

Evaluation of Serum Adenosine Deaminase Levels as Diagnostic Marker in Pulmonary and Extra Pulmonary Tuberculosis Cases

Asia Omar¹, Md. Shams Tabrez², Sude Kumar Singh³, Ajit Kumar⁴, Shankar Dayal Singh⁵, Abu Nafe⁶

ABSTRACT

Introduction: There is growing interest in developing biochemical tests that measure the body's metabolic reaction in tuberculosis (TB) infection. Both pulmonary and extrapulmonary TB can be diagnosed using these tests, which seems to be an appealing approach. Adenosine deaminase (ADA), an enzyme involved in purine breakdown, is present in T lymphocytes. It has been shown that tuberculosis leads to elevation in the T lymphocytes and eventually causes an elevation in ADA activity. Aim: To evaluate the diagnostic potential of serum ADA concentration in detecting pulmonary and extra pulmonary tuberculosis cases.

Methods and Materials: For this study, 336 patients in a variety of age groups who were admitted were chosen. In this investigation, 112 patients of pulmonary tuberculosis were considered. This study comprised 112 cases of extrapulmonary TB in total. This study comprised 112 control volunteers who were matched for age and sex. 46 of them served as healthy controls for this study; they had a normal skiagram chest, no previous history of pulmonary or extrapulmonary tuberculosis, and no other chronic illnesses. This study includes 66 diseased controls with empyema, pneumonia, and cancer were included. ADA was calculated using a commercial ADA-MTB kit produced by Tulip Diagnostics (P) Ltd.'s MICROXPRESS division.

Results: Mean Serum ADA concentration was 45.78±3.33 IU/L, 27.31±4.21 IU/L and 14.43± 1.84 in pulmonary TB participants, diseased controls and healthy controls respectively. Mean Serum ADA concentration was 44.74±3.12 IU/L, 29.95±3.64 IU/L and 14.42 ±1.86 in extra pulmonary TB participants, diseased controls and healthy controls respectively. It was observed that serum ADA was significantly greater in pulmonary TB and extra pulmonary TB study participants as compared to disease controls and healthy controls. (p<0.05). The overall accuracy was 95.32% in detecting pulmonary tuberculosis. The overall accuracy was 94.16% in detecting pulmonary tuberculosis. Fischer exact revealed statistically significant diagnostic ability of serum ADA concentration in identification of pulmonary TB and extra pulmonary TB.

Conclusion: Serum ADA concentration can be important diagnostic tool in identification of pulmonary TB and extra pulmonary TB.

Keywords: Serum Adenosine Deaminase, Pulmonary Tuberculosis, Extra Pulmonary Tuberculosis

their overall health.¹⁻³ The prompt diagnosis and treatment of tuberculosis (TB) is the top goal of successful TB management, according to the WHO framework assessment. However, the primary obstacle to successful TB management is the absence of defined diagnostic guidelines in the initial stages of TB infection.⁴⁻⁶ Because the clinical signs of tuberculosis can occasionally be incredibly ambiguous and nonspecific, an identification of the disease can be very easily overlooked. Sometimes the worry of discrimination prevents the elicitation of previous instances of contact.⁶⁻⁸

To monitor the efficaciousness of chemotherapy and to stop the disease from spreading further, an accurate identification of the tuberculosis is necessary.^{9,10} Even though sputum assessment is regarded as the "gold standard" and is a straightforward and reasonably quick method of identifying the presence of TB, its efficacy is reduced because accurate diagnosis requires in excess of ten bacilli per milliliter of sputum.¹¹⁻¹³ Sputum recuperation is challenging in cases of childhood TB and doesn't constitute the best specimen in cases of extrapulmonary TB. Many efforts have been undertaken to use diverse modern strategies to increase the accuracy and rapidity of tubercle bacilli or their ingredient identification. However, there are cost or responsiveness limitations on all of these tests.¹⁴⁻¹⁶

Furthermore, newer methods are harder to come by and need trained people, both of which are impractical in underdeveloped nations. Not all patients are willing to undergo an intrusive procedure for obtaining a specimen, which is necessary for an accurate identification of extrapulmonary tuberculosis.¹⁷⁻¹⁹ For patients who visit hospitals, a precise and quick diagnosis is therefore necessary. As a result, there

