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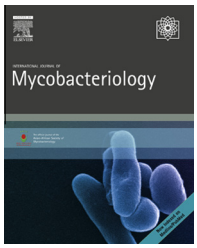

Incidence of antituberculosis-drug-induced hepatotoxicity and associated risk factors among tuberculosis patients in Dawro Zone, South Ethiopia: A cohort study

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ABSTRACT

Background: Antituberculosis drugs cause hepatotoxicity in some individuals leading to acute liver failure, which results in death. Such phenomena limit the clinical use of drugs, contributing to treatment failure that possibly causes drug resistance. Furthermore, associated risk factors for the development of antituberculosis-drug-induced hepatotoxicity (anti-TB-DIH) are found to be controversial among different study findings.

Methods: A prospective cohort study was conducted from May 2014 to October 2014 in Dawro Zone, Tercha District Hospital Laboratory, South Ethiopia. One hundred and twenty-four new tuberculosis-positive individuals available from Tercha Hospital and five health centers during data collection were consecutively included. The sociodemographic data and anthropometric measurement were obtained. Then, 5 mL of venous blood was drawn from each individual, and the alanine transaminase, aspartate transaminase, and total bilirubin were measured photometrically at baseline, and then continuously monitored by measuring these liver enzymes every 2 weeks for 2 months. Data were analyzed with SPSS version 20 for Windows (SPSS Inc., Chicago, IL, USA).

Results: The incidence of anti-TB-DIH was found to be 8% (10 patients out of 124). Raised serum transaminase and bilirubin level, as well as signs and symptoms of hepatotoxicity (nausea, anorexia, vomiting, malaise, and jaundice), were observed in the cases. The onset of hepatotoxicity ranged from 13 days to 58 days (median, 26 days) after treatment was initiated. Of the various risk factors analyzed, only high alcohol intake was associated with the incidence of anti-TB-DIH (odds ratio = 9.3, 95% confidence interval 1.8–47, $p < .007$). Age, gender, extent of tuberculosis disease, and malnutrition were not significantly associated with anti-TB-DIH.

Conclusion: The incidence of anti-TB-DIH in Dawro Zone was high. The drug responsible for the hepatotoxicity was not known. However, chronic high alcohol intake was associated with the development of anti-TB-DIH.

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Introduction

Tuberculosis (TB) continues to remain a significant infectious disease across much of the world. It poses a formidable socioeconomic burden on the individual and on the society. There were 8.6 million newer TB cases and an estimated 1.3 million deaths that occurred worldwide in 2012 [1]. New cases of TB-infected individuals are treated by a combination of four drugs: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol [2]. However, a variety of adverse reactions of these drugs have been reported; one of the well-known toxic effects is hepatotoxicity [3]. Antituberculosis-drug-induced hepatotoxicity (anti-TB-DIH) may result from the direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response, affecting hepatocytes, biliary epithelial cells, and/or liver vasculature [4,5]. Most types of anti-TB-DIH is due to metabolic idiosyncrasy due to the metabolites released or accumulated during the metabolic process. These hypersensitivity or metabolic reactions occur largely independent of the dose [6].

Anti-TB-DIH is confirmed by an elevated level of aspartate transaminase (AST) or alanine transaminase (ALT) to five times the upper limit of normal (ULN), in the absence of jaundice or other symptoms, or up to three times the ULN in the presence of symptoms of hyperbilirubinemia (bilirubin 2 times the ULN) [7]. Although a vast majority of patients tolerate the drugs, some 3–25% develops anti-TB-DIH worldwide. Anti-TB-DIH accounts for 7% of reported drug adverse effects, 2% of jaundice in hospitals, and approximately 30% of fulminant liver failure [8,9]. The spectrum of anti-TB-DIH is diverse, ranging from asymptomatic rise in transaminase (to fivefold) in 2.3–28% to acute liver failure in approximately <0.01% of the individuals [10].

There are factors that contribute to the development of anti-TB-DIH [2,3,7]. Some studies reported that the history of chronic alcohol intake is a predisposing factor for anti-TB-DIH [11,12]. Several studies reported that old age is a potential risk factor for anti-TB-DIH [3,7,13]. However, a study in Nepal revealed that the incidence of anti-TB-DIH was higher in younger patients [3]. Some studies suggested that female gender is an independent predictor of anti-TB-DIH [3,14]. However, a recent report suggested that males have a higher risk of developing anti-TB-DIH [15]. A study reported that there was no significant association between the extent of TB disease and the incidence of anti-TB-DIH [16]. However, extrapulmonary organ involvement was reported to be associated with the incidence of anti-TB-DIH in studies from India [17,18]. Some studies from Nepal [3], Spain [28], and India [11,18] showed that malnourishment had a significant association with the incidence of anti-TB-DIH.

