A Cross Sectional Survey on Tissue Transglutaminase Auto-Antibodies in Patients with Pulmonary and Extra Pulmonary Tuberculosis

Iraj Shahramian, Ameneh Rezaei Keikhaei, Omolbanin Sargazi Aval, Mojtaba Delaramnasab and Ali Bazi

1Pediatric Gastroenterology and Hepatology Research Center, Zabol University of Medical Sciences, Zabol, Iran

Corresponding author: Clinical Research Development Unit, Amir-Al-Momenin Hospital, Zabol University of Medical Sciences, Zabol, Iran. Email: m.baziali@gmail.com

Received 2018 November 05; Revised 2020 January 23; Accepted 2020 February 09.

Abstract

Background: Mycobacterium tuberculosis (TB) is a widespread life-threatening infection worldwide. There is an uncertainty in the association between the emergence of autoimmune antibodies and TB.

Objectives: We hereby aimed to screen anti-tissue transglutaminase (anti-tTG) IgA in patients with TB in an Iranian population.

Methods: This was a cross sectional study conducted on smear positive TB patients admitted to the Respiratory Diseases Management Center of the city of Zabol, Sistan and Baluchestan Province of Iran during 2017 - 2018. Anti-tTG IgA level was determined using an ELISA kit (Pars Azmoun, Iran). Statistical analyses were performed in SPSS 19 software.

Results: Overall, 162 patients were evaluated. Females and males constituted 87 (53.7%) and 75 (46.3%) of the patients respectively. The mean age was 51.7 ± 22.3 years (range of 1 - 83). Afghan patients constituted 16 (9.9%) and the remaining were Iranians. The therapy course was successfully completed in 78 (48.1%) patients, and 67 (41.4%) improved following treatments. Overall, 5 patients had active TB with 2 drug-resistant cases. Pulmonary tuberculosis was diagnosed in 127 (78.4%) while 35 (21.6%) had extra-pulmonary disease. The mean titer of anti-tTG IgA was 22.59 ± 107.7 (range of 0.8 - 940). Overall, 19 (11.9%) of the patients showed elevated levels of the antibody. There was no significant association between anti-tTG IgA titer with neither demographic nor clinical variables.

Conclusions: Although anti-tTG IgA antibody test was positive in a relatively high ratio of our patients with TB, the clinical implications of this phenomenon were not significant.

Keywords: Tuberculosis, Celiac Disease, Tissue Transglutaminase, Mycobacterium tuberculosis

1. Background

Mycobacterium tuberculosis (TB) is a frightening infectious disease affecting nearly one-third of the world’s population (1). Although pulmonary TB is the most common clinical subtype, TB can also orchestrate multi-organ dysfunction by invading extra-pulmonary tissues. Tuberculosis is also a major health concern in Iran. Especially, an increased rate of drug-resistant infections has been encountered in recent years in the country (1). Tuberculosis is particularly common in the South-Eastern Regions of Iran (2). Accordingly and with an estimated rate of 3.6% and annual incidence rate of 0.48%, Sistan and Baluchestan Province is an endemic region of TB in Iran (3).

Infectious diseases have been noted as potential culprits in the development of autoimmune conditions (4). Accordingly, patients infected with mycobacterial infections have been detected with higher susceptibility to autoimmune conditions and the emergence of autoantibodies (5-8). A relationship has been noted between celiac disease (CD) and TB (9-11). Celiac disease is a common autoimmune etiology of intestinal atrophy. Generally, CD is diagnosed as a cause of malnutrition in 1% of Mediterranean populations (12). Association of CD with genetic determinants has been well established during years of extensive research. In particular, CD has been associated with human leukocyte antigen (HAL)-DQ2 and DQ8 haplotypes (13, 14). Autoimmunity against intestinal enterocytes in CD is promoted by gluten (i.e. gluten triggered enteropathy) and is mediated by IgA antibodies targeting tissue transglutaminase (tTG). Serological evaluation of anti-tTG IgA antibody is the most common test used for CD screening (12, 14). Celiac disease is usually alleviated by administering gluten-free diet; however, there is a necessity for screening other malnutrition conditions in non-responders (15).

2. Objectives

The association of TB with the development of autoantibodies necessitates routine screening of these patients...
and divulging the clinical importance of these antibodies in the clinical course of TB. There was no study on the clinical implications anti-tTG IgA antibody in TB affected individuals. Considering that CD is a common clinical condition in Sistan and Baluchestan Province of Iran (16), we here aimed to screen anti-tTG IgA antibodies in patients with TB in this region.