¹Final year PG, Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, ²Final year PG, Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, ³Professor. & HEAD, Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, ⁴Second year PG, Dept. of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, ⁵First year PG, Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, ⁶Associate Professor, Department of Periodontics and Implantology, M.M.Dental College and Hospital, Darbhanga

Corresponding author: Dr Asia Omar, Final year PG, Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga

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INTRODUCTION

One of the most ancient and pervasive infectious illnesses, tuberculosis is wreaking havoc on public well-being and posing problems for emerging nations' economies as well as

is growing interest in creating tests that measure the body's metabolic reaction to tuberculosis infection. Both pulmonary and extrapulmonary tuberculosis can be diagnosed using these tests, which seems to be an appealing approach.²⁰⁻²² An indirect biochemical measurement is used to estimate the enzyme activity of adenosine deaminase in serum.

It has been shown that TB leads to elevation in the T cell population. Additionally, ADA, an enzyme involved in purine breakdown, is present in lymphocytes (10 times more than erythrocytes) and eventually causes an elevation in ADA activity.¹⁹⁻²² ADA activity has previously been investigated in tubercular meningitis (TBM), tubercular lymphadenitis, and tubercular pleural fluid; Results indicated ninety percent to hundred percent diagnostic accuracy as well as sensitivity for tuberculosis. ADA activity is quite easy to measure. It is a quick diagnostic test for tuberculosis early identification.²³⁻²⁵ It can distinguish TBM from pyogenic meningitis and other CNS illnesses, in addition to distinguishing pulmonary tuberculosis from other infections of the lower respiratory tract. Conversely, hardly much research has been done on ADA.²⁴⁻²⁷

This study has been carried out to evaluate the potential of serum biochemical marker ADA in detecting pulmonary and extra pulmonary tuberculosis cases

MATERIALS AND METHOD

This investigation was a case-control, observational, non-interventional study. Ethical clearance was obtained from the institutional ethical committee before starting the study.

Requirements for inclusion:

For this study, 336 patients in a variety of age groups who were admitted to a tertiary care hospital were chosen. In this investigation, 112 instances of pulmonary tuberculosis were considered. The sputum from each of these instances tested positive for acid fast bacilli (AFB). This study comprised 112 cases of extra-pulmonary TB in total. Included were 41 cases of tubercular meningitis, identified by positive CSF microscopy results or positive AFB cultures. Based on either positive pleural fluid microscopy or positive pleural fluid culture for AFB, 35 instances of tubercular pleural effusion were included.

This study also included 36 patients with tubercular lymphadenitis based on the results of their cytology. This study comprised 112 control volunteers who were matched for age and sex. 46 of them served as healthy controls for this study; they had a normal skiagram chest, no previous history of pulmonary or extrapulmonary tuberculosis, and no other chronic illnesses. This study includes 66 diseased controls with comparable clinical characteristics. 66 age- and sex-matched diseased controls with empyema, pneumonia, and cancer were included.

Exclusion criteria

The following conditions were excluded from this study: extensive muscle injury, infectious mononucleosis, diabetes mellitus, chronic malnutrition, kidney diseases, organ transplantation, typhoid, leprosy, lymphocytic lymphoma,

Q fever pneumonia, and corticosteroid treatment. Samples of blood and bodily fluids are collected, processed, and stored.

Estimation of serum ADA

ADA was calculated using a commercial ADA-MTB kit produced by Tulip Diagnostics (P) Ltd.'s MICROXPRESS division. Fundamental: Adenosine is hydrolyzed to produce ammonia and isosine by adenosine deaminase. Sodium nitroprusside serves as a catalyst when the ammonia generated subsequently combines with phenol and hypochlorite in an alkaline solution to generate a blue indophenol complex. The quantity of ADA contained in the sample is directly correlated with the intensity of the blue-colored indophenol complex that forms.

STATISTICAL ANALYSIS

SPSS 17.0 was used for the analysis, and a 5% significance threshold was applied to the findings. Findings were presented in the form of means, standard deviation, standard error mean, percentages. Z-Test and Fisher's Exact Test was used for statistical analysis. p value ≤ 0.05 was taken as statistically significant.

RESULTS

112 study participants with diagnosis of pulmonary tuberculosis, 112 study participants with diagnosis of extra pulmonary tuberculosis, 66 age and gender matched disease controls including patient having no history of pulmonary or extra pulmonary TB, but suffering from empyema, pneumonia, and cancer, 46 age and gender matched healthy controls with no history of any disease including pulmonary or extra pulmonary TB.

