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# Impact of Anti Tubercular Drugs on Biochemical Changes in Newly Diagnosed Tuberculosis Patients

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**Abstract** **Original Research Article**

***Background:*** The disease tuberculosis (TB) continues to be a major global health concern, with high rates of morbidity and mortality, particularly in developing nations. It affects multiple organs and has the ability to alter metabolic processes. The purpose of this study was to ascertain how patients' serum biochemical markers were affected by tuberculosis and the medications used to treat it. ***Objective:*** The aim of this study is to evaluate impact of anti-tubercular drugs on biochemical changes in newly diagnosed tuberculosis patients. ***Methods:*** The cross-sectional observational study was conducted in Netrokona Medical College Hospital, Netrokona, from 1st January 2022 to 31st December 2023. A total of 120 newly diagnosed cases of pulmonary tuberculosis were enrolled and analyzed in this study. The questionnaire was pretested, corrected and finalized. Data were collected by face-to-face interview and analyzed by appropriate computer based programmed software Statistical Package for the Social Sciences (SPSS), version 24. ***Results:*** In this study, majority 48 (40.0%) of the patients were in 31 - 40 years age group and 28 (23.3%) patients were in 41 - 50 years age group, Mean±SD of age was 36.13±11.03 years. Most of the patients 69 (57.50%) were male and 51 (42.50%) patients were female. Most of the patients 87 (72.5%) were in normal range (18.5 – 29.9 kg/m2), 15 (11.7%) of the patients were underweight (<18.5) and 19 (15.8%) of the patients were overweight (>30). Serum Glutamic Oxaloacetic Transaminase and Serum Glutamic Pyruvic Transaminase level were 18.00 (4.01), 21.04 (3.16) before treatment but after treatment the level became 20.10 (3.52), 22.57 (4.41). Urea and Creatinine level were 18.20 (2.31), 0.63 (0.15) before treatment but after treatment 20.01 (5.34) and 0.53 (0.13). After treatment by anti-tubercular drug gastrointestinal adverse drug effects were nausea 3 (2.5%), vomiting 6 (5.0%), diarrhea 3 (2.5%) and abdominal pain 5 (4.2%), followed by itching in 4 (3.3%) patients but before treatment by anti-tubercular drug gastrointestinal adverse drug effects were nausea 1 (0.8%), vomiting1 (0.8%), no diarrhea and abdominal pain 1 (0.8%), followed by itching in 1 (0.8%) patient. Decrease in sodium (123mmol/L Vs 140.4mmol/L), potassium levels (3.3mmol/L Vs 4.2mmol/L), chloride levels (97.6mmol/L Vs 101.9mmol/L) and bicarbonate values (19.3 Vs 20.6mmol/L) in tuberculosis patients. Treatment with antitubercular drugs normalized sodium (137.3mmol/L Vs 123mmol/L), potassium (4.0mmol/L Vs 3.3mmol/L) chloride (101.6mmol/L Vs 97.6mmol/L) and bicarbonate levels (21.6mmol/L Vs 19.3mmol/L). ***Conclusion:*** In this study, there was a significant decrease in blood albumin, serum sodium, and serum calcium in patients with tuberculosis and normalized with receiving Anti tubercular drugs.

**Key words:** Tuberculosis, Anti-tuberculosis Drugs, Mycobacterium tuberculosis, Biochemical changes.



## INTRODUCTION

Millions of people worldwide are killed by tuberculosis (TB), an infectious disease brought on by Mycobacterium tuberculosis [1]. Although it can affect every organ in the body, tuberculosis is mostly a lung disease [2]. Mycobacterium tuberculosis is an aerobic, rod-shaped, nonspore-forming bacterium that spreads through microscopic airborne droplets produced by a person with pulmonary tuberculosis coughing, sneezing, talking, or singing [3].

About one-third of the world's population is infected by tuberculosis (TB), a serious public health issue [4]. 1.6 million people passed away from TB in

2021. After coronavirus disease, tuberculosis is the second most prevalent cause of infection-related death worldwide [1]. It ranks 13th in terms of mortality. With an estimated incidence of 378 new cases per 100,000 people, Ethiopia ranked third in Africa and seventh in the world for tuberculosis burden [5, 6].

