Original Research Article

Study of various biochemical parameters in tuberculosis patients: A hospital based cross-sectional study

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Abstract

Background: Tuberculosis is a major cause of morbidity and mortality worldwide. Various strategy for management of tuberculosis in the form of directly observed treatment short course (DOTS) is followed in association of Govt of India, World Health Organization (WHO) and World Bank. Many antitubercular drugs and disease itself may have ill effect on various biochemical parameters. Based on this the current study was aimed to analyze various biochemical parameters in tuberculosis subjects and to compare with healthy controls. **Method:** A cross sectional analysis of randomly selected 75 subjects of pulmonary tuberculosis and 50 age and gender matched healthy controls were analyzed for various biochemical parameters in serum. Statistical analysis was done by SPSS V16. **Result:** We found significantly higher serum levels of fasting blood sugar, total and indirect bilirubin, SGPT, SGOT, alkaline phosphatase, uric acid, creatinine, phosphorous and magnesium in tuberculosis patients as compared to control subjects. There were significantly lower levels of albumin and sodium in tuberculosis patients compared to control subjects, however no significant difference was observed in levels of direct bilirubin, protein, urea, potassium, chloride, cholesterol, triacylglycerol, HDL, LDL and calcium between both groups. **Conclusion:** We conclude that there is hepatotoxicity, nephrotoxicity, and altered mineral metabolism in TB patients compared to controls. We suggest a periodic evaluation of these parameters to prevent or timely intervention of these altered organ functions in tuberculosis patients.
Key Words: Anti-tuberculosis Treatment, Biochemical Parameters, Tuberculosis.

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INTRODUCTION

Tuberculosis (TB) remains a major cause of global health problem. It causes ill-health among millions of people each year and one of the top 10 causes of the death all over the world. The latest estimates included that there were 10 million new tuberculosis cases in 2017 and 1.3 million deaths due to tuberculosis. Most of the tuberculosis cases and death occurs among men, but the burden of disease among women is also high. 27% of the total tuberculosis cases were reported from in India in 2013.[1] Tuberculosis is an infectious disease caused by the bacillus, mycobacterium tuberculosis. It primarily affects lung but it can also affect intestine, meninges, bones, joints, lymph nodes, skin and other tissues of the body. It affects mostly adults of economically productive age groups. Transmission of tuberculosis is still a problem for a variety of reasons, most due to social, economic and environmental factors. The disease spread by aerosol when tuberculosis infected patient coughs or sneezes [2]. Directly observed therapy (DOT) is the world health organization (WHO) standard for treatment of tuberculosis disease. The revised national tuberculosis control program (RNTCP), based on the internationally recommended directly observed treatment short-course

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(DOTS) strategy, was launched in India in 1997, and expanded pan India in a phased manner. Full national wide coverage was achieved in march 2006.[2,3]

Various drugs are used for the treatment of tuberculosis have been associated with increased incidence of side effects. These side effects may be mild to fatal. This leads to discontinuation of the drug therapy.[4] The major side effects are ototoxicity, hepatotoxicity, neuropsychiatric manifestations, hyperuricemia, nephrotoxicity, hypercalcemia, and hypokalemia.[4-7] In addition to this, possible changes may occur in phosphorous, magnesium, electrolytes and lipid profile concentrations [8,9] in tuberculosis patients. Based on present knowledge, our study was primarily aimed to study the changes in various biochemical parameters in tuberculosis patients receiving anti-tuberculosis treatment (ATT) compared to healthy controls.

MATERIALS AND METHODS

The present study was carried out in the Biochemistry and Clinical Biochemistry department of tertiary care teaching hospital, Surat. A total of 125 subjects were taken up for this study. A total 75 tuberculosis subjects were selected from outdoor and indoor units of Tuberculosis and chest department. 50 apparently healthy individual comprised of attendants of patients, colleagues and from society. Study subjects included male as well as female between the age group of 20 to 60 years. Subjects having metabolic disorders like diabetes mellitus, hypertension, cardiovascular disease, HIV/AIDS were excluded from the study. All the subjects were enrolled in the study by taking oral and written consent. Blood sample was collected by taking proper aseptic precautions. Blood was allowed to clot and then centrifuged at 3000 rpm for 5 minutes and then separated serum was immediately used for analysis of biochemical parameters. Serum was analyzed on fully automated clinical chemistry analyzer ERBA-EX-640 (Erba Mannheim Ltd, Germany) for calcium, magnesium, phosphorous, glucose, urea, uric acid, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, SGPT, SGOT, cholesterol, triacylglyceride, HDL-cholesterol and LDL-cholesterol. For estimation of electrolytes viz. sodium, potassium and chloride, AFT-500 electrolyte analyzer (Meizhou Cornley Hi-Tech Co. Ltd) was used.

RESULTS

Table 1: Demographic profile of the study subjects

Characteristics		Case (N=75)	Control (N=50)
Age	≤ 50 years	49 (65.3%)	40 (80%)
	> 50 years	26 (34.7%)	10 (20%)
Gender	Male	62 (82.7%)	38 (76%)
	Female	13 (17.3%)	12 (24%)
Food Habits	Pure Vegetarian	15 (20%)	31 (62%)
	Non-Vegetarian (Mixed Diet)	60 (80%)	19 (38%)

The study was conducted on total 125 subjects out of which 75 subjects were patients of pulmonary tuberculosis and 50 were apparently healthy controls. As shown in table 1, out of total 75 cases, 49 subjects were 50 years or lower age group whereas 26 subjects were older than 50 years similarly out of total 50 control subjects, 40 subjects age was 50years or lower and 10 subjects were more than 50 years old. As per gender distribution, 62 males and 13 females were included in case group whereas 38 male and 12 females were included in control group. As per food habits, in case group 15 subjects were pure vegetarian and 60 subjects were taking non-vegetarian (mixed diet) food whereas in control group 31 subjects were vegetarian and 19 subjects were non-vegetarian (mixed diet).

Table 2: Comparison of Biochemical Parameters in Tuberculosis patients and Control Subjects

Parameter	Tuberculosis Patient(N=75)	Controls (N=50)	p value
Glucose (mg/dl)	97.22 ±19.05	91.1 ± 15.33	<0.05*
Total Bilirubin (mg/dl)	0.80±0.23	0.678±0.166	<0.05*
Direct Bilirubin (mg/dl)	0.40±0.15	0.38±0.122	0.538
Indirect Bilirubin (mg/dl)	0.40±0.15	0.29±0.10	<0.05*
SGPT (IU/L)	44.34±29.47	24.39±14.24	<0.05*
SGOT (IU/L)	41.70±26.61	27.24±5.89	<0.05*
ALP (IU/L)	194.82±93.72	94.44±22.06	<0.05*
Total Protein (gm/dl)	6.34±1.01	6.47±0.90	0.451
Albumin (gm/dl)	3.10±0.64	4.03±0.48	<0.05*
Urea (mg/dl)	24.26±12.74	24.12±7.19	0.942
Uric Acid (mg/dl)	2.98±2.33	0.88±0.48	<0.05*
Creatinine (mg/dl)	3.11±2.31	1.46±1.40	<0.05*

Sodium (Na) (mEq/L)	133.32±21.60	139.38±3.61	<0.05*
Potassium (K) (mEq/L)	4.33±0.60	4.43±0.42	0.322
Chloride (Cl) (mEq/L)	98.78±7.8	102.28±3.67	0.13
Total Cholesterol (mg/dl)	160.16±55.14	154.10±28.41	0.475
Triglycerides (TG) (mg/dl)	79.43±53.21	89.80±39.44	0.24
HDL-Cholesterol (mg/dl)	45.29±14.69	47.14±15.13	0.498
LDL-Cholesterol (mg/dl)	100.70±51.24	109.59±49.40	0.336
Calcium (Ca) (mg/dl)	11.01±2.85	11.06±12.42	0.975
Phosphorus (P) (mg/dl)	4.09±0.65	3.14±0.24	<0.05*
Magnesium (Mg) (mg/dl)	4.06±2.21	2.75±0.833	<0.05*

In present study we have analyzed various biochemical parameters like Fasting blood sugar, Bilirubin (Total and Direct), Total Protein, Albumin, Urea, Creatinine, Uric acid, Alkaline phosphatase (ALP), SGOT, SGPT, Cholesterol, Triacylglycerol, HDL- and LDL-Cholesterol, Calcium, Phosphate, and Magnesium in serum of both healthy controls as well as tuberculosis positive cases. Data of various biochemical parameters are expressed as mean ± SD in table 2. We observed significant difference in glucose level (97.22 ± 19.05 mg/dl) in tubercular subjects compared to controls (91.1± 15.33 mg/dl). The level of total bilirubin in tubercular subjects and control subjects were 0.80 ± 0.23 mg/dl and 0.67 ± 0.166 mg/dl respectively and this difference was significant. The level of direct bilirubin in tuberculosis subjects and controls were 0.40±0.15 mg/dl and 0.38±0.122 mg/dl respectively and it was not significant however the observed difference between indirect bilirubin of tuberculosis subjects (0.40±0.15 mg/dl) and control subjects (0.29±0.10 mg/dl) was found to be significant. The levels of SGPT in tubercular subjects and in controls, 44.34 ± 29.47 IU/L and 24.39 ± 14.24 IU/L, and of SGOT in tubercular subjects 41.70 ± 26.61 IU/L and in controls were 27.24 ± 5.89 IU/L. Both parameters, SGOT and SGPT were significantly higher in the tubercular subjects. There were significantly high levels of ALP in tubercular subjects than in control, 194.82 ± 93.72 IU/L and 94.44 ± 22.06 IU/L respectively. We observed no significant difference in total protein between in tubercular subjects and controls 6.34± 1.01gm/dl and 6.47± 0.90 mg/dl respectively. The levels of albumin in tubercular subjects and controls was 3.10 ± 0.64 mg/dl, 4.03 ± 0.48 mg/dl respectively and found to be significant. The levels of uric acid in tubercular subjects and controls were 2.98 ± 2.33 mg/dl, 0.88 ± 0.48 mg/dl respectively, and creatinine was 3.11 ± 2.31 mg/dl and 1.46 ± 1.40 mg/dl respectively both, Uric acid and creatinine found significantly elevated in tubercular subjects. However, no significant difference was observed in urea (tubercular subjects: 24.26 ± 12.74 mg/dl, control: 24.12 ± 7.19 mg/dl). The levels of sodium in tubercular subjects and controls were 133.32 ± 21.60 mEq/L and 139.38 ± 3.61 mEq/L respectively which shows significant difference. However, no significant change observed in potassium level in tubercular subjects and controls 4.33 ± 0.60 mEq/L, 4.34 ± 0.42, p=0.322 mEq/L respectively and chloride were 98.7.8 ± 78 mEq/L in tubercular subjects and in controls were 102.28 ± 3.67 which also showed no significant difference between two groups. The levels of total cholesterol in tubercular subjects and in controls were 160.16 ± 55.14 mg/dl and 154.10 ± 28.41 mg/dl, TG levels were 79.43 ± 53.21 mg/dl in tubercular subjects and controls were 89.80 ± 39.44 mg/dl, levels of HDL-cholesterol were in tubercular subjects and controls were 45.29± 14.69 mg/dl and 47.14± 15.13 mg/dl respectively and LDL levels in tubercular subjects and controls were 100.70 ± 51.24 mg/dl and 109.59 ± 49.40mg/dl respectively. These differences were not significant for all these lipid profile variables. The levels of calcium in tubercular subjects and controls were 11.01 ± 2.85 mg/dl and 11.06 ± 12.42 mg/dl respectively, magnesium were in tubercular subjects 4.06 ± 2.21 mg/dl and controls were 2.75 ± 0.833 mg/dl and levels in phosphorus in tubercular subjects were 4.09 ± 0.65 mg/dl and in controls were 3.14 ± 0.24 mg/dl. Out of these three minerals, phosphorous and magnesium level shoed significant difference between tubercular and non-tubercular group however, no such significant difference was observed in calcium level.

DISCUSSION

Tuberculosis (TB) is one of the oldest diseases known to affect humans and is a major cause of death worldwide. TB remains a major global health problem, despite the fact that the causative organism was discovered more than 100 years ago and highly effective drugs and vaccines are available making tuberculosis, a preventable and curable diseases [3]. During the late 1980s and early 1990s, numbers of reported cases of tuberculosis increased in industrialized countries. These increases were related largely to immigration from countries with a high prevalence of tuberculosis, infection with HIV, social problems, such as increased urban poverty, homelessness, and drug abuse and dismantling of tuberculosis services. During the past few years, numbers of reported cases have begun to decline again or

stabilized in industrialized nations [2].Patients with active pulmonary tuberculosis may be asymptomatic, have mild or progressive dry cough, or present with multiple symptoms, including fever, fatigue, weight loss, night sweats, and a cough that produces bloody sputum. Directly Observed Therapy (DOT) is the World Health Organization (WHO) standard for treatment of tuberculosis. Directly observed treatment short course (DOTS) chemotherapy is strategy to ensure cure by providing the most effective medicine and confirming that it is taken. It is the only strategy which has been documented to be effective worldwide on programme basis. Globally the DOTS strategy has been recognized as the best cost-effective approach to tuberculosis control [3]. The Govt. of India, WHO and World Bank together reviewed the Notational Tuberculosis Programme (NTP) in the year 1992. Based on findings of that review a revised strategy called, 'Revised National Tuberculosis Control Programme (RNTCP)' was evolved [3].These anti-tubercular drugs have many side effects ranging from mild to fatal. As anti-tuberculosis drugs lead to side effects making patients to discontinue the treatment ultimately leading to increased morbidity and mortality [4]. Alterations in many biochemical parameters have been seen in tuberculosis patients i.e. pre and post anti-tuberculosis treatments. Tuberculosis patients may develop hypercalcemia, hypoalbuminemia [6]. In addition to these possible changes may occurs in phosphorus, magnesium [8], electrolytes and lipid profile concentrations [7] in tuberculosis patients. We observed altered liver function tests (LFTs) in tuberculosis patients compared to healthy controls. In our study there was significantly increased total bilirubin in tuberculosis subjects (0.80 ± 0.23 mg/dl) compared to controls (0.67 ± 0.166 mg/dl) and indirect bilirubin subjects (0.40 ± 0.15 mg/dl) compared to controls (0.24 ± 0.10 mg/dl). There was no significant difference in the level of direct bilirubin in tuberculosis subjects (0.40 ± .15 mg/dl) compared to controls (0.38 ± 0.12 mg/dl). Liver enzymes levels were increased significantly in tubercular cases compared to healthy controls. SGPT (tubercular subjects: 44.34 ± 29.47 IU/L Vs control: 24.39 ± 14.24 IU/L), SGOT (tubercular subjects: 41.70 ± 26.61IU/L Vs controls: 27.24 ± 5.89 IU/L) and ALP (tubercular subjects: 194.82 ± 93.72 IU/L Vs controls: 94.44 ± 22.06 IU/L). We observed significantly high levels of LFTs suggesting liver damage may be due to tuberculosis treatment. Our findings correlate with the studies of Singla el al (2009) [10] and Smik *et al* (2006) [11]. Singla el al (2009) [10] observed that bilirubin is altered in tuberculosis due to ATT which may cause hepatoxicity. They reported that drug-induced liver injury is a problem increasing due to treatment of tuberculosis infection. The liver has a central role in drug metabolism and detoxification, and is consequently vulnerable to injury. Isoniazid and rifampicin given together produce hepatotoxicity more frequently than either drug alone. The reported incidence is 8-36% in India [11]. The study done by Smik *et al* (2006) [11] shows that drugs are responsible for 10 to 30% of cases of acute liver failure. Factors that have been associated with a higher risk of ATT-induced liver disease include female sex, age >35 years, oriental race, extent of tuberculosis, pre-existing liver disease, alcohol consumption, nutritional status defined by low body mass index and serum albumin level, certain anti tuberculosis drugs or combinations thereof and the dosage of drugs in relation to body weight. There was no significant difference in the level of total protein between tubercular subjects (6.34± 1.01gm/dl) and controls (6.47± 0.90 gm/dl). We observed significantly decreased albumin concentration in tuberculosis subjects (3.10 ± 0.64gm/dl) compared to control (4.03 ± 0.48 gm/dl). Our study shows hypoalbuminemia in tuberculosis and our observations are in correlation with that of the study by Khan *et al* (2012) [12] and Liam *et al* (1998) [6]. In case of the levels of total protein our results differ from that of Khan *et al* (2012) [12], in which he observed increased levels of total protein in tuberculosis patients. The decrease in serum albumin of tuberculosis patients may be attributed to the loss of appetite in tuberculosis patients due to endotoxins produced by bacteria and lack of exercise disturb the metabolic process of the patients, which results in low intake of proper diet thus leading to malnutrition. Liam *et al* (1998) [6] found that Protein-calorie malnutrition and hypoalbuminemia are common observations in patients with active tuberculosis. The relatively high frequency of hypoalbuminemia among tuberculosis patients could have been related to malnutrition, which was partly due to the low socio-economic background of tuberculosis patients and partly because of chronic ill-health as a result of tuberculosis. A significantly higher level of uric acid was observed in tuberculosis group compared to control subjects. Creatinine was significantly increased in tubercular subjects (3.11 ± 2.31 mg/dl) as compared to control subjects (1.46 ± 1.40mg/dl) with no significant change in urea level between tubercular subjects (24.26 ± 12.74 mg/dl) and controls (24.12 ± 7.19 mg/dl). Our observation regarding significantly increased uric acid level in tuberculosis patients was in line with study by Koju D *et al* (2005) [13] and Zierski M *et al* (1980) [14] which showed slight increase in uric acid level after treatment when compared to pre-treatment. Finding of our study regarding increased creatinine level in TB patient is in agreement with other studies [14-17]. The cause of such reaction is postulated to be due to generation of

