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A correlative study of serum adenosine deaminase (ADA) and liver function test (LFT) in untreated and treated patients of pulmonary tuberculosis

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Abstract
Aim and Objective: Correlation between Adenosine Deaminase (ADA) and Liver Function Tests in untreated and treated patients of pulmonary tuberculosis.
Introduction: Tuberculosis as a chronic granulomatous disease caused by Mycobacterium tuberculosis usually affects the lungs but all other system as well. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary tuberculosis.
Material and Method: Detailed data was collected regarding age, sex, socioeconomic status & history of the disease etc. Serum Adenosine Deaminase activity and Liver function test was determined by standard method after taking sample from subjects.
Result and discussion: Among 50 healthy controls, there were 25 males (50%) and 25 females (50%), most of them in the age group (21-50) years. The mean serum ADA activity in control was observed to be 15.7 $\pm$ 4.43 U/L. No significant difference in serum ADA activity was observed in control subjects with respect to age and sex. In untreated phase, the serum ADA activity was observed significantly higher than healthy control (36.4 $\pm$ 16.9, $p<0.001$) and treated pulmonary tuberculosis patients too (19.4$\pm$ 4.92, $p<0.001$). The serum activities of the liver enzymes (SGOT, SGPT and ALP) were found significantly higher in treated patients compared to untreated patients of Pulmonary Tuberculosis (61.5$\pm$47.39 v/s 23.1 $\pm$ 7.1; 61.80 $\pm$ 46.97 v/s 28.03 $\pm$ 8.04; 157.9 $\pm$ 67 v/s 91.1$\pm$ 21.10, $p<$ 0.001)respectively.
Conclusion: Thus, it can be concluded that serum ADA activity is increased in untreated patients of pulmonary tuberculosis and liver enzymes-ALT, AST and ALP activity increased in treated patients of pulmonary tuberculosis. No significant difference in activities of liver enzymes-ALT, AST and ALP in untreated cases of PTB and control subjects were found.

Keywords: Serum ADA, Pulmonary Tuberculosis, Liver function test.

Introduction
Globally, 9.4 million people are suffering from active tuberculosis (guidelines for national programmes, WHO, 2009). Tuberculosis as a chronic granulomatous disease caused by Mycobacterium tuberculosis usually affects the lungs but all other system as well. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary tuberculosis (Anthony *et al*; 2008) [1].
Signs of Tuberculosis include:

- Clubbing of the fingers or toes (in people with advanced disease)
- Swollen or tender lymph nodes in the neck or other areas
- Fluid around a lung (pleural effusion)
- Unusual breath sounds (crackles)

The diagnostic efficiency of serum ADA activity determination has been evaluated in cases of sputum negative culture positive patients of pulmonary tuberculosis who pose a problem of diagnosis in routine practice, when sputum smear results are negative. (Goldman L *et al.*, 2011) [2].

Drug induced liver injury may occur as a consequence of providing drug regimens and is a problem of increasing significance but has been a long standing concern in the treatment. Liver has a central role in drug metabolism and detoxification and is consequently vulnerable to injury (Suzuki Y *et al.*, 1999) [3].
Thus, this study was undertaken to correlate the levels of ADA and Liver function test in untreated and treated patients and their comparison with normal control subjects and to know the effectiveness of serum ADA in the prognosis of untreated and treated pulmonary tuberculosis patients.

Material and Method

Subject selection and study design: The study was conducted on 150 subjects of varying age groups and both male and female, out of which 50 were newly diagnosed pulmonary tuberculosis cases and 50 were those who have undergone anti-tuberculosis treatment and 50 were healthy control without any clinical symptom and disease.
This study was conducted in Department of Biochemistry, Pacific Medical College and Hospital, Udaipur. Subjects were selected from Department of T.B. and chest PMCH, Udaipur. The study is planned to carry out in two steps.

Physical examination: It includes age, sex, socioeconomic status & history of the disease etc.

Biochemical examination
Blood Collection: 5 ml of blood was collected in plain vials from subjects and serum samples were separated.
Following investigations were done in subjects of Experimental group and controls.

1. **Determination of Serum Adenosine Deaminase activity by kit reagents (supplied by Tulip diagnostics) on Semi autoanalyzer.**

Method: Colorimetric method (Guisti G., and Galanti B., 1969) [4]

2. **Determination of Liver function test**

- Estimation of Bilirubin
- Estimation of Alanine Aminotransferase (ALT)/ Serum Glutamate Pyruvate Transaminase (SGPT)
- Estimation of Aspartate aminotransferases (AST)/ Serum Glutamate Oxaloacetate Transaminase (SGOT)
- Estimation of Total protein
- Estimation of Serum Albumin
- Determination of serum globulin
- Estimation of serum Alkaline Phosphatase (ALP)

Method: The estimation of enzymes was carried out on fully automatic analyzer (MIURA 200).

