ORIGINAL ARTICLE

AFRICAN JOURNAL OF CLINICAL AND EXPERIMENTAL MICROBIOLOGY SEPTEMBER 2015 ISBN 1595-689X VOL16 No.3
AJCEM/1518 http://www.ajol.info/journals/ajcem

AFR. J. CLN. EXPER. MICROBIOL. 16(3): 104-110 http://dx.doi.org/10.4314/ajcem.v16i3.4

RENAL AND HEPATIC PROFILES IN NIGERIAN MULTIDRUG RESISTANT TUBERCULOSIS PATIENTS WITH OR WITHOUT HIV CO-INFECTION

Ige, O[1].,Yaqub S.A[2]Edem V.F[2] and *Arinola O.G[2]

[1]Department of Medicine, College of Medicine, University of Ibadan, Nigeria; [2]Department of Chemical Pathology, College of Medicine, University of Ibadan, Nigeria

***For Correspondence: drarinolaog64@yahoo.com Tel: +2348023451520**

ABSTRACT

Tuberculosis (TB) is primarily a lung disease (pulmonary tuberculosis, PTB) but the bacilli can also develop in other places in the body, such as the bones, liver and kidney as extra pulmonary tuberculosis. Hepatic and renal involvements in PTB patients are mostly secondary to TB chemotherapy that is potentially hepato- and nephro- toxic. In this study, the biochemical parameters that indicate renal and hepatic involvements were analyzed in the sera of MDR-TB patients with and without HIV co-infection prior to commencement of chemotherapy. Out of 115 MDR-TB patients (76 males and 39 females) recruited for the study, 22 patients (11 males and 11 females) were co-infected with HIV. Serum levels of sodium (Na^+), potassium (K^+), chloride (Cl^-) were analyzed using Easylite (ISE technology), bicarbonate (HCO_3^-) was analysed using back titration method, urea and creatinine were determined spectrophotometrically using Diacetlymonoxime (DAM) method and Jaffe's alkaline picrate method respectively. Total and direct bilirubin, serum glutamate oxaloacetate transferase (SGOT), serum glutamate pyruvate transferase (SGPT), alkaine phosphatase(ALP), total protein (TP) and albumin (Alb) were determined using Hitachi 912 autoanalyzer. There were no statistical significant differences in the renal and hepatic parameters of TB patients with HIV compared with TB patients without HIV. However, significantly higher proportions (89%) of MDR-TB patients had their SGOT within reference range. The mean values indicate that HIV infection did not significantly alter renal and hepatic profiles in MDR-TB patients prior to treatment.

Key words: Kidney, Liver, Electrolytes, Tuberculosis, Human Immunodeficiency Virus, Co-infection.

LES PROFILS RENALS ET HEPATIQUES DANS MULTIRESISTANTE PATIENTS TUBERCULEUX NIGERIANS AVEC OU SANS CO – INFECTION PAR LE VIH.

Ige, O[1]., Yaqub S.A[2]., Edem V. F[2]., et Arinola O.G[2]. ; [1]Departement de médecine, Collège de médecine, Université d'Ibadan, Nigeria ; [2]Departement de pathologie chimique, Collège de médecine, Université d'Ibadan, Nigeria.

Pour correspondance : drarionlaog64@yahoo.com Téléphone : +2348023451520.

RESUME :