3. Methods

3.1. Patients

This was a cross sectional study performed during November 2017-June 2018. The study was performed on patients with confirmed smear-positive TB diagnosed in the Respiratory Diseases Management Center of Zabol. The diagnoses had also been approved by chest radiography. The diagnosis and clinical management of these patients had been performed according to the national guidance on diagnosis and management of TB (17). All the eligible patients registered at the center were enrolled by accessible sampling method. Informed consent was acquired from the patients before gathering their data. The study was approved by the local Ethical Committee of Medical Researches of Zabol University of Medical Sciences.

3.2. Measuring Anti-tTG IgA

Blood samples (3 mL) were drawn in fasting condition. The samples were immediately transferred to the laboratory of the center for separating sera. The serum samples were then stored at -80°C until use. The level of anti-tTG IgA antibody was determined using a specific ELISA kit (Pars Azmoun, Iran) as noted in our previous study (18). Antibody titer > 18 IU/L was considered as positive.

3.3. Statistical Analysis

Statistical methods were performed in SPSS 19 software. Kolmogorov-Smirnov test was applied for checking the data distribution. Univariate analyses were applied as independent samples student t-test (normally distributed quantitative variables) and Mann-Whitney U test (non-normally distributed quantitative variables, i.e. anti-tTG titer). The P value < 0.05 was considered as statistically significant.

4. Results

From a total of 162 recruited patients; 100 (61.7%) were married, 30 (18.5%) were widowed or divorced and 32 (19.8%) were single. Females and males constituted 87 (53.7%) and 75 (46.3%) respectively. The mean age was 51.7 ± 22.3 years old (range of 1 - 83). The means of height and weight were 160 ± 17.8 cm and 50.8 ± 14.4 kg respectively. Afghan patients constituted 16 (9.9%) and the remaining were Iranians.

The therapy course was successfully completed in 78 (48.1%) patients, and 67 (41.4%) of them showed improved symptoms following treatments. Eight patients (4.9%) died of disease-related complications. Three patients (1.9%) did not receive any treatment, 3 (1.9%) were currently under treatment, and 2 (1.2%) did not respond to the treatments. One (0.6%) patient was incorrectly diagnosed as TB. A history of contact with a person diagnosed with TB was recorded in 47 (29%).

Pulmonary TB was diagnosed in 127 (78.4%) while 35 (21.6%) had extra-pulmonary disease. The mean titer of anti-tTG antibody was 22.59 ± 107.7 IU/mL (range of 0.8 - 940). The mean titer of anti-tTG IgA antibody were 21.9 ± 112.7 IU/mL and 24.8 ± 87.9 IU/mL for pulmonary and extra-pulmonary TB, respectively (P > 0.05, Table 1). Overall, 19 (11.9%) of the patients showed positivity for anti-tTG. Seven patients had borderline results (titer of 12 - 18). In replication, they rendered negative results summing up the negative cases to 143 (88.1%). There was no significant association between anti-tTG positivity with neither demographic nor clinical variables (Table 2).

5. Discussion

We hereby have assessed a potential relationship between TB clinical course and seropositivity for anti-tTG IgA antibody. Overall, 19 (11.9%) patients rendered seropositivity for anti-tTG IgA Antidbody. However, there were no significant associations between the seropositivity for anti-tTG IgA and either demographic or clinical features. There was no significant difference in the antibody titer between pulmonary and extra-pulmonary TB.

An elevated risk of TB as high as 2-fold has been reported in biopsy verified CD patients, especially within the first year (11). TB itself can present as an intestinal disease mimicking a malnutrition status (19). In fact, intestinal TB may be misdiagnosed as a malabsorption syndrome (20-26). In one study, 13% and 9% of severely malnourished children were diagnosed with CD and TB respectively (27). The common genetic signature at HLA class II locus can be causative for both CD (as an autoimmune entity) and TB (as an inflammatory disease) (28). Furthermore, the HLA-B8 allele has been reported as a risk factor for both TB and CD (29). In this study, although 19 out of 162 (11.9%) TB patients showed anti-tTG seropositivity, no one revealed clinical symptoms of CD. Nevertheless, we could not rule out this condition without intestinal biopsy. Overall, clinically insignificant elevation of anti-tTG IgA antibody without overt CD in the course of TB should be carefully monitored by physicians.
Table 1. Demographic Variables and Anti-Tissue Transglutaminase Titer in Patients with Pulmonary and Extra-Pulmonary Mycobacterium tuberculosis

