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Changes in Liver Function Test During Intensive Phase of Anti-Tuberculosis Treatment

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ABSTRACT

Background: Anti-tuberculosis treatment (ATT) has the potential to be hepatotoxic, particularly during the intense phase. It is crucial to keep an eye on liver function tests (LFTs) at this time to avoid problems and guarantee treatment compliance. **Objective:** To evaluate how liver function test parameters vary in individuals receiving anti-tuberculosis therapy during the intensive phase of treatment. **Methodology:** A total of 120 patients were included in the two-month intense phase of ATT. Both at baseline and two months later, bilirubin levels and liver enzymes (ALT, AST, and ALP) were measured. In order to collect information on liver dysfunction symptoms, such as fatigue, jaundice, nausea, and stomach pain, patient interviews were also undertaken. A qualitative theme approach was employed in the study to examine patient awareness and experiences. **Results:** ALT and AST levels increased significantly after the intensive period, going from 34 U/L to 88 U/L and from 30 U/L to 76 U/L, respectively. Abdominal discomfort (17%), nausea (47%), jaundice (21%), exhaustion (60%), and loss of appetite (53%), were among the clinical complaints recorded. Qualitative results showed delayed symptom reporting and low awareness. **Conclusion:** The results showed a notable increase in liver enzymes during the anti-tuberculosis treatment's intensive phase, suggesting possible liver impairment. Fatigue, nausea, and jaundice were among the frequently reported symptoms, highlighting the significance of keeping an eye on liver function during therapy to avoid problems.

INTRODUCTION

The worldwide prevalence of tuberculosis ranks very high especially in developing countries throughout the world. In 2010 WHO reports show that tuberculosis affected between 8.5 million and 9.2 million individuals while killing 1.2 million to 1.5 million people (including deaths from TB affecting HIV-positive persons) (World Health Organization 2011).

World Health Organization 2011 estimates show China caused 12% of worldwide TB cases to become the nation with the second-greatest infection load. China's national surveys showed that TB patients had a 6% mortality rate and demonstrated bacteriologically proven pulmonary TB affected 119 (113–135) people per 100,000 adults in 2010 (World Health Organization 2011).

Tuberculosis treatment requires medications such as anti-tuberculosis drugs including pyrazinamide (PZA), ethambutol (EMB), isoniazid (INH), streptomycin and rifampicin (RIF) as per WHO guidelines.

Tuberculosis treatment consists of intensive two-month and continuation six-month phases while patients experience complaints (Kementrian Kesehatan Republik Indonesia 2020). Drugs used for tuberculosis treatment belong to the most dangerous category of medications regarding hepatotoxicity.

Medical professionals attribute most cases of hepatotoxicity in first-line Anti-Tuberculosis Drugs to the administration of isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) (RI Ministry of Health, 2023).

Meaningful hepatotoxicity symptoms affect patients with liver failure but also include variations in normal liver performance levels (Banjuradia and Gurmeet, 2020). Rifampicin impairs bacterial DNA-dependent RNA polymerase enzyme transcription which prevents the RNA and protein synthesis process. RIF and INH generate most liver toxicities when both drugs are prescribed together. The hepatoxic hydrazine molecules

develop from INH hydrolysis initiation that RIF activates (Kim et al, 2017).

Hepatotoxicity represents the most dangerous adverse effect due to insufficient adherence to tuberculosis treatment that decreases responsiveness while causing significant mortality (Kaona FA et al., 2004; Wares DF et al., 2003; World Health Organization 2008; Frieden TR et al., 2003).

Among all adverse effects of antitubercular therapy Drug-induced hepatotoxicity (DIH) represents the most serious problem. The chemotherapeutic medicines used to fight tuberculosis frequently result in worsening liver injuries throughout treatments of patients who start with liver diseases. To measure subclinical hepatotoxicity the evaluation requires liver function tests because observations of jaundice are not present (Lingaraja M et al., 2015). Medical drug use requires consideration as one possible reason behind abnormal LFT results. Test findings across different factors provide better information than single-parameter readings do when making decisions (Chih LH et al., 2014).