Recent data show that current pharmacotherapy for TB is inadequate to achieve therapeutic drug serum levels [7,8]. Therefore, there is a necessity to identify a new molecule for the control of TB. Piperine and Isoniazid is available for the treatment of tuberculosis. By adding Piperine, the dose of rifampicin is reduced to 200 mg which possesses to achieve the therapeutic serum level of Rifampicin as of 450 mg [9]. Since the dose of Rifampicin is reduced and the toxicity of Rifampicin is also reduced and thereby better patient compliance is expected. Thus, defaulter rate and development of drug resistance can be reduced. Many studies have considered this point and evaluated the relationship of Piperine and Rifampicin. However, limited data are available in clinical practice [10]. The present study was undertaken to find out the superiority of piperine included FDC in TB management.

Early in the 1980s, a number of in vitro and in vivo investigations revealed that rifabutin (RBT) showed promise in the management of mycobacterial infections in humans. RBT is 2- to 2Q-fold more active against Mycobacterium TB [11] than rifampicin (RMP) and exhibits activity against around one-third of RMP-resistant strains of M. tuberculosis [12].

Despite having a similar chemical makeup to RMP, RBT is more lipophilic, which leads to a greater intracellular penetration, a longer elimination half-life (45 h), and a wider tissue distribution [13].

For instance, the ratio of RBT's intracellular to extracellular concentrations is 9.2-14.6, whereas RMP's is 5-5.4. Additionally, RBT's toxicity is equal to that of RMP. Patients who have experienced hepatic toxicity from RMP can safely receive RBT at a dose of 300 mg/d; additionally, it does not seem to exacerbate the liver toxicity caused by isoniazid. Thus, patients with abnormal liver function and tuberculosis may benefit from RBT [14].

The World Health Organization (WHO) has approved the treatment of newly diagnosed pulmonary tuberculosis, which is now well established in many nations. It consists of an initial 8-week phase of daily drug administration (isoniazid, RMP, pyrazinamide, and ethambutol), followed by intermittent administration (isoniazid and RMP) for 16 weeks [15]. Treatment adherence to the prescribed schedule may be improved by intermittent regimens, which are simpler to use and need fewer dosages.

Based on its pharmacological and pharmacokinetic properties, RBT seems like a good option for treating tuberculosis on a daily or intermittent basis. In fact, RBT has been shown to be quite successful when given daily or sporadically to mice infected with experimental tuberculosis.

Research has indicated that tuberculosis (TB) has been linked to biochemical alterations [16], including low serum albumin, low sodium, low/high calcium, and low/high potassium levels, among other changes [17]. Additionally, two investigations have shown certain biochemical alterations linked to anti-TB medications [18, 19]. Studies on the metabolic alterations brought on by tuberculosis infection are scarce. This led to the conduct of this study, which evaluated the effects of TB infection and the anti-TB drugs used to treat it on serum albumin, calcium, sodium, and potassium in order to start taking action to prevent negative effects from these.

## METHODOLOGY

The cross-sectional observational study was conducted in Netrokona Medical College Hospital, Netrokona, from 1st January 2022 to 31st December 2023. A total of 120 newly diagnosed cases of pulmonary tuberculosis were enrolled and analyzed in this study. Patients who matched the inclusion and exclusion criteria were approached for participation in the study. Patients who were not willing to give consent were excluded. Purposive sampling was done according to the availability of the patients who fulfilled the selection criteria. Face to face interview was done to collect data with a semi-structured questionnaire. After collection, the data were checked and cleaned, followed by editing, compiling, coding, and categorizing according to the objectives and variable to detect errors and to maintain consistency, relevancy and quality control. Statistical evaluation of the results used to be obtained via the use of a window-based computer software program devised with Statistical Packages for Social Sciences (SPSS-24).

## RESULT

**Table I: Distribution of the patients according to age (n = 120)**

| Age group | Frequency | % |
|---|---|---|
| 20 – 30 years | 17 | 14.2 |
| 31 - 40 years | 48 | 40.0 |
| 41 - 50 years | 28 | 23.3 |
| 51 - 60 years | 23 | 19.2 |
| 61 - 70 years | 12 | 10.0 |
| Total | **120** | **100.0** |
| Mean + SD: 36.13±11.03 Years | | |

Table I shows that, majority 48 (40.0%) of the patients were in 31 - 40 years age group and 28 (23.3%) patients were in 41 - 50 years age group, Mean±SD of age was 36.13±11.03 years.