The mean age of study participants was 43.39 ± 8.34 years, 43.13 ± 9.25 years, 44.41 ± 8.01 years and 43.16 ± 8.67 years in pulmonary TB participants, extra pulmonary TB participants, diseased controls and healthy controls respectively. There was no statistically significant difference in age of study participants in different categories. ($p > 0.05$). M:F was 1:1, 1:0.95, 1:1.05 and 1:1 in pulmonary TB participants, extra pulmonary TB participants, diseased controls and healthy controls respectively. There was no statistically significant difference in M:F of study participants in different categories. ($p > 0.05$). (table 1)

Mean Serum ADA concentration was 45.78 ± 3.33 IU/L, 27.31 ± 4.21 IU/L and 14.43 ± 1.84 in pulmonary TB participants, diseased controls and healthy controls respectively. It was observed that serum ADA was significantly greater in pulmonary TB study participants as compared to disease controls. ($p < 0.05$). The mean serum ADA concentration was maximum in pulmonary TB participants, while it was minimum in healthy controls. The serum ADA was significantly greater in pulmonary TB study participants as compared to healthy controls also ($p < 0.05$). (table 2).

Mean Serum ADA concentration was 44.74 ± 3.12 IU/L, 29.95 ± 3.64 IU/L and 14.42 ± 1.86 in extra pulmonary TB participants, diseased controls and healthy controls

Group	Pulmonary TB	Extra pulmonary TB	Disease Controls	Healthy Controls
No.	112	112	66	46
Age (Mean ±SD) years	43.39 ± 8.34	43.13 ± 9.25	44.41 ± 8.01	43.16 ± 8.67
z-value	5.41			
p-value	p > 0.05			
M:F	1:1	1:0.95	1:1.05	1:1
z-value	6.53			
p-value	p > 0.05			

Table-1: Demographic details of study participants

Group	Pulmonary TB	Disease Controls	Healthy Controls
No.	112	66	46
Mean	45.78	27.31	14.43
Std. Deviation	3.33	4.21	1.84
Std. Error Mean	0.34	1.24	0.33
z-value	12.30		
p-value	p < 0.05		

Table-2: Comparison of concentration Serum ADA in pulmonary tuberculosis cases, disease controls and healthy controls

	Pulmonary TB	Disease Controls	Healthy Controls
No.	112	66	46
Mean	44.74	29.95	14.42
Std. Deviation	3.12	3.64	1.86
Std. Error Mean	0.31	1.16	0.55
z-value	-	16.12	42.31
p-value	-	p < 0.05	p < 0.05

Table-3: Comparison of concentration Serum ADA in extra pulmonary tuberculosis cases, disease controls and healthy controls

	Pulmonary tuberculosis	Extra-pulmonary tuberculosis (n=112)		
		Tubercular pleural effusion (TPE)	Tubercular meningitis (TBM)	Tubercular lymphadenitis (TLN)
No assayed	112	35	41	36
No showing ADA levels above 40 IU/L	105 (93.75%)	33 (94.28%)	39 (95.12%)	34 (94.45%)

Table-4: Detection potential of serum ADA in pulmonary and extra pulmonary tuberculosis

	Disease control n=66	Lung malignancy (LM)	Pneumonia (PN)	Viral meningitis (VM)	Reactive lymphadenitis (RLN)	Healthy controls N= 46
No assayed	11	11	12	17	15	46
No showing ADA levels above 40 IU/L	2 (18.18%)	0 (0.00%)	0 (0.00%)	2 (11.76%)	2 (13.33%)	0 (0.00)

Table-5: Detection potential of serum ADA in disease control and healthy controls

	Sensitivity	Specificity	PPV	NPV	LR	Accuracy	Fisher's Exact Test
Pulmonary TB	95.10	97.36	97.16	91.93	32.81	95.32	p < 0.0001
Extra pulmonary TB	95.21	94.32	94.21	94.31	15.49	94.16	p < 0.0001

PPV: Positive predictive value, NPV: Negative predictive value, LR: Likelihood ratio

