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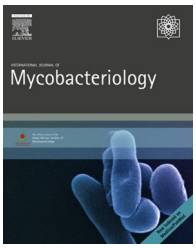

Full Length Article

Risk assessment of hepatotoxicity among tuberculosis and human immunodeficiency virus/AIDS-coinfected patients under tuberculosis treatment

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ABSTRACT

Objective/background: Tuberculosis (TB) is a worldwide public health problem. It is a contagious and grave disease caused by *Mycobacterium tuberculosis*. Current drugs such as isoniazid, pyrazinamide, and rifampicin used for the treatment of tuberculosis are potentially hepatotoxic and can lead to drug hepatitis. In order to improve the follow-up of TB patients in Cameroon, we carried out a study which aimed to evaluate the hepatotoxicity risk factors associated with anti-TB drugs.

Methods: The studies were performed on 75 participants who had visited the Loum District Hospital located in the littoral region of Cameroon for their routine consultation. Participants have been selected based on pre-established criteria of inclusion and exclusion. Prior to the informed consent signature, patients were given compelling information about the objective and the result output of the study. They were questioned about antioxidant food and alcohol consumption as well as some clinical signs of hepatotoxicity such as fever, nausea, vomiting, and tiredness. The collected blood was tested for the determination of biochemical markers (transaminases and C-reactive protein) using standard spectrophotometric methods.

Results: Biochemical analysis of samples showed a significant increase ($p < .05$) of aspartate aminotransferase and alanine aminotransferase values in TB patients coinfected with human immunodeficiency virus/AIDS (33.28 ± 16.58 UI/L and 30.84 ± 17.17 UI/L, respectively) compared with the respective values of the controls (16.35 ± 5.31 UI/L and 16.45 ± 4.83 UI/L). Taking individually, the liver injury patient percentage of TB patients was significant compared to TBC when considering alanine aminotransferase and aspartate aminotransferase parameters. When considering risk factors, antioxidant food

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consumption significantly reduced the liver injury patient percentage for the above parameters, whereas an opposite situation was observed with alcohol consumption between TB-coinfection and TB patients. Regarding the C-reactive protein results, the percentage of positive tests was very high among coinfected patients (40%) compared with the control (15%). The interactions between parameters related to alcohol consumption and intake of antioxidant foods showed a slight decrease in activity compared with interactions without food.

Conclusion: The results showed that human immunodeficiency virus status and alcohol consumption constitutes aggravating factors for the occurrence of hepatic toxicity. In addition, the consumption of antioxidant foods simultaneously with TB drugs help in reducing the hepatotoxic effects of these drugs.

Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium called *Mycobacterium tuberculosis*. It usually affects the lungs (pulmonary TB) but can affect other organs, such as bones and lymph nodes (extrapulmonary TB). The disease is spread through air when TB patients expel the bacteria, by coughing for example [1]. TB remains a major global health problem in Africa and Asia. It affects the health of millions of people annually throughout the world and ranks as the second disease leading to death among infectious diseases worldwide after human immunodeficiency virus (HIV)/AIDS [2]. The World Health Organization estimated in 2012 that there were up to 8,600,000 new TB cases and 1.3 million deaths. Just under the 1.0 million people who died were HIV-negative and 0.3 million deaths were people coinfected with HIV [3]. Most TB cases and deaths occur in men, but the burden of disease in women is also high. In Cameroon, approximately 35,000 of TB cases are recorded every year and 40% of these patients are also diagnosed HIV-positive/AIDS. Between 2009 and 2013, among the 100,000 habitants hospitalized in Cameroon, 238 were suffering from TB, including 83 cases of pulmonary TB, with a mortality rate of 30.94% [4]. The recommended treatment regimen for new cases of TB includes four drugs (isoniazid [I], rifampicin [R], ethambutol [E], and pyrazinamide [Z]) for 6 months. Three of these drugs (I, Z, and R) are potentially hepatotoxic and can lead to drug-induced hepatitis [3]. A study carry out in India on the use of different schemes of TB regimen in adults demonstrated 2.6% liver toxicity with I coadministrated with R and 1.1% and 1.6% with R and I alone, respectively [5]. Similar studies conducted in Turkey and Singapore showed that the reintroduction of Z was more likely to lead to a recurrence of hepatotoxicity [6]. As hepatotoxicity caused by these drugs is related to the administration of higher doses of drugs, a lower daily dose is recommended or a reduction in the frequency of the drugs to three times weekly [7].

