Mod Care J. 2017 April; 14(2):e64569. doi: 10.5812/modernc.64569.

Published online 2017 April 30. **Research Article**

Alterationsinserum Antitrypsin Level and Its Association with Pulmonary Complications Among Patients with Lung Tuberculosis

Reza Eslami Manoochehri,[1] Sayyed Gholamreza Mortazavimoghaddam,[2,*] Mohammad Hasan Namaei,[3] and Mahmod Zardast[4]

[1]Department of Internal Medicine, Vali-e-Asre Hospital, School of Medicine, Birjand University of Medical Sciences, Birjand, IR Iran
[2]Pulmonary Division, Department of Internal Medicine, Vali-e-Asre Hospital, School of Medicine, Birjand University of Medical Sciences, Birjand, IR Iran
[3]Department of Microbiology, School of Medicine, Birjand University of Medical Sciences, Birjand, IR Iran
[4]Department of Pathology, Vali-e-Asre Hospital, School of Medicine, Birjand University of Medical Sciences, Birjand, IR Iran

[*]*Corresponding author*: Sayyed Gholamreza Mortazavimoghaddam, Department of Internal Medicine, Vali-e-Asre Hospital, School of Medicine, Birjand University of Medical Sciences, Birjand, IR Iran. E-mail: gmortazavi@yahoo.com

Received 2017 January 29; **Accepted** 2017 March 04.

Abstract

Background: Antitrypsin is one of the factors that increases during inflammatory responses. The aim of this study was to monitor alterations in serum antitrypsin level during pulmonary tuberculosis treatment and determine its association with pulmonary function and fibrotic changes.

Methods: This quasi-experimental study was done on all 40 patients who had pulmonary tuberculosis and were referred in 2015 - 2017 to a tuberculosis care center in Birjand, Iran. Sampling was done through the census method. After the establishment of tuberculosis diagnosis, all patients received tuberculosis treatment for 6 consecutive months. Before, 2 and 6 months after treatment onset, 5-milliliter blood samples were obtained from each patient for antitrypsin measurement. Moreover, chest radiography was performed for each patient both before and 6 months after treatment onset, while pulmonary function test or spirometry was done 2 and 6 months after treatment onset. The one-way analysis of variance, independent-sample t-test, Mann-Whitney U, Friedman, and Kruskal-Wallis tests were performed for statistical data analysis.

Results: From the 40 recruited patients, only 24 completed the study. The mean of serum antitrypsin level at baseline was 201.72 $\pm$ 47.66, which significantly decreased to 157.61 $\pm$ 36.98 and 141.10 $\pm$ 26.76, at respectively 2 and 6 months after treatment onset ($P < 0.001$). Post-treatment chest radiography showed that 15 patients had fibrotic residue and 9 had normal chest radiography. The mean of serum antitrypsin among patients with fibrotic residue was not significantly different from that of patients with normal chest radiography (75.05 $\pm$ 13.51 vs. 36.57 $\pm$ 14.22; $P = 0.7$). Pulmonary dysfunction was observed among 75% of patients. The prevalence rates of post-treatment restrictive, obstructive, and normal spirometry patterns were 41.7%, 33.3%, and 25%, respectively. There was no significant difference among patients with restrictive, obstructive, and normal spirometry patterns respecting the amount of decrease in the mean of serum antitrypsin (56.12 $\pm$ 64.41, 63.27 $\pm$ 35.6, and 64.60 $\pm$ 54.14, respectively; $P = 0.94$).

Conclusions: The serum level of antitrypsin decreases during pulmonary tuberculosis treatment. Therefore, antitrypsin, as an acute-phase protein, can be used for the follow-up assessment of response to treatment among patients with pulmonary tuberculosis.

Keywords: Tuberculosis, Antitrypsin, Spirometry, Pulmonary Fibrosis

1. Background

Tuberculosis is a widespread disease, which is prevalent particularly in less developed countries. Pulmonary tuberculosis (PTB) is the most prevalent form of tuberculosis. Either with or without treatment, patients with PTB may develop persistent pulmonary complications (1) such as fibrosis and pulmonary dysfunction. Pulmonary dysfunction among patients with PTB may have different forms, chiefly chronic obstructive pulmonary disease (COPD) (2, 3). While smoking has been considered as the most important risk factor for COPD (3), PTB is also considered important (1).