rifampicin antibodies. These antibodies make complex with rifampicin which gets deposited in renal interstitium, blood vessels and causes damage to glomerular membrane there by decreasing renal functions.[17] We observed no significant change in serum calcium between tuberculosis subjects (11.01 ± 2.85 mg/dl) and control (11.06 ± 12.42 mg/dl) which is in agreement with study done by Yusra *et al* (2017).[18] Probable cause of such observation in our study may be due to proper diet taken by patients, because high protein and balanced diet is recommended by the treating physician during ATT. However, the observations by various authors is contradictory. Ijaz *et al*[19] observed hypocalcemia and Abbassi *et al* (1979)[20] observed hypercalcemia in tuberculosis patients. This can be explained by many factors e.g. ethnic differences, malnutrition and malabsorption associated with patients of pulmonary tuberculosis. Abbasi *et al* (1979)[20] suggested that hypercalcemia might be related to the intake of vitamin D, but they also went on to suggest that possibly more than one mechanism is acting in all cases of hypercalcemia associated with granulomatous disease. Other possible mechanisms might include bone or adrenal involvement by tuberculosis. We observed significant increases in phosphorus levels between tubercular subjects (4.09 ± 0.65 mg/dl) and controls (3.14 ± 0.24 mg/dl), but the values were within normal range in both tubercular subjects and controls. Our observation is supported by Kardjito *et al* (1984) [8] who showed that there was an increase in phosphorus level in tuberculosis patient receiving ATT. In our study there was significant increase in magnesium levels in tubercular subjects (4.06 ± 2.21mg/dl) compared to controls (2.75 ± 0.833mg/dl) however the studies by other authors [21-23] are not in agreement with our study. The findings of our study may be attributed to patients receiving magnesium supplementations which was not studied. There was no any significant difference in Total Cholesterol, triacylglycerol, HDL-Cholesterol, and LDL-Cholesterol between tuberculosis patients compared to controls. Whereas many studies found significant low levels of lipid profile in tuberculosis patients [9,24]. Oyedeji *et al* (2013) [9] observed significantly low levels of triglycerides, total cholesterol and LDL- cholesterol among tuberculosis patients and they further reported that increased lipid peroxidation in all categories of tuberculosis patients may be responsible for reduction in the serum lipid levels. This could further lead to wasting and weight loss which is often observed in tuberculosis patient. In our study we observed significantly low level of sodium in study subjects (133.32 ± 21.60 mEq/L) compared to controls (139.38 ± 3.61 mEq/L), with no significant changes in potassium (tubercular subjects: 4.33 ± 0.60 mEq/L Vs controls 4.34 ± 0.42mEq/L) and chloride (tubercular subjects: 98.7.8 ± 78 mEq/L Vs controls 102.28 ± 3.67 mEq/L). our findings about low sodium level was in agreement with study by Olalekan AW *et al* (2015) [25] but they observed hyperkalemia and hypochloremia which were not in agreement with our study.

CONCLUSION

We conclude that there is significant damage to the organs viz. liver and kidney associated with altered mineral metabolism in TB patients. The correction or treatment of these altered biochemical parameters may help the diseases outcome. We suggest that these biochemical parameters should periodically analyzed in tuberculosis patients to monitor the adverse effect of ATT therapy.

LIMITATIONS

Lack of detailed diet and nutrition history is the limitation of our study. Further prospective studies are necessary to confirm our findings.

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