Liver Function Monitoring during the Intensive Phase of Tuberculosis Treatment: A Case Study in Western Kenya

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ABSTRACT

Background: Tuberculosis (TB) remains a major public health concern worldwide, despite the availability of effective therapies for many decades. It continues to contribute significantly to illness, disability and mortality. While treatment is effective, adverse drug reactions affecting the liver can complicate management and undermine therapeutic success. Establishing multifaceted pharmacovigilance approaches provides the most viable avenues of understanding patient needs and appropriate response.

Objective: This study aimed to assess the prevalence of hepatic impairment caused by anti-tuberculosis drugs among newly diagnosed patients receiving treatment for drug-sensitive tuberculosis.

Methodology: The study was conducted among participants aged 18 years and above.

Results: The Aspartate Transaminase (AST) and Alanine Transaminase (ALT) individually presented no noticeable significance both at initial and during treatment. However, the AST/ALT ratio remained significantly high possibly due to slow recovery after TB induced muscle wastage. There was a significant elevation of alkaline phosphatase (ALP) for cases at baseline, median 269.5 U/L, p value < 0.0001 but reduced to 243.0, p value 0.056. Total protein was within reference range but with low albumin and higher globulin values at baseline, p value < 0.0001, this improved over treatment duration, p = 0.093

Conclusion: Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) tests provided additional value in the diagnosis of extra pulmonary tuberculosis and treatment monitoring.

Keywords: Tuberculosis, Safety, surveillance.

INTRODUCTION

Tuberculosis (TB) is an infectious disease that significantly contributes to global illness and remains one of the top causes of death from a communicable disease worldwide. It is caused by the Mycobacterium tuberculosis complex bacteria [1]. In 2022, tuberculosis affected approximately 10.6 million people globally, leading to around 1.3 million deaths. This is quite regrettable for a disease that is curable and preventable. Sub-Saharan Africa and South-East Asia carry the greatest burden of tuberculosis worldwide. Studies showed that TB is not evenly distributed in the World and even within each country, there are variations both at National and Sub national level [2]. According to NTLDP report of 2020, an estimated 32,000 died from the disease [3]. Preventive strategies in Kenya include TB Preventive therapy to asymptomatic contacts of bacteriologically confirmed patients and special groups such as HIV infected clients, health care workers and other hospital staff members, prisoners and prison staff for 3 months using Isoniacid/Rifapentine or 6 months of Isoniacid therapy based on different patient categories [4].

Control of TB requires that patients are diagnosed early using World Health Organization (WHO) recommended diagnostic tools and right therapies to be initiated [5]. The standard treatment regimen for drug-sensitive tuberculosis (TB) involves a six-month course using isoniazid, rifampicin, pyrazinamide and ethambutol, followed by a four-month treatment phase with isoniazid and rifampicin (2RHZE/4RH). The concurrent administration of multiple drugs is a risk factor for liver injury [6, 7, 8].

Globally, liver injury due to anti-tuberculosis treatment ranges from 2% to 28% with considerable variation observed across different populations and geographic regions [7, 8]. This makes it important to conduct ongoing monitoring of medication safety through post-marketing surveillance as adverse drug reactions (ADR) can still appear after randomized controlled trials have concluded [9,10].

The liver is the major organ for metabolism through phase I and phase II reactions and secretion of the hydrophilic drug metabolites into the blood for excretion from the body [11]. However in Kenya, routine liver function tests are not offered to patients on drug-sensitive TB patients.

Therefore, the aim of this study was to determine the effect of anti-tuberculosis drug therapy on the liver injury among patients who were newly diagnosed with tuberculosis and initiated on TB treatment in Western Kenya. Currently, only multi drug resistance TB patients are monitored for organ dysfunction including the liver.