La tuberculose est principalement une maladie du poumon (Tuberculeuse pulmonaire TBP) mais les bacilles peuvent être également se développer dans d'autres endroits dans le corps, tels que les os, le foie et les reins comme la tuberculose extra pulmonaire. L'atteinte hépatique et rénale chez les patients atteints de TBP est surtout secondaire a la chimiothérapie de la tuberculose(TB) qui est potentiellement hépato – et néphro – toxique. Dans cette étude, les paramètres biochimiques qui indiquent les implications rénales et hépatiques ont été analyses dans les sérums des patients atteints de MDR – TB avec ou sans Co – infection par le VIH avant le commencement de la chimiothérapie. Sur les 115 patients atteints de MDR – TB (76 males et femelles), recrutés pour l'étude, 22 patients (11 males et femelles) ont été co – infectes par le VIH. Le niveau sérique de sodium (Na^+), de potassium (K^+), le chlorure($C1^-$) ont été analyses en utilisant Easylite(technologie ISE), le bicarbonate ($HC0_3^-$) a été analyse en utilisant la méthode de titrage de retour, l'urée et de la créatinine ont été déterminés spectrophotométrie rn utilisant la méthode Diacétyle monoxime(DAM) et la méthode de picrate alcaline de Jaffer respectivement. Bilirubine totale et directe, glutamate oxaloacetate transférase sérique(SGOT), transférase sérique de glutamate pyruvate(SGPT), phosphatase alcaline(ALP), protéines totale(TP) et albumine(Alb) ont été déterminés en utilisant Hitachi 912 autoanalyseur. Il n' ya pas de différence statistiquement significative dans les paramètres rénales et hépatiques des patients tuberculeux vivant avec ke VIH par rapport aux patients atteints de tuberculose sans VIH. Néanmoins, les proportions significativement élevées (89%) des patients atteints de MDR – TB ont eu leurs SGOT a porté de référence. Les valeurs moyennes indiquent que l'infection par le VIH n'a pas modifié significativement les profils rénaux et hépatiques chez les patients de TB – MRD.

Mots – clés : Les reins, le foie, l'électrolyte, la tuberculose, Virus de l'immunodéficience humaine, Co – infection.

INTRODUCTION

TB is an air-borne infectious disease caused by bacteria *Mycobacterium tuberculosis*, which primarily affects the lungs. The World Health Organization (WHO) declared Tuberculosis (TB) a global emergency in 1993 and it remains one of the world's major causes of illness and death. One third of the world's population carries the TB bacteria and more than nine million of these become sick each year with active TB (1). TB disproportionately affects people in resource-poor settings, particularly in Africa and Asia during their most productive years (2). Coupled with the pandemic of HIV, TB has become an important cause of morbidity and mortality world-wide (3). TB is a major public health problem in Nigeria, with the country ranking 5th among the 22 high TB burden countries which collectively bear 80% of the global burden of TB. The TB burden in Nigeria is further compounded by HIV/AIDS epidemic and the emergence of multi-drug resistant tuberculosis (MDR-TB) (2).

It was reported that systemic effects especially on vital organs such as the kidneys and liver are later events that characterize tuberculosis (TB) and Human Immunodeficiency (HIV) infections. There can be direct renal and hepatic involvement in TB patients but this rarely causes marked impaired renal and hepatic functions. Occasionally, local signs and symptoms may be prominent in renal and hepatic tuberculosis, and may constitute the initial or sole presenting feature of the disease (4). Anti- tubercular drugs was reported to cause renal and hepatic injuries. Rifampicin, pyrazinamide, isoniazid and ethambutol were shown to benephro- and hepato-toxic drugs (5). A study showed that patients with chronic kidney and liver disease can also develop tuberculosis (6), thus posing special management problems for the TB. Since many of the potent anti-tubercular drugs are nephrotoxic and hepatotoxic, they may aggravate the underlying disease processes. Thus, anti-TB drug regimens need to be monitored to prevent further renal and hepatic insult in the patients.

Moreover, literatures have shown that a single anti-TB drug has side effects on liver and kidney (5, 6), thus it is likely that combination of drugs in MDR-TB patients or co-existence of MDR-TB with HIV may have severe effects on kidneys and liver of these patients. This therefore demands for the need to evaluate the status ofliver and kidney functions in MDR-TB patients before commencement of multi-drug treatment.

