

Changes of serum adenosine deaminase level in new cases of pulmonary tuberculosis before and after intensive phase treatment

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ABSTRACT

Background and Objectives: Tuberculosis (TB) continues to be a public health crisis with an estimated 10 million people developing TB disease in 2017. Adenosine deaminase (ADA) level in serum and pleural fluid as a biomarker may be used to diagnose pulmonary TB (PTB), but it is not always easy to obtain those samples at the end of treatment. This study was conducted to analyze the changes of serum ADA level in the new case of PTB patients with acid-fast bacilli (AFB) smear-positive sputum and sputum conversion status as treatment monitoring in PTB patients. **Materials and Methods:** This was a prospective observational analytic study conducted in Dr. Soetomo General Hospital, Surabaya, from January 2018 to May 2018. Participants were all new cases of PTB patients with AFB smear-positive sputum, and a positive rapid molecular test for *Mycobacterium tuberculosis*. Blood serums were taken at the same time on the 1st day of TB treatment and also taken at the end of intensive phase treatment to analyze the changes of serum ADA level. **Results:** There were 26 TB patients and 26 healthy control people. Serum ADA level at the beginning of TB treatment was higher than the level at the end of intensive phase treatment. There was a significant difference between serum ADA level before and after the intensive phase of TB treatment ($P < 0.001$). **Conclusions:** The examination of serum ADA levels can be used to evaluate the PTB treatment response.

KEY WORDS: Pulmonary tuberculosis, serum adenosine deaminase, sputum conversion

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INTRODUCTION

Tuberculosis (TB) is a major health problem with an estimated 10 million people having developed TB disease causing 1.3 million deaths in 2017. Indonesia was ranked third high TB burden country in 2017 with 842,000 TB cases.^[1] Acid-fast bacilli (AFB) and culture

of *Mycobacterium tuberculosis* from sputum samples were commonly used for TB diagnosis and monitoring. The culture of *M. tuberculosis* has better sensitivity and specificity than smear examination.^[2,3] However, the time needed to obtain culture results is around

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8 weeks^[4] which cause significant delays in diagnosis and starting treatment, also monitoring treatment response. Sputum conversion can be a strong prediction and an early indication of treatment success. There were different times for sputum conversion in every patient, even though treated with the same standard regimen. According to Rutta *et al.*, sputum conversion occurred in the 2nd month of intensive phase treatment. Sputum conversion in patients is also associated with predictions of antituberculosis drug (ATD) resistance.^[5] Meanwhile, some patients have problems from the beginning with the examination of sputum specimens, so that evaluation of therapy response monitoring is only based on clinical and chest X-ray series.

Adenosine deaminase (ADA) is an enzyme which plays a role in purine catabolism which catalyzes the conversion of adenosine to inosine and deoxyadenosine to deoxyinosine. The examination of ADA activity is fast, affordable, and has high sensitivity and specificity to be used as a supporting diagnosis of pulmonary TB (PTB).^[4] Elevated serum ADA levels in PTB patients conform to the severity of the disease, high bacterial isolation, and lung tissue damage. This suggests that ADA measurement is an additional criterion in assessing the response of TB treatment and is used as a prognosis in PTB patients.

Studies of serum ADA levels comparison in TB patients during TB treatment in Indonesia are limited. This study was conducted to analyze changes in serum ADA levels in new PTB cases with smear positive tuberculosis who experienced sputum conversion, so as to assess its utility as a possible treatment monitoring method in PTB.

MATERIAL AND METHODS

This was a prospective observational analytic study conducted in TB clinic Dr. Soetomo Hospital, Surabaya, from January 2018 to May 2018. All samples were taken from new PTB cases with sputum-positive smear with positive GeneXpert for *M. tuberculosis* that were put on treatment with standard WHO regimen at Dr. Soetomo Hospital. Sputum smear examination was done using Ziehl–Neelsen staining according to the WHO recommendation. AFBs identified were graded according to the International Union against Tuberculosis and Lung Disease and the WHO smear grading scale. Serum ADA levels were analyzed using the enzymatic colorimetric method, using Erba XL 600. Results of serum ADA levels of TB patients were analyzed and compared to serum ADA levels of healthy people. Participants of this study were healthy control people and PTB patients who agreed and signed written informed consent form. This study was approved by the Ethics Committee of Dr. Soetomo Hospital with ethical clearance number 0005/KEPK/I/2018 and was approved on January 22, 2018.