The association of PTB and COPD has been assessed in different ways. A review study noted PTB-COPD comorbidity and reported COPD as the second most principal PTB-associated problem after diabetes mellitus. Moreover, this study showed that PTB-COPD comorbidity is more common among older patients and concluded that COPD increases the risk of drug resistance, the need for critical care, and the rate of mortality among patients with PTB (4). Another study also indicated that patients with a past history

Copyright © 2017, Modern Care Journal. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/) which permits copy and redistribute the material just in noncommercial usages, provided the original work is properly cited.

of PTB develop COPD and experience death 5 years earlier than those without such history (5). A study in Columbia also showed that PTB-COPD association is more prevalent than smoking-COPD association (6).

One of the factors in COPD etiology is antitrypsin deficiency (7). Antitrypsin is an acute-phase protein, which increases during inflammatory reactions such as PTB (8, 9). In PTB, inflammatory reactions are provoked and matrix metalloproteinase is produced. Matrix metalloproteinase is known to contribute to lung tissue degeneration (10-12) as well as COPD development. Therefore, PTB can be a potential risk factor for COPD. On the other hand, regenerative reactions, scar formation, and pulmonary fibrosis, due to delayed PTB diagnosis and treatment can restrict pulmonary function and cause restrictive lung disease (13).

It is unknown whether antitrypsin has protective effects against metalloproteinase production in PTB or is a contributing factor to PTB-related fibrotic changes in lung tissue. Some studies showed the significant increase of serum antitrypsin level during active PTB (14). However, no study has yet assessed the serum antitrypsin level during PTB treatment and its association with pulmonary complications. The aim of this study was to monitor alterations in the serum antitrypsin level during PTB treatment and determine its association with pulmonary function and fibrotic changes.

2. Methods

This quasi-experimental study was done on all 40 patients with PTB who were referred in 2015 - 2017 to a tuberculosis care center in Birjand, Iran. Sampling was done through the census method. The eligibility criteria included: consent for participation, easy accessibility throughout the study, no tobacco use, and no history of malignancy, COPD, asthma, sarcoidosis, interstitial lung disease, as well as non-PTB fibrotic disorders. Patients were excluded if they voluntarily withdrew from the study, discontinued treatment, or were resistant to treatment.

PTB diagnosis was established after ruling out other differential diagnoses and based on the presence of PTB clinical manifestations, PTB-related manifestations in chest radiography, and 1 of the following diagnostic criteria:

- 2 positive sputum-smear testsfor Acid fast bacili;

- A positive sputum-smear test along with a positive sputum culture for Acid fast bacili; or

- A positive bronchoalveolar lavage (BAL) acid-fast bacilli test along witha positive BAL culture or a positive sputum culture.

Before the onset of treatment, a 5-milliliter blood sample was obtained from each patient. Then, PTB pharmacological treatment was provided for 6 consecutive months. Two and 6 months after treatment onset, pulmonary function test or spirometry was done and blood sampling for antitrypsin assessment was repeated. The serum part of each blood sample was separated and immediately placed in the freezer at a temperature of less than -20°C. At the end of each weak during the study, the collected samples were transferred to a central laboratory where they were kept in freezer at a temperature of -70°C. At the end of treatment, all blood samples were studied, respecting the serum antitrypsin level. Antitrypsin measurements were done using enzyme-linked immunosorbent assay (ELISA) kits (Roche Diagnostic, Germany) and an INTEGRA 400 device. Moreover, chest radiography was performed and interpreted both before and 6 months after treatment onset.

Data analysis was made via the SPSS software (v. 23.0). The independent-sample t, Mann-Whitney U, Kruskal-Wallis, Chi-square tests, as well as the one-way analysis of variance were used for between-group comparisons. Moreover, Friedman test was used for within-group comparisons.