In Cameroon very few studies have been conducted regarding the potential hepatotoxicity risks of TB treatment either in TB patients or in coinfected TB/HIV patients. Therefore, it was important to carry out this study to identify and understand the hepatotoxic risks of TB drugs in order to manage the treatment.

Material and methods

Ethical consideration

This study was approved by the Ethics Research Committee of the Cameroon Bioethics Initiative (CAMBIN) located in Yaounde – Cameroon and the ethical clearance was obtained under the reference number CBI/317/CARE/CAMBIN. This approval helped receive authorization from the hospital center under the reference number 176/L/MSP/DRSPL/DSL/HDL. Patient gave "informed consent" in order to give details relating to the understanding of the purpose, any profit if involved in the study, as well as their right to be included or not in the study.

Patients and drug consumption

Descriptive and analytical retrospective and prospective studies were conducted in TB patients with ages ranging from 15 years to 65 years, under anti-TB drugs under Directly Observed Treatment, Short course, visiting Loum District Hospital. The study was conducted from June 2014 to February 2015. Composed of some voluntary participants without TB or/and HIV infection (control), both TB patients coinfected with HIV/AIDS or not coinfected were included in the study. The patients fulfilled the following criteria: (1) they were on anti-TB drugs at least 2 months; (2) were not receiving any other hepatotoxic drugs parallel with anti-TB treatment as well as without hepatitis B or C; and (3) had normal findings of liver function parameters at the beginning of the treatment. TB patients were given a 6-month regimen of four first-line drugs: I, R, E, and Z divided into two phases: 2 months of RIEZ and 4 months of RI. Coinfected patients with HIV/AIDS received 9 months divided into two phases: 2 months of I/R/Z ± E and 7 months of I/R. Some hepatotoxicity clinical signs such as fever, nausea, vomiting, and tiredness were monitored. Patients were given a questionnaire about some antioxidant foods and alcohol consumption levels. Antioxidant food was well explained to the patients in relation to their physio-pathological situation, to help them understand that this type of food plays a big role in the elimination of excess of free radicals that can sometimes mediate hepatotoxicity according to Yew and Leung [8]. Ambreen et al.

Table 1 – Sociodemographic characteristics of the study population.

Characteristics	Interval	(%)
Age (y)	<45	65.33
	⩾45	34.67
Sex	Male	60
	Female	40
Alcohol	Male patients	25.45*
	Female patients	5.45

Note. Chi-square test was used to compare frequencies. y = year.
* Difference is significant at $p < .05$.

[9] as well as Yew and Leung [8] revealed that alcohol is one of the most common risk factors that have been found to be associated with anti-TB dug-induced hepatotoxicity (DIH).

Follow-up and parameter measurements

Patients were positively diagnosed using a sputum examination in which bacterium were directly observe under a microscope. To evaluate the occurrence of hepatotoxicity, blood samples were collected into dried tubes under a temperature of 4 °C and immediately centrifuged at 1509*g* for 5 min to obtain serum. This was then kept at −8 °C until use. The different sera obtained were used to for biochemical analysis. Liver function was tested transversally after the treatment. Liver function parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and C-reactive protein [CRP]) were measured in blood serum by utilizing an autoanalyzer in the pathology lab. Transaminases (AST and ALT) were determined using spectrophotometry following the kinetic method previously described. The CRP was measured qualitatively and semiquantitatively with the slide agglutination test CRP-latex reagent (Arlington Scientific, Inc.™, Springville, UT, USA) in which the particles are coated with anti-human CRP antibodies. According to Ambreen et al. [9], the presence of at least one of the following criteria was used to define anti-TB-DIH: a rise to more than two times the normal level of CRP, ALT, and/or AST; any increase in ALT and/or AST above pretreatment levels together with anorexia, nausea, vomiting, and jaundice. Liver function parameters included ALT, AST, and CRP. The liver injury patient percentage (LIP) helps to find people with hepatotoxicity based on the above criteria.

