Cholecalciferol for Prophylaxis against Antituberculosis Therapy-Induced Liver Disorders among Naïve Patients with Pulmonary Tuberculosis: A Randomized, Comparative Study

Ahmad Farooq Alsayed Hasanain, Ali Abdel-Azeem Hasan Zayed, Reem Ezzat Mahdy, Amany Mohamed Adawi Nafee

Department of Tropical Medicine and Gastroenterology, 'Chest Diseases, 'Internal Medicine and 'Microbiology and Immunology, Assiut University, Assiut, Egypt

Abstract

Background: Patients in countries endemic for chronic viral hepatitis are more vulnerable to antituberculosis therapy-induced liver disorders (ATT-LDs). The aim of this study was to explore the role of cholecalciferol in prophylaxis against ATT-LD among patients with pulmonary tuberculosis (TB) receiving ATT. Material and Methods: We conducted a hospital-based, prospective, randomized, comparative study which included 300 consecutive, naïve patients with pulmonary TB eligible for ATT. The patients were randomly allocated to Group A (150 patients who received ATT) and Group B (150 patients who received ATT with cholecalciferol) who had clinical evaluation, laboratory investigations, and imaging studies. Statistical analysis used student’s t-test and Chi-square test were used as appropriate to compare the variables between the study groups. Results: The study population mean age was 35.6 ± 15.3 years. The overall incidence rate of ATT-LD among the study population was 9.3%; the incidence rate was significantly higher among Group A patients compared to those of Group B (13.3 vs. 5.3%; P = 0.001). The onset of ATT-LD was significantly earlier among patients of Group A compared to those of Group B (31.4 vs. 58.7 days, P = 0.027), while the duration of ATT-LD was significantly longer among patients of Group A compared to those of Group B (34.8 vs. 16.9 days, P = 0.009). No adverse effects related to cholecalciferol use were observed. Conclusions: Adjuvant cholecalciferol supplementation may be protective against ATT-LD without extra adverse effects. Before recommending the routine use of cholecalciferol supplementation for prevention of ATT-LD, larger scale studies are recommended.

Keywords: Antituberculosis therapy, cholecalciferol, liver disorders

INTRODUCTION

In developing countries including Egypt, tuberculosis (TB) is an endemic disease and is recognized with increasing incidence, mainly among the immunocompromised patients.[1] Antituberculosis therapy (ATT) including isoniazid (INH), rifampin (RIF), and pyrazinamide (PZA), although effective for treatment, carries the risk of liver disorders; it may be severe enough to result in discontinuation of therapy or exacerbation of underlying liver disease. The spectrum of ATT-induced liver disorders (ATT-LDs) encompasses a range of elevated levels of aminotransferases to acute liver failure.[2,3] The prevalence of ATT-LD is up to 4.28% in Western countries;[4] its risk factors include extensive TB, older age, polymorphism and reduced activity of liver N-acetyl-transferase-2 genes and glutathione-S-transferase, slow acetylation, inappropriate use of drugs, underlying liver disease, severe malnutrition (including baseline hypoalbuminemia), alcohol excessive intake, and human immunodeficiency virus (HIV) infection.[5-9] Relation of Vitamin D to the severity of liver disease has been reported among liver disorders other than ATT-LD. Patients with nonalcoholic steatohepatitis (NASH) have significantly lower levels of Vitamin D.[10] In addition, Vitamin D deficiency is associated with the histopathological severity of NASH.[11] Animal studies demonstrate that elevated level of Vitamin D using phototherapy results in lower severity of nonalcoholic fatty liver disease (NAFLD) as indicated by baseline hypoalbuminemia, alcohol excessive intake, and human immunodeficiency virus (HIV) infection.[5-9]

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms. For reprints contact: reprints@medknow.com

How to cite this article: Hasanain AF, Zayed AA, Mahdy RE, Nafee AM. Cholecalciferol for prophylaxis against antituberculosis therapy-induced liver disorders among naïve patients with pulmonary tuberculosis: A randomized, comparative study. Int J Mycobacteriol 2017;6:149-55.
less necroinflammation, fibrosis, and apoptosis.\textsuperscript{[12]} Vitamin D receptor (VDR) gene polymorphisms involved in Vitamin D synthesis and activation are associated with Vitamin D status and the severity of liver disease.\textsuperscript{[13]} In Egypt, VDR BsmI genotype distribution among healthy individuals is 57% for genotype Bb, 34% for bb, and 9% for BB, with b allele among 62.5% compared to 37.5% for B allele.\textsuperscript{[14]}

The only measure to manage ATT-LD is discontinuation of the ATT; it is reintroduced after normalization of the aminotransferases levels.\textsuperscript{[15]} There is no standard recommendation for prophylaxis against ATT-LD. The contribution of Vitamin D to prevention of ATT-LD has not been studied before. The aim of this study was to explore the role of cholecalciferol (Vitamin D\textsubscript{3}) supplementation in prophylaxis against ATT-LD among naïve patients with pulmonary TB receiving ATT. The study objective was to compare incidence rate of ATT-LD among patients receiving ATT with cholecalciferol supplementation to that of a matching group receiving ATT only.

**Materials and Methods**

**Study design**

We conducted a hospital-based, prospective, randomized, comparative study.

**Study location**

We recruited the study population in the inpatient sectors and outpatient clinics of the Departments of Chest Diseases, Tropical Medicine, and Internal Medicine.

**Study duration**

We recruited the study population during the period from October 2014 to May 2016.

**Study population**

The study included 300 consecutive, naïve patients with pulmonary TB eligible for ATT. The patients were randomly allocated to two groups. Group A included 150 patients who received ATT only while Group B included another 150 patients who received ATT with cholecalciferol supplementation.

Pulmonary TB was diagnosed based on positive sputum culture on Lowenstein–Jensen medium performed by an experienced microbiologist, with or without the radiological evidence on chest radiography.\textsuperscript{[16]} ATT-LD was diagnosed according to the International Union Against TB and Lung Disease based on the presence of one or more of the following criteria: (1) a rise to more than two times the upper limit of normal (ULN) of alanine transaminase (ALT; ULN is 41 IU/L) level and/or aspartate transaminase (AST; ULN is 38 IU/L) level; (2) a rise in total serum bilirubin level to more than 25.7 μmol/L or 1.5 mg/dl; (3) any increase in AST and/or ALT levels above pretreatment levels together with anorexia, nausea, vomiting, and jaundice. In addition, normalization of laboratory abnormalities and resolution of signs and symptoms of liver disease after discontinuation of ATT were needed for diagnosis.\textsuperscript{[17]}

**Inclusion criteria**

The study included adult (18 years or more) patients with pulmonary TB eligible for ATT who accepted to be enrolled in the study.

**Exclusion criteria**

Pregnant female patients or those with previous ATT were excluded from being enrolled. In addition, patients with pre-existing elevated liver chemistry (ALT, AST, and bilirubin), hepatitis C virus (HCV) infection, hepatitis B virus infection, Human immunodeficiency virus (HIV) infection, evidence of fatty liver disease, liver cirrhosis or portal hypertension, any alcohol intake, receiving hepatotoxic drugs other than ATT, renal disorder (elevated serum creatinine level), and hemolytic anemia were excluded as well as those receiving corticosteroids or antimetabolites for any other indication.

**Methods**

All the patients enrolled had pretreatment evaluation including clinical evaluation (medical history and physical examination with estimation of weight and height), imaging studies (chest radiography and abdominal ultrasonography), and laboratory investigations (liver chemistry panel, virology panel, kidney chemistry panel, and complete blood count). Body mass index (BMI) was calculated as the following: body weight (kg)/(height [m])\textsuperscript{2}. Liver chemistry panel included estimation of serum levels of ALT, AST, and bilirubin. Virology panel included testing for serum antibody to HCV, hepatitis B surface antigen, antibody to hepatitis B core, and anti-HIV. For patients with criteria of ATT-LD, the following were performed to confirm the diagnosis: testing for serum antibody to hepatitis A virus of immunoglobulin-M type and markers of autoimmune hepatitis (antinuclear and anti-smooth muscle antibodies).

All the study patients received the World Health Organization (WHO)-recommended therapy: INH (5 mg/kg/day; maximum dose was 300 mg/day), RIF (10 mg/kg/day; maximum dose was 600 mg/day), PZA (30 mg/kg/day; maximum dose was 2000 mg/day), and ethambutol (EMB) (20 mg/kg/day; maximum dose was 1600 mg/day) for 2 months, followed by INH and RIF for four more months.\textsuperscript{[18]} Group B patients, in addition to ATT, received cholecalciferol supplementation during the whole treatment period (600 IU/day, orally, immediately after lunch). The dose of cholecalciferol was determined according to the recommended dietary allowances for persons 19–70 years old.\textsuperscript{[19]} Taking Vitamin D with the largest meal improves its absorption.\textsuperscript{[20]} Cholecalciferol supplementation was produced by the same pharmaceutical company.

Follow-up included clinical evaluation and laboratory investigations. Daily clinical evaluation during the period of hospital admission and weekly clinical and laboratory evaluation (liver chemistry panel) at the outpatient clinic for the first 2 months of the treatment period and then monthly for rest of the period were carried out. Therapeutic failure of
ATT was defined as positive sputum culture at the 4th month or later during the treatment period.[21]

For the study patients with elevated levels of ALT and/or AST (three times the ULN or more with symptoms or five times the ULN with or without symptoms) during the first 2 months of ATT, RIF and PZA were discontinued immediately. Liver-friendly drugs (EMB and streptomycin [SM]) were used in addition to INH until RIF and PZA were resumed after decrease of ALT and/or AST levels to less than two times the ULN. The dose of SM was 15 mg/kg/day by intramuscular injection with a maximum daily dose of 1000 mg. For patients with the same criteria but after the first 2 months of ATT, RIF was replaced by EMB temporarily until it was be resumed according to the previously mentioned rules.[18]

Statistical analysis
Data were collected in a specialized data collection form and then entered and analyzed using the Statistical Package for Social Sciences (SPSS, version 22.0; SPSS Inc., Chicago, IL, USA) for Windows. Results were expressed as mean ± standard deviation or frequency (percentage) as appropriate. Student’s t-test and Chi-square test were used as appropriate to compare the variables between the study groups. P < 0.05 was considered statistically significant.

Ethical considerations
The study was approved by the Faculty of Medicine Clinical Research Ethical Committee (Assiut University) and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Before enrollment in the study, all participants signed a consent certificate. Before signing, they were able to discuss in detail with investigators the certificate subjects and the study aim. Participants were clearly informed that refusing to participate in the study will not affect having full benefit of the available medical service and treatment. Data were collected by personal interview of investigators with participants taking in consideration data confidentiality.

Results
The study included 300 naïve patients with pulmonary TB. Their mean age was 35.6 ± 15.3 years; female patients represented 57% of them.

Pretreatment characteristics of the study population
Pretreatment demographic, clinical, radiological, and laboratory characteristics of the two groups of the study population with pulmonary TB are shown in Table 1. No statistically significant difference was observed between the patients of Group A and Group B; the two groups were matching.

Antituberculosis therapy induced liver disorders among the study population
Out of 300 patients with pulmonary TB, 28 (9.3%) developed ATT-LD. Table 2 shows the pattern of ATT-LD among the two groups of the study population with pulmonary TB. Out of 28 patients with ATT-LD, 20 (71.4%) were of Group A patients [Figure 1]. The incidence rate of ATT-LD was significantly higher among patients of Group A compared to patients of Group B (13.3 vs. 5.3%; P = 0.001). The most frequent type of ATT-LD among patients who developed ATT-LD was elevated level of ALT more than two times of the UNL (18 out of 28, 64.3%), which also was the most frequent among Group B patients with ATT-LD (5 out of 8, 62.5%). All patients with elevated levels of AST and/or bilirubin had concomitant ALT level elevation. Symptoms associated with elevated aminotransferases levels were anorexia, nausea, and vomiting, which were more common among patients of Group A with ATT-LD (10 out of 20, 50%) compared to those of Group B (3 out of 8, 37.5%). Interestingly, patients of Group B with ATT-LD had no single case of elevated bilirubin. Even among Group A patients with elevated bilirubin level, jaundice was not detected.

The onset of ATT-LD was significantly earlier among patients of Group A compared to those of Group B (31.4 vs. 58.7 days, P = 0.027) while the duration of ATT-LD was significantly longer among patients of Group A compared to those of Group B (34.8 vs. 16.9 days, P = 0.009). Complete cure was ultimate for all the patients who developed ATT-LD.

The mean peak serum levels of ALT, AST, and bilirubin among the study population of the two groups are shown in Table 3. The aminotransferases levels were significantly higher among patients of Group A compared to those of Group B, especially for ALT (62.5 vs. 36.9 IU/L, P = 0.024).

| Table 1: Pretreatment demographic, clinical, radiological, and laboratory characteristics of the study population |
| --- |
| **Age** | Group A (n=150) | Group B (n=150) | P |
| 34.3±14.7 | 37.5±16.3 | 0.193 |
| Male gender | | | |
| 60 (40) | 69 (46) | 0.227 |
| Rural residence | 93 (62) | 109 (72.7) | 0.104 |
| Tobacco smoking | 43 (72) | 38 (55) | 0.083 |
| Coffee consumption | 98 (65.3) | 87 (58) | 0.194 |
| BMI | 26.3±3.6 | 27.6±4.1 | 0.484 |
| Cavitary pulmonary TB | 42 (28) | 48 (32) | 0.397 |
| Pleural effusion | 3 (2) | 5 (3.3) | 0.792 |
| ALT (IU/L) | 32.7±7.8 | 29.9±5.2 | 0.373 |
| AST (IU/L) | 34.1±5.3 | 36.4±3.8 | 0.291 |
| Bilirubin (µmol/L) | 13.6±5.6 | 12.3±5.9 | 0.417 |
| Serum albumin (g/L) | 43.2±6.5 | 45.4±4.3 | 0.381 |
| Hemoglobin (g/dL) | 11.4±2.1 | 10.7±1.8 | 0.298 |
| WBC (×10³/mm³) | 9.6±1.3 | 10.2±1.6 | 0.437 |
| Serum creatinine (µmol/L) | 89.3±17.4 | 95±19.7 | 0.203 |

Age, BMI, ALT, AST, bilirubin, serum albumin, hemoglobin, WBC, and serum creatinine are expressed as mean±SD; the rest or variables are expressed as frequency (%). Group A: Patients with antituberculosis therapy only, Group B: Patients with antituberculosis therapy and cholecalciferol supplementation, TB: Tuberculosis, BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, WBC: White blood cell count, SD: Standard deviation.
Hasanain, et al.: Cholecalciferol for antituberculosis liver disorders

Table 2: Pattern of antituberculosis therapy induced liver disorders among the study population

| ATT-LD                                | Total (n=300) | Group A (n=150) | Group B (n=150) | P       |
|----------------------------------------|---------------|-----------------|-----------------|---------|
| Total (%)                              | 28 (9.3)      | 20 (13.3)       | 8 (5.3)         | 0.001*  |
| Elevated ALT >2 × ULN with or without symptoms | 18 (6)        | 13 (8.7)        | 5 (3.3)         |         |
| Elevated AST >2 × ULN with or without symptoms | 13 (4.3)      | 10 (6.7)        | 3 (2)           |         |
| Elevated ALT ≤2 ULN with symptoms      | 10 (3.3)      | 7 (4.7)         | 3 (2)           |         |
| Elevated AST ≤2 ULN with symptoms      | 6 (2)         | 4 (2.7)         | 2 (1.3)         |         |
| Elevated bilirubin >25.7 µmol/L        | 3 (1)         | 3 (2)           | 0               |         |
| Onset of ATT-LD after start of ATT (days) | 46±20.6 | 31±19.2 | 58±22.5 | 0.027** |
| Duration of ATT-LD (days)              | 25±7.2        | 34±9.1          | 16±3.3          | 0.009** |

*Statistically significant using Chi-square test. **Statistically significant using Student’s t-test. Onset and duration of ATT-LD are expressed as mean±SD; the rest of the variables are expressed as frequency (%). Group A: Patients with antituberculosis therapy alone, Group B: Patients with antituberculosis therapy and cholecalciferol supplementation. ATT-LD: Antituberculosis therapy-induced liver disorder, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, SD: Standard deviation, ULN: Upper limit of normal

Table 3: Peak levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin among the study population with antituberculosis therapy-induced liver disorders

|                  | Total (n=300) | Group A (n=150) | Group B (n=150) | P       |
|------------------|---------------|-----------------|-----------------|---------|
| ALT (IU/L)       | 47.3±9.8      | 62.5±16.2       | 36.9±5.7        | 0.024*  |
| AST (IU/L)       | 39.9±6.3      | 57.2±10.5       | 35.6±3.4        | 0.046*  |
| Bilirubin (µmol/L) | 14.8±2.6 | 19.6±4.8        | 13.1±1.2        | 0.061   |

*Statistically significant using Student’s t-test. Group A: Patients with antituberculosis therapy only, Group B: Patients with antituberculosis therapy and cholecalciferol supplementation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Therapeutic outcome of pulmonary tuberculosis among the study population

Discontinuation of the WHO-recommended ATT temporarily due to elevation of ALT and/or AST of triple the ULN or more with symptoms was inevitable in 5 out of 20 patients (25%) of Group A with ATT-LD while no single patient of Group B patients with ATT-LD had to. Hepatotoxic drugs (RIF and PZA) were replaced by liver-friendly ones (SM and EMB). Therapeutic failure among the study population with pulmonary TB was 23% (69 out of 300 patients). Therapeutic failure was more frequent among Group A patients compared to those of Group B (27.3% vs. 18.7%); however, it did not reach the statistical significance level although it was close to P = 0.057 [Table 4]. No adverse effects related to cholecalciferol supplementation were observed among Group B patients. Figure 2 shows the therapeutic outcome according to the presence or absence of ATT-LD.

Discussion

We believe that the use of cholecalciferol with ATT should be considered. Based on our results, cholecalciferol needs to be incorporated as an adjuvant therapy for patients receiving ATT although not being recommended by the currently available studies. Patients with TB in areas endemic for chronic viral hepatitis are rendered more vulnerable to ATT-LD with higher risk of liver-related morbidity and mortality and more chance of mycobacterial resistance due to discontinuation of the standard of care-ATT.

The overall incidence rate of ATT-LD among our study population receiving the WHO-recommended ATT for pulmonary TB was 9.3%. This incidence rate was lower than that reported by Makhloff et al. (15%) among 100 Egyptian patients with TB who were followed up for the same period.[22] The lower incidence rate of ATT-LD among our study patients could be attributed to the study population; while our study was restricted to patients with pulmonary TB, theirs included patients with both pulmonary and extrapulmonary TB. Furthermore, the nutritional status might have played a role; the mean BMI of their study population was 20 which was lower than that of ours (26), reflecting more potential for malnourishment among their study patients. Globally, the incidence rate of ATT-LD is variable with higher rates among patients in developing countries as a consequence of endemicity of chronic viral hepatitis, medications abuse, especially antimicrobials and nonsteroidal anti-inflammatory drugs, and worse nutritional conditions.[23,24] In Africa, the reported incidence of ATT-LD was 16.4% among Nigerian
patients\textsuperscript{25} with worldwide variation between 4%\textsuperscript{26} and 20%\textsuperscript{27}, approximately, due to different study populations, medications, monitoring methods, and definitions of ATT-LD.\textsuperscript{17} Regarding the pattern of ATT-LD, the most frequent disorder was elevated ALT level regardless of the degree of elevation or the presence or absence of symptoms among our study patients (9.3%) as well as those of the study by Makhlouf\textit{et al.} (15%). No serious ATT-LD was reported among our study population compared to a single case of mortality due to fulminant liver failure reported by Makhouf\textit{et al.}. The onset of ATT-LD among our study population was after 46 days, in agreement with the reported range among Egyptian (15–60 days)\textsuperscript{22} and Nepalese patients receiving ATT (12–60 days).\textsuperscript{28} Regarding the duration of ATT-LD, it was 26 days among our study population which was also within the reported range among Egyptian patients with TB (15–45 days).\textsuperscript{22}

Among our study population, Group B patients who received adjuvant cholecalciferol supplementation had significantly lower incidence rate of ATT-LD compared to those of Group A without the supplementation (5.3% vs. 13.3%, \( P = 0.001 \)), near to the lowest reported globally (4%).\textsuperscript{28} Moreover, patients of Group B had significantly more late onset (59 vs. 31 days, \( P = 0.027 \)) and shorter duration (17 vs. 35 days, \( P = 0.009 \)) of ATT-LD compared to those of Group A. Regarding the liver chemistry panel, Group B patients had significantly lower levels of ALT (37 vs. 63 IU/L, \( P = 0.024 \)) and AST (~36 vs. 57 IU/L, \( P = 0.046 \)) compared to those of Group A. Considering both groups of our study were matching, we can suggest that adjuvant cholecalciferol supplementation for Group B patients has contributed to less development, later onset, and shorter duration of ATT-LD among such patients compared to Group A patients who did not receive the supplementation, reflecting a potential hepatoprotective property of cholecalciferol. Although it was not reported previously, several studies described the role of Vitamin D in liver disease severity and progression. The prevalence of Vitamin D deficiency (serum 25-hydroxycholecalciferol concentrations <20 ng/mL) among the general population is 20%–100%\textsuperscript{29}, while it is 64%–92% among patients with chronic liver disease where it is inversely correlated to liver disease progression.\textsuperscript{30,31} In addition to the role of Vitamin D in calcium and bone metabolism, its extraskeletal effects associated with chronic disease have been discovered.\textsuperscript{32} Regardless of the etiology of chronic liver disease, it was found that Vitamin D deficiency is highly prevalent\textsuperscript{33} and is associated with liver dysfunction and liver-related mortality.\textsuperscript{34} It has been suggested that Vitamin D deficiency can aggravate liver damage;\textsuperscript{35,36} Vitamin D plays a pivotal role in the progression of liver necroinflammation and fibrosis.\textsuperscript{32} Vitamin D deficiency (25-hydroxycholecalciferol <10 ng/mL) was a predictor of advanced liver fibrosis among patients with chronic liver disease.\textsuperscript{37} Among patients with genotype-1 chronic HCV infection, a significant inverse correlation between 25-hydroxycholecalciferol serum level and stage of fibrosis has been reported. Moreover, low level of 25-hydroxycholecalciferol was a predictor of higher necroinflammation grade and fibrosis stage.\textsuperscript{38} This observation was corroborated by the finding that lower 25-hydroxycholecalciferol concentration was associated with hepatic steatosis, necroinflammation, and fibrosis among patients with NAFLD.\textsuperscript{39,40} Oral administration of

![Figure 2: Therapeutic outcome of the study population. TB: tuberculosis, ATT: antituberculosis therapy, n: number, ATT-LD: antituberculosis therapy-induced liver disorder, TF: therapeutic failure.](image)

**Table 4: Therapeutic outcome among the study population**

| Variable                        | Total (n=300) | Group A (n=150) | Group B (n=150) | P     |
|--------------------------------|--------------|----------------|----------------|-------|
| Temporary discontinuation of WHO-recommended ATT | 5 (1.7)      | 5 (3.3)        | 0              |       |
| Therapeutic failure            | 69 (23)      | 41 (27.3)      | 28 (18.7)      | 0.057 |

Variables are expressed as frequency (%). Group A: Patients with antituberculosis therapy only, Group B: Patients with antituberculosis therapy and cholecalciferol supplementation, WHO: World Health Organization, ATT: Antituberculosis therapy.
1α-hydroxycholecalciferol for 6 weeks in rat model with diet-induced NASH showed dose-dependent amelioration of NASH progression, suggesting that the active form of Vitamin D may be beneficial as an adjunctive therapy for NASH.[12]

The potential hepatoprotective effect of Vitamin D could be explained by its significant role in immune system response. Vitamin D has been demonstrated to modulate the activation of lymphocytes toward a Th2 anti-inflammatory profile.[14] In addition, activated macrophages produce 1,25-dihydroxycholecalciferol and express VDR. Thus, 1,25-dihydroxycholecalciferol produced by the liver can practice a negative feedback effect on inflammation contributing to its suppression.[42] Moreover, Vitamin D inhibits monocytes activation and subsequent expression of the key inflammatory markers of NAFLD-related liver injury (tumor necrosis factor alpha and interleukin-1) while its deficiency promotes NAFLD progression through the activation of Toll-like receptor 2, 4, and 9 leading to more severe necroinflammation.[43] It has been suggested that the active form of Vitamin D could suppress the activation of stellate cells based on in vitro and in vivo models.[44] In experimental model, it was found that Vitamin D inhibits proliferation of primary hepatic stellate cells, suppresses the expression of collagen, and prevents thioacetamide-induced liver fibrosis.[45]

The overall therapeutic failure rate among out study population was 23%. This rate was lower than previously reported (29%) among 133 Egyptian patients with pulmonary TB who received the WHO-recommended ATT. This may be attributed to the absence of some potential risk factors of therapeutic failure (liver cirrhosis and renal failure) among our study patients compared to those recruited by Hasanain et al.[46] Although it was not statistically significant, our study Group B patients had a less frequent therapeutic failure rate compared to those of Group A (19% vs. 27%). This may point to a potential, additional, beneficial role of adjuvant cholecalciferol supplementation among patients with TB receiving ATT. 1,25-dihydroxycholecalciferol promotes the antimicrobial properties of macrophages and monocytes; this may play a role in combatting pathogens such as Mycobacterium tuberculosis indirectly through Toll-like receptor signaling, monocytes-induced cytochrome (CYP2B1), inflammatory response in macrophages with enhanced secretion of cytokines, enhanced capacity of monocyte-derived macrophages,[47] and VDR activity, or directly by modulating gene expression in favor of cathelicidin production.[48] Production of human cathelicidin is upregulated in response to infection to destroy lipoprotein membranes of microbes.[49]

Our study has a weakness; estimation of Vitamin D level was not performed to assess the pretreatment Vitamin D status of the study population due to financial limitations. Lower pretreatment level of Vitamin D among patients of Group A might have contributed to the higher incidence rate of ATT-LD. However, this study is unique in being the first one to explore the potential role of Vitamin D₃ supplementation for protection against ATT-LD.

## Conclusions

Adjuvant cholecalciferol supplementation may be protective against ATT-LD without extra adverse effects. Before recommending the routine use of cholecalciferol supplementation for prevention of ATT-LD, larger scale studies are recommended. The potential contribution of cholecalciferol supplementation to ATT therapeutic response needs further studies to be explored. Being inexpensive and safe, the use of Vitamin D supplementation within the recommended dietary allowance range cannot be discouraged among patients with TB receiving ATT.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

1. Cantwell MF, Snider DE Jr., Cauthen GM, Onorato IM. Epidemiology of tuberculosis in the United States, 1985 through 1992. JAMA 1994;272:535-9.
2. Durand F, Bermuau J, Pessaye D, Samuel D, Belaiche J, Degott C, et al. Delerious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment including isoniazid. Hepatology 1995;21:929-32.
3. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifamip and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J 1996;9:2026-30.
4. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest 1971;99:465-71.
5. Franks AL, Binkin NJ, Snider DE Jr., Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep 1989;104:151-5.
6. Hussain Z, Kar P, Hussian SA. Antituberculosis drug-induced hepatitis: Risk factors, prevention and management. Indian J Exp Biol 2003;41:1226-32.
7. Fernández-Villar A, Sopheha B, Fernández-Villar J, Vázquez-Gallardo R, Ulloa F, Leiro V, et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2004;8:1499-505.
8. Sakauskonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006;174:935-52.
9. Singla R, Sharma SK, Mohan A, Makharia G, Sreenivas V, Jha B, et al. Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity. Indian J Med Res 2010;132:81-6.
10. Wang X, Li W, Zhang Y, Yang Y, Qin G. Association between Vitamin D and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: Results from a meta-analysis. Int J Clin Exp Med 2015;8:17221-34.
11. Nelson JE, Roth CL, Wilson LA, Yates KP, Aouizerat B, Morgan-Stevenson V, et al. Vitamin D deficiency is associated with increased risk of non-alcoholic steatohepatitis in adults with non-alcoholic fatty liver disease: Possible role for MAPK and NF-κB? Am J Gastroenterol 2016;111:852-63.
12. Nakano T, Cheng YF, Lai CY, Hsu LW, Chang YC, Deng JY, et al. Impact of artificial sunlight therapy on the progress of non-alcoholic fatty liver disease in rats. J Hepatol 2011;55:413-25.
13. Grünhage F, Hochrath K, Krawczyk M, Höblinger A, Obermayer-Pietsch B, Geisel J, et al. Common genetic variation in Vitamin D metabolism is
associated with liver stiffness. Hepatology 2012;56:1883-91.
14. Azab SF, Ali YF, Farghaly MA, Hamed ME, Allah MA, Emam AA, et al. Vitamin D receptor gene BsmI polymorphisms in Egyptian children and adolescents with systemic lupus erythematosus: A case-control study. Medicine (Baltimore) 2016;95:e5233.
15. Telean MD, Chee CB, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis 2002;6:699-705.
16. Eillner JJ. Tuberculosis. In: Goldman L, Schaffer AI, editors. Goldman-Cecil Medicine. Philadelphia: Elsevier-Saunders; 2016. p. 2159-64.
17. Tahaoglu K, Ataç G, Sevim T, Tärün T, Yazıcıoğlu O, Horzum G, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2001;5:65-9.
18. World Health Organization. Treatment of Tuberculosis: Guidelines for National Programs. WHO/HTM/TB/2009.420. 4th ed. Geneva: World Health Organization; 2009.
19. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press; 2010.
20. Mulligan GB, Licata A. Taking Vitamin D with the largest meal improves absorption and results in higher serum levels of 25-hydroxyvitamin D. J Bone Miner Res 2010;25:928-30.
21. World Health Organization. Definitions and Reporting Framework for Tuberculosis, 2013 Revision. WHO/HTM/TB/2013.2. Geneva: World Health Organization; 2013 Revision. Available from: http://www.who.int/ht/publications/definitions/en/. Last updated 2014 Dec.
22. Makhlouf HA, Helmy A, Fawzy E, El-Attar M, Rashed HA. A prospective study of antituberculous drug-induced hepatotoxicity in an area endemic for liver diseases. Hepatol Int 2008;2:353-60.
23. Mehta S. Malnutrition and drugs: Clinical implications. Dev Pharmacol Ther 1990;15:159-65.
24. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: A case-control study. Thorax 1996;51:132-6.
25. Isa SE, Ebonyi AO, Shehu NY, Idoko P, Anejo-Okopi JA, Simji G, et al. Antituberculosis drugs and hepatotoxicity among hospitalized patients in Jos, Nigeria. Int J Mycobacteriol 2016;5:21-6.
26. Steele MA, Burk RF, DesPrez RM. Hepatitis with INH and RMP: A meta-analysis. Chest 1991;99:465-71.
27. Mahmood K, Hussain A, Jairamani KL, Talib A, Abbasi B, Salkeen S. Hepatotoxicity with antituberculosis drugs: The risk factors. Pak J Med Sci 2007;23:33-8.
28. Shakyra R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antituberculous medicines and assessment of risk factors. Ann Pharmacother 2004;38:1074-9.
29. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.
30. Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. Clin Gastroenterol Hepatol 2007;5:513-20.
31. Arteh J, Narra S, Nair S. Prevalence of Vitamin D deficiency in chronic liver disease. Dig Dis Sci 2010;55:2624-8.
32. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
33. Stokes CS, Volmer DA, Grünhage F, Lammert F. Vitamin D in chronic liver disease. Liver Int 2013;33:338-52.
34. Putz-Bankuti C, Pizl S, Stojakovic T, Scharnagl H, Pieber TR, Trauner M, et al. Association of 25-hydroxyvitamin D levels with liver dysfunction and mortality in chronic liver disease. Liver Int 2012;32:845-51.
35. Rahman AH, Branch AD. Vitamin D for your patients with chronic hepatitis C? J Hepatol 2013;58:184-9.
36. Kwok RM, Torres DM, Harrison SA. Vitamin D and nonalcoholic fatty liver disease (NAFLD): Is it more than just an association? Hepatology 2013;58:1166-74.
37. Ko BJ, Kim YS, Kim SG, Park JH, Lee SH, Jeong SW, et al. Relationship between 25-hydroxyvitamin D levels and liver fibrosis as assessed by transient elastography in patients with chronic liver disease. Gut Liver 2016;10:818-25.
38. Petta S, Cammá C, Scaczone C, Tripodo C, Di Marco V, Bono A, et al. Low Vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. Hepatology 2010;51:1158-67.
39. Targher G, Bertolmi L, Scala L, Cigolini M, Zenari L, Falezza G, et al. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2007;17:517-24.
40. Lager M, Kruschitz R, Kienbacher C, Traussnigg S, Langer F, Schindler K, et al. Prevalence of liver fibrosis and its association with non-invasive fibrosis and metabolic markers in morbidly obese patients with Vitamin D deficiency. Obes Surg 2016;26:2425-32.
41. Baek F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: Modulator of the immune system. Curr Opin Pharmacol 2010;10:482-96.
42. Hayes CE, Nashold FE, Spach KM, Pedersen LB. The immunological functions of the Vitamin D endocrine system. Cell Mol Biol (Noisy-le-grand) 2003;49:277-300.
43. Roth CL, Ellers CT, Figlewicz DP, Melhorn SJ, Morton GI, Hoofnagle A, et al. Vitamin D deficiency in obese rats exacerbates nonalcoholic fatty liver disease and increases hepatic resistin and Toll-like receptor activation. Hepatology 2012;55:1103-11.
44. Ding N, Yu RT, Subramaniam N, Sherman MH, Wilson C, Rao R, et al. A Vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response. Cell 2013;153:601-13.
45. Abramovitch S, Dahan-Bachar L, Sharvit E, Weisman Y, Ben Tov A, Brazowski E, et al. Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats. Gut 2011;60:1728-37.
46. Hasanain AF, Zayed AA, Mahdy RE, Nafee AM, Attia RA, Mohamed AO. Hookworm infection among patients with pulmonary tuberculosis: Impact of co-infection on the therapeutic failure of pulmonary tuberculosis. Int J Mycobacteriol 2015;4:318-22.
47. Eklund D, Persson HL, Larsson M, Welin A, Idh J, Paues J, et al. Vitamin D enhances IL-1β secretion and restricts growth of Mycobacterium tuberculosis in macrophages from TB patients. Int J Mycobacteriol 2013;2:18-25.
48. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the Vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. FASEB J 2005;19:1067-77.
49. Ramanathan B, Davis EG, Ross CR, Blecha F. Cathelicidins: Microbicidal activity, mechanisms of action, and roles in innate immunity. Microbes Infect 2002;4:361-72.