This study was approved by the ethics committee of Birjand University of Medical Sciences, Birjand, Iran (with the approval number of IR.BUMS.REC.1395.70). Information about PTB and the aim of the study were provided to all patients and written informed consent was obtained as well.

3. Results

From the 40 TBP patients recruited to this study, 16 were excluded due to voluntary withdrawal from the study, death, or drug side effects. Therefore, 24 patients completed the study and were included in the final analysis. Among these 24 patients, 9 (37.5%) were male and 15 (62.5%) were female. They aged 60.87 $\pm$ 21.50, on average. They had been diagnosed with PTB based on 2 positive sputum-smear tests (9 cases, 37.5%), 2 positive acid-fast bacilli tests and positive BAL-sample mycrobacterium tuberculosis culture (9 cases, 37.5%), or positive mycrobacterium tuberculosis culture for patients with clinical and radiographic findings of PTB (6 cases, 25%). Two and 6 months after treatment onset, respectively, 4 (16.7%) and 6 (25%) patients had normal spirometry results (Table 1).

Chest radiography results showed that 13 (54.2%) patients had right lung PTB involvement and 11 (45.8%) had left lung PTB involvement. PTB involvement of different anatomical lobes of the lung are shown in Table 2.

At the onset of treatment, the mean of serum antitrypsin level was 201.72 $\pm$ 47.66; 2 and 6 months after treatment onset, the value significantly decreased to 157.61 $\pm$ 36.98 and 141.10 $\pm$ 26.76, respectively ($P < 0.001$; Table 3).

Table 1. The Frequency of Spirometry Patterns Among Study Participants[a]

Pattern	Time	
	Two Months After	Six Months After
Restrictive	12 (50)	10 (41.7)
Obstructive	8 (33.3)	8 (33.3)
Normal	4 (16.7)	6 (25)
Total	24 (100)	24 (100)

[a]Values are expressed as No. (%).

Table 2. The Involvement Frequency of Different Anatomical Lobes of the Lungs Based on Chest Radiography Findings

		Side Lobe	
		Left Lung	Right Lung
1.	Upper lobe	5 (20.8)	7 (29.2)
2.	Middle lobe	5 (20.8)	4 (16.7)
3.	Lower lobe	1 (4.2)	2 (8.3)
Total		11 (45.8)	13 (54.2)

Table 3 shows the mean levels of serum antitrypsin among patients with restrictive, obstructive, and normal spirometry patterns. Six months after treatment onset, these 3 groups of patients did not differ significantly from each other, respecting the amount of decrease in the mean of serum antitrypsin during the study (56.12 $\pm$ 64.41, 63.27 $\pm$ 35.6, and 64.60 $\pm$ 54.14, respectively; P = 0.94).

Baseline serum antitrypsin levels among patients with fibrotic residue and patients with normal chest radiography were respectively, 211.45 $\pm$ 55.60 and 185.51 $\pm$ 25.46, with no significant between-group difference (t = 1.31 and P = 0.20). Six months after treatment onset, these values were respectively, 136.40 $\pm$ 20.90 and 148.93 $\pm$ 34.41, again with no significant between-group difference (Z = 1.13 and P = 0.27; Table 4). In total, 15 patients had fibrotic changes. Six month after treatment onset, 6 of these 15 patients (40%) showed restrictive spirometry pattern, 5 (33.3%) showed obstructive pattern, and 4 (26.7%) showed normal pattern (P = 0.96).

Table 4 shows the mean serum antitrypsin levels among patients with normal chest radiography and patients with fibrotic changes. Six months after treatment onset, the mean decrements from the serum antitrypsin levels among patients with normal chest radiography and patients with fibrotic changes were 36.57 $\pm$ 14.22 and 75.05 $\pm$ 13.51.

