Original Research Article

ASSESSMENT OF SERUM GAMMA GLUTAMYL TRANSFERASE, ASPARTATE AMINOTRANSFERASE AND ALBUMIN IN TUBERCULOSIS PATIENTS UNDER TREATMENT IN EDSUTH, EDO STATE, NIGERIA

ABSTRACT

Background: Tuberculosis (TB) remains a significant health burden globally, particularly in developing nations like Nigeria. The use of anti-tubercular drugs, while effective, is associated with potential hepatotoxic effects, which can be monitored using specific serum biomarkers.

Aim: This study aimed to assess serum levels of Gamma-glutamyl transferase (GGT), Aspartate aminotransferase (AST), and Albumin in TB patients undergoing treatment at Edo State University Teaching Hospital, Auchi, Edo State, Nigeria.

Study design: This cross-sectional study was conducted on tuberculosis patients who were selected by simple random sampling.

Methods:A total of 70 tuberculosis patients aged 10 years and above out of which 48 were being treated with rifampicin, and 22 were being treated with Pyrazinamide for six months and above, as well as 50 healthy controls, participated in this study. Blood samples were analyzed for GGT, AST, and Albumin levels using standard spectrophotometric method. Data was presented as mean ± standard deviationand comparisons between TB patients and controls were made using the independent Student's t-test. Significance level was taken at $p<0.05$.

Results: The serum levels of GGT and AST were significantly elevated in TB patients under treatment compared to controls. Albumin levels were significantly lower in TB patients compared to controls. Statistically significant increase was observed in the serum GGT and AST ($p<0.05$) of patients treated with rifampicin and Pyrazinamide drugs from 6 months and above compared to those not on the treatment. In the long-term treatment phase, serum albumin levels in both drug groups decreased significantly ($p<0.05$), with Rifampicin showing slightly lower levels compared to Pyrazinamide.

Conclusion: Prolonged TB treatment, especially beyond 6 months, is associated with elevated liver enzyme levels and reduced albumin levels, suggesting potential hepatic stress.

Keywords: Gamma-glutamyl transferase (GGT), Aspartate aminotransferase (AST), Albumin, Tuberculosis, Rifampicin, Pyrazinamide.

1. INTRODUCTION

Tuberculosis (TB) is an airborne disease caused by bacteria belonging to the Mycobacterium tuberculosis complex (MTBC)[1,2]. Tuberculosis (TB) remains a significant public health challenge worldwide, especially in developing countries like Nigeria. The World Health Organization (WHO) reported that in 2021, approximately 10 million people fell ill with TB globally, with Africa accounting for a substantial portion of these cases [3]. TB treatment typically involves a combination of drugs administered over a period of six months or more. However, these drugs can cause significant side effects, including hepatotoxicity, which may lead to treatment discontinuation or failure [4,5].

Serum biomarkers, such as Gamma-glutamyl transferase (GGT), Aspartate aminotransferase (AST), and Albumin, are vital indicators of liver function and overall health status[4,6]. GGT is a sensitive marker of hepatobiliary disease and is often elevated in conditions involving liver injury or cholestasis [7]. AST, an enzyme found in the liver and other tissues, is released into the bloodstream in response to liver damage, making it a crucial marker for assessing liver injury [8,9]. Albumin, a protein synthesized by the liver, reflects the synthetic function of the liver and is often reduced in chronic liver diseases [10,11].The assessment of these serum biomarkers in TB patients undergoing treatment is essential for early detection of drug-induced hepatotoxicity. Such monitoring can help in timely intervention, thereby preventing severe liver damage and ensuring the continuation of effective TB treatment. In Nigeria, particularly in Edo State, there is limited research on the impact of anti-tubercular treatment on liver function, as indicated by serum GGT, AST, and Albumin levels. This study aimed to fill this gap by evaluating these biomarkers in TB patients under treatment, providing insights into the hepatic effects of TB therapy and guiding clinical practice in the region.

2. MATERIALS AND METHODS

Study design and population

This cross-sectional study was conducted at Edo State University Teaching Hospital, Auchi, Edo State, Nigeria. The study population consisted of 70 TB patients undergoing anti-tubercular treatment and 50 healthy controls matched for age and duration of tuberculosis treatment who were randomly selected.

Inclusion criteria

TB patients confirmed by sputum microscopy TB diagnosis and under anti-tubercular treatment for at least one month.

Exclusion criteria

Patients with known liver diseases, HIV infection, or those on other hepatotoxic medications.