MATERIALS AND METHODS

Study Site: The study was carried out in Lurambi Sub-County, located within Kakamega County, where the Kakamega County General Hospital (KCGH), which is the regional referral facility. Kakamega County is situated in the western region of Kenya, approximately 400 km from the Capital city of Nairobi. The County spans about 3,051.3 square kilometers. Based on the 2019 Kenya Population and Housing Census [12], Kakamega

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had a population of 1,867,579, ranking as the fourth most populous county after Nairobi. With a fertility rate of 3.4%, its projected population for the year 2025 is about 2,072,565.

The main economic activities are crop production (maize, sugar cane, cassava, beans & horticulture), Livestock rearing, entrepreneurship and artisanal mining. The County has an absolute poverty rate of 35.8%, slightly below the national rate of 36.1%. In terms of monetary poverty rate, it stands at 35.1% against the Kenyan rate at 35.7%. However, the food poverty rate is a bit higher at 33.3%, while the national rate stands at 32.0% [13].

Study design: Study design is a broad plan of how the research objectives shall be answered [14]. This was a longitudinal observational study with healthy control population.

Study population: The study population consisted of male and female participants aged 18 years and above, who were recently diagnosed with tuberculosis (TB), initiated treatment within the first two weeks of diagnosis and had no prior history of TB treatment. *C*onsecutive sampling technique was used to recruit patients into the study. This involved recruiting any patient who consented to be included as they presented themselves for health care.

Patients were identified through a positive laboratory result for TB using either Molecular Genexpert test or microscopy. Those with a negative laboratory results, TB signs and symptoms and a suggestive imaging result were classified as clinically diagnosed, hence recruited as study participants. Healthy individuals (control group) usually from blood transfusion unit were enrolled after screening for TB signs and symptoms. Biodata and venous blood collection was done to all the consented participants.

Exclusion criteria: Patients who had been on treatment for more than two weeks, or had previously completed a full course of TB therapy with relapse and individuals who declined to give consent or chose to withdraw before the study was completed were also excluded.

Sample size determination: A sample refers to a subset of individuals or elements selected from a larger population, possessing the relevant study characteristics, and is used to make inferences about the entire population. The size of the sample has an effect on the application and use of results. If the sample size is too small, it does not rule out a result effect due to random variations while a large sample size may give a statistically significant result if when the difference is not meaningful, may also require a lot of resources [15]. An annual average of 541 drug-sensitive TB patients for the period 2017 – 2019 in Lurambi Sub County [16]. Sample size was determined using power of 80%, sample size effect of 0.4 (medium effect) and at significance level (α) 0.05. An G-Power electronic calculator tool was used and gave the sample size of 44 participants.

Laboratory procedures: Liver function tests (LFTs) were performed using Humastar 100™ automated clinical chemistry analyzer as per the stated principles. The specimens were analyzed based on the general principle of enzyme kinetic test for ASA and ALT where NADH substrate was converted to NAD. The rate of NADH loss was measured spectrophotometrically at 340 nm. The ALP principle was based on the ability of the ALP enzyme to catalyze the hydrolysis of colourless p-nitrophenyl phosphate to a coloured p-nitrophenol compound. The color intensity generated during the reaction is directly related to the enzyme's activity and was measured at a wavelength of 405 nm. The estimation of GGT is based on its catalytic action on specific substrates, such as L-γ-Glutamyl-3-Carboxy-4-nitroanilide, which results in the formation of a colored product detectable at 405 nm. The depth of the color formed reflects the concentration of GGT in the sample. Serum total protein was determined using the Biuret method, where peptide bonds interact with Copper (II) sulfate in an alkaline environment to yield a purple-colored complex, which was quantified at 540 nm. The intensity of this color is directly proportional to the protein concentration in the specimen. Albumin was estimated using the Bromo-Creseol Green (BCG) reaction. BCG dye binds to albumin in a slightly acidic medium to form a green coloured compound which was detected at 620 nm. The colour intensity directly corresponds to the albumin concentration in the specimen. Both total and conjugated bilirubin were analyzed on the principle of Modified Jaffe' reaction. Bilirubin reacts with diazotized Sulphanilic acid to form a purple coloured Azobilirubin, which was measured at 540 nm. The measurement of unconjugated bilirubin which is a component of total bilirubin utilizes the same principle, however an accelerator was required e.g. Methanol/DMSO for it to react. The intensity of the resultant colour is directly proportional to the bilirubin concentration [17].

Ethical Consideration and safety: Permission to undertake this study was granted by MMUST Directorate of Post Graduate Studies Ref: MMU/COR: 509099. Ethical approval for the study was obtained from the Institutional Ethics Review Committee (IERC) of Masinde Muliro University of Science and Technology (MMUST), Ref No: MMUST/IERC/32/19 and the National Commission for Science, Technology and Innovation (NACOSTI), Ref No. 923427. Informed consents were obtained from the study participants. The patients' safety during specimen collection was safeguarded by use of competent personnel. Standard phlebotomy

procedures were employed. Confidentiality of the clients' information or results was assured by use of their unique registration numbers for identity. This study did not introduce any foreign products to the participants. Therefore, the only foreseeable risks were some level of discomfort during specimen collection and rarely infection at puncture site. The research followed the guidelines laid out in the Declaration of Helsinki.

Statistical Analysis

Data for patients' demographics and clinical characteristics were collected using a laboratory questionnaire. All the participants' data were transcribed to Microsoft excel document before analysis. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20. The Mann–Whitney U test was used for continuous variables and results were presented as numbers, median, ranges. Percentages were used to establish those below or above the reference ranges. P value ≤ 0.05 was deemed significant.

RESULTS

Evaluation of LFT markers concentration among study participants for both patients and healthy controls

The cases at baseline did not show any significant difference in the values for both ALT compared to controls (20 U/L, 4.0 – 90.0 U/L; 22.0 U/L, 14.0 – 51.0 U/L; p=0.052)) or cases AST (29.5U/L, 6.0 – 131.0 U/L; controls 29.0, 8.0 – 82.0 U/L; p = 0.415). The AST/ALT ratio at baseline was significant for cases who had n = 30 (63.5%) with a value above 1.3 but with significantly high range (1.6; 0.2 – 5.3,) unlike the controls who had n = 13 (25.0 %) but with range (0.9; 0.9 – 2.0) very close to the reference value for the same value. This big variation in AST/ALT ratio was most likely associated with muscle wastage due to TB cachexia. After eight weeks of treatment in the case group, no significant changes were observed in the levels of transaminases (ALT: 20 U/L, 7.0 – 45.0 U/L; p = 0.785; AST: 32 U/L, 18.0 – 61.0 U/L p = 0.567). There was no significant change in the AST/ALT ratio at endpoint than at baseline (median 0.9, p-value 0.0001) where 26 (55.3%) cases recorded a ratio above 1.3, unlike at baseline which had a record of 30 (63.8%) (Table 1).

The GGT value at baseline was not significant in relation to the control population (29.0 U/L, 6.0 – 156.0 U/L; 37.0 U/L, 8.0 – 362.0 U/L; p=0.317) compared to endpoint value for cases (71.0 U/L, 7.0 – 189.0; p=0.033). Since GGT is a liver specific marker, this demonstrates that the medicines had an effect on the liver. The values for ALP were significantly high for cases at baseline (269.5 U/L, 160 – 767 U/L; ALP > ref range; n=41, 87.2%) when compared to controls (180.5 U/L, 103 – 307 U/L; ALP > ref range; n=30, 57.7%) p = <0.00001. At endpoint, the value for cases was significantly reduced towards the reference value (243 U/L, 91.0 – 441 U/L; p = 0.056). This indicates that the bacterial activity had an impact on the production of ALP in the body (Table 1).

At baseline, the value of both direct bilirubin for cases versus the controls (Median = 4.4 umol/L; 5.4 umol/L, p value 0.026) and total bilirubin (median 10.2 umol/L; 14.4 umol/L, p value <0.0001). The values below the reference range for bilirubin do not have any medical significance. These values were still within the population reference ranges. The result compared well with the fact that bilirubin is a delayed marker for liver disease (Table 1).

Both total bilirubin (median 13.1 umol/L, p-value 0.234) and direct bilirubin (median 4.8 umol/L, p-value 0.582) did not have any notable significance for cases at endpoint versus the baseline report (Table 1).

Total protein for cases at baseline (median = 77.0 g/L) was not significant in relation to controls (median= 73.0 g/L). Albumin was relatively low for cases at baseline (median = 37.0 g/L) versus the controls (median= 48.0 g/L). Hypoalbunemia was more pronounced in cases at baseline (n = 23, 48.9%) than in controls (n = 1, 2.1%). Cases at baseline had a higher concentration of globulin (median 41.0 g/L) than controls that had a median of 26.0 g/L. The frequency of hyperglobulinemia was higher for cases at baseline, (n=35, 74.5%), while controls recorded an insignificant value (n = 5, 9.6%). TB bacteria has a high ability to act as a super antigen that leads to the production of non-specific immunoglobulins. Additionally, TB infection causes both humoral and cell-mediated immunological response. The cytokines produced such as IL-6 have ability to increase permeability of blood vessels and cause excessive leakage of albumin, TB infection is accelerated in under nutrition status. This explains some the mechanism for reduced albumin in the body (Table 1).

In the case group, endpoint measurements of total protein, albumin, globulin, and the albumin-to-globulin ratio (81.0 g/L, p = 0.100; 39.5 g/L, p = 0.093; 41.0 g/L, p = 0.157; and 1.0, p = 0.579, respectively) did not show significant differences compared to baseline values. There were 17 cases with low albumin values, down from 23 cases at baseline. Additionally, the cases at endpoint with high globulin levels and albumin globulin ratio dropped from 35 to 30 and 30 to 25 cases. These results suggest that liver function tests are a useful tool as a pointer to disease status and may provide additional information especially in extra-pulmonary TB where TB bacilli may not be demonstrated by laboratory techniques (Table 1).

Table (1): Evaluation of liver function parameters for healthy controls and patients at baseline and during follow-up

Analyte	Baseline		p*	8 weeks	p**
	Controls	Cases		Cases	
ALT (U/l)	22.0 (14.0 – 51.0)	20.0 (4.0 – 90.0)	0.052	20.0 (7.0 – 45.0)	0.785
Ref range - 5 – 55U/L					
<ref range (n, %)	2 (3.8)	3 (6.4)	0.249	2 (4.3)	0.476
>ref range (n, %)	6 (11.5)	2 (4.3)		0 (0.0)	
AST (U/l)	29.0 (8.0 – 82.0)	29.5 (6.0 – 131.0)	0.415	32.0 (18.0 – 61.0)	0.567
Ref range – 15.0 – 40U/L					
<ref range (n, %)	2 (3.8)	3 (6.4)	0.586	0 (0.0)	0.257
>ref range (n, %)	6 (11.5)	12 (25.5)		8 (17.0)	
AST/ALT ratio:	0.9 (0.9 – 2.0)	1.6 (0.2 – 5.3)	**<0.0001**	1.5 (0.7 – 6.8)	0.601
>1.3 (No., %)	13 (25.0)	30 (63.8)		26 (55.3)	
GGT (U/l)	37.0 (8.0 – 362)	29.0 (6.0 – 156.0)	0.317	71.0 (7.0 – 189.0)	**0.033**
Ref range 10 – 90U/L					
<ref range (n, %)	3 (5.8)	3 (6.4)	0.617	1 (2.1)	0.162
>ref range (n, %)	3 (5.8)	4 (8.5)		9 (19.1)	
ALP (U/l)	180.5 (103 – 307)	269.5 (160 – 767)	**<0.0001**	243.0 (91 – 441)	0.056
Ref range 47 – 174U/L					
<ref range (n, %)	0 (0.0)	0 (0.0)	**<0.0001**	0 (0.0)	**<0.0001**
>ref range (n, %)	30 (57.7)	41 (87.2)		34 (72.3)	
Total bilirubin (μmol/l)	14.4 (1.6 – 76.4)	10.2 (3.1 – 53.9)	**<0.0001**	13.1 (2.6 – 33.1)	0.234
Ref range 5.3 – 43.0umol/L					
<ref range (n, %)	3 (5.8)	7 (14.9)	0.175	1 (2.1)	0.889
>ref range (n, %)	3 (5.8)	1 (2.1)		0 (0.0)	
Direct bilirubin (μmol/l)	5.4 (1.5 – 13.7)	4.4 (0.0 – 31.8)	**0.026**	4.8 (0.1 – 26.8)	0.582
Ref range 1.1 – 8.8 umol/L					
<ref range (n, %)	0 (0.0)	5 (10.6)	**0.020**	2 (4.3)	0.167
>ref range (n, %)	8 (21.2)	4 (8.5)		7 (14.9)	
Total protein (g/l)	73.0 (59.0 – 96.0)	77.0 (58 – 98.0)	0.304	81.0 (42.0 – 102.0)	0.100
Ref range 67.0 – 83.0g/L					
< Ref range (n, %)	3 (5.8)	7 (14.9)	0.600	3 (6.4)	0.156
>Ref range (n, %)	6 (11.5)	12 (25.5)		15 (31.9)	
Albumin (g/l)	48.0 (40.0 – 63.0)	37.0 (18 – 55.0)	**<0.0001**	39.5 (25.0 – 61.0)	0.093
Ref range 39.0 – 50.0					
Hypoalbuminaemia (n, %)	1 (2.1)	23 (48.9)	**<0.0001**	17 (36.2)	0.377
Hyperalbuminaemia (n, %)	17 (36.2)	3 (6.4)		4 (8.5)	
Globulin (g/l)	26.0 (13.0 – 89.0)	41.0 (15.0 – 73.0)	**<0.0001**	41.0 (17.0 – 69.0)	0.157
Ref range 28.0 – 33.0 (g/L)					
Hypoglobulinemia (n, %)	31 (59.6)	4 (8.5)	**<0.0001**	6 (12.8)	0.317
Hyperglobulinemia (n, %)	5 (9.6)	35 (74.5)		30 (63.8)	
Albumin/globulin ratio	2.0 (0.8 – 4.2)	1.0 (0.3 – 3.3)	**<0.0001**	1.0 (0.5 – 3.2)	0.579
>Ref range (n, %)	3 (5.8)	30 (63.8)		25 (53.2)	

Continuous variables are presented as median values with ranges, while categorical variables are expressed as counts (n) and percentages (%). **ALT** refers to alanine aminotransferase, **AST** to aspartate aminotransferase, **GGT** to gamma-glutamyl transferase and **ALP** to alkaline phosphatase. Comparisons were carried out between cases and controls at baseline (p*) and between baseline and endpoint within cases (p**) using the Mann–Whitney U test. Statistically significant values are highlighted in bold at p ≤ 0.05.