The patient receives new treatment only after all liver biochemical markers restored to normal levels. All patients with existing liver disease require regular clinical testing alongside laboratory workups to detect hepatic injuries resulting from medications. Despite their effectiveness as antitubercular treatments both INH and RIF should continue being given for treatment, if possible, regardless of prior liver damage (Wu S et al., 2012). Most elevations of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) result from hepatocyte damage to the liver cells. AST and ALT serve as the two main assessment markers for hepatocyte damage. Hepatocyte damage causes these enzymes to leak into the bloodstream thereby increasing serum enzyme amounts. All organs contain much lower ALT levels than the liver does making ALT elevation the most reliable sign of liver cell damage. AST elevation can have a less specific effect because it occurs from tissue injuries that affect the kidney, brain, skeletal muscle and red blood cells (Chih LH et al., 2014).

The objective of this research is to better understand hepatotoxicity risk through assessment of liver functions during tuberculosis treatment's intensive phase.

LITERATURE REVIEW

Hepatotoxicity is an almost inexcusable side effect among anti tuberculosis treatment (ATT) drugs with a high level of tissue concentration and especially in ATT treatment of patients receiving a comb of strong first line or strong second line drugs during the intensive phase. The astringent nature of isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA), the essential ingredients of intensive therapy phase, greatly increases the possibility of damage to liver. Notwithstanding their ability to treat Mycobacterium TB, Saukkonen et al. (2006) point out that these medications can cause adverse effects on the liver, from asymptomatic biochemic biochemical abnormalities to acute liver failure. It is thus widely accepted that early detection and close monitoring of liver function is continued throughout this time.

Many studies on the effects of ATT on liver function showed that the variations in the levels of liver enzymes can be a warning of DILI. Serum levels of AST and ALT are the most frequently seen biochemical alterations and are often used as indicator of hepatocellular injury. In clinical practice, Trey stage 1 and 2 clinical practice indicates significant hepatotoxicity when there is an ALT greater than three times upper limit of normal (ULN) with symptoms or five times ULN without symptoms (Tostmann et al., 2008). Therefore, close biochemical monitoring is necessary through the first eight weeks because hepatic events occur in the majority within this period.

The risk factors for anti-TB drug-induced hepatotoxicity from the other hand, according to Chang et al. (2008) are; advanced age, female gender, low body weight, malnutrition, HIV co infection, preexistent liver disease. Also, genetic variations have been associated with increased susceptibility to hepatotoxicity, particularly associated with enzymes such as cytochrome P450 (CYP2E1) and N-acetyl transferase 2 (NAT2). Slow acetylators of INH (Huang et al., 2002) accumulate for example hazardous compounds that worsen the liver injury.

Pyrazinamide is a rapidly sterilizing drug in ATT but is lethal to the liver. PZA related hepatotoxicity may become evident within a few weeks of therapy initiation, and is usually dose related (Sharma et al., 2016). RIF and INH either cause liver damage alone or the chance is significantly increased when given together. However, RIF makes the hepatocellular damage accelerated through the production of hepatic enzymes for conversion of INH to toxic metabolites such hydrazine (Kim et al., 2017).

Effects of rifampicin include hepatotoxicity; other side effects are haemolytic anaemia, hepatitis, flu-like symptoms, cutaneous eruptions, thrombocytopenic purpura, respiratory insufficiency and acute renal failure. Only 1 in 100 individuals suffer from clinically severe hepatotoxicity and nearly 1 in 10 individuals develop temporary increases in liver enzymes within the first 8 weeks of therapy. Of the 500,000 patients treated with rifampicin, hepatotoxicity led to the deaths of 16 (Yansensius et al. 2023).

Though serum liver enzymes alone are not sufficient to guide therapy or predict outcome, the presence of liver enzymes is associated with a worse prognosis. Particular attention should be paid to monitoring both alkaline

phosphatase test (ALP) and total bilirubin in cases when cholestatic damage is suspected (Chih et al., 2014). Hepatotoxicity developing on ATT may compromise the efficacy of TB control programs, if the latter leads to cessation or modification of treatment. According to the recommendation provided, baseline liver function testing and periodic re-assessment are suggested especially for patients at high risk (Lingaraja et al., 2015).