RESULTS

There were 26 new cases of TB patients with *M. tuberculosis* detected results and positive AFB, with mean age 42.85 years and 26 healthy control people with mean age 39.69 years. TB patients were 21/26 (80.8%) men and 5/26 (19.2%) women [Table 1].

All TB patients had sputum conversion and showed a decreased in serum ADA levels after the end of the intensive phase of TB treatment. Patients with AFB + 3 have a higher mean value of serum ADA level before and after the end of the intensive phase of TB treatment. After the end of intensive phase of TB treatment, serum ADA levels of TB patients with baseline AFB + 1 had the closer value (15.51 IU/L) to the serum ADA levels of healthy people (10.18 IU/L) [Table 2].

Mann–Whitney test showed that there was a significant difference in serum ADA levels of TB patients before and after the intensive phase of TB treatment, compared to healthy people with $P < 0.001$ [Table 3].

All patients experienced sputum conversion after the intensive phase of TB treatment. Examination of serum ADA levels showed that the mean value of serum ADA levels before treatment was higher than after receiving ATDs with (26.40 IU/L vs. 19.67 IU/L). Paired *t*-test results showed a significant difference in serum ADA levels before and after the intensive phase of TB treatment with $P < 0.001$ [Table 4].

Table 5 shows that serum ADA levels of TB patients decreased after the intensive phase of TB treatment

Table 1: Profile of study participants

	TB patients (n=26), n (%)	Healthy control people (n=26), n (%)
Age (year), mean±SD	42.85±14.66	39.69±8.21
Gender		
Men	21 (80.8)	25 (96)
Women	5 (19.2)	1 (4)

SD: Standard deviation, TB: Tuberculosis

Table 2: Serum adenosine deaminase levels before and after the end of the intensive phase of tuberculosis treatment

	Mean±SD (IU/L)
AFB+1 before treatment (n=8)	
Baseline test	19.99±5.267
After the end of intensive phase	15.51±4.630
AFB+2 before treatment (n=9)	
Baseline test	24.44±8.085
After the end of intensive phase	19.02±7.360
AFB+3 before treatment (n=9)	
Baseline test	34.04±9.400
After the end of intensive phase	24.02±9.693
Healthy people (n=26)	10.18±2.39

SD: Standard deviation, AFB: Acid-fast bacilli

implying that serum ADA levels decreased as patients were on TB treatment and the value of serum ADA levels became closer to the serum ADA levels of healthy people.

DISCUSSION

There were 26 TB patients in this study with an average age of 42.85 years from 21/26 (80.8%) men to 5/26 (19.2%) women. PTB is common in men, and this is due to the greater smoking habits in men increased risk of incident TB^[6] and the high mobility causes the high transmission.

All study participants before getting TB treatment showed positive AFB sputum and after receiving treatment for 2 months, all the study participants experienced smear sputum conversion. The success of treatment for PTB is directly related to the microbiological status of the sputum specimen of the patient during treatment. Sputum conversion has been widely reported as a predictor of treatment success.^[7,8]

Our study found that the highest mean value of serum ADA levels before TB treatment was among AFB + 3 with 34.04 IU/L, followed by AFB + 2 with 24.44 IU/L, and AFB + 1 with 19.99 IU/L. Previous study reported the same results that the mean value of serum ADA level was higher among 3+graded sputum-positive patients. This is due to the stimulation of cell-mediated immunity.^[9]

Table 3: The difference in serum adenosine deaminase test results of tuberculosis patients before and after the intensive phase of tuberculosis treatment compared to healthy people

Serum ADA levels	Median (minimum–maximum)	P*
Pre-TB treatment (n=26)	24.95 (10–56)	<0.001
Healthy people (n=26)	10.35 (7–18)	
Postintensive phase of TB treatment (n=26)	20.33 (10–44)	<0.001
Healthy people (n=26)	10.35 (7–18)	

*Mann–Whitney test. ADA: Adenosine deaminase, TB: Tuberculosis

Table 4: Differences in serum test results in tuberculosis patients before and after the intensive phase of tuberculosis treatment

Serum ADA levels	Mean±SD (IU/L)	P*
Pre (n=26)	26.40±9.619	<0.001
Post (n=26)	19.67±8.118	

*Pair t-test. ADA: Adenosine deaminase, SD: Standard deviation

Table 5: Differences in serum test results before and after the intensive phase of tuberculosis treatment compared to healthy people

Serum ADA levels	Mean±SD (IU/L)
TB patients before treatment (n=26)	26.40±9.619
TB patients after the intensive phase of TB treatment (n=26)	19.67±8.118
Healthy people (n=26)	10.18±2.39

ADA: Adenosine deaminase, TB: Tuberculosis, SD: Standard deviation

In this study, serum ADA levels increased in higher AFB load in sputum smears of TB patients. Serum ADA levels in PTB patients decreased by TB treatment and suggest that serum ADA levels can be used as a prognostic marker. Higher AFB sputum smear shows the severity of the disease based on the number of bacterial loads. Saini *et al.* stated that the average level of serum ADA levels increased significantly in PTB patients, although there was no statistically significant difference in the value of serum ADA levels related to the level of bacterial load on sputum smear.^[10] This shows that the measurement of ADA serum does not have a role in determining the bacteriological burden of the disease. A study by Pandey *et al.* reported that the increase in serum ADA levels along with the increase of the sputum AFB grading, and the increase in serum ADA level was caused by stimulation of cell mediated immunity.^[9]

All participants in this study experienced sputum conversion. The results of the examination of ADA serum levels after the end of the intensive phase of TB treatment have decreased. This indicates that examination of ADA serum levels can be used in monitoring TB therapy response. Kartaloglu *et al.* reported that there was a significant decrease in serum ADA levels in PTB patients who had received ATDs therapy after the intensive phase. There was an increase in serum ADA in the 1st month but decreased during treatment.^[11] ADA serum levels were expected to increase twice in PTB patients at the time of diagnosis and subsequently experienced a significant decrease in the mean value of ADA serum levels after treatment in PTB patients.^[12] ADA serum levels decreased to normal levels after 1 month of effective treatment in patients with PTB. A decrease in ADA serum levels can be caused by changes in the number of lymphocytes induced by *M. tuberculosis*.^[13] Significant differences were obtained in ADA serum activity before and after treatment, and also from older TB patients and healthy control patients, indicating that ADA serum activity was increased in PTB patients.^[14]

Serum ADA levels decreased during TB treatment, although there is a significant difference, compared to serum ADA levels in healthy people with $P < 0.001$ [Table 3], this is because the TB treatment is not completed yet till the end of continuation phase. It was shown that after the end of intensive phase of TB treatment, serum ADA levels decreased and reached closer to the mean value of serum ADA levels in healthy people (19.67 IU/L after the end of the intensive phase of TB treatment and 10.18 IU/L in healthy people) as presented in Table 5.

In this study, the mean serum ADA levels in PTB patients before receiving TB treatment was 26.40 IU/L and decreased during PTB treatment with serum ADA levels of 19.67 IU/L. Paired *t*-test showed a significant difference in serum ADA levels before TB treatment and after the end of the intensive phase of TB treatment with $P < 0.001$. These data suggests that ADA measurement is an additional marker in assessing therapy response or

treatment monitoring in PTB patients. Rao *et al.* reported the decrease in serum ADA levels during PTB treatment. Serum ADA levels showed a significant difference between serum ADA levels before and after the 2nd month of TB treatment with $P < 0.001$ (41.48 U/L vs. 29.66 U/L). The measurement of serum ADA could help the evaluation of therapy response.^[15] Other study reported the same results that serum ADA levels decreased during TB treatment.^[16,17]

Changes of serum ADA levels can be used as a therapeutic response marker. Serial examination of serum ADA levels can be used to monitor therapy response of TB treatment, especially in patients with negative sputum microscopic examination results. The future study was needed by measuring the serum ADA levels at the baseline before therapy and followed up till the end of TB treatment.

CONCLUSIONS

The mean value of serum ADA levels was significantly decreased after the end of the intensive phase of TB treatment. The examination of serum ADA levels can be used to evaluate the response of PTB treatment.

Limitations of the study

The present study had several limitations. TB diagnosis is based on GeneXpert and AFB microscopy examination. The culture of *M. tuberculosis* as a gold standard for TB diagnosis was not used. Furthermore, sputum conversion in only based on AFB microscopy examination, not with serial culture.

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Conflicts of interest

There are no conflicts of interest.

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