| Parameters               | Mycobacterium tuberculosis | P  |
|--------------------------|-----------------------------|----|
|                          | Pulmonary (N = 127)         |    |
|                          | Extrapulmonary (N = 35)     |    |
| Gender                   | Male 54 (42.5) | 21 (60) | 0.1 |
|                         | Females 73 (57.5) | 14 (40) |
| Nationality              | Iranian 112 (88.2) | 34 (97.1) | 0.09 |
|                         | Afghan 15 (11.8) | 1 (2.9) |
| Marital status           | Married 75 (59.1) | 25 (71.4) | 0.02 |
|                         | Single 23 (18.1) | 9 (25.7) |
|                         | Widowed/divorced 29 (22.8) | 1 (2.9) |
| History of contact with infected person | Yes 34 (26.8) | 13 (37.1) | 0.1 |
|                         | No 93 (73.2) | 22 (62.9) |
| Age                      | 55.9 ± 21.4 | 36.5 ± 18.9 | < 0.001 |
| Weight                   | 49.2 ± 13 | 56.3 ± 17.5 | 0.01 |
| Anti-tTG IgA, IU/mL      | 21.9 ± 12.2 | 24.8 ± 87.9 | 0.4 |

\(^a\)Values are expressed as No. (%) or mean ± SD. 
\(^b\)Fischer exact test. 
\(^c\)Mann-Whitney U test.

Infection-induced alterations in immunoregulatory processes can potentially be associated with aberrant responses against auto-antigens. The risk of autoimmunity in TB patients can be influenced by genetic variations in immune system genes such as IFN-\(\gamma\) and CD14 (30-33). The role of Th-17 lymphocytes is yet to be explored as a possible dominant modulator of inflammatory autoimmunity in the context of TB infection (34).

It seems that antibodies against TB derived proteins such as heat shock protein 65 (Mt-Hsp65) (35, 36) and chaperonin 10 (m-Cpn10) (37) can promote cross-reactions with human antigens triggering autoimmunity in this condition (38). Also, immune reactions against Mt-Hsp70 has been shown to activate T cell-mediated autoimmunity (39). Identification of antigens that can promote antibody cross-reactions can assist to better understand the pathogenesis of TB and its potential associations with autoimmune conditions.

An interaction between CD and TB diseases can be assumed by some evidence from researches. As a malnutrition status, CD can be associated with deficiencies in multiple micro-nutrients and vitamins, in particular vitamin D, both as a result of general malabsorption and vitamin-deficit regimens (40). Vitamin D has a crucial role in augmenting immune responses against microbial pathogens and suppressing the growth of intracellular microorganisms such as TB within phagocytes (41). Furthermore, TB infection may contribute to CD by inducing gluten-sensitivity through accelerating the transportation of gluten across the intestine (11). The altered biology and distribution of drug metabolizing enzymes in the gastrointestinal wall of CD patients can further modulate the efficiency of medications in TB (42). Accordingly, Shetty and McKendrick (43) reported two patients with pulmonary TB who did not respond to treatment while both of them suffered from co-existing CD. In our study, two non-responder patients had anti-tTG titers of 1.1 IU/L and 5.3 IU/L respectively; negating this hypothesis. This indicates that treatment response in TB is a multifactorial phenomenon and under influence of other potential molecular and environmental factors.

In this study, we had no access to details on therapeutic regimens, the duration of treatments and follow-up, clini-
cal features of those in whom treatment failed, and other relevant clinical data. Nevertheless, the number of anti-tTG positive cases did not get high enough to allow us for a good statistical analysis on the relevance of these clinical variables. In any future study, we recommend providing a complete clinical picture of TB patients and its potential association with anti-tTG positivity.

5.1. Conclusions

According to our observation, seropositivity for anti-tTG IgA antibody is relatively common in patients with TB. Although we found no association between this serologic marker and TB clinical parameters, it is advisable to further explore the implication of this observation on the clinical course of TB patients.

Acknowledgments

Thanks to the patients and the staff of the Respiratory Diseases Management Center of Zabol City for their cooperation.

Footnotes

Authors’ Contribution: Iraj Shahramian did concept and design. Ameneh Rezaei Keikhaei did clinical evaluations and data collection. Omolbanin Sargazi Ava did data collection. Mojtaba Delaramnasab did data collection. Ali Bazi did data analysis and drafting the manuscript.

Conflict of Interests: None of the authors have any conflict of interests.

Ethical Approval: The study was approved by the local Ethical Committee of Medical Researches of Zabol University.

Funding/Support: The study was supported by the Zabol University of Medical Sciences.

Informed Consent: Informed consent was acquired from the patients before gathering their data.

References

1. Rafiee S, Besharat S, Jabbari A, Golalipour F, Nasermoadeili A. Epidemiology of tuberculosis in northeast of Iran: A population-based study. Iran J Med Sci. 2009;34(3):93-7.
2. Zahedi Bialvaei A, Asgharzadeh M, Aghazadeh M, Nourazarian M, Samadi Kafi H. Challenges of tuberculosis in Iran. Jundishapur J Microbiol. 2017;10(3). e37866. doi: 10.5812/jpmi.37866.
3. Haghdoost AA, Afghari M, Baneshi MR, Goyou MM, Nasehi M, Movahedi M. Estimating the annual risk of tuberculosis infection and disease in southeast of Iran using the bayesian mixture method. Iran Red Crescent Med J. 2014;16(9). e15308. doi: 10.5812/ircmj.15308. [PubMed: 25593722]. [PubMed Central: PMC4270654].
4. Samarkos M, Vaiopoulos G. The role of infections in the pathogenesis of autoimmune diseases. Curr Drug Targets Inflamm Allergy. 2005;4(1):99-103. doi: 10.2174/1568010053622821. [PubMed: 15720242].
5. Ghosh K, Patwardhan M, Pradhan V. Mycobacterium tuberculosis infection precipitates SLE in patients from endemic areas. Rheumatol Int. 2009;29(9):1047-50. doi: 10.1007/s00296-009-0903-x. [PubMed: 19160412].
6. Pradhan V, Patwardhan M, Athavale A, Taushid S, Ghosh K. Mycobacterium tuberculosis triggers autoimmunity? Indian J Tuberc. 2012;59(1):49-51. [PubMed: 22670553].
7. Doffinger R, Helbert MR, Barcanes-Morales G, Yang K, Dupuis S, Ceron-Gutierrez I, et al. Autoantibodies to interferon-gamma in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. Clin Infect Dis. 2004;38(1):e10-4. doi: 10.1086/400453. [PubMed: 14679495].
8. Kakumanu P, Yamagata H, Sobel ES, Reyes WH, Chan EK, Satoh M. Patients with pulmonary tuberculosis are frequently positive for anti-cyclic citrullinated peptide antibodies, but their sera also react with unmodified arginine-containing peptide. Arthritis Rheum. 2008;58(6):1576-81. doi: 10.1002/art.23514. [PubMed: 18512773]. [PubMed Central: PMC3621955].
9. Urganci N, Kalyoncu D. Tuberculosis and tuberculin skin test reactivity in pediatric patients with celiac disease. Minerva Pediatr. 2017;69(3):30-5. doi: 10.23736/S0026-4946.16.04210-9. [PubMed: 28102654].
10. Sarghini K, Oubaha S, Samlani Z, Krati K. [Relationship between coeliac disease and multifocal tuberculosis: About a case and literature review]. Pan Afr Med J. 2017;27:214. doi: 10.11604/pamj.2017.27.214.212847. [PubMed: 28979616]. [PubMed Central: PMC5622824].
11. Ludwigsson JF, Sanders DS, Mauerer M, Jonsson J, Grunewald J, Wahlstrom J. Risk of tuberculosis in a large sample of patients with coeliac disease—a nationwide cohort study. Aliment Pharmacol Ther. 2011;33(6):658-96. doi: 10.1111/j.1365-2036.2010.04572.x. [PubMed: 21250209].
12. Sanders DS, West J, Whyte MK. Coeliac disease and risk of tuberculosis: A population-based cohort study. Thorax. 2007;62(1):12-3. doi: 10.1136/thx.2006.062158. [PubMed: 1789527]. [PubMed Central: PMC211272].
13. Noori NM, Shahramian I, Dehghani SM, Teimouri A, Etaolah M, et al. Evaluation of celiac disease in children with dilated cardiomyopathy. Int Cardiovasc Res J. 2017;11(1):2-5.
14. Ahmad A, Mazhar AU, Usman M, Mazhar M. Evaluation of celiac disease serological markers in children presenting with features of malabsorption. Pakistan Paediatr J. 2011;31(3):281-8.
15. DeGeorge KC, Frye JW, Stein KM, Rollins LK, McCarter DF. Celiac disease and gluten sensitivity. Prim Care. 2017;44(1):193-7. doi: 10.1016/j.pop.2016.07.011. [PubMed: 29132529].
16. Bahari A, Karimi M, Sanei-Moghaddam I, Firouzi F, Hashemi M. Prevalence of celiac disease among blood donors in Sistan and Baluchestan Province, Iran. Iran J Med Sci. 2009;34(3):193-7. doi: 10.5812/ijms.9784. [PubMed: 19523258].
17. Barberi A, Karimi M, Sanei-Moghaddam I, Firouzi F, Hashemi M. Prevalence of celiac disease among blood donors in Sistan and Baluchestan Province, Iran. Arch Iran Med. 2010;13(9):1234-8. doi: 10.1016/j.aim.2010.09.007. [PubMed: 20597563].
18. Shahramian I, Haghjhat M, Noori NM, Teimouri AR, Sharafi E, Kalli M, et al. TTG IgA in functional constipation: Is it rational to be evaluated? Arch Cardiovasc Dis. 2016;109(1):4-7. doi: 10.31771/jbasm.2016.02.002.001. [PubMed: 27310344].
19. Ashraf H, Ahmad Z. Histologic findings in biopsies/resection specimens from the small intestine with special emphasis on celiac disease: experience from a developing country in South Asia. Ann Diagn Pathol. 2012;16(6):436-40. doi: 10.1016/j.anndiagpath.2012.03.003. [PubMed: 22464354].
20. Singh S, Khichi S, Bhangale D, Agarwal SP. Intestinal tuberculosis in a celiac disease patient. Indian J Tuberc. 2010;57(4):216-9. [PubMed: 21413431].
21. Parfenov AI, Krums LM, Sivash ES, Tsaregorodtseva TM, Poleva NI, Ruchkina IN, et al. [Algorithm for diagnosis of small intestinal diseases]. Ter Arkh. 2008;80(4):46-51. Russian. [PubMed: 18491580].
22. Ramakrishna BS, Venkataraman S, Mukhopadhyaya A. Tropi- cal malabsorption. Postgrad Med J. 2006;82(974):779-87. doi: 10.1366/pgmj.2006.048579. [PubMed: 17148698]. [PubMed Central: PMC2653921].