Sample collection and analysis

Five millilitres of venous blood samples were collected from the cubital vein of each participant after an overnight fast using standard venipuncture technique and dispensed into plain labelled containers.Blood samples were left at room temperature for about 10 minutes to clot after which serum was obtained by centrifugation for 5 minutes at 4000rpm and stored at -20^{o}c prior to analysis. GGT and AST levels were measured using enzymatic methods, while Albumin was quantified using the bromocresol green dye-binding method.

Statistical analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the data. Data was presented as mean ± standard deviation and comparisons between TB patients and controls were made using the independent t-test. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

Table 1 shows the serum Gamma Glutamyl Transferase level (GGT) (U/L) in TB patients treated with rifampicin and Pyrazinamide over a 6 months period. The mean gamma glutamyl transferase (GGT) values showed a statistically significant increase in patients treated with rifampicin (10.08±0.08), as compared to Pyrazinamide (7.64±0.94) treated patient in the period of less than a monthand 1-2 months (Rifampicn: 11.08±4.55) , Pyrazinamide: (8.11±1.47) of treatment respectively. Whereas, there was no statistically significant difference was observed in rifampicin (11.53±4.68) treated patients as compared with tuberculosis patients treated with Pyrazinamide(14.27±8.41) in 3-5 months (P=0.23) and 6 months and above (Rifampicin: 29.16±3.99; Pyrazinamide: 32.8±1.56) respectively. Statistically significant decrease was observed in the groups of less than a month and 1-2 months as compared with the control group. Conversely, there was significant increase in tuberculosis patient treated with rifampicin and Pyrazinamide in 6 months and above as compared with the control.

Table 1: Comparison of serum levels of Gamma Glutamyl Transferase (GGT) (U/L) ± SD in tuberculosis patients treated with Rifampicin and Pyrazinamide.

Duration of Treatment	Tuberculosis Treated Patients (n = 70)		
	Rifampicin	Pyrazinamide	P-value
< 1 month	10.08±0.08	7.64±0.94	0.02*
1-2 months	11.08±4.55	8.11±1.47	0.03*
3-5 months	11.53±4.68	14.27±8.41	0.23
6 months and above	29.16±3.99	32.8±1.56	0.04*
Control	11.98±4.55		

SD = standard deviation, n = number, *=statistically significant at p<0.05

Table 2 shows the serum level of Aspartate Aminotransferase (AST) in tuberculosis patients treated with Rifampicin and Pyrazinamide from less than 1 month to 6 months and above.

In the first month of treatment, AST levels are higher in patients treated with Pyrazinamide (13.67 ± 0.61 U/L) compared to those treated with Rifampicin (11.52 ± 0.47 U/L). During the 1-2 month period, AST levels increase for both drugs, with Rifampicin showing an average of 18.44 ± 6.99 U/L and Pyrazinamide showing 19.44 ± 4.75 U/L. However, the P-value of 0.31 indicates that the difference between the two is not statistically significant. In the 3-5 month period, AST levels further increase for both Rifampicin (21.25 ± 10.55 U/L) and Pyrazinamide (21.82 ± 11.18 U/L). The P-value of 0.55 indicates no statistically significant difference between the two drugs. In the late phase of treatment (6 months and above), AST levels are substantially elevated in both groups, with Rifampicin-treated patients showing 47.63 ± 10.94 U/L and Pyrazinamide-treated patients showing 50.64 ± 11.34 U/L. The P-value of 0.63 indicates no significant difference between the two drugs.

Table 2: Comparison of serum levels of aspartate aminotransferase (AST) (U/L) ± SD in tuberculosis patients treated with rifampicin and Pyrazinamide.

Duration of Treatment	Tuberculosis Treated Patients		
	Rifampicin	Pyrazinamide	P-value
< 1 month	11.52±0.47	13.67±0.61	0.01*
1-2 months	18.44±6.99	19.44±4.75	0.31
3-5 months	21.25±10.55	21.82±11.18	0.55
6 months and above	47.63±10.94	50.64±11.34	0.63
Control	20.02±5.92		

SD = standard deviation, n = number, *=statistically significant at p<0.05

Table 3 shows the albumin in TBpatients treated with rifampicin and Pyrazinamide fromless than 1 month to 6 months and above.