Inclusion criterion for Pulmonary Tuberculosis

- Case diagnosed as 'new case' of tuberculosis: Possessing at least two sputum smear test positive for Acid Fast Bacilli; Radiographic abnormalities consistent with pulmonary tuberculosis.
- Patients treated with standard anti-tuberculosis treatment as per RNTCP (DOTS) regimen were categorized as treated patients.

Exclusion criterion for Pulmonary Tuberculosis

- Patients with extra pulmonary TB/or patients requiring surgical intervention were excluded.
- Drop out patients were also excluded from study group.
- Patients having liver abnormalities were also excluded.

Statically analysis: The data in this study is expressed as mean ± S.D. The statistical analysis was performed using analysis of variance (ANOVA) test which is confined not only for comparing two sample means, but more than two samples drawn from corresponding controls. $p < 0.001$ was considered as statistically significant.

Result and Discussion

Among 50 healthy controls, there were 25 males (50%) and 25 females (50%), most of them in the age group (21-50) years. The mean serum ADA activity in control was observed to be 15.7 ± 4.43 U/L. No significant difference in serum ADA activity was observed in control subjects with respect to age and sex.

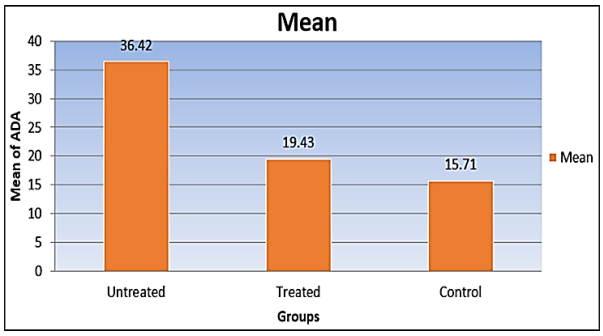

Fig 1: Change in serum ADA activity between Control, Untreated, Treated groups by ANOVA test

In untreated phase, the serum ADA activity was observed significantly higher than healthy control (36.4 ± 16.9, $p<0.001$) and treated pulmonary tuberculosis patients too (19.4± 4.92, $p<0.001$) as shown in figure 1
There is statistically significant difference in liver function test of untreated and treated patients of PTB compared to control. The serum activities of the liver enzymes (SGOT, SGPT and ALP) were found significantly higher in treated patients compared to untreated patients of Pulmonary Tuberculosis (61.5±47.39 v/s 23.1 ± 7.1; 61.80 ± 46.97 v/s 28.03 ± 8.04; 157.9 ± 67 v/s 91.1± 21.10, $p<$ 0.001)respectively (fig:2,fig:3,fig:4).

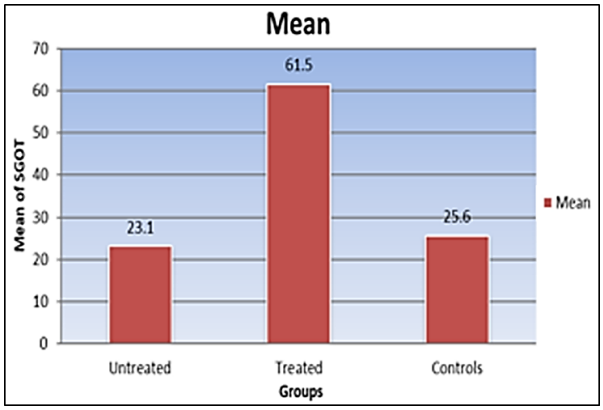

Fig 2: Change in serum SGOT activity between Control, Untreated, Treated groups by ANOVA test

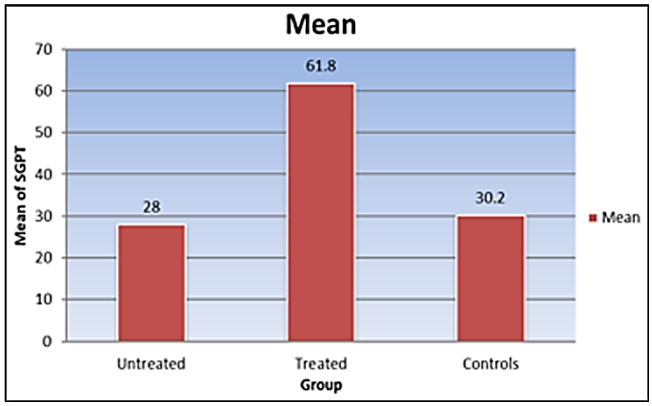

Fig 3: Change in serum SGPT activity between Control, Untreated, Treated groups by ANOVA test