23. Thakur B, Mishra P, Desai N, Thakur S, Alexander J, Sawant P. Profile of chronic small-bowel diarrhea in adults in Western India: A hospital-based study. Trop Gastroenterol. 2006;27(2):84-6. [PubMed: 17085608].

24. Yachha SK, Misra S, Malik AK, Nagi B, Mehta S. Spectrum of malabsorption syndrome in north Indian children. Indian J Gastroenterol. 1993;12(4):120-5. [PubMed: 8270289].

25. Ghoshal UC, Mehrotra M, Kumar S, Ghoshal U, Krishnani N, Misra A, et al. Spectrum of malabsorption syndrome among adults & factors differentiating celiac disease & tropical malabsorption. Indian J Med Res. 2012;136(3):451-9. [PubMed: 23047399]. [PubMed Central: PMC3508982].

26. Dutta AK, Balebuduru A, Chacko A. Spectrum of malabsorption in India-tropical sprue is still the leader. J Assoc Physicians India. 2011;59:420-2. [PubMed: 22315745].

27. Kumar P, Mishra K, Singh P, Rai K. Should we screen children with severe acute malnutrition for celiac disease? Indian Pediatr. 2012;49(4):330-1. [PubMed: 22565083].

28. Mangalam AK, Rajagopalan G, Taneja V, David CS. HLA class II trans- tors differentiating celiac disease & tropical malabsorption. Indian J Gastroenterol. 2010;29(2):126-31. doi: 10.1007/s12048-010-0121-x. [PubMed: 20946904].

29. Selby R, Barnard JM, Buehler SK, Crumley J, Larsen B, Marshall WH. Tuberculosis associated with HLA-B8, BS in a Newfoundland community study. Tissue Antigens. 1998;51(5):403-8. doi: 10.1034/j.1399-0039.1998.t01-5.18.x. [PubMed: 994904].