In the first month of treatment, patients treated with Rifampicin have statistically significant higher serum albumin levels compared to those treated with Pyrazinamide (P = 0.0001). During the 1-2 month treatment period, albumin levels in patients treated with Rifampicin are slightly higher than those treated with Pyrazinamide, but the difference is not statistically significant (P = 0.25). In the 3-5 month treatment period, there is a notable increase in the mean albumin levels for patients treated with Rifampicin (5.70±7.17 g/dl) compared to those treated with Pyrazinamide (4.12±0.75 g/dl). Despite higher albumin levels observed in the Rifampicin group, the large standard deviation (7.17) suggests considerable variability, making the difference between the two treatments non-significant. In the long-term treatment phase (6 months and above), the patients treated with Rifampicin show statistically significant lower albumin levels compared to those treated with Pyrazinamide (P = 0.0002).A statistically significant decrease was observed in tuberculosis patients treated with rifampicin as compared to Pyrazinamide treated patients in 6 months of treatment and the control.

Table 3: Comparison of serum levels of albumin (g/dl) ± SD in tuberculosis patients treated with Rifampicin and Pyrazinamide.

Duration of Treatment	Tuberculosis Treated Patients		
	Rifampicin	Pyrazinamide	P-value
<1 month	4.23±0.15	3.47±0.76	0.0001
1-2 months	4.45±0.70	4.27±0.44	0.25
3-5 months	5.70±7.17	4.12±0.75	0.82
6 months and above	3.29±0.35	3.73±0.57	0.0002
Control	4.47±0.39		

SD = standard deviation, n = number, statistically significant at p<0.05

4. Discussion

Rifampicin and Pyrazinamide are known for hepatotoxicity overtime and might contribute to the initial increase in GGT levels and subsequent adjustments as the body adapts[5]. The impact on AST levels could be indicative of the medication's influence on liver inflammation and cellular health. Albumin levels might reflect the overall nutritional status and response to treatment. It is important to recognize that these results might vary based on individual patient characteristics and the specific dynamics of tuberculosis infection. The fluctuations in enzyme levels over time might also depend on factors such as disease severity, patient compliance, and potential interactions with other medications[6].

From this study, the observed result for gamma glutamyl transferase (GGT) values of the tuberculosis patients treated with Rifampicin and Pyrazinamide over a 6-months period showed that the GGT significantly increasedwith increased duration of treatment and they were higher than the observed mean GGT values of control. This finding is similar to the work of [12] who reported mean GGT values of 27.95 U/L in evaluating the preventive use of a hepatoprotectant against anti-tuberculosis drug-induced liver injury in China.This may be as a result of extensive metabolism in the liver by various enzymes that can lead to the formation of reactive metabolites[13]. These reactive metabolites may cause direct damage to hepatocytes or trigger an immune response, which involves the activation of T cells, release

of pro-inflammatory cytokines, and recruitment of immune cells to the liver [14]. This immune-mediated response can contribute to liver inflammation and injury[14]. It may also result from oxidative stress in hepatocytes,which leads to the generation of reactive oxygen species(ROS) and deplete cellular antioxidant defenses, leading to an imbalance between oxidants and antioxidants, which can result in cellular damage, lipid peroxidation, protein oxidation, and DNA damage, contributing to hepatocellular injury[15]. The sharp rise in GGT levels after 6 months indicates that prolonged exposure to these drugs may significantly impact liver function. Pyrazinamide, which is known for its hepatotoxic potential, appears to have a more pronounced effect in the long term compared to Rifampicin. This highlights the need for careful monitoring of liver function in patients undergoing extended tuberculosis treatment.

The comparison with the control group suggests that both rifampicin and Pyrazinamide can impact GGT levels, but the effects vary over time and between the two drugs.

The study also suggested that both Rifampicin and Pyrazinamide have a significant impact on liver function, as evidenced by elevated AST levels throughout the treatment duration. The increase in AST levels, particularly after prolonged treatment, indicates potential liver damage or stress, which is a known risk with these drugs. Rifampicin, as an enzyme inducer, may contribute to liver stress, particularly with long-term use, which is reflected in the elevated AST levels. Pyrazinamide, known for its hepatotoxic potential, its impact is evident from the early stages, with significantly higher AST levels compared to Rifampicin in the first month. The findings of this present study agree with the work of [16] from LAUTECH Teaching Hospital, Ogbomoso, Nigeria.The significant rise in AST levels in the late phase of treatment reflects considerable liver stress or damage associated with prolonged exposure to both Rifampicin and Pyrazinamide. This indicates a need for close monitoring of liver function, particularly in patients undergoing long-term treatment.This may also result from extensive metabolism in the liver by various enzymes that can lead to the formation of reactive metabolites, immune response and oxidative stress which can lead to hepatocellular injury thereby increasing the levels of AST[17].These results are consistent with previous studies that have reported hepatotoxicity as a common side effect of anti-tubercular therapy [18].