Table-6: Diagnostic parameters of serum ADA in detection of pulmonary and extra pulmonary TB

respectively. It was observed that serum ADA was significantly greater in extra pulmonary TB study participants as compared to disease controls. ($p < 0.05$). The mean serum ADA concentration was maximum in extra pulmonary TB participants, while it was minimum in healthy controls. The serum ADA was significantly greater in extra pulmonary TB study participants as compared to healthy controls also ($p < 0.05$). (table 3)

Using a 2X2 table in pulmonary TB and extra pulmonary TB and a 40 IU/L concentration of ADA as the detection cutoff, we assessed the potential for serum ADA detection. It was observed that 105 (93.75%) participants with pulmonary tuberculosis showed ADA levels above 40 IU/L. In extra pulmonary cases, 33 (94.28%) study participants with tubercular pleural effusion showed ADA levels above 40 IU/L, 39 (95.12%) study participants with Tubercular meningitis showed ADA levels above 40 IU/L, 34 (94.45%) study participants with Tubercular lymphadenitis showed ADA levels above 40 IU/L. (table 4)

Only 2 (18.18%) cases of emphysema, 2 (11.76%) cases of viral meningitis and 2 (13.33%) under disease control group showed ADA levels above 40 IU/L. While none of the cases of lung malignancy, pneumonia and healthy control showed ADA levels above 40 IU/L. (table 5). (table 5)

The sensitivity of serum ADA in detecting pulmonary TB was 95.10%. The specificity was 97.36%, PPV was 97.16%, NPV was 91.93%, LR was 32.81 and overall accuracy was 95.32% in detecting pulmonary tuberculosis. The sensitivity of serum ADA in detecting pulmonary TB was 95.21%. The specificity was 94.32%, PPV was 94.21%, NPV was 94.31 %, LR was 15.49 and overall accuracy was 94.16% in detecting pulmonary tuberculosis. Fischer exact revealed statistically significant diagnostic ability of serum ADA concentration in identification of pulmonary TB and extra pulmonary TB. (table 6).

DISCUSSION

Millions of individuals have lost their lives to TB. The tubercle bacillus still kills more people than any other infectious agent, even with the availability of the Bacilli Calmette Guerin (BCG) vaccination and efficient short-course chemotherapy (DOTS).⁴⁻⁷ Examinations include cytological, radiographic, bacteriological, and clinical tests are crucial in the diagnosis of tuberculosis. Limitations of direct microscopy of sputum for bacilli include insensitivity, lack of utility in extra-pulmonary TB, and challenge in obtaining sputum sample in pediatric tuberculosis cases.⁸⁻¹¹ The culture process is labor-intensive, time-consuming, and prone to contamination. Biochemical markers don't require specialist laboratory equipment and are simple, inexpensive, and faster to perform.¹²⁻¹⁴ In order to assess serum ADA's potential for detection in cases of pulmonary and extrapulmonary tuberculosis, we assessed it in this study. In this study, 112 study participants with diagnosis of pulmonary tuberculosis, 112 study participants with diagnosis of extra pulmonary tuberculosis, 66 age and gender matched disease controls including patient having no

history of pulmonary or extra pulmonary TB, but suffering from empyema, pneumonia, and cancer, 46 age and gender matched healthy controls with no history of any disease including pulmonary or extra pulmonary TB.

The mean age of study participants was 43.39 ± 8.34 years, 43.13 ± 9.25 years, 44.41 ± 8.01 years and 43.16 ± 8.67 years in pulmonary TB participants, extra pulmonary TB participants, diseased controls and healthy controls respectively. There was no statistically significant difference in age of study participants in different categories. ($p > 0.05$). M:F was 1:1, 1:0.95, 1:1.05 and 1:1 in pulmonary TB participants, extra pulmonary TB participants, diseased controls and healthy controls respectively. There was no statistically significant difference in M:F of study participants in different categories

The majority of mammalian tissues naturally contain the enzyme adenosine deaminase (ADA; EC 3.5.4.4), with the maximum activity found in organs that contain several lymphoid tissues.¹⁴⁻¹⁶ Although it is widely distributed throughout the human body, lymphoid tissue has a particularly significant physiological role for it. Its concentration in lymphocytes is ten times greater than that of erythrocytes, especially in T lymphocytes, though it varies depending on the stage of cellular differentiation.¹⁷⁻¹⁹ Adenosine deaminase, or ADA as Spencer referred to it, is a purine catabolism enzyme. Adenosine is hydrolytically cleaved irreversibly by ADA, yielding inosine and ammonia.²⁰⁻²³

Mean Serum ADA concentration was 45.78 ± 3.33 IU/L, 27.31 ± 4.21 IU/L and 14.43 ± 1.84 in pulmonary TB participants, diseased controls and healthy controls respectively. It was observed that serum ADA was significantly greater in pulmonary TB study participants as compared to disease controls. ($p < 0.05$). The serum ADA was significantly greater in pulmonary TB study participants as compared to healthy controls also ($p < 0.05$).