The risk factors that contribute to the development of anti-TB-DIH are still obscure and controversial. Understanding anti-TB-DIH is restricted by the difference in study population, definition of hepatotoxicity, and monitoring practices. There was no study that determined the incidence of anti-TB-DIH and assessed the risk factors of anti-TB-DIH among TB patients in Dawro Zone. Therefore, this study was aimed to determine the incidence of anti-TB-DIH and identify the possible risk factors of anti-TB-DIH among TB patients in Dawro Zone, South Ethiopia.

Materials and methods

Study setting and study participants

A prospective cohort study was conducted from May 2014 to October 2014 in Southern Ethiopia. One hundred and twenty-four newly TB-infected individuals with negative hepatitis B surface antigen, anti-hepatitis C virus (HCV) antibodies, and human-immunodeficiency-virus test, and having complete recorded data were included in this study consecutively. Patients who had ALT and AST values greater than two times the ULN (i.e., ULN > 42 U/L and 37 U/L, respectively), and patients positive for hepatitis B surface antigen, anti-HCV antibodies, as well as retreatment case of TB were excluded from the study.

Data collection and laboratory testing

The sociodemographic and clinical data were collected using a structured questionnaire and checklist. Then, 5-mL venous blood samples were collected using test tubes that contain separator gels and allowed to clot for 30 min. After retracting the clot, the samples were centrifuged at 3000 g for 10 min. Pure serum samples were transferred to Nunc tubes, and screened for hepatitis B and C virus using rapid hepatitis B surface antigen and rapid anti-HCV test kits, respectively. The baseline measurements of ALT, AST, and total bilirubin were performed photometrically using Mindray BS-200E Chemistry Analyzer machine (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.) before the initiation of anti-TB treatment. After the initiation of anti-TB treatment, the patients were examined both physically and biochemically every week for 2 months. The standard operating procedures and manufacturer instructions were strictly followed throughout the procedures, and all reagents were prepared according to the manufacturer's instruction. A quality-control run was undertaken for all laboratory tests in this study.

Statistical analysis

Data were coded, entered, and cleaned using statistical software (EpiData, version 3.1), and then exported to and analyzed with SPSS, version 20 for Windows (SPSS Inc., Chicago, IL, USA). The mean standard deviation (SD) and frequency of variables were calculated. The bivariate and multivariate logistic regression was calculated to evaluate the possible association of the variables, and $p < .05$ was considered as statistically significant.

Ethical consideration

The ethical clearance was obtained from the Jimma University Ethical Review Committee, and an official letter was written to Dawro Zone Health Bureau. For voluntary participation, the research participants signed an informed consent based

on the explicit information of any possible risk, harm, and even discomfort caused by data/sample collection procedures, as well as any benefits. Moreover, issues concerning intervention especially in the case of induced hepatotoxicity were discussed with concerned bodies to continue or discontinue treatment.

Results

Demographic and anthropometric data

One hundred and twenty-four TB patients taking anti-TB drugs were involved in this study and were followed for 2 months. Among them, 66 (53.2%) were females. The ages of the cases ranged from 10 years to 80 years with the mean (±SD) age being 34.5 (±15.2 years), but the highest number of participants was found in the age group of 20–49 years, which is 84 (67.7%). The body-mass-index (BMI) measurement of the participants ranged from 17.08 kg/m^2 to 24.78 kg/m^2, the mean value being 20.60 kg + 1.77 kg. The BMI measurement of the majority (119 [96%]) of the participants was within the normal range (i.e., 18.5–24.00 kg/m^2 [Table 1]).

Clinical and laboratory data, and hepatotoxicity of study patients

Out of 124 participants, 13 of them were taking different antibiotics during the study period, of which nine (69%) were males and four (31%) were females. None of them were reported to be taking paracetamol or other potentially hepatotoxic drugs during the study or 1 month prior to the study period. Among the 124 participants, eight (6.5%) were reported to be alcoholics, of whom six (75%) were females and two (25%) were males. Smear-positive pulmonary TB accounted for 99 (79.8%) of all cases, and extrapulmonary TB accounted for about 25 (20.2%) cases.

During the 5-month study period, 10 patients out of 124 developed anti-TB drug hepatotoxicity, which was confirmed by clinical examination and liver function test. They showed elevated serum concentrations of ALT, AST, and total bilirubin beyond five times the ULN with or without symptoms. Patients with anti-TB-DIH had their ALT, AST, and bilirubin total values (mean ± SD) were 22.70 ± 9.71 U/L, 21.60 ± 6.67 U/L, and 0.34 ± 0.21 mg/dL, respectively, at baseline measurement, and their peak values during treatment were 304.80 ± 93.67 U/L, 261.80 ± 66.07 U/L, and 1.86 ± 0.91 mg/dL, respectively (Table 2).

