13) are at lower levels in children with PPD (+) (6,7). While contradictory results have been reported in many of the studies carried out afterwards. Hence, the most possible interpretation of the results of this study is that the converse relationship between atopy and tuberculin response reflects the Th-1/Th-2 balance of the host rather than the causal relationship between infection and atopy (13). In Sweden, Stensballe et al. determined that BCG vaccination at early stages of life has no impact on atopy development in school-age children (14). However, the relationship between atopy and PPD was not examined in this study. It is reported that the difference in the results compared with those of Shirakawa et al. may be related with the fact that BCG vaccine develops a moderate PPD response in addition to the low environmental exposure to tuberculosis in Sweden (15). While the BCG vaccination rates were similar in our study between the atopy and control groups, PPD response level and PPD positivity were observed to be different at a statistically significant level. Tanner et al. did not observe a correlation between PPD and atopy among 14-year-old individuals with BCG vaccination and 20-44 age individuals (16). Based on the studies in Sweden and Germany, the researchers considered that there is actually no relation between exposure to tuberculosis and atopy and that such a relationship if any may be unique to individuals vaccinated during early childhood (17, 18).

Conversely, a correlation could not be determined between PPD and atopy as a result of 2 studies carried out in different regions of our country where all individuals are vaccinated during early stages of their lives (19,20). A study in Australia put forth that there are no differences in the allergic sensitivity of the 7-14 age group between those subject to BCG vaccination after birth and those that were not (21). It was observed when the studies that did not determine a correlation between atopy and tuberculosis that the communities evaluated were either subject to tuberculosis only by way of BCG vaccination or that they are comprised of individuals at the age intervals when they have not been exposed except the vaccination as was the case in Turkey (16,17). However, the effectiveness of BCG vaccination can change and while PPD (+) ratio is in 80 % of the cases 3 months after the BCG vaccination, this ratio decreases down to 60 % after 10 years (22). The relationship between atopy and exposure to tuberculosis cannot be explained only by way of immunity due to BCG vaccination since the level and intensity of environmental exposure to tuberculosis are also important factors. Tuberculosis incidence is less than 1/100.000 in Norway where the mean PPD response is 4.8mm (23,24). Yılmaz et al. determined the mean PPD response as 6.8±5.6mm in the atopic group and as 7.4±5.9mm in the nonatopic group (18). While these values were determined in our study as 8.12 ± 6.05mm and 14.59 ± 6.58 mm respectively. It was put forth during the study carried out in Japan in which a correlation

was determined between atopy and exposure to tuberculosis that incidence was high (52.1/100.000) in 1994 (25,26). It was determined in another study supporting this finding that atopy indicators are lower in patients with active tuberculosis compared to those with inactive tuberculosis (27).

Yii et al. carried out a study examining the impact of gender on the correlation between exposure to tuberculosis and atopy in which it was determined that the prevalence of asthma and other allergic diseases decrease during the later stages in the lives of women who had tuberculosis infection when aged 16 and below; however, the same correlation could not be observed for men (28). We also determined a converse relationship between atopy and PPD response in women, however could not determine a statistically significant relationship in men. The gender difference with regard to the natural course of asthma and allergy may partially explain this finding. While asthma and allergic rhinitis are observed more frequently in men before school age, the converse is true afterwards. The early onset in men results in the early domination of Th2 type immune response and greater resistance against the immunomodulation that may develop in later years (29). This can also be explained by the mechanical characteristics of boys. The diameter of the airway is narrower in men before puberty, airway tonus is greater and IgE is higher. However, asthma prevalence becomes equal for both girls and boys following the change in the pulmonary structure of boys during puberty (30).

A statistically significant converse relationship was determined between asthma prevalence and tuberculosis ratios during a multicentric study; however, a relationship could not be determined between rhinitis and atopic eczema and tuberculosis (31). Marks et al. determined among cases with rhinitis and eczema in the family anamnesis that asthma prevalence is lower for those with BCG vaccination in comparison with those who have not been vaccinated. It was reported as a result of the study that the intervention to the immune system by way of external factors (BCG vaccination) during the newborn period affects asthma development in later periods but that the impact is most likely modified via genetic factors (32). These findings lead us to think that tuberculosis is related more with asthma development rather than atopy. Our study included atopic asthma patients but the cases were not evaluated after being classified into subgroups based on their different atopic characteristics (skin, nasal and ocular). The relationship between exposure to tuberculosis and atopy develops after exposure to tuberculosis that leads to a certain PPD value. Based on our findings, atopy prevalence decreases most likely at PPD values of >10mm but a boundary value has still not been determined. Even though it has been reported as a result of some experiments on animals that allergic sensitivity decreases following BCG vaccination, the

dose used is not known exactly (33). Studies on humans put forth that BCG vaccination does not provide sufficient immune modulation by itself (34).