MATERIALS AND METHODS

After obtaining informed consent, a total of 115 TB patients consisting of 76 males (37±11 years) and 39 females (30±8 years) admitted into MDR-TB Treatment Center, University College Hospital, Ibadan, Nigeria, were recruited into the study. Twenty-two(22) patients (33±9 years) made up of 11 males ((32±9 years) and 11 females(26±8years)were co-infected with HIV. Five (5) ml of blood samples were collected to plain bottles. Serum was obtained following centrifugation. Serum bilirubin was estimated by photometric method based on the diazo reaction. This was based on the principle that bilirubin reacts with diazotized sulphanilic acid to form the red colour azobilirubin (7).Serum protein was analyzed using Biuret method in which divalent copper reacts in alkaline solution with protein peptide bonds to form the characteristic purple-coloured Biuret complex. The colour intensity is directly proportional to the protein concentration which was determined photometrically (8). Albumin was determined by dye binding method whereat a pH value of 4.1 albumin displays a sufficiently cationic character to be able to bind with bromocresol green (BCG), an anionic dyestuff to form a blue –green complex (9). Urea was estimated using Diacetyl monoxime method where heating urea with substances such as diacetyl formed coloured compound measurable spectrophotometrically at 520nm (10). Creatinine was determined using Jaffe's alkaline picrate method where creatinine reacts with picric acid in an alkaline solution toproduce a deep yellow complex directly proportional to the level of creatinine present in the sample (10). ALP activity was assayed using kinetic methodby measuring the concentration of p-nitrophenol released from the cleavage of p-nitrophenyl phosphate into phosphate and p-nitrophenol(11). ASTand ALT activitywere determined following the principle described by Reitman and Frankel(1953). AST was measured by monitoring the concentration of oxaloacetate hydrazone formed with 2, 4-dinitrophenylhydrazine while ALT was measured by monitoring the concentration of pyruvate hydrazone formed with 2, 4-dinitrophenylhydrazine (12). GGTactivity was assayed by monitoringthe concentration of 5-amino-2-nitrobenzoate released (13). Serum levels of sodium (Na^+), potassium (K^+), chloride (Cl^-) were analyzed using Easylite (ISE technology), bicarbonate ($HC0_3^-$) was determined using back titration method (14). The data were presented in mean ± S.D. The differences between the means were compared using Mann-whitney U test.

RESULTS

Table 1 shows demographic characteristics of MDR-TB patients with and without HIV infection and their gender distribution. Age, height, weight and BMI were similar in MDR-TB patients compared with patients having MDR-TB/HIV co-infection.

Table 2 shows that there were no significant differences in renal and hepatic profiles of the MDR-TB patients compared with patients having MDR-TB/HIV co-infection.

Table 3 shows percentage of parameters below, within and above reference range (RR). SGOT was significantly above normal reference range in most(74.2%) of MDR-TB patients.

TABLE 1: DEMOGRAPHIC CHARACTERISTICS OF MDR-TB PATIENTS AND MDR-TB/HIV PATIENTS

	MDR-TB (n= 93)	MDR-TB/HIV (n= 22)	p-values
Age (yrs)	**35.44±11.07**	**33.18±9.18**	**0.377**
BMI (kg/m²)	**16.95±4.91**	**18.13±2.58**	**0.276**
Height (m)	**1.63±0.26**	**1.66±0.11**	**0.617**
Weight (kg)	**48.40±13.26**	**50.27±8.75**	**0.530**
Gender (males)	**65**	**11**	
Gender (females)	**28**	**11**	

TABLE 2: RENAL AND HEPATIC PROFILES IN MDR-TB PATIENTS AND MDR-TB/HIV PATIENTS

	MDR-TB (n= 93)	MDR-TB/HIV (n= 22)	p-values
Urea (mg/dl)	**31.83±9.66**	**29.45±8.62**	**0.293**
Creatinine (mg/dl)	**0.80±0.24**	**0.81±0.21**	**0.804**
Sodium (mmol/l)	**129.77±5.81**	**130.91±2.62**	**0.374**
Potassium (mmol/l)	**3.62±0.51**	**3.55±0.54**	**0.591**
Chloride (mmol/l)	**97.49±2.48**	**97.00±1.20**	**0.366**
Bicarbonate (mmol/l)	**22.88±1.92**	**22.95±1.56**	**0.869**
Total Bilirubin(mg/dl)	**0.62±0.26**	**0.56±0.28**	**0.362**
Direct Bilirubin(mg/dl)	**0.29±0.18**	**0.33±0.22**	**0.351**
SGOT (IU/l	**51.45±23.45**	**55.77±22.62**	**0.436**
SGPT (IU/l)	**38.18±16.08**	**39.91±18.81**	**0.662**
ALP (IU/l)	**88.94±34.99**	**86.23±23.63**	**0.731**
Total protein (g/dl)	**6.55±0.85**	**6.36±0.56**	**0.204**
Albumin (g/dl)	**4.73±0.26**	**4.75±0.14**	**0.699**