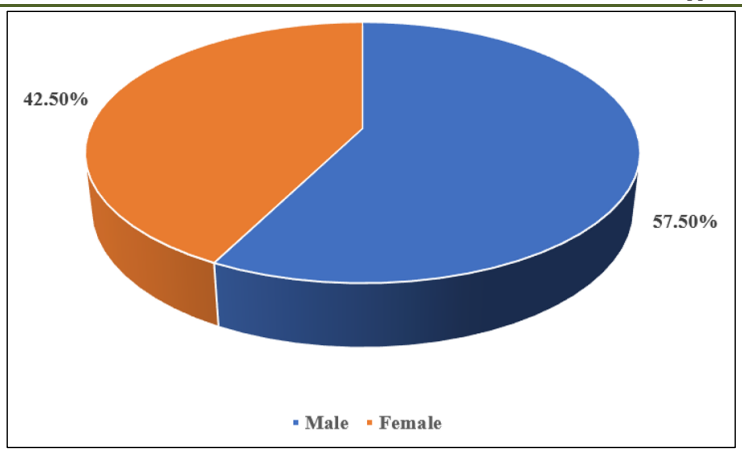


**Figure I: Distribution of the patients according to sex (n=120)**

Figure I shows that, most of the patients 69 (57.50%) were male and 51 (42.50%) patients were female.

**Table II: Distribution of the patients according to comorbidity (n = 120)**

| Body Mass Index (kg/m2) | Frequency | % |
|---|---|---|
| <18.5 | 14 | 11.7 |
| 18.5 – 24.9 | 55 | 45.8 |
| 25.0 – 29.9 | 32 | 26.7 |
| >30 | 19 | 15.8 |
| Total | **120** | **100.0** |

Table II shows that, most of the patients 87 (72.5%) were in normal range (18.5 – 29.9 kg/m2), 15 (11.7%) of the patients were underweight (<18.5) and 19 (15.8%) of the patients were overweight (>30).

**Table III: Distribution of the patients according to Liver function test and Renal function test (n = 120)**

| Sputum conversion rate | | Before treatment | After treatment |
|---|---|---|---|
| LFT (U/L) | SGOT | 18.00 (4.01) | 20.10 (3.52) |
| | SGPT | 21.04 (3.16) | 22.57 (4.41) |
| RFT (mg/dl) | Urea | 18.20 (2.31) | 20.01 (5.34) |
| | Creatinine | 0.63 (0.15) | 0.53 (0.13) |

Table III shows that, Serum Glutamic Oxaloacetic Transaminase and Serum Glutamic Pyruvic Transaminase level were 18.00 (4.01), 21.04 (3.16) before treatment but after treatment the level became 20.10 (3.52), 22.57 (4.41). Urea and Creatinine level were 18.20 (2.31), 0.63 (0.15) before treatment but after treatment 20.01 (5.34) and 0.53 (0.13)

LFT: Liver Function Test; SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; RFT: Renal Function Test.

**Table IV: Distribution of the patients according to Adverse Drug Events (n = 120)**

| Organ system involved | Type of ADEs | After treatment by anti-tubercular drug | Before treatment by anti-tubercular drug |
|---|---|---|---|
| Gastrointestinal | Nausea | 3 | 1 |
| | Vomiting | 6 | 1 |
| | Diarrhea | 3 | 0 |
| | Abdominal pain | 5 | 1 |
| Cutaneous | Itching | 4 | 1 |

Table IV shows that, after treatment by anti-tubercular drug gastrointestinal adverse drug effects were nausea 3 (2.5%), vomiting 6 (5.0%), diarrhea 3 (2.5%) and abdominal pain 5 (4.2%), followed by itching in 4 (3.3%) patients but before treatment by anti-tubercular drug gastrointestinal symptoms were nausea 1 (0.8%), vomiting1 (0.8%), no diarrhea and abdominal pain 1 (0.8%), followed by itching in 1 (0.8%) patient

**Table V: Distribution of the patients according to Serum electrolyte levels (n = 120)**

| Electrolytes (mmol/L) | Before treatment | | After treatment | | p-value |
|---|---|---|---|---|---|
| | Mean±SD | Hypo | Mean±SD | Hypo | |
| Serum Sodium | 123.0±2.16 | | 137.3±2.04 | | <0.001 |
| Serum Potassium | 3.3±0.6 | | 4.0±0.3 | | <0.001 |
| Serum Chloride | 97.6±8.3 | | 101.6±5.6 | | 0.01 |
| Serum Bicarbonate | 19.3±2.16 | | 21.6±2.0 | | <0.001 |

Table V shows that, decrease in sodium (123mmol/L Vs 140.4mmol/L), potassium levels (3.3mmol/L Vs 4.2mmol/L), chloride levels (97.6mmol/L Vs 101.9mmol/L) and bicarbonate values (19.3 Vs 20.6mmol/L) in tuberculosis patients. Treatment with antitubercular drugs normalized sodium (137.3mmol/L Vs 123mmol/L), potassium (4.0mmol/L Vs 3.3mmol/L) chloride (101.6mmol/L Vs 97.6mmol/L) and bicarbonate levels (21.6mmol/L Vs 19.3mmol/L)