30. Pagan AJ, Ramakrishnan L. Immunity and Immunopathology in the Tuberculous Granuloma. Cold Spring Harb Perspect Med. 2014;5(9). doi: 10.1101/cshperspect.a018499. [PubMed: 25377442]. [PubMed Central: PMC4564014].

31. Elkington P, Tehruegger M, Mansour S. Tuberculosis: An infection-initiated autoimmune disease? Trends Immunol. 2016;37(12):685-8. doi: 10.1016/j.it.2016.09.004. [PubMed: 27735684]. [PubMed Central: PMC5193557].

32. Hashemi M, Sharifi-Mood B, Nezamdoost M, Moazeni-Roodi A, Naderi M, Kouhpayeh H, et al. Functional polymorphism of interferon-gamma (IFN-gamma) gene +874T/A polymorphism is associated with pulmonary tuberculosis in Zahedan, Southeast Iran. Prrague Med Rep. 2012;112(1):38-43. [PubMed: 21470497].

33. Alavi-Naini R, Salimi S, Sharifi-Mood B, Davoodikia AA, Moody B, Naghavi A. Association between the CD4 gene C-159T polymorphism and serum soluble CD14 with pulmonary tuberculosis. Int J Tubercul Lung Dis. 2012;16(10):1383-7. doi: 10.5588/ijtlld.11.0827. [PubMed: 2307636].

34. Sutton CE, Lalor SJ, Sweeney CM, Bereton CF, Lavelle EC, Mills KH. Interleukin-1 and IL-23 induce innate IL-17 production from gamma (IFN-gamma) gene +874T/A polymorphism is associated with pulmonary tuberculosis. Autoimmun Rev. 2009;8(12):1331-41. doi: 10.1016/j.autrev.2009.08.001. [PubMed: 19682929].

35. Dubaniewicz A. Mycobacterium tuberculosis heat shock proteins and autoimmunity in sarcoidosis. Autoimmun Rev. 2009;8(6):419-24. doi: 10.1016/j.autrev.2009.11.015. [PubMed: 19931650].

36. Munk ME, Schoel B, Modrow S, Karr RW, Young RA, Kaufmann SH. T lymphocytes from healthy individuals with specificity to self-epitopes shared by the mycobacterial and human 65-kilodalton heat shock protein. J Immunol. 1989;143(9):2844-9. [PubMed: 2505958].

37. Minto M, Galli G, Gianazza E, Eberini I, Legname G, Fossati G, et al. Mycobacterial Cpn10 promotes recognition of the mammalian homologue by a mycobacterium-specific antiserum. Biochim Biophys Acta. 1999;1430(2):126-34. doi: 10.1016/s0006-2977(98)00003-4. [PubMed: 9630938].

38. Kaufmann SH, Flesch IE, Munk ME, Wand-Wurttenberger A, Schoel B, Koga T. Cell-mediated immunity to mycobacteria: A double-sided sword? Rheumatol Int. 1989;9(3-5):181-6. doi: 10.1007/bf00271877. [PubMed: 2481876].

39. Salvetti M, Ristori G, Buttinelli C, Fiori P, Falcone M, Britton W, et al. The immune response to mycobacterial 70-kDa heat shock proteins frequently involves autoreactive T cells and is quantitatively disregulated in multiple sclerosis. J Neuroimmunol. 1996;65(2):143-53. doi: 10.1016/0165-5728(96)00015-x. [PubMed: 8964896].

40. Kikut J, Konecka N, Szczuko M. Quantitative assessment of nutrition and nutritional status of patients with celiac disease aged 13-18. Rocz Panstw Zakl Hig. 2019;70(4):359-67. doi: 10.32394/rpzh.2019.0084. [PubMed: 31960667].

41. Shapira Y, Agmon-Levin N, Shoenfeld Y. Mycobacterium tuberculosis, autoimmunity, and vitamin D. Clin Rev Allergy Immunol. 2016;50(2-3):169-77. doi: 10.1007/s12016-016-8504-0. [PubMed: 25954859].

42. Drozdzik M, Oswald S. Expression and regulation of drug transporters and metabolizing enzymes in the human gastrointestinal tract. Curr Med Chem. 2016;23(39):4468-89. doi: 10.2174/0929867323666616102454457. [PubMed: 2778942].

43. Shetty A, McKendrick M. TB and coeliac disease. J Infect. 2004;48(1):109-11. doi: 10.1016/j.jinf.2003.08.004. [PubMed: 14667800].