Among the total 10 anti-TB-DIH cases, female patients account for the highest number [6 (60%)]. Most of the patients who had developed ant-TB-DIH showed the same signs and symptoms (malaise, anorexia, vomiting, nausea, and jaundice). The most common symptoms being nausea and anorexia (90% and 80%, respectively), followed by malaise and jaundice being 60% and 40%, respectively (Table 4). The time interval from the initiation of treatment to the onset of hepatotoxicity was 13–58 days (median of 26 days) (see Tables 3 and 6).

Table 1 – Demographic and anthropometric data of study participants at Dawro Zone Tercha Hospital and five health centers, Southern Ethiopia, from May 2014 to October 2014.

Characteristics		No. (%)
Gender	Male	58 (46.8)
	Female	66 (53.2)
	Total	124 (100)
Age (y)	10–19	20 (16.1)
	20–49	84 (67.8)
	>50	20 (16.1)
	Total	124 (100)
BMI (kg/m^2)	Underweight	4 (3.2)
	Normal	119 (96)
	Overweight	1 (0.8)
	Total	124 (100)

Note: BMI = body mass index; y = year.

Table 2 – Laboratory Data (mean ± standard deviation) of patients at Dawro Zone among Tercha Hospital and five health centers, Southern Ethiopia, from May 2014 to October 2014.

Laboratory test		Patients with anti-TB-DIH (n = 10)	Patients without anti-TB-DIH (n = 114)
ALT (U/L)	Baseline	22.70 ± 9.71	23.34 ± 3.67
	During treatment (peak value)	304.80 ± 93.67	33.90 ± 5.21
AST (U/L)	Baseline	21.60 ± 6.67	27.74 ± 4.54
	During treatment (peak value)	261.80 ± 66.07	30.13 ± 2.22
Total bilirubin (mg/dL)	Baseline	0.34 ± 0.21	0.45 ± 0.33
	During treatment (peak value)	1.86 ± 0.91	0.65 ± 0.77

Note: ALT = alanine transaminase; anti-TB-DIH = antituberculosis-drug-induced hepatotoxicity; AST = aspartate transaminase.

Table 3 – Laboratory data (mean + standard deviation) based on gender of patients at Dawro Zone among Tercha Hospital and five health centers, Southern Ethiopia, from May 2014 to October 2014.

Parameters	Cutoff value			Patients with DIH (n = 10), No. (%)
AST (U/L)	>3 × ULN + symptoms	Male	111	3 (30)
		Female	93	1 (10)
	>5 × ULN with/without symptom	Male	185	4 (40)
		Female	155	2 (20)
ALT (U/L)	>3 × ULN + symptoms	Male	126	1 (10)
		Female	96	3 (30)
	>5 × ULN with/without symptom	Male	210	3 (30)
		Female	160	3 (30)
Total bilirubin (mg/dL)	>2 × ULN	Male	2.4	2 (20)
		Female	2.4	3 (30)

Note: ALT = alanine transaminase; AST = aspartate transaminase; DIH = drug-induced hepatotoxicity; ULN = upper limit of normal.

Table 4 – Clinical presentations of antituberculosis-drug-induced hepatotoxicity in patients at Dawro Zone Tercha Hospital and five health centers, Southern Ethiopia, from May 2014 to October 2014.

Signs & symptoms	Patients with anti-TB-DIH, No. (%)
Vomiting	4 (40)
Jaundice	4 (40)
Anorexia	8 (80)
Nausea	9 (90)
Malaise	6 (60)

Note: Anti-TB-DIH = antituberculosis-drug-induced hepatotoxicity.

Those who had developed anti-TB-DIH were followed weekly for 3 weeks with liver function test (AST, ALT, and total bilirubin) until their liver-enzyme levels returned to normal or the baseline state. Liver toxicity resolved within 21 days (median of 20 days; Table 5), and continued treatment.

Factors associated with hepatotoxicity

Alcoholism (which is defined as consuming >35 units and >28 units of alcohol per week for at least 10 years for men and women, respectively) was found to be significantly associated with the incidence of anti-TB-DIH (crude odds ratio = 9.343, 95% confidence interval 1.8–47.3). According to this study, BMI (kg/m^2), extent of TB disease, gender, and age had no significant association with the incidence of anti-TB-DIH (Table 7).