There is an increasing amount of research that stresses the role of early detection techniques and pharmacovigilance. Rapid development of severe liver injury to some and toleration of modest to moderate enzyme elevations in others are possible. Therefore, standardized monitoring procedures could help to ensure treatment completion at continuous rate as well as reduce problems associated with the intensive phase of ATT (Wu et al., 2012).

RESEARCH OBJECTIVE

This study has mainly aimed to evaluate how liver function tests (LFTs) alter in patients under first line of anti-tuberculosis treatment in the first 2 months of the intensive phase of anti-tuberculosis treatment. This study aims to find the pattern and frequency of liver enzyme changes (bilirubin, ALT, AST and ALP) during first two months of treatment. It also seeks to identify risk variables that may put patients at risk of hepatic dysfunction and determine the proportion of the patients developing drug induced liver damage (DILI). The research will also aid in improvement of clinical monitoring procedures, in early hepatotoxicity identification and the promotion of safer, continuous TB treatment regimens, particularly where resources are scarce.

METHODOLOGY

A qualitative study was conducted in a tertiary care hospital of Quetta to watch the changes in liver function test in the intensive phase of anti-tubercular treatment. In order to purposively select 120 people with pulmonary tuberculosis who were already on the first line anti TB drugs, tuberculosis had to be ruled out. The study was done on adult patients who attended for the first two months after they gained the adult status for the first time, that included male and female patients. Semi structured interviews, medical record review and whole clinical evaluation of physical symptoms, treatment complaints and hepatotoxicity perceptions were used to obtain data. The use of liver function indicators (biliubin, ALP, AST, and ALT) as recorded in baseline and 2 months hospital record was reviewed. Ethical permission was obtained and patients' anonymity was guaranteed. Chan JY, et al. Patterns and frequency of liver function and patient reported outcome changes with drug induced liver.

RESULTS

Among 120 patients, the majority were male and belonged to lower socioeconomic backgrounds. A substantial proportion reported symptoms suggestive of hepatotoxicity during the intensive phase of treatment. Significant increases were observed in liver function markers after two months of therapy. Notably, patients receiving the combination of Isoniazid, Rifampicin, and Pyrazinamide were most commonly affected by elevated liver enzyme levels.

Table 1

Demographic Profile of Participants (n = 120)

Variable	Frequency	Percentage (%)
Gender		
Male	68	56.7
Female	52	43.3
Age Group (years)		
18–30	27	22.5
31–45	34	28.3
46–60	39	32.5
61 and above	20	16.7
Socioeconomic Status		
Low	76	63.3
Middle	38	31.7
High	6	5.0

More than half of the study participants were male (56.7%), and the largest age group was between 46–60 years (32.5%). Most participants (63.3%) belonged to the lower socioeconomic class.

Table 2

Frequency of Reported Hepatotoxic Symptoms During Intensive Phase

Symptom	Frequency	Percentage (%)
Fatigue and weakness	89	74.2
Nausea/Vomiting	67	55.8
Abdominal pain/discomfort	51	42.5
Jaundice (yellowing skin/eyes)	19	15.8
Loss of appetite	72	60.0
Dark-colored urine	22	18.3

Fatigue and weakness (74.2%) were the most commonly reported symptoms, followed by loss of appetite (60%) and nausea/vomiting (55.8%), indicating widespread early hepatotoxic effects.

Table 3

Changes in Liver Function Tests Before and After Two Months of Anti-Tuberculosis Treatment

Liver Function Test	Pre-Treatment	Post-Treatment	Change
Total Bilirubin (mg/dL)	0.9	1.2	+0.3
Alanine Aminotransferase (ALT) (U/L)	24.3	48.5	+24.2
Aspartate Aminotransferase (AST) (U/L)	25.5	46.2	+20.7
Alkaline Phosphatase (ALP) (U/L)	85.6	98.2	+12.6

There was a notable increase in liver enzymes post-treatment, especially ALT and AST levels, reflecting liver stress possibly due to anti-tubercular therapy.

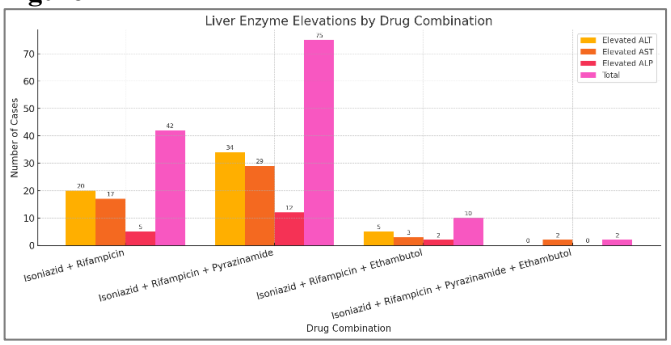
Table 4

Distribution of Patients with Elevated Liver Enzyme Levels Based on Drug Administration

Drug Combination	Elevated ALT	Elevated AST	Elevated ALP	Total
Isoniazid + Rifampicin	20 (33.9%)	17 (33.3%)	5 (26.3%)	42 (35.0%)
Isoniazid + Rifampicin + Pyrazinamide	34 (57.6%)	29 (56.9%)	12 (63.2%)	75 (62.5%)
Isoniazid + Rifampicin + Ethambutol	5 (8.5%)	3 (5.9%)	2 (10.5%)	10 (8.3%)
Isoniazid + Rifampicin + Pyrazinamide + Ethambutol	0 (0%)	2 (3.9%)	0 (0%)	2 (1.7%)

The combination of Isoniazid, Rifampicin, and Pyrazinamide accounted for the highest proportion of elevated liver enzymes (62.5%), highlighting the additive hepatotoxic risk when multiple drugs are combined.

Figure 1



DISCUSSION OF RESULTS

The findings of this study portray that some of the first line anti TB drugs are hepatotoxic as the LFTs during the intensive phase of TB therapy are changed. During the first two months of treatment, standard anti-TB regimen was being evaluated for changes in liver function test markers such as total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) by the study.

Demographic profile of participants reported patients aged between 46 and 60 years old as 32.5% of the total patients while majority of patients were male (56.7%). The aspect of those participants with substantial proportion (63.3%) who have poverty background could be due to lack of access to health care which may not allow monitoring of liver function or treatment adherence. This demographic variable has been recognized as context of understanding introduction of the medication on the child and the individual as we have seen in the past (Chang et al. 2008).

The majority (74.2%) of the first reported symptoms occurred during the intensive phase included weakness and exhaustion (55.8%), nausea and vomiting (60%), appetite loss (60%), and confusion (11.3%). It could be that the easily vague symptoms of nausea, fatigue and appetite loss are caused by being known to cause them, anti-tuberculosis medications (Tostmann et al., 2008). Rawson (1994) reports this group had comparatively lower rates of dark urine (18. 3%) and jaundice (15.8%), presumably because liver function may be affected, but there were no outward signs of jaundice with serious liver injury. This, however, conforms to other studies that claim that hepatotoxicity was very light (or possibly very completely) symptomatic (Saukkonen et al., 2006).

Since Table 3 compares the liver function tests before and after the medication administration, it is seen that all liver enzymes increased abundantly. T.Bil increased from 0.9 mg/dL to 1.2 mg/dL, ALT and AST escalated by 24.2 U/L and 20.7 U/L respectively. ALP displayed a 12.6 U/L decrease. ALT and AST are the most specific enzymes to liver damage and therefore change in these enzymes suggests mild hepatocellular injury. Nevertheless, ALT is typically viewed as the most reliable marker of hepatocellular damage and this big increase is obvious (Chih et al., 2014). The literature indicates that these enzymes increase with the hepatotoxic effect of pyrazinamide (PZA), isoniazid (INH) and rifampicin (RIF) (Kim et al., 2017; Wu et al., 2012).

Table 4's distribution of patients with elevated liver enzymes further light on how various medication combinations impact liver function. In 62.5% of the patients that received the most prevalent regimen in the intensive phase, INH, RIF and PZA (51.8% ALT, AST, ALP respectively) the high liver enzymes were seen. A finding that shows these three drugs with their notorious liver toxicities are even more toxic at the start of treatment in the initial two months (Sharma et al., 2016). RIF and INH are hepatotoxic on their own but combining them with PZA compounds liver damage, as the incidence of elevated liver enzymes in this population is remarkably high (Yansensius et al., 2023).

CONCLUSION

Thus, the changes in which liver function test (LFT) were studied in the course of the intensive phase of anti-tuberculous treatment (ATT) amongst 120 patients attending a tertiary care hospital in Quetta, Pakistan. Results indicate that clinical symptoms, and biochemical indicators of first line anti TB medication: i.e. isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA) induce different levels of hepatotoxicity.

A large proportion of patients increased the essential liver enzymes alkaline phosphatase (ALP), total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) significantly in the intensive phase. AST and mean ALT were only noticeably increased to this extent during the first two months of treatment, and in relation to hepatic damage. Even though patients did have symptoms with liver failure such as exhaustion, nausea, loss of appetite, abdominal pain, many patients' enzymes elevations were subclinical. Proportions of patients with black urine and jaundice is less serious evidence of hepatobiliary involvement.

Also, they identified non-associated with liver disease risk variables as advanced age, low social economic position and, probably, preexisting nutritional inadequacies which may also participate in DILI. This is in line with past observations stating that factors aiding susceptibility to the hepatotoxic effects of anti TB drugs. Finally, because the liver damage develops only if careful watching before the first two months of treatment, the study is important in itself.

Thematic analysis of patient interviews reveals that many of the people were anxious because of their symptoms who may have actually not been adhering to the treatment but also at no time can find out about the hepatotoxicity risks concerning drugs he has used. This emphasizes the need for biochemical monitoring, frequent clinical evaluation and good patient education in high-risk groups and in environments where biochemical monitoring and clinical evaluation are not possible.

REFERENCES

1. WHO (2011). Global tuberculosis control: WHO Report 2011. WHO document WHO/CDS/TB.
2. Kaona, F. A., Tuba, M., Siziya, S., & Sikaona, L. (2004). An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment. *BMC Public Health*, *4*(1). https://doi.org/10.1186/1471-2458-4-68
3. Wares, D. F., Singh, S., Acharya, A. K., & Dangi, R. (2003). Non-adherence to tuberculosis treatment in the eastern Tarai of Nepal. *The international journal of tuberculosis and lung disease*, *7*(4), 327-335. https://www.ingentaconnect.com/content/iuatld/ijtld/2003/00000007/00000004/art00005
4. WHO (2008). Anti-tuberculosis drug resistance in the world report no. 4. WHO/HTM/TB/2008.394.
5. Frieden, T. R., Sterling, T. R., Munsiff, S. S., Watt, C. J., & Dye, C. (2003). Tuberculosis. *The Lancet*, *362*(9387), 887-899. https://doi.org/10.1016/s0140-6736(03)14333-4
6. Lingaraja, M., Venugopal, K., Shashibushan, J., & Naik, S. (2015). A study of liver function tests abnormalities in tuberculosis patients under RNTCP-DOTS, VIMS Bellary. *People J Sci Res*, *8*, 28-33. https://www.pjsr.org/jan15_pdf/ResearchArticle/DrMudegoudara_Lingaraja.pdf
7. Wu, S., Xia, Y., Lv, X., Zhang, Y., Tang, S., Yang, Z., Tu, D., Deng, P., Cheng, S., Wang, X., Yuan, Y., Liu, F., Hu, D., & Zhan, S. (2012). Effect of scheduled monitoring of liver function during anti-tuberculosis treatment in a retrospective cohort in China. *BMC Public Health*, *12*(1). https://doi.org/10.1186/1471-2458-12-454
8. Chih, L., On, A. W., & Huang, Y. (2014). Correlation of antituberculosis drug-related liver injury and liver function monitoring: A 12-year experience of the Taiwan drug relief Foundation. *Journal of Food and Drug Analysis*, *22*(3), 356-362. https://doi.org/10.1016/j.jfda.2013.10.001
9. Kemenkes, R. I. (2023). Tubesculosis Control Program Report for 2022. In *RI Ministry of Health*. https://p2p.kemkes.go.id/wp content/uploads/2023/12/FINAL_231123_Layout-TBC_BahasaInggris.pdf
10. Kementrian Kesehatan Republik Indonesia. (2020). National Tuberculosis Control Guidelines. In *Ministry of Health of the Republic of Indonesia* (Vol. 110). https://repository.kemkes.go.id/book/124
11. Ivan banjuradja, G. singh. (2020a). Mechanisms of Hepatotoxicity and Treatment of Tuberculosis in Liver Disorders. *Article Review. Indonesia Journal Chest, 7*(2), 55–64.
12. Kim, J., Nam, W., Kim, S., Kwon, O., Seung, E., Jo, J., Shresha, R., Lee, T., Jeon, T., Ki, S., Lee, H., & Lee, S. (2017). Mechanism investigation of rifampicin-induced liver injury using comparative Toxicoproteomics in mice. *International Journal of Molecular Sciences*, *18*(7), 1417. https://doi.org/10.3390/ijms18071417
13. Come, Y. F., Buntoro, I. F., Setiono, K. W., & Setianingrum, E. L. (2023). Pengaruh Pemberian Terapi Obat anti Tubekulosis Fase Intensif Terhadap Kadar hemoglobin pada Penderita Tuberkulosis Di Kota Kupang. *Cendana Medical Journal*

(CMJ), *11*(1), 24-32. https://doi.org/10.35508/cmj.v11i1.10515

14. Chang, K. C., Leung, C. C., Yew, W. W., Lau, T. Y., & Tam, C. M. (2008). Hepatotoxicity of Pyrazinamide. *American Journal of Respiratory and Critical Care Medicine*, *177*(12), 1391-1396. https://doi.org/10.1164/rccm.200802-355oc
15. Chih, L.H., Zhang, S., Zhang, M. (2014). Patterns of liver function test abnormalities during anti-TB therapy. *BMC Infect Dis*, 14, 212.
16. Huang, Y., Chern, H., Su, W., Wu, J., Lai, S., Yang, S., Chang, F., & Lee, S. (2002). Polymorphism of the N -acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology*, *35*(4), 883-889. https://doi.org/10.1053/jhep.2002.32102
17. Kim, H.J., Kim, Y.S., Kim, S.I., Park, Y.S., Yoon, H.I., Lee, C.T., Lee, J.H. (2017). The incidence and risk factors of hepatotoxicity induced by antituberculosis drugs. *Respirology*, 22(2), 361–368.
18. Lingaraja, M., Kaleem, A., Mujeeb, S., Haroon, K. (2015). Evaluation of hepatotoxicity in pulmonary tuberculosis patients undergoing DOTS therapy. *J Clin Diagn Res*, 9(10), FC01–FC04.
19. Saukkonen, J. J., Cohn, D. L., Jasmer, R. M., Schenker, S., Jereb, J. A., Nolan, C. M., Peloquin, C. A., Gordin, F. M., Nunes, D., Strader, D. B., Bernardo, J., Venkataramanan, R., & Sterling, T. R. (2006). An official ATS statement: Hepatotoxicity of Antituberculosis therapy. *American Journal of Respiratory and Critical Care Medicine*, *174*(8), 935-952. https://doi.org/10.1164/rccm.200510-1666st
20. Wu, S., Lin, J., Pan, W. (2012). Hepatotoxicity of first-line anti-TB drugs and monitoring liver function during treatment. *Clin Respir J*, 6(3), 167–172.