DISCUSSION

Regarding the effect of Anti-TB drugs on the development of liver dysfunction, The ALT and AST enzymes are markers of acute liver cell damage [18]. There were no significant differences between the markers at baseline for cases as well as during intervention. The AST/ALT (De Ritis) ratio is often used to assess the extent of liver cell damage, with higher values generally indicating a poorer prognosis. An elevated ratio is commonly linked to liver injury. Increasing ratio of more than 1.3 was used to classify the degree of damage to hepatocytes indicative of increasing degree of liver cirrhosis, while a ratio equal or below 1.3 was considered normal [19,20]. There was statistically significant elevated AST/ALT ratio at baseline mostly likely associated with TB cachexia than at endpoint, which showed marked improvement caused by disease clearance. An earlier study established that the risk of liver injury or failure for patients occurring in > 8 weeks were higher than those that occurred within 8 weeks during anti-TB treatment, even in patients not at high risk of liver injury [21]. The level of ALP at baseline was significantly high but the values declined during follow – up. This result correlates well with another study that demonstrated that 72.2% of patients with cervical TB lymphadenitis had increased values, which showed gradual decline at the rate of 33.4U/L reduction every 15 days [22].

The level of Gamma-glutamyl transferase (GGT) showed a significant increase from baseline with 8.5% of the patients being above reference range to 19.1% of patients above reference range and an elevated median of 71.0 U/L against the baseline median of 37.0 U/L. The findings of this study align with another report in Nigeria, which documented a progressive rise in median GGT levels over a six-month period among patients undergoing treatment with either Pyrazinamide or Rifampicin [23]. Both medications are recognized for their hepatotoxic potential and are thought to cause an early elevation in GGT, followed by gradual adjustment as the body adapts. GGT, an enzyme predominantly located in the liver, is essential for regulating intracellular glutathione levels and is frequently employed as a biomarker for liver or biliary tract disorders. Glutathione itself is a naturally occurring antioxidant that supports the detoxification of reactive metabolites [24].

There was no significant observation in the levels of bilirubin at both baseline and follow-up. Also, there was no significance noted in total protein at baseline and during treatment at follow-up. However, albumin value was significantly low at baseline with no significance at follow-up. This affected the albumin/globulin ratio to be also significantly high at baseline but showed improvement at follow-up. During infection, more antibodies (globulins) are produced to fight the infection leading to increased levels which reduces as the infection is cleared from the body. The synthesis of albumin can be suppressed by pro-inflammatory mediators, including interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α). These cytokines lead to increased capillary leakage responsible for the vascular permeability, which is a result of various factors including the effects of cytokines such as TNF-alpha and IL-6, chemokines, prostaglandins and complement components [25]. In tuberculosis, the infection influences how Interleukin-6 (IL-6) is produced. Accumulation of IL-6 and other cytokines as IL-1 and TNF are important in the induction of acute phase response [26]. On the other hand, most patients presented with under-nutrition, which affect albumin synthesis, but during treatment, there was significant improvement in nutrition status, hence improved albumin levels.

The results for patients indicated low albumin median levels of 37.0 g/L at treatment initiation though there was a steady increase during the 2 months of treatment follow-up to 39.5 g/L. These results are supported by other studies [19, 27], which demonstrated a steady increase from median albumin concentration during treatment towards the health control median. The increase in albumin was closely linked to better patient outcomes as low albumin levels were associated with higher prevalence of Anti-Tuberculosis drug-induced liver injury as a result of malabsorption of medicines from circulation for long and cause toxicity [28]. Majority of patients **(**74.5%) had globulin value that was significantly raised at initiation as compared to 63.8% after 2 months of treatment. These results are consistent with a cross sectional study done in India where globulins, especially gamma fraction was elevated in patients newly diagnosed with pulmonary TB, while total protein and albumin was significantly reduced [29].

CONCLUSION AND RECOMMENDATIONS

There was significant increase in alkaline phosphatase (ALP) values at baseline line evaluation and gradually reduced towards the reference ranges during treatment. Gamma-glutamyl transferase (GGT) values increased considerably during the two months treatment follow-up with not much increase in ALP. This was indicative of liver injury due to TB medicines that may have been coupled with other patient dynamics. This study; therefore, recommends that performing ALP provides an added advantage especially in supporting diagnosis of EPTB. The study further recommends estimation of liver function markers to detect any challenges early and correct them.

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