Discussion

One hundred and twenty-four cohorts of newly diagnosed TB patients who were negative for human immunodeficiency virus and hepatitis B and C, and started taking anti-TB drugs were included in this study. The analysis in this study showed the incidence of anti-TB-DIH to be 8.1%. This incidence is almost similar to previous reports of a study in St. Peter's TB Specialized Hospital, Addis Ababa, Ethiopia (8.9%) [19] and to reports from Asia (8.0–19.8%) [3,13]. However, this incidence is lower than that from Egypt (15% [2]) and higher than that of the Western world (4.3% [19]). The variation in the incidence of anti-TB-DIH worldwide may be attributed to the differences in patients' characteristics, indiscriminate use of drugs, and the definition criteria of hepatotoxicity [20].

According to this study, the time interval for the onset of hepatotoxicity after the initiation of treatment was 13–58 days (median, 26 days). This is similar to the result reported in Nepal (12–60 days [median, 28 days]) [3]. One study also reported that the onset of anti-TB-DIH to be 15–60 days (median, 30 days) [2], which is similar to the result of this study. But, another study [21] reported that the onset of anti-TB-DIH in almost two-thirds of their patients (61.2%) was within 14 days from the start of therapy.

Table 5 – Follow-Up result of patients who had antituberculosis-drug-induced hepatotoxicity (mean ± standard deviation, n = 10) at Dawro Zone Tercha Hospital and five health centers, Southern Ethiopia, from May 2014 to October 2014.

Test	1st week	2nd week	3rd week
ALT (U/L)	324 ± 60.10	135.35 ± 24.12	47.34 ± 8.21
AST (U/L)	268 ± 48.42	107.08 ± 14.76	36.33 ± 7.98
Total bilirubin (mg/dL)	1.92 ± 0.710	1.25 ± 0.53	0.95 ± 0.34

Note: ALT = alanine transaminase; AST = aspartate transaminase.

Table 6 – Baseline characteristics of patients with antituberculosis-drug-induced hepatotoxicity and without antituberculosis-drug-induced hepatotoxicity (mean ± standard deviation) at Dawro Zone Tercha Hospital and five health centers, Southern Ethiopia, from May 2014 to October 2014.

Characteristics		No. of patients (%)	Patients with DIH, No. (%)	Patients without DIH, No. (%)	COR (95%) CI
Gender	Male (ref)	58 (46.8)	4 (3.2)	54 (43.5)	1.3 (.36–5.04)
	Female	66 (53.2)	6 (4.8)	60 (48.3)	.74 (.12–2.34)
Extent of disease	Pulmonary (ref)	99 (79.8)	7 (5.6)	92 (74.2)	1.79 (.42–7.49)
	Extrapulmonary	25 (20.2)	3 (2.4)	22 (17.7)	.76 (.11–1.54)
Alcohol status	Alcoholic	8 (6.5)	3 (2.4)	5 (4)	9.343 (1.84–47.3)
	Nonalcoholic (ref)	116 (93.5)	7 (5.6)	109 (87.9)	.064 (.13–7.5)
Age (y)	10–19	20 (16.1)	2 (1.6)	18 (14.5)	.11 (.4–3.76)
	20–49 (ref)	84 (67.8)	7 (5.6)	67 (54)	.818 (.157–4.27)
	>50	20 (16.1)	1 (0.8)	19 (15.3)	.474 (.039–5.688)
BMI	<18.5	4 (3.2)	3 (2.4)	1 (0.8)	0
	18.5–24.99 (ref)	119 (96)	7 (5.6)	112 (90.3)	0
	>25	1 (0.8)	0 (0)	1 (0.8)	0

Note: BMI = body mass index; CI = confidence interval; COR = crude odds ratio; DIH = drug-induced hepatotoxicity; ref = reference group; y = year.

Table 7 – Association of predictors with incidence of antituberculosis-drug-induced hepatotoxicity in patients taking antituberculosis drugs in Dawro Zone Tercha Hospital and five health centers, Southern Ethiopia, from May 2014 to October 2014.

Variables		COR	95% CI	*p*
Gender	Male	1.3	.36–5.04	.65
	Female	.74	.12–2.34	.56
Age (y)	10–19	.11	.4–3.76	.838
	20–49	.818	.15–4.27	.81
	>50	.474	.039–5.7	.556
BMI (kg/m^2)	<18.5	161,547,162	0	.999
	18.5–25	11,643,038	0	.99
	>25	1,454,367	0	.999
Extent of disease	Pulmonary	1.792	.42–7.4	.424
	Extrapulmonary	.76	.11–1.54	.89
Alcohol status	Alcoholic	9.3	1.8–47.3	.007
	Nonalcoholic	.064	.13–7.5	.92

Note: BMI = body mass index; CI = confidence interval; COR = crude odds ratio; y = year.