In the long-term treatment phase, serum albumin levels in both drug groups decreased, with Rifampicin showing slightly lower levels compared to Pyrazinamide. The decrease in albumin levels in this phase may be indicative of cumulative liver stress or nutritional depletion due to prolonged illness and treatment. However, the difference between the two drugs remains non-significant, suggesting that both drugs exert a similar impact on liver function over extended treatment periods. Regular monitoring of serum albumin levels remains important to ensure that TB treatment does not lead to significant nutritional or liver function deterioration.

5. CONCLUSION

The study demonstrated that prolonged TB treatment, especially beyond 6 months, is associated with elevated liver enzyme levels and reduced albumin levels, suggesting potential hepatic stress. While Rifampicin and Pyrazinamide both impact liver function, the differences between the drugs were not statistically significant. Regular monitoring of liver function markers in TB patients is essential for early detection and management of drug-induced hepatotoxicity, allowing for timely intervention and adjustment of therapy to prevent severe liver damage, thereby improving treatment outcomes.

6. RECOMMENDATION

The findings suggest the need for further research into strategies for minimizing hepatotoxicity in TB treatment.

CONSENT

A written informed consent was obtained from all participants prior to inclusion in this study.

ETHICAL APPROVAL

Ethical approval was obtained from the Ethics Committee of Edo State University Teaching Hospital.

Disclaimer (Artificial intelligence)
Option 1:
Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

REFERENCES

[1] Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, Ginsberg A, Swaminathan S, Spigelman M, Getahun H, Menzies D, Raviglione M. Tuberculosis. Nat Rev Dis Primers. 2016; 2:16076. Doi: 10.1038/nrdp.2016.76

[2] Furin J, Cox H, Pai M. Tuberculosis. The Lancet. 2019; 393(10181):1642-56.

[3] World Health Organization. (2021). Global tuberculosis report 2021. Retrieved from https://www.who.int/publications/i/item/9789240037021

[4] Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM.An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respiratory Critical Care Med, 2006;174(8):935-52.

[5] Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: mechanisms and management. J ClinExpHepatol. 2013; 3(1):37-49. Doi: 10.1016/j.jceh.2012.12.001

[6] Vagvala SH, O'Connor SD. Imaging of abnormal liver function tests. Clin Liver Dis. 2018; 11(15):128-34.

[7] Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci.2001;38(4):263-355.

[8] Ramaiah SK. A toxicologist guide to the diagnostic interpretation of hepatic biochemical parameters. Food and Chemical Toxicol.2007; 45(9):1551-7.

[9] Oh RC, Hustead TR, Ali SM, Pantasari MN. Mildly elevated liver transaminase levels: causes and evaluation. Am Fam Physician. 2017; 96(11):709-15.

[10] Levitt DG, Levitt MD. Human serum albumin homeostasis: a new look at the role of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. Int J Gen Med. 2016; 9:229-55.

[11] Panditt A, Pandey AK. Liver dysfunction in pulmonary tuberculosis patients on dots: a study and review. J GastroenterolHepatol Res. 5(6):2254-60.

[12] Zhang Y, Shi W, Zhang W, Mitchison D. Mechanisms of Pyrazinamide Action and Resistance. MicrobiolSpectr. 2013; 2(4):1-12.

[13] Claesson A, Spjuth O. On mechanisms of reactive metabolite formation from drugs. Mini-Rev Med Chem. 2016; 13(5):720-29.

[14] Woolbright BL, Jaeschke H. Mechanisms of inflammatory liver injury and drug-induced hepatotoxicity. CurrentPharmacol Rep. 2018; 4:346-57.

[15] Torino C, Mattace-Raso F, van Saase JL, Postorino M, Tripepi GL, Mallamaci F, Zoccali C, Progredire Study Group. Oxidative stress as estimated by gamma-glutamyl transferase levels amplifies the alkaline phosphatase-dependent risk for mortality in EKSD patients on dialysis. Oxidative Med Cell Long. 2016; 2016:8490643.

[16] Olaniyan OA, Olowookere AK, Adelakun AA, Olaniyi, JO, Zakariyau TO, Adeniji TW, Olaniyan AM, Oguntola AM, Taiwo SS. Assessment of selected liver enzyme activity in patients with rifampicin-resistant tuberculosis receiving treatment at a tertiary healthcare facility, southwest Nigeria. Afri J ExpMicrobiol.2022; 23(2):209-14.

[17] Patel A, McKeown DA. Hepatotoxicity of tuberculosis therapy: implications for public health.J Clin Tuberculosis and Other Mycobacterial Dis.2012; 8(1):10-6.

[18] Singh R, Dwivedi SP, Sharma V. Hepatotoxicity induced by anti-tuberculosis drugs and its management. J ClinExpHepatol.2011;1(3):213-26.