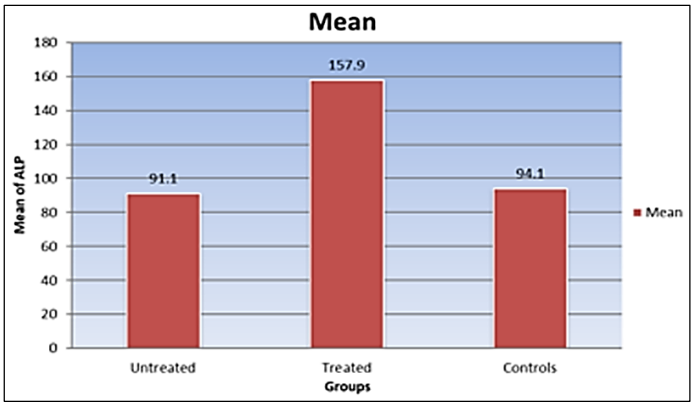

Fig 4: Change in serum ALP activity between Control, Untreated, Treated groups by ANOVA test

No significant difference in activities of liver enzymes (SGOT, SGPT and ALP) in untreated cases of PTB and control subjects (23.1 ± 7.1 v/s 25.1 ± 6.5; 28.03± 8.04 v/s 30.27 ± 7.7; 91.1 ± 21.10 v/s 94.14± 27.5; p < 0.001)respectively were found (fig-2,fig-3,fig-4).

Pre-treatment serum total protein level was found to be significantly lower than both control (5.90 ± 1.1 v/s 6.53 ± 0.86; p< 0.001)as well as treated cases of PTB (5.90 ± 1.1 v/s 7.07 ± 0. 84; p<0.001). However in both cases and controls, pre-treatment values were within the acceptable levels for serum total protein.

There was no statistically significant variation in the level of serum albumin between untreated, treated cases and control subjects respectively (3.7 ± 0.85 v/s 3.8 ± 0.62 v/s 3.9 ± 0.54; p>0.05).

Statistical analysis of the results in control subjects and treated cases showed poor degree of negative correlation between ADA activity and Bilirubin. Henceforth, correlation was found to be not significant (p >0.05) while untreated cases showed negative correlation but was found to be statistically significant (p <0.05) (fig:5, fig:6, fig:7)

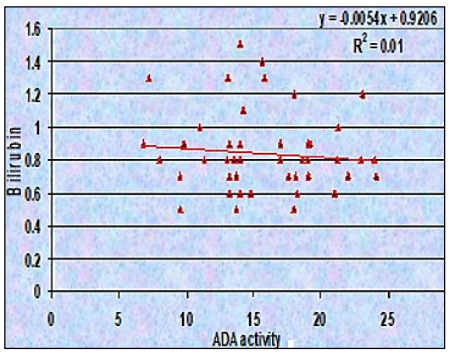

Fig 5: For controlled group

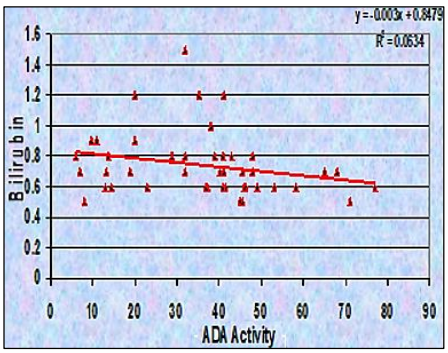

Fig 6: For untreated group

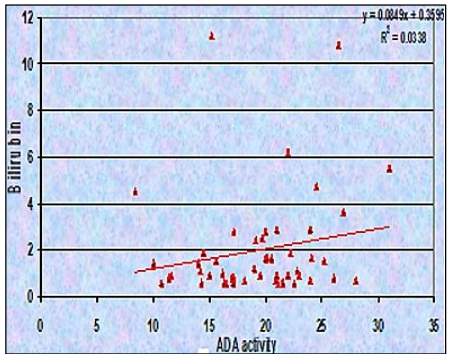

Fig 7: For treated group

No significant correlation between serum ADA and (SGOT, SGPT, TP) were found among untreated, treated cases and control subjects (p > 0.05)

Serum ADA activity was negatively correlated with albumin level and results were found to be statistically significant in treated cases of pulmonary tuberculosis (P < 0.05) (fig. 8).