TABLE 3: RENAL AND HEPATIC PARAMETERS IN MDR-TB AND MDR-TB/HIV PATIENTS WITHIN AND OUTSIDE REFERENCE RANGES (RR)

	MDR-TB	MDR-TB/HIV	N	p-values
Urea:				
Within RR	**89(80.2%)**	**22(19.8%)**	**111**	**1.000**
Above RR	**4 (100%)**	**0 (0.0%)**	**4**	
Creatinine:				
Within RR	**81(81.8%)**	**18(18.2%)**	**99**	**0.504**
Above RR	**12(75.0%)**	**4 (25.0%)**	**16**	
Potassium:				
Below RR	**32(76.2%)**	**10(23.8%)**	**42**	**0.333**
Within RR	**61(83.6%)**	**12(16.4%)**	**73**	
Chloride:				
Below RR	**3(100.0%)**	**0(0.0%)**	**3**	**1.000**
Within RR	**90(80.4%)**	**22(19.6%)**	**112**	
Bicarbonate:				
Within RR	**93(80.9%)**	**22(19.1%)**	**115**	
Total Bilirubin:				
Within RR	**88(81.5%)**	**20(18.5%)**	**108**	**0.617**
Above RR	**5(71.4%)**	**2(28.6%)**	**7**	
Direct Bilirubin:				
Within RR				
Above RR	**87(82.1%)**	**19(17.9%)**	**106**	**0.370**
SGOT:	**6(66.7%)**	**3(33.3%)**	**9**	
Within RR				
Above RR	**44(89.8%)**	**5(10.2%)**	**49**	**0.036***
SGPT:	**49(74.2%)**	**17(25.8%)**	**66**	
Within RR				
Above RR	**34(77.3%)**	**10(22.7%)**	**44**	**0.440**
ALP:	**59 (83.1%)**	**12(16.9%)**	**71**	
Within RR				
Above RR	**70(79.5%)**	**18(20.5%)**	**88**	**0.515**
Total protein:	**23(85.2%)**	**4(14.8%)**	**27**	
Below RR				
Within RR	**47(77.0%)**	**14(23.0%)**	**61**	**0.268**
Albumin:	**46(85.2%)**	**8(14.8%)**	**54**	
Below RR				
Within RR	**1(100.0%)**	**0(0.0%)**	**1**	**1.000**
	92(80.7%)	**22(19.3%)**	**114**	

Renal and hepatic profiles of male MDR-TB compared with female MDR-TB patients were shown in Table 4. Serum creatinine was significantly raised in male MDR-TB patients compared with female MDR-TB patients. Tables 5 and 6 respectively show hepatic and renal profiles in male or female MDR-TB patients compared with MDR-TB/HIV co-infection. There were no statistical significant differences between the parameters in male patients compared with female patients.

TABLE 4: RENAL AND HEPATIC PROFILES IN MALE AND FEMALE MDR-TB PATIENTS

	Male (n= 76)	Female (n= 39)	p-values
Urea (mg/dl)	31.84±9.48	30.46±9.53	0.462
Creatinine (mg/dl)	0.84±0.25	0.73±0.17	0.013*
Sodium (mmol/l)	130. 03±5.38	129.92±5.37	0.923
Potassium (mmol/l)	3.63±0.51	3.55±0.52	0.440
Chloride (mmol/l)	97.49±2.18	97.23±2.53	0.574
Bicarbonate (mmol/l)	23.05±1.91	22.59±1.70	0.205
Total Bilirubin (mg/dl)	0.62±0.25	0.58±0.28	0.500
Direct Bilirubin (mg/dl)	0.28±0.18	0.33±0.22	0.259
SGOT (IU/l	52.24±23.09	52.36±23.89	0.979
SGPT (IU/l)	39.16±15.86	37.26±18.00	0.562
ALP (IU/l)	87.11±32.08	90.97±35.14	0.555
Total protein (g/dl)	6.55±0.86	6.44±0.68	0.474
Albumin (g/dl)	4.72±0.27	4.78±0.16	0.200