A study carried out by David Strachan in 1989 on the increase in the prevalence of asthma and other allergic diseases attracted significant attention. According to Strachan, "the fact that the size of families have gradually decreased during the last century, that domestic comfort has increased along with personal hygiene standards resulted in the decrease of cross infections among the younger family members. This may be the reason for the increased prevalence of atopic diseases". Even though it is not the only explanation for the increase in allergic diseases, the hygiene theory has been supported by many epidemiologic and experimental studies. Atopy, eczema, allergic rhinitis and asthma are observed less frequently among individuals living in non-hygienic and crowded families. The essence of the hygiene hypothesis is as such; the individual is born with a Th-2 type cellular profile during the early childhood period. The microorganisms that the baby naturally comes into contact with in the coming months transform the Th-2 type cytokine profile of the baby to Th-1 thus resulting in normal immune system maturation. However, if the child does not encounter these microorganisms in a highly hygienic environment, this cellular transformation will not take place, Th-2 type domination will take place leaving the child open to atopy and asthma development (35).

CONCLUSION

The relationship that we determined between atopy and exposure to tuberculosis cannot be explained solely by BCG vaccination. Genetic characteristics, intensity and severity of the environmental exposure to tuberculosis are probably among significant factors. The impact of BCG vaccination can be measured more accurately by eliminating or at least reducing the impact of these factors. If the BCG doses at which atopy prevalence can be reduced are determined, immunomodulation at an early period can be attained thus protecting the children against such diseases especially in families that are considered as risky with regard to atopy. In addition, we are of the opinion that hormone studies for evaluating gender difference which was determined to have an impact on the relationship between atopy and exposure to tuberculosis may also shed light on this issue.

REFERENCES

1. Wright RJ, Subramanian SV. Advancing a multi leve lframework for epidemiologic research on asthma disparities. Chest. 2007;132(5 suppl):757S–769S.
2. AkinbamiL J, Rossen LM, Fakhouri THI, Fryar CD. 2–19 yaş arası ABD'li çocuklarda kilo durumuna göre astım prevalansı eğilimleri, 1988-2014. Pediatr Obes. 2018; 13 (6): 393 – 396.

3. Byrne AL, Marais BJ, Mitnick CD, Garden FL, Lecca L, Contreras C, Yauri Y, Garcia F, Marks GB. Asthma and atopy prevalence are not reduced among former tuberculosis patients compared with controls in Lima, Peru. BMC Pulm Med. 2019; 13;19(1):40.
4. Burbank AJ, Sood AK, Kesic MJ, Peden DB, Hernandez ML. Environmental determinants of allergy and asthma in early life. J Allergy Clin Immunol 2017;140: 1-12.
5. Schlaud M, Schmitz R, Poethko-Müller C, Kuhnert R. Vaccinations in the first year of life and risk of atopicdisease results from the KiGGSstudy. Vaccine 2017; 35:5156-62.
6. Shirakawa T, Enomoto T, Shimazu S et al. The inverse association between tuberculin responses and atopic disorder. Science 1997; 275:77-9.
7. K. Palosuo, A. K. Kukkonen, A. S. Pelkonen, and M. J. Mäkelä, Gal d 1-specific IgE predicts allergy to heated egg in Finnish children, Pediatric Allergy and Immunology 2018; vol. 29, no. 6, pp. 637–643.
8. B. Kim, T.H. Kim, Fundamental role of dendritic cells in inducing Th2 responses, Korean J. Intern. Med. 2018; 33: 483–489.
9. Milner JD. TCR signaling abnormalities in human Th2-associated atopic disease. Front Immunol. 2018; 9:2–6. doi: 10.3389/fimmu.2018.00719
10. Muflihah H, Florido M, Lin LCW et al. Sequential pulmonary immunization with heterologous recombinant influenza A virüs tuberculosis vaccines protects against murine M. Tuberculosis infection. Vaccine 2018; 36: 2462-70.
11. Guibas GV, Tsolia M, Christodoulou I, Stripeli F, Sakkou Z, Papadopoulos NG. Distinction between rhinovirus-induced acute asthma and asthma-augmented influenza infection. Clin Exp Allergy. 2018; 48: 536- 543.
12. Martorano LM, Grayson MH. Respiratory viral infections and atopic development: From possible mechanisms to advances in treatment. Eur J Immunol. 2018 Mar;48(3):407- 414.
13. Renz H, Herz U. The bidirectional capacity of bacterial antigens to modulate allergy and asthma. Eur Respir J 2002; 19: 158-71.
14. L.G. Stensballe, E. Nante, I.P. Jensen, P.E. Kofoed, A. Poulsen, H. Jensen, et al., Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea-Bissau: a beneficial effect of BCG vaccination for girls' community based case-control study, Vaccine 2005; 23 (10):1251–1257.

15. R Bennet, S Nejat, M Eriksson. Foreign background and older age of children were associated with infection in Swedish tuberculosis contacts. Acta Paediatrica, 2020; 00:1-6.
16. Tanner, R, Villarreal-Ramos, B, Vordermeier, H.M, McShane, H. The Humoral Immune Responseto BCG Vaccination. Front. Immunol. 2019; 10, 1317.
17. Kowalewicz Kulbat M, Locht C. BCG and protection against inflammatory and auto-immune diseases. Expert Rev Vaccines. 2017;16:1–10. doi: 10.1080/14760584.2017.1333906
18. Linehan MF, Nurmatov U, Frank TL, et al. Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis. J Allergy Clin Immunol 2014; 133: 688–695.
19. Füsun S, Esra E, Gulden P, Pınar Y. Erişkin astımlılarda atopik durum ile tüberkülin yanıtı arasındaki ters ilişki. Tuberk Toraks 2012; 60(3): 218-223.
20. Yonca N, Cagatay N, Mavusen I, Sevil O. The Association Between Delayed Type Hypersensitivity to Mycobacterium Tuberculosis and Atopy in Children with Asthma. Medeniyet Med J. 2002; 17(1): 21-23.
21. M. Singh, R.R. Das, L. Kumar, R. Kumar. Bacille Calmette-Guerin vaccination is associated with lower prevalence of allergic diseases in Indianchildren. Am J Rhinol Allergy, 27 (4) 2013; pp. e107-e112.
22. Cruz AT, Hwang KM, Birnbaum GD, Starke JR. Adolescents with tuberculosis: a review of 145 cases. Pediatr Infect Dis J 2013;32(9):937–941.
23. Beltran-Beck, B. J. Fuente, J. M. Garrido, A. Aranaz, I. Sevilla, M. Villar, M. Boadella, R. C. Galindo, J. M. Lastra, J. A. Moreno-Cid, I. G. de Mera, P. Alberdi, G. Santos, C. Ballesteros, K. P. Lyashchenko, E. Minguijón, B. Romero, L. de Juan, L. Domínguez, R. Juste, and C. Gortázar, 2014: Oral vaccination with heat in activated Mycobacterium bovis activates the complement system to protect against tuberculosis. PLoS ONE 9, e98048.
24. Kayaoğlu SÇ, Esin MN. Tüberküloz hastalığında doğrudan gözetimli tedavi uygulamaları: Sistematik inceleme. İzmir Göğüs Hastanesi Dergisi 2013; 27 (1).
25. Balbay Ö, Isıkhan V, Annakkaya AN, Arbak P, Bilgin C, Bulut Y ve ark. Sosyal ve Ekonomik Boyutuyla Türkiye' deki Tüberküloz Hastaları. Düzce Tıp Fakültesi Dergisi 2004; 2: 5-14.
26. Üner S, Melek A, Koşan A. Günümüzde verem savaşı ve DOTS. Hacettepe Toplum Hekimliği Bülteni 2003; 24 (1): 4-6.

27. Ohmori M, Ozasa K, Mori T, Wada M, Yoshiyama T, Aoki M, Uchimura K, Ishikawa N: Trends of delays in tuberculosis case finding in Japan and associated factors. Int J Tuberc Lung Dis. 2005, 9 (9): 999-1005.
28. Yii AC, Soh AZ, Chee CBE, et al. Asthma, sinonasal disease, and the risk of active tuberculosis. J Allergy Clin Immunol Pract. 2019;7(2):641–648.e1. doi: 10.1016/j.jaip.2018.07.036
29. Kankaanranta H, Tuomisto LE, Ilmarinen P. Age-specificincidence of new asthma diagnoses in Finland. J Allergy Clin Immunol Pract 2017; 5: 189–191.
30. Stempel DA, Spahn JD. Pediatric asthma. Pediatr Clin N Am, 2003; 50: 523-731.
31. Matheson MC, Dharmage SC, Abramson MJ, et al. Early-life risk factors and incidence of rhinitis: results from the European Community Respiratory Health Study an international population- based cohort study. J Allergy Clin Immunol. 2011; 128:816.
32. Homaira N, Briggs N, Pardy C, Hanly M, Oei JL, Hilder L, Bajuk B, Lui K, Rawlinson W, Snelling T, Jaffe A. (2017) Association between respiratory syncytial viral disease and the subsequent risk of the firs tepisode of severe asthma in different subgroups of high-risk Australian children: a whole-ofpopulation-based cohort study. BMJ Open 7.
33. Sallusto, F. 2016. Heterogeneity of human CD4(+) T cells against microbes. Annu. Rev. Immunol. 34: 317–334.
34. Muraro, R.F. Lemanske Jr., P.W. Hellings, C.A. Akdis, T. Bieber, T.B. Casale, et al. Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma&Immunology. J Allergy Clin Immunol, 2016;137:1347-1358
35. Novakovic B, Messina N, Curtis N. Chapter 6 the heterologouseffects of bacillus Calmettee Guerin (BCG) vaccine and trained innate immunity. In: Faustman DL, editor. The value of BCG and TNF in autoimmunity. 2nd ed. New York: AcademicPress. 2018; 71-90.