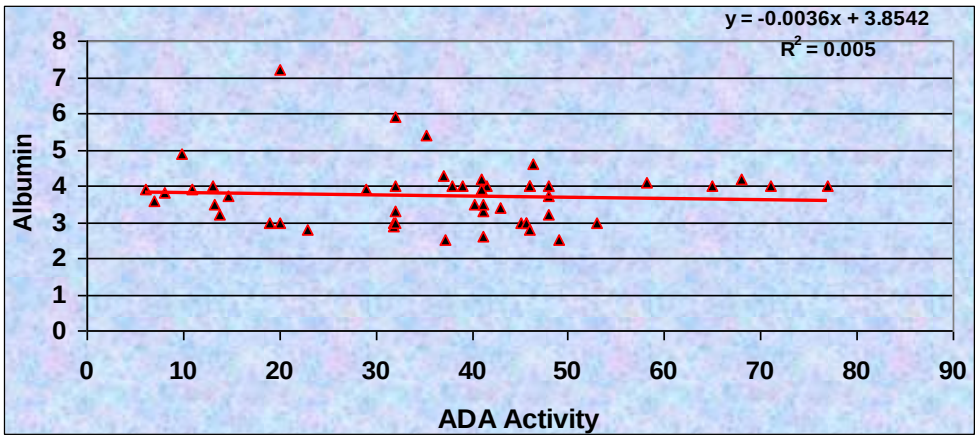

Fig 8: Correlation between ADA activity & Albumin of Untreated group subjects

Positive correlation between serum ADA activity and globulin level as well as ALP activity was found in treated as well as untreated cases respectively (p<0.05).

Alatas F. *et al.* (2003) [5] determined the role of serum ADA activity in the diagnosis and follow up of pulmonary tuberculosis and monitoring the efficiency of therapy. A significant difference was observed in ADA activity before and after treatment, also from old Tuberculosis patients and subjects.

Srinivasa Rao K. *et al.* (2012) [6] evaluated the effectiveness of serum ADA activity in prognosis of pulmonary tuberculosis at different durations of the therapy in relation with other diagnostic test of tuberculosis. The values of serum ADA activity were significantly higher in the study group than in control group.

According to Swami Kamlesh K. *et al.* (2011) [7], the serum ADA activity in PTB patients was significantly higher than the healthy controls and followed up subjects because in pathological conditions, the clearance capacity of lungs is decreased leading to increased number of cells and the recirculation of the activated lymphocytes may cause a high serum ADA activity in patients with pulmonary diseases for detoxification of toxic metabolites.

Gupta *et al.* (2012) [8] reported higher values of ADA in all three groups i.e. sputum positive, sputum negative and extra pulmonary tuberculosis but the rise was much more in sputum positive pulmonary tuberculosis signifying the higher antigenic load.

Our observations are similar with Alatas F. (2003) [5] and Swami Kamlesh (2011) [7]. Thus, a falling level of ADA activity indicates improvement and may be used as a good prognostic indicator.

The serum activities of the liver enzymes (SGOT, SGPT and ALP) were also found significantly higher in treated patients compared to untreated patients may be due to the drug induced hepatotoxicity (DIH).However, the mechanism underlying to DIH is unknown.

The result was in accordance with study done by Rohit Singla *et al.* (2010) [9] who claimed that the higher activities of the serum liver enzymes might be the result of ethnic susceptibility, inherent peculiarity of drug metabolism and/or the presence of various known risk factors such as HBV infection or malnutrition.

It was also found that serum Bilirubin level was within their normal range and also was approximately similar among both untreated and treated cases as well as control subjects too. The result was not in accordance with a study done in urban Nepalese population by Dinesh Koju *et al.* (2005) [10] as significant rise in bilirubin total, bilirubin direct was observed after anti tuberculosis treatment.

Rohit singla *et al.* (2010) [9] revealed that pre-treatment serum total protein and serum albumin level were significantly lower among cases as compared to control but were within their acceptable levels.

Our findings were different from others but similar with Rohit Singla *et al.* (2010) [9] because in our study also, serum total protein level and serum albumin level were within acceptable levels before treatment and after treatment as well as in control subjects too.

Conclusion

From the results of this study following conclusions were drawn:

- Increased serum ADA activity was found in untreated patients of pulmonary tuberculosis as compared to treated patients and healthy control subjects.
- Increased activity of liver enzymes-ALT, AST and ALP in serum were found in treated patients of pulmonary tuberculosis.
- No significant difference in activities of liver enzymes-ALT, AST and ALP in untreated cases of PTB and control subjects were found.
- Serum total proteins level was found lower in untreated patients than treated patients and control subjects.
- Increased Bilirubin level was found in treated patients as compared to untreated patients. However, no significant difference was observed in Bilirubin level between untreated patients and control subjects.
- No significant variation was observed in the level of serum albumin, serum globulin among untreated, treated cases and control subjects.
- So, the assay of serum ADA activity is simple, easy and cost effective. Hence, it should be considered in the battery of routine investigations for the prognosis of PTB.

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