## DISCUSSION

Tuberculosis (TB), a complex socioeconomic disease, remains a global health threat in Bangladesh and accounts nearly one third of prevalent cases worldwide. TB remains as a major cause of morbidity and mortality. TB is a curable disease if diagnosed and treated properly with anti-tuberculosis therapy (ATT). In addition to benefits, poor and variable bioavailability of ATT drugs produces a challenge to successful anti-tubercular program [20]. Rifampicin is the first line drug of choice in the chemotherapy of TB since 1960s and it is a potent inducer of CYP-450 enzymes. This leads to a number of adverse drug interactions. In addition, this results in over expression of P-glycoprotein-drug efflux pumps. Both these effects lead to sub-therapeutic levels, which are seen usually after continuous use of rifampicin for 10–14 days. Apart from this, conventional rifampicin is poorly tolerable. Nausea, vomiting, upper abdominal discomfort, hepatotoxicity and gastrointestinal are most common adverse effects of rifampicin.

The cross-sectional observational study was conducted in Netrokona Medical College Hospital, Netrokona, from 1st January 2022 to 31st December 2023. A total of 120 newly diagnosed cases of pulmonary tuberculosis were enrolled and analyzed in this study.

In this study, majority 48 (40.0%) of the patients were in 31 - 40 years age group and 28 (23.3%) patients were in 41 - 50 years age group, Mean±SD of age was 36.13±11.03 years. Most of the patients 69 (57.50%) were male and 51 (42.50%) patients were female. Most of the patients 87 (72.5%) were in normal range (18.5 – 29.9 kg/m2), 15 (11.7%) of the patients were underweight (<18.5) and 19 (15.8%) of the patients were overweight (>30). In another study, total of 72 patients attended the screening phase for sputum positive newly diagnosed pulmonary tuberculosis, out of which 66 patients met the study criteria. The patients who got enrolled after giving written informed consent were randomized into two groups. In the UC group, out of 34 patients, 32 patients completed the study and in the IC group, out of 32 patients, 31 patients completed the study. Finally, 63 patients completed all the follow-up visits.

Baseline characteristics like age, body mass index (BMI), gender, sputum conversion rate, liver and renal function tests were done. No significant difference was observed with respect to baseline characteristics of patients between the study groups (p>0.05). Measurement of sputum conversion rate was the primary efficacy outcome. The mean (SD) values of UC and IC group patients during baseline were found to be 1.947 (0.84) and 1.912 (0.87) respectively. The same on END IP was found to be 0.632 (0.91) and 0.118 (0.48). During MID CP, the value of UC group was 0.105 (0.31) whereas in the intervention group it was zero. During END CP period, both the groups showed zero bacteria detection [21]. In another study conducted in India shows majority of the patient were in the age group of 14-78 years mean age being 52 ±13.6 years Mean age of females was slightly more (53.1± 14.3) than that of male, but the difference was statistically insignificant.

In present study, Serum Glutamic Oxaloacetic Transaminase and Serum Glutamic Pyruvic Transaminase level were 18.00 (4.01), 21.04 (3.16) before treatment but after treatment the level became 20.10 (3.52), 22.57 (4.41). Urea and Creatinine level were 18.20 (2.31), 0.63 (0.15) before treatment but after treatment 20.01 (5.34) and 0.53 (0.13). In another study, assessment of Liver Function Tests (LFT) and Renal Function Tests (RFT) values were the secondary measures to assess the tolerability of liver and kidney. From Table 2, it is shown that, the base value (pretreatment) and final review value (END CP) for SGOT and SGPT have significantly increased to higher values, but when we observe both values, the rate of increase is much higher in the UC group (p<0.0001) than the Interventional group (p<0.05) indicating that Rifampin 200 mg with Piperine 10 mg (FDC) is safer to liver than the Rifampin 450 mg (control group regimen).

Urea and creatinine have also increased from pre-treatment to END CP. However, the significance is shown only in urea level in the UC group (p<0.01). No significant increase was observed in creatinine level in both groups. It is evident from Table 3 that IC group is safer to liver and kidney. A significant change is observed in SGOT and SGPT parameters in between

group analysis (Table 3) and no significant difference with respect to urea and creatinine.