This study showed that the history of high alcohol intake was a potential risk factor for anti-TB-DIH ($p < .007$, odds ratio = 9.3). Similarly, one study [12] reported that the history of chronic alcohol intake was common among the cases. Other studies also reported high alcohol intake as a predisposing factor for anti-TB-DIH [11,22]. On the contrary, a study report from Dossing, Wilcke, Askgaard, and Nybo [23] and a study done in Egypt [2] showed that high alcohol intake had no correlation with the incidence of anti-TB-DIH. This difference can be explained by the fact that high alcohol intake as a predisposing factor for anti-TB-DIH has been considered as the most equivocal. However, according to some study reports, higher alcohol consumption as a risk factor was ascribed to malnutrition and glutathione store depletion [24].

Several studies reported that old age is a potential risk factor for anti-TB-DIH [3,7,13]. A study done in Egypt [21] reported that the older age group was affected more than the younger age group. By contrast, a study done in Nepal [3] reported that the incidence of anti-TB-DIH was higher in younger patients. The current study showed that there was no correlation between age and anti-TB-DIH. In agreement to this, another study reported that age had no significant relation to anti-TB-DIH [25]. The discordance between our findings and the studies done in Nepal and Egypt may be explained by the fact that the age categorization for young and old people is different.

Several studies suggested that female gender is an independent predictor of anti-TB-DIH [3,14]. However, a recent report suggested that males have a higher risk of developing anti-TB-DIH [15]. The reason for female susceptibility was believed to be variations in pharmacokinetics and slower acetylation status [26]. However, gender showed no correlation with anti-TB-DIH in the current study. This difference may be explained by the fact that females are slow acetylators, and INH is cleared by acetylation. Thus, the females in our study might have developed anti-TB-DIH by an anti-TB drug other than INH. Some other studies are in agreement with this current-study finding [2,27].

The extent of TB disease or the involvement of extrapulmonary organ had no significant association with the

incidence of anti-TB-DIH according to the current study. In congruence to this, another study reported that there was no significant association between the extent of TB disease and the incidence of anti-TB-DIH [16]. However, extrapulmonary organ involvement was reported to be associated with the incidence of anti-TB-DIH in studies from India [17,18]. This difference may be attributed to the fact that extrapulmonary TB may not necessarily indicate severity of the disease.

In this study, malnutrition, as assessed by BMI < 18.5 kg/m^2, had no significant association with anti-TB-DIH. Despite, some studies from Nepal [3], Spain [28], and India [11,18] showed that malnourishment had a significant association with the incidence of anti-TB-DIH. This might be due to the depletion of glutathione stores, which makes patients more vulnerable to oxidative injuries. The reason for the deviation of our finding may be explained by the fact that the majority of patients included in our study were not malnourished.

In this study, since there was no severe hepatotoxicity, no death was recorded. During the study period, 100% of patients who developed anti-TB-DIH had their transaminase level below tenfold of the ULN. Patients having signs and symptoms suggestive of hepatotoxicity were put under close follow-up, and had their liver function tests monitored and physical examination done regularly. For confirmed hepatotoxic cases, anti-TB drugs were discontinued for some time until it was normalized. Fortunately, all of the cases recovered after a few days and continued treatment.

Although as a result of meta-analysis, the incidence rate of hepatotoxicity was shown to be high with INH followed by PZA and RIF [19]. TB patients who were included in the current study were taking a combination of four anti-TB drugs: INH, RIF, PZA, and ethambutol. Therefore, it was difficult to infer which drug was responsible for the cause of hepatotoxicity. The role of N-acetyltransferase 2 gene/enzyme polymorphisms on the metabolism of INH plays a role on susceptibility to anti-TB-DIH [7]. But, we could not determine genetic polymorphism because of the resource in this study. Most of the time, anti-TB-DIH was expected to happen during the initial phase (the first 2 months) of treatment, although it may develop during the continuous phase. In the current study, liver function test for monitoring of TB patients was done only for the initial phase of treatment. We could not get enough financial and time resources to follow the patients during their continuation phase, and thus, we were unable to describe the incidence during this phase.

Conclusions

Hepatotoxicity developed within the first 2 months after initiating treatment. Patients taking anti-TB drugs should be followed biochemically more frequently during the initial phase of treatment than during the continuous phase. Chronic high alcohol consumers had an increased risk of developing anti-TB-DIH rates.

Conflicts of interest

The authors declare that they have no competing interests.

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