4. Discussion

Serum antitrypsin level at baseline was 201.72 $\pm$ 47.66. Two and 6 months after treatment onset, it significantly decreased to 157.61 $\pm$ 36.98 and 141.10 $\pm$ 26.76, respectively. Antitrypsin level can increase by 3 - 4 times during inflammatory reactions to infectious or non-infectious diseases, malignancies, and acute inflammatory reactions (15). Therefore, antitrypsin is considered as an acute-phase protein and an inflammatory biomarker (9, 13). Our findings also revealed significant decreases in the level of serum antitrypsin among PTB patients who were responsive to treatment. Therefore, antitrypsin can be considered as a proper marker for the follow-up assessment of PTB patients. Matalon et al. also assessed post-colectomy levels of serum antitrypsin among patients with ulcerative colitis for the purpose of pouchitis diagnosis and found that serum antitrypsin level is directly associated with the incidence and the severity of pouchitis (16). As antitrypsin is an acute-phase protein, effective infection or inflammation management may be associated with significant decrease in its level in 3 - 4 days (15). Increases in antitrypsin level during the acute phase of diseases may have some benefits. For instance, some studies reported antitrypsin as an anti-inflammatory, anti-infective immunomodulator, and a tissue-regenerative agent (17).

Study findings also indicated that at the end of the 6-month treatment, the level of serum antitrypsin among patients with fibrotic residue was slightly higher than those with normal radiography, though the difference was not statistically significant. Moreover, the amount of decrease in antitrypsin level among patients with fibrotic residue was more than patients with normal radiography. This slightly higher level of post-treatment serum antitrypsin level among patients with fibrotic residue may be due to the higher level of antitrypsin at baseline and can be indicative of severer inflammation among these patients. Moreover, this hypothesis can be suggested that increased tissue, regenerability among patients with higher level of serum antitrypsin, might have caused more fibrotic changes. It is noteworthy that while antitrypsin deficiency can reduce lung tissue regenerability and cause emphysema (17), its high levels can improve regenerability and cause fibrosis (17).

The relative frequency of patients with abnormal spirometry patterns in the present study was 75% at end of successful treatment. Restrictive spirometry pattern was also more common than the obstructive one. Similarly, a study in Tanzania showed that 74% of post-treatment spirometry patterns were abnormal. However, the difference between these 2 studies was in the frequencies of different functional disorders of the lung. In other

Table 3. The Mean Serum Antitrypsin Levels at Different Time Points Among Patients with Different Spirometry Patterns (post treatment)[a]

		Time			
Pattern		**Baseline**	**Two Months After**	**Six Months After**	**P value < 0.05 Between Time of Tests**
Restrictive	N = 10	203.28 ± 50.55	158.49 ± 34.42	147.16 ± 34.74	(1 vs. 2 and 1 vs. 3)
Obstructive	N = 8	203.16 ± 42.29	162.32 ± 49.14	139.88 ± 23.23	(1 vs. 2 and 1 vs. 3)
Normal	N = 6	197.21 ± 57.58	149.86 ± 25.25	132.61 ± 14.313	(1vs. 3)
Statistic		0.96	0.61	0.66	
Total	N = 24	201.72 ± 47.66	157.61 ± 36.89	141.10 ± 26.67	(1vs. 2, 1 vs. 3, and 2 vs. 3)

[a]Values are expressed as mean ± SD.

Table 4. The Mean Serum Antitrypsin Levels at Different Time Points Among Patients with Different Final Chest Radiography Findings (post treatment)[a]

		Time			
Radiography Findings		**Baseline**	**Two Months After**	**Six Months After**	**P value < 0.05 Between Time of Tests**
Normal radiography	N = 9	185.51 ±25.46	150.28 ± 20.23	148.93 ± 34.41	(1 vs. 2 and 1 vs. 3)
Fibrotic residue	N = 15	211.45 ±55.60	162.00 ± 44.12	136.40 ± 20.90	(1 vs. 2, 1 vs. 3, and 2 vs. 3)
Statistic		T = 1.31; P = 0.2	Z = 0.59; P = 0.55	Z = 1.13; P = 0.26	(1 vs. 2, 1 vs. 3, and 2
Total	N = 24	201.72 ± 47.66	157.61 ± 36.89	141.10 ± 26.67	vs. 3)