After treatment by anti-tubercular drug gastrointestinal adverse drug effects were nausea 3 (2.5%), vomiting 6 (5.0%), diarrhea 3 (2.5%) and abdominal pain 5 (4.2%), followed by itching in 4 (3.3%) patients but before treatment by anti-tubercular drug gastrointestinal adverse drug effects were nausea 1 (0.8%), vomiting1 (0.8%), no diarrhea and abdominal pain 1 (0.8%), followed by itching in 1 (0.8%) patient. In another study, tolerability assessment is also performed by monitoring adverse drug events (ADEs). ADEs gauged during six-month treatment period are summarized in Table 4. A total of 5 different ADEs was reported by the study patients. All the ADEs were of minor clinical importance in both the groups. The number of patients reported ADEs was less in the IC group (22.22%) when compared to UC group (36.84%). All the suspected adverse events were assessed for causality using Naranjo's algorithm and it was confirmed by the panel of experts that most of the ADEs were possibly related to the study medications. No patients withdrew their consent from the study due to adverse events.

Decrease in sodium (123mmol/L Vs 140.4mmol/L), potassium levels (3.3mmol/L Vs 4.2mmol/L), chloride levels (97.6mmol/L Vs 101.9mmol/L) and bicarbonate values (19.3 Vs 20.6mmol/L) in tuberculosis patients. Treatment with antitubercular drugs normalized sodium (137.3mmol/L Vs 123mmol/L), potassium (4.0mmol/L Vs 3.3mmol/L) chloride (101.6mmol/L Vs 97.6mmol/L) and bicarbonate levels (21.6mmol/L Vs 19.3mmol/L). In another study, in newly diagnosed tuberculosis patients, there was a significant ($p<0.001$) decrease in sodium, potassium, chloride and bicarbonate values compared to after treatment. Treatment with antitubercular drugs normalized sodium, potassium and bicarbonate levels significantly compared to values before treatment [22]. Their findings revealed that there was a significant decrease in sodium (124mmol/L Vs 140.4mmol/L), potassium levels (3.4mmol/L Vs 4.2mmol/L), chloride levels (97.7mmol/L Vs 101.9mmol/L) and bicarbonate values (19.4 Vs 20.6mmol/L) in tuberculosis patients. Treatment with antitubercular drugs normalized sodium (137.4mmol/L Vs 124mmol/L), potassium (4.1mmol/L Vs 3.4mmol/L) chloride (107.7mmol/L Vs 97.7mmol/L) and bicarbonate levels (21.7mmol/L Vs 19.4mmol/L) significantly compared to values before treatment [23].

The mean chloride value was significantly ($p<0.001$) lowered in newly diagnosed TB cases. After treatment with anti-tubercular drugs, these levels returned to normal levels. The mean serum potassium value was significantly ($p<0.001$) lower in tuberculosis patients. Treatment with anti-tuberculosis drugs, serum sodium levels were increased significantly. Similarly, the mean serum bicarbonate value was also decreased significantly ($p<0.001$) in newly diagnosed TB cases. After treatment bicarbonate levels returned to normal levels.

Mean sodium value was significantly ($p<0.001$) lower in the newly diagnosed patients. After anti-tuberculosis treatment for 3 months, mean sodium value was significantly ($p<0.001$ compared to before treatment) increased and was found to be within normal limits (136-146 mmol/L).

The hyponatremia seen among newly diagnosed TB patients was 72%, the odds of having hyponatremia was 2.57 higher among newly diagnosed TB patients than among the treated TB cases. Hypokalemia, seen among newly diagnosed TB patient was 48%. The odds being 0.9. Hypochloremia seen among newly diagnosed TB patient was 24% the odds being 0.3. Low serum bicarbonate among newly diagnosed TB patient was 72%. The odds being 2.57 [24].

A study by SS Warke *et al.*, (2004) conducted on patients in India evaluated the effect of treatment of antitubercular drugs on blood pH, electrolytes and osmolality, found mean value of serum Na+ concentration found to be 134 mmol/L which was increased after treatment and reached to 143 mmol/L. similarly Chloride level was increased 4-month post treatment suggesting the decrease in reabsorptive capacity of uriniferous tubules towards chloride ions in tuberculosis [25].

A study survey done on 110 patients in southwestern Nigeria to assess the electrolytes imbalance among tuberculosis patients who are receiving treatment. This study suggested that initiation of treatment on TB patients seems to bring about improvement in hyponatremia, hyperkalemia, hypochloremia and hypercarbonemia [26].

## CONCLUSION

In this study, there was a significant decrease in blood albumin, serum sodium, and serum calcium in patients with tuberculosis and normalized with receiving Anti tubercular drugs. There is a need for clinicians to search for abnormalities of serum sodium, serum potassium, serum calcium and serum albumin in tuberculosis patients in routine clinical practice.

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