Statistical analysis

The data collected were entered in Microsoft Office Excel 2007 (Microsoft Corporation Corporate Headquarters Redmond, WA, USA) and checked for any inconsistencies. Analysis of variance followed by Tukey post hoc were used to compare the means of the enzymatic parameters. The interactions between these biochemical parameters and risk factors (age, sex, and alcohol) were analyzed using multivariate testing general linear model. Chi-square test was used to compare the frequencies of single factors or interactions. Also, a bivariate correlation was made through the Spearman rho test. A p value <.05 was considered significant. All the analysis was carried out using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of the patients are given in Table 1. From the 75 participants in the study, 30 were TB only, 25 were TB coinfected, and there were 20 controls. In this study men were most represented (60%). The age group younger than 45 years was the most represented (65.33%) compared with the group equal or greater than 45 years (34.67%). The mean age was 37 years for men and 34 years for women. Taking into account the risk of hepatotoxicity associated with alcohol intake, it is clear that the frequency of alcohol consumption was significantly higher ($p < .05$) in male patients (25.45%) than in female patients (5.45%).

Table 2 shows variation of parameters ALT, AST, and CRP in both TBC and TB patients compared with the control group. There is a significant difference ($p < .001$) of the mean values of transaminases (AST and ALT) in TBC groups compared with the controls and TB-only patients. The same observation was made with the percentage of positive tests for CRP although this was not significant. In spite of the fact that some slight differences were observed between values, it remains clear that no significant difference is noticeable with reference values. However, concerning the ALT parameter, nine TBC patients out of 25 (12%) presented with hepatotoxicity based on the criteria used (they presented twice with the biochemical parameter values compared with the control). Moreover, three TB patients out of 30 (10%) presented with hepatotoxicity based on the criteria used (they presented twice with the biochemical parameter values compared with the control). Furthermore, the difference between TBC patients and TB patients is significant ($p < .001$).

The LIP helps to find people with hepatotoxicity based on the criteria used (they presented twice with the biochemical parameter values compared with the control). Concerning the AST parameter, 10 TBC patients out of 25 (40%) presented hepatotoxicity based on the criteria used (they presented twice with the biochemical parameter values compared with the control). Moreover, three TB patients out of 30 (10%) presented with hepatotoxicity. Furthermore, the difference between TBC patients and TB patients is significant ($p < .05$; Table 2). LIP for the food and alcohol consumption between TBC and TB patients is also presented in the text and tables.

The effects of different factors such as alcohol intake, sex, and age on the previous biochemical parameters were also evaluated using multivariate general linear model and the results presented in Table 3 show that the interaction

Table 2 – Effect of patient group on some biochemical parameters.

Groups (sample size)	AST (UI/L)		ALT (UI/L)		CRP (% of positive tests)
	Reference value (35–38)	LIP (%)	Reference value (35–38)	LIP (%)	
Control (20)	16.35 ± 5.31[a]	0.0	16.45 ± 4.83[a]	0.0	15.0
TB (30)	20.43 ± 15.01[a]	10	21.3 ± 11.4[a]	10	36.66
TBC (25)	33.28 ± 16.58[b]	40*	30.84 ± 17.17[b]	12*	40.0

Note. The analysis of variance followed by Tukey post hoc were used to compare the means of the enzymatic parameters. The value subscripted with the same letter in the columns show no significant difference. Chi-square was used to compare the frequencies of liver injury patient percentage and C-reactive protein between tuberculosis and tuberculosis coinfection. ALT = alanine aminotransferase; AST = aspartate transaminase; CRP = C-reactive protein; LIP = liver injury patient percentage; TB = tuberculosis; TBC = tuberculosis coinfection.
* Difference is significant at $p < .05$.

Table 3 – Influence of sex and patient group on some biochemical parameters.

Groups (sample size)	AST (UI/L), reference value (35–38)		ALT (UI/L), reference value (35–38)		CRP (% of positive tests)	
	Men	Women	Men	Women	Men	Women
Control (20)	15.71 ± 5.62	15.68 ± 4.88	15.00 ± 5.10	16.67 ± 4.71	12.5	12.5
TB (30)	21.88 ± 17.21	17.91 ± 12.05	18.56 ± 9.8	21.41 ± 10.91	43.75	37.5
TBC (25)	32.07 ± 19.19	31.89 ± 12.96	31.03 ± 18.66	27.82 ± 16.22	43.75	50.0

Note. The interactions between biochemical parameters and risk factor (sex) were analyzed using multivariate testing general linear model. ALT = alanine aminotransferase; AST = aspartate transaminase; CRP = C-reactive protein; TB = tuberculosis; TBC = tuberculosis coinfection.

between different parameters (ALT, AST, and CRP) with sex brings about a slight increase of ALT and CRP in men compared with women. The influence of sex on some biochemical parameters presented in Table 4 shows a nonsignificant difference on all the parameters studied in the group of patients consuming alcohol or not compared with controls. The multivariate testing general linear model indicated that age was not a significant ($p > .05$) risk factor for anti-TB-DIH. Further, the analysis shown in Table 5 shows that CRP was very high even though it was not significant in patients aged older than 45 years.

At follow-up of the patients, we observed that certain clinical signs associated with hepatotoxicity were evaluated in these patients. These results, shown in Table 6, demonstrate a high percentage gap between the TBC and TB groups for symptoms (fatigue, fever, nausea, and vomiting). Among these a significant variation ($p < .05$) was noted in people with fever symptoms. However, the percentages of the various symptoms observed were higher among TB patients compared with TBC patients. Furthermore, it was noted that the time of appearance of these signs was between 10 days and 45 days.

In order to assess the influence of some antioxidants present in the diet on the occurrence of hepatotoxicity, the quality of food consumption (fruits and vegetables) was estimated in all participants of the various study groups. Table 7 depicts the influence of diet on risk factors for hepatotoxicity while taking TB drugs or not, compared with the control. Using multivariate testing general linear model, from Table 7 it appears that the interaction between different parameters (ALT, AST, and CRP) and foods show a slight decrease in different groups (28.75 ± 14.39 UI and 37.00 ± 17.89 UI for AST). When food is not taken into account, the values of these parameters become high (26.25 ± 14.4 UI and 34.57 ± 18.9 UI for AST) but not significant. The same observation was made with alcohol consumption. When looking at the percentage of LIP (liver injury patients) based on the above criteria, it appears from Table 7 that the percentage of TB patients with LIP decreases

Table 4 – Influence of alcohol and patient groups on some biochemical parameters.

Groups (sample size)	AST (UI/L), reference value (35–38)			ALT (UI/L), reference value (35–38)			CRP (% of positive tests)	
	Alcohol	LIP (%)	No alcohol	Alcohol	LIP (%)	No alcohol	Alcohol	No alcohol
Control (20)	15.71 ± 5.62	0.0	15.68 ± 4.88	15.00 ± 5.10	0.0	16.67 ± 4.71	12.5	12.5
TB (30)	21.88 ± 17.21	66.67	17.91 ± 12.05	18.56 ± 9.8	66.67	21.41 ± 10.91	43.75	37.5
TBC (25)	32.07 ± 19.19	50.0*	31.89 ± 12.96	31.03 ± 18.66	55.55*	27.82 ± 16.22	43.75	50.0

Note. The interactions between biochemical parameters and risk factors (alcohol) were analyzed using multivariate testing general linear model. Chi-square was used to compare the frequencies of liver injury patient percentage and C-reactive protein when consuming alcohol between tuberculosis and tuberculosis coinfected.
ALT = alanine aminotransferase; AST = aspartate transaminase; CRP = C-reactive protein; LIP = liver injury patient percentage; TB = tuberculosis; TBC = tuberculosis coinfection.
* Difference is significant at $p < .05$.

Table 5 – Effect of age and patient group on some biochemical parameters.

Groups (sample size)	AST (UI/L), reference value (35–38)		ALT (UI/L), reference value (35–38)		CRP (% of positive tests)	
	<45 y	>45 y	<45 y	>45 y	<45 y	>45 y
Control (20)	16.5 ± 5.64	17.75 ± 2.87	16.81 ± 5.48	16.5 ± 1.73	4	8
TB (30)	20.76 ± 17.37	19.2 ± 9.04	20.81 ± 9.78	17.7 ± 10.71	20	28
TBC (25)	28.46 ± 15.43	40.5 ± 17.23	25.13 ± 13.87	39.4 ± 19.01	16	24

Note. The interactions between biochemical parameters and risk factors (alcohol) were analyzed using multivariate testing general linear model. ALT = alanine aminotransferase; AST = aspartate transaminase; CRP = C-reactive protein; TB = tuberculosis; TBC = tuberculosis coinfection.

Table 6 – Change in some clinical symptoms based on some factors.

Symptoms	Groups	%	Symptoms/alcohol (%)	Symptoms/antioxidant food (%)
Tiredness	TBC	42.9	44.0	36.0
	TB	57.1	60.0	50.0
Fever	TBC	6.7	12.0	7.6
	TB	93.3*	96.67	88.33
Nausea	TBC	20.0	28.0	12.0
	TB	80.0	83.33	73.33
Vomiting	TBC	20.0	24.0	16.0
	TB	80.0	83.33	76.67

Note. Chi-square analysis and multivariate logistic regression. TB = tuberculosis; TBC = tuberculosis coinfection; Symptoms/alcohol = when taking alcohol into consideration; Symptoms/antioxidant food = when food is taken into consideration.
* Difference is significant at $p < .05$.

Table 7 – Role of some antioxidant foods on aspartate transaminase (AST), alanine aminotransferase (ALT), and C-reactive protein (CRP) parameters.

Groups	AST (UI/L), reference value (35–38)			ALT (UI/L), reference value (35–38)			CRP (% of positive tests)	
	Alt	No Alt	LIP (%)	Alt	No Alt	LIP (%)	Alt	No Alt
Controls (20)	16.3 ± 5.31	16.4 ± 5.60	0.0	16.4 ± 5.25	16.5 ± 4.67	0.0	5.88	33.33
TB (30)	19.94 ± 17.50	20.53 ± 12.10	33.33	20.12 ± 9.55	22.23 ± 14.3	66.67	10.0	80.0
TBC (25)	28.75 ± 14.39	37.0 ± 17.89	70.0*	26.25 ± 14.4	34.57 ± 18.9	55.56*	13.33	80.0

Note. The values for transaminases are expressed as means ± standard deviation. Chi-square was used to compare the frequencies of liver injury patient percentage and CRP when antioxidant food are not consuming between tuberculosis and tuberculosis coinfected. Alt = antioxidant food; LIP = liver injury patient percentage; TB = tuberculosis; TBC = tuberculosis coinfected.
* Difference is significant at $p < .05$.

significantly from TBC patients with LIP ($p < .001$) when consuming antioxidant food and no alcohol consumption. These observations are reversed when not consuming antioxidant food but with a considerable alcohol consumption (Tables 4 and 7).

Discussion

Diet, clinical symptoms, biochemical parameters, and some risk factors such as alcohol intake, age, and sex, are generally taken into account when monitoring the health of TB patients in the Loum District Hospital and these parameters were evaluated to better understand the effect of the TB drugs on liver toxicity. The three main drugs usually used by TB patients (I, Z, and R) are potentially hepatotoxic [3]. ALT and AST are mainly synthesized in the liver and located in the cytoplasm and mitochondrion respectively. After synthesis, these enzymes can be found in the blood in a lower concentration. The high level of AST and ALT in serum can explain liver damage [10]. In this study, we found that there was a significant increase ($p < .05$) in ALT and AST values among coinfected and noncoinfected TB patients compared with controls (Table 2). The elevation of these enzyme activities could be due to the use of TB drugs. TBC patients showed a slight increase in ALT and AST activities. In fact, when taking TB drugs, I hydrolysis by R produces isonicotinic acid releasing hydrazine. Once this is released it undergoes an acetylation reaction in the presence of isonicotinic acid to give hydrazine monoacetyl which subsequently undergoes a cascade of reactions including oxidation which is accelerated by alcohol intake and produces hepatotoxic compounds [11]. Koné [12], during a comparative study on HIV/TB coinfected patients in Mali, indicated an acceleration of liver enzymes and progression to cirrhosis in coinfected patients compared with

controls. Similarly, Pukenyte et al. [1] showed that the decrease in immune status of HIV patients could be link with the increase of risk of liver toxicity.

The effects of different factors such as alcohol intake, sex, and age on these parameters (ALT, AST, and CRP) were also assessed as well as the role of food or noninteraction with alcohol. Of all these factors, alcohol had the greatest influence by increasing the values of these parameters. The same observation was made with the age factor only for CRP, but this was not significant. Moreover, the intake of some foods (fruits and vegetables) decreased the effect of alcohol. Foods consumed on this medication could be responsible for the decline of activities/observed frequencies.

The state of malnutrition according to the National Institute of Nutrition [13] is suggested as a risk factor for anti-TB drugs inducing hepatotoxicity. The same observation was made by Khoharo et al. [14] and Senaratne et al. [15] in their studies showed that diet plays a role in the occurrence of hepatotoxicity. Moreover, other authors suggested that hepatotoxicity of TB drugs induced by malnutrition may be due to the depletion of glutathione reserves, making patients vulnerable to oxidation and thus to oxidative stress which is a mediator of hepatotoxicity [7,16,17]. A previous study on Ethiopian patients with TB and coinfected with HIV demonstrated that the development of hepatotoxicity due to TB drugs is significantly associated with a decrease in nutritional status. This result corroborates with our study which shows no significant increase in the parameters studied in relation to alcohol intake. It is therefore important to note that the foods consumed by patients can have a strong antioxidant potential and thus protect liver cells against toxicity.

The age group older than 45 years was not significantly influenced by increasing percentages of positive tests of CRP in patients compared with controls. Studies conducted by Durand et al. [18] and Senaratne et al. [15], showed that advanced age may be a risk factor for hepatotoxicity in TB treatment. By contrast, studies carried by Marzuki et al. [5], Javadi et al. [19], and Sharifzadeh et al. [20] showed that advanced age was not a risk factor for hepatotoxicity in patients taking anti-TB inducing drugs. This could be explained not only through compliance with medication doses and frequencies, but also nutrition that helps cope with oxidative stress—the main pathway mediated hepatotoxicity associated with taking TB drugs.

Some patients experienced nausea, vomiting, fatigue, and fever. This clinical evidence was significant ($p < .05$) due to the fact that these patients had not complied with the prescribed diet and the prescription of alcohol intake. The first clinical signs of liver toxicity were observed at the interval 10–45 days. Makhlouf et al. [16] worked on the hepatotoxicity of Z and E in the treatment of latent TB and also observed similar clinical manifestations when taking anti-TB-HID in patients within the 15–60-day time interval.

Conclusion

Regarding the results obtained in this study we can conclude that advanced age (older than 45 years), HIV/AIDS status, and regular alcohol consumption were identified as factors aggravating the occurrence of hepatotoxicity when taking TB drugs. Also, we found that regular consumption of foods such as fruits and vegetables highly rich in antioxidant molecules reduce the risk of liver dysfunction while taking TB drugs.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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