[a]Values are expressed as mean ± SD.

words, the relative frequencies of restrictive, obstructive, and restrictive-obstructive patterns in Tanzania were respectively 13%, 42%, and 19% (18), while the frequencies of restrictive, obstructive, and normal patterns in the present study were 50%, 33.3%, and 26.7%, respectively. A study in the United States also showed that 59% of spirometry patterns after PTB treatment were abnormal, 31% of which were restrictive, 15% were obstructive, and 13% were restrictive-obstructive (19). The values from a study done in Pakistan, on patients who suffered from dyspnea after PTB treatment, were 29%, 55%, and 7% (20). High prevalence of abnormal restrictive and obstructive spirometry patterns after PTB treatment is a finding of paramount importance.

The type of post-treatment pulmonary disorders depends on the types of degenerative changes in the lung, in that fibrotic changes can reduce lung compliance and cause restrictive pattern, while degenerative changes, which are due to protease activation and anti-protease deficiency, can reduce lung elasticity and cause air trapping with obstructive pattern. However, objective evidence for this hypothesis was not found in the present study. In other words, there were no significant differences between patients with fibrotic changes and patients with normal chest radiography, respecting the rates of restrictive and obstructive spirometry patterns. Similarly, the serum antitrypsin level among patients with different abnormal spirometry patterns did not significantly differ from that of patients with normal spirometry pattern. Of course, patients with obstructive spirometry pattern had slightly lower antitrypsin level than those with restrictive pattern, though this difference was not significant. However, as 1% - 5% of patients with COPD suffer from antitrypsin deficiency (21), no increase in antitrypsin level during lung tissue inflammation can be considered as a predictor of obstructive disease, while antitrypsin increase can be a predictor of fibrotic changes. Further studies with larger samples of patients are still needed to determine the cutoff point of antitrypsin and the effects of serum antitrypsin on pulmonary function.

4.1. Study Limitations

The most important limitation of the present study was the lack of eligible patients for producing more credible results despite the 2-year extension of the study.

4.2. Conclusions

As an acute-phase protein, antitrypsin can be used for the follow-up assessment of response to treatment among PTB patients. Large-scale studies can produce more credible results respecting the power of antitrypsin in predicting pulmonary fibrotic changes and functional disorders.

Acknowledgments

We would like to thank the staff of both Shafa laboratory and tuberculosis care center, Birjand, Iran, particularly Mr. Salari. We also acknowledged the financial support of this study by the Research Administration of Birjand University of Medical Sciences, Birjand, Iran.

References

1. Chakaya J, Kirenga B, Getahun H. Long term complications after completion of pulmonary tuberculosis treatment: A quest for a public health approach. *J Clin Tuberculosis Other Mycobacterial Dis*. 2016;**3**:10–2. doi: 10.1016/j.jctube.2016.03.001.
2. Hassan IS, Al-Jahdali HH. Obstructive airways disease in patients with significant post- tuberculous lung scarring. *Saudi Med J*. 2005;**26**(7):1155–7. [PubMed: 16047080].
3. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, Gold Scientific Committee . Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med*. 2001;**163**(5):1256–76. doi: 10.1164/ajrccm.163.5.2101039. [PubMed: 11316667].
4. Chakrabarti B, Calverley PM, Davies PD. Tuberculosis and its incidence, special nature, and relationship with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2007;**2**(3):263–72. [PubMed: 18229564].
5. Yakar HI, Gunen H, Pehlivan E, Aydogan S. The role of tuberculosis in COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;**12**:323–9. doi: 10.2147/COPD.S116086. [PubMed: 28176901].
6. Caballero A, Torres-Duque CA, Jaramillo C, Bolivar F, Sanabria F, Osorio P, et al. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). *Chest*. 2008;**133**(2):343–9. doi: 10.1378/chest.07-1361. [PubMed: 17951621].
7. MacNee W. Pathogenesis of chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2005;**2**(4):258–66. discussion 290-1. doi: 10.1513/pats.200504-045SR. [PubMed: 16267346].
8. Welle I, Bakke PS, Eide GE, Fagerhol MK, Omenaas E, Gulsvik A. Increased circulating levels of alpha1-antitrypsin and calprotectin are associated with reduced gas diffusion in the lungs. *Eur Respir J*. 2001;**17**(6):1105–11. [PubMed: 11491151].
9. McCarthy C, Saldova R, Wormald MR, Rudd PM, McElvaney NG, Reeves EP. The role and importance of glycosylation of acute phase proteins with focus on alpha-1 antitrypsin in acute and chronic inflammatory conditions. *J Proteome Res*. 2014;**13**(7):3131–43. doi: 10.1021/pr500146y. [PubMed: 24892502].
10. Lomas DA. Does Protease-Antiprotease Imbalance Explain Chronic Obstructive Pulmonary Disease?. *Ann Am Thorac Soc*. 2016;**13 Suppl 2**:S130–7. doi: 10.1513/AnnalsATS.201504-196KV. [PubMed: 27115947].
11. Ong CW, Elkington PT, Friedland JS. Tuberculosis, pulmonary cavitation, and matrix metalloproteinases. *Am J Respir Crit Care Med*. 2014;**190**(1):9–18. doi: 10.1164/rccm.201311-2106PP. [PubMed: 24713029].
12. Navratilova Z, Kolek V, Petrek M. Matrix Metalloproteinases and Their Inhibitors in Chronic Obstructive Pulmonary Disease. *Arch Immunol Ther Exp (Warsz)*. 2016;**64**(3):177–93. doi: 10.1007/s00005-015-0375-5. [PubMed: 26611761].
13. Khara NV, Patel BM, Kshatriya RM, Patel SN, Paliwal RP. Post TB Pulmonary Disability: An Ongoing Challenge for India. *Nat J Med Res*. 2016;**6**(3):247–50.
14. Grange JM, Kardjito T, Setiabudi I. A study of acute-phase reactant proteins in Indonesian patients with pulmonary tuberculosis. *Tubercle*. 1984;**65**(1):23–39. [PubMed: 6428016].
15. Janciauskiene SM, Bals R, Koczulla R, Vogelmeier C, Kohnlein T, Welte T. The discovery of alpha1-antitrypsin and its role in health and disease. *Respir Med*. 2011;**105**(8):1129–39. doi: 10.1016/j.rmed.2011.02.002. [PubMed: 21367592].
16. Matalon S, Elad H, Brazowski E, Santo E, Tulchinsky H, Dotan I. Serum alpha-1 antitrypsin: a noninvasive marker of pouchitis. *Inflamm Bowel Dis*. 2015;**21**(3):589–95. doi: 10.1097/MIB.0000000000000308. [PubMed: 25659085].
17. de Serres F, Blanco I. Role of alpha-1 antitrypsin in human health and disease. *J Intern Med*. 2014;**276**(4):311–35. doi: 10.1111/joim.12239. [PubMed: 24661570].
18. Manji M, Shayo G, Mamuya S, Mpembeni R, Jusabani A, Mugusi F. Lung functions among patients with pulmonary tuberculosis in Dar es Salaam - a cross-sectional study. *BMC Pulm Med*. 2016;**16**(1):58. doi: 10.1186/s12890-016-0213-5. [PubMed: 27107713].
19. Pasipanodya JG, Miller TL, Vecino M, Munguia G, Garmon R, Bae S, et al. Pulmonary impairment after tuberculosis. *Chest*. 2007;**131**(6):1817–24. doi: 10.1378/chest.06-2949. [PubMed: 17400690].
20. Baig IM, Saeed W, Khalil KF. Post-tuberculous chronic obstructive pulmonary disease. *J Coll Physicians Surg Pak*. 2010;**20**(8):542–4. [PubMed: 20688021].
21. Marciniuk DD, Hernandez P, Balter M, Bourbeau J, Chapman KR, Ford GT, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. *Can Respir J*. 2012;**19**(2):109–16. [PubMed: 22536580].