The results of this study are having similarity with the findings of studies by Conde MB et al²⁰, Dilmaç A et al²¹, Rasooli Nejad M et al²². They also found that serum ADA was significantly greater in pulmonary TB study participants as compared to disease controls

Increased blood ADA levels were also discovered in patients with non-tubercular pulmonary illnesses and pulmonary tuberculosis by Agarwal MK et al¹⁴ and Jhamaria JP et al¹³. However, compared to non-tubercular pulmonary illnesses, the rise in blood ADA level was significantly greater in patients of pulmonary tuberculosis.¹³⁻¹⁵ For the same rationale as was previously mentioned in the case of pulmonary tuberculosis, we also noticed significantly higher serum ADA activity in instances of extra pulmonary tuberculosis (EPTB) when compared to healthy controls.¹⁶⁻¹⁹ Mean Serum ADA concentration was 44.74 ± 3.12 IU/L, 29.95 ± 3.64 IU/L and 14.42 ± 1.86 in extra pulmonary TB participants, diseased controls and healthy controls respectively. It was observed that serum ADA was significantly greater in extra pulmonary TB study participants as compared to disease controls and healthy controls.

Our results were similar to those observed in previous studies

carried out by Jhamaria JP et al¹³ and Agarwal MK et al¹⁴. They also found that serum ADA was significantly greater in extra pulmonary TB study participants.

Using a 2X2 table in pulmonary TB and extra pulmonary TB and a 40 IU/L concentration of ADA as the detection cutoff, we assessed the potential for serum ADA detection. It was observed that 105 (93.75%) participants with pulmonary tuberculosis showed ADA levels above 40 IU/L. In extra pulmonary cases, 33 (94.28%) study participants with tubercular pleural effusion showed ADA levels above 40 IU/L, 39 (95.12%) study participants with Tubercular meningitis showed ADA levels above 40 IU/L, 34 (94.45%) study participants with Tubercular lymphadenitis showed ADA levels above 40 IU/L.

The findings of present study are in accordance with the findings of previous studies by Agarwal MK et al¹⁴, Jhamaria JP et al¹³ and Stevanovic G et al¹⁵ who also found major proportion of patients of pulmonary TB and extra pulmonary TB showed ADA levels above 40 IU/L.

In our study, the sensitivity of serum ADA in detecting pulmonary TB was 95.10%. The specificity was 97.36% and overall accuracy was 95.32% in detecting pulmonary tuberculosis. The sensitivity of serum ADA in detecting pulmonary TB was 95.21%. The specificity was 94.32% and overall accuracy was 94.16% in detecting pulmonary tuberculosis. Fischer exact revealed statistically significant diagnostic ability of serum ADA concentration in identification of pulmonary TB and extra pulmonary TB.

Some of the studies like Gupta BK et al¹⁹ also found sensitivity of ADA in detecting pulmonary TB and extra pulmonary TB similar to that observed in our study. These studies found overall accuracy of ADA in detecting pulmonary TB and extra pulmonary TB similar to that observed in our study.

The present global tuberculosis epidemic, especially in developing nations, has highlighted the need for more affordable and efficient diagnostic methods. The two most often used techniques for diagnosing tuberculosis in impoverished countries, acid fast stain and X-ray, are ineffective in identifying paucibacillary and extrapulmonary tuberculosis.²⁰⁻²⁴ According to our findings, measuring serum Adenosine deaminase (ADA) has a good potential for detecting PTB and EPTB. To generalize the findings of this study, however, further research of this kind must be done in other settings and with a variety of populations.²⁵⁻²⁷

CONCLUSION

Serum ADA concentration can be important diagnostic tool in identification of pulmonary TB and extra pulmonary TB.

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