TABLE 5: HEPATIC AND RENAL PROFILES IN MALE MDR-TB PATIENTS AND MDR-TB/HIV PATIENTS

	MDR-TB (n= 65)	MDR-TB/HIV (n= 11)	p-values
Urea (mg/dl)	31.74±9.66	32.45±8.78	0.819
Creatinine (mg/dl)	0.84±0.25	0.87±0.24	0.646
Sodium (mmol/l)	129.74±5.70	131.73±2.33	0.260
Potassium (mmol/l)	3.64±0.51	3.55±0.56	0.600
Chloride (mmol/l)	97.62±2.29	97.73±1.19	0.214
Bicarbonate (mmol/l)	23.02±1.96	23.27±1.68	0.682
Total Bilirubin(mg/dl)	0.62±0.26	0.57±0.23	0.532
Direct Bilirubin(mg/dl)	0.27±0.17	0.34±0.21	0.279
SGOT (IU/l	51.62±23.19	55.91±23.19	0.572
SGPT (IU/l)	39.32±16.03	38.18±15.50	0.827
ALP (IU/l)	86.77±33.28	89.09±24.98	0.826
Total protein (g/dl)	6.59±0.91	6.32±0.53	0.334
Albumin (g/dl)	4.71±0.29	4.73±0.17	0.789

TABLE 6: HEPATIC AND RENAL PROFILES IN FEMALE MDR-TB PATIENTS AND MDR-TB/HIV PATIENTS

	MDR-TB (n= 28)	MDR-TB/HIV (n= 11)	p-values
Urea (mg/dl)	**32.04±9.83**	**26.45±7.70**	**0.100**
Creatinine (mg/dl)	**0.72±0.18**	**0.75±0.15**	**0.562**
Sodium (mmol/l)	**129.86±6.15**	**130.09±2.74**	**0.905**
Potassium (mmol/l)	**3.55±0.53**	**3.55±0.54**	**0.966**
Chloride (mmol/l)	**97.21±2.91**	**97.27±1.19**	**0.949**
Bicarbonate (mmol/l)	**22.57±1.81**	**22.64±1.43**	**0.916**
Total Bilirubin(mg/dl)	**0.60±0.27**	**0.55±0.32**	**0.619**
Direct Bilirubin(mg/dl)	**0.33±0.21**	**0.33±0.25**	**0.977**
SGOT (IU/l	**51.07±24.46**	**55.64±23.16**	**0.598**
SGPT (IU/l)	**35.54±16.17**	**41.64±22.26**	**0.348**
ALP (IU/l)	**93.96±38.84**	**83.36±23.04**	**0.404**
Total protein (g/dl)	**6.45±0.71**	**6.40±0.61**	**0.828**
Albumin (g/dl)	**4.78±0.18**	**4.77±0.11**	**0.920**

DISCUSSION

Chemotherapy is the basic approach to clinical tuberculosis control. Previous study have reported that antituberculosis therapy (ATT) causes derangement of hepatic and renal functions (15) but influence of HIV co-infection and combination of ATT on renal and hepatic profile was not reported. The primary purpose of this study was to determine the base line serum levels of renal and hepatic parameters in MDR-TB patients without HIV infection compared with MDR-TB/HIV co-infection before commencement of multi-drug therapy for MDR-TB patients. This allows early detection of possible hepatic or renal defect and thus necessitating more appropriate management strategies.

To the best of our knowledge, this is the first study that will monitor renal and kidney functions in patients with co-infection of MDR-TB and HIV at initiation of therapy in this environment. Renal- and hepatic- parameters measured in MDR-TB patients with HIV infection were not statistically different compared with MDR-TB patients without HIV infection. However, higher proportions of MDR-TB patients have their SGOT above normal reference range.Previous authors have reported raised transaminases as early sign of liver involvement in TB/HIV pathology (16). Also, renal- and hepatic-parameters in male or female MDR-TB patients with HIV infection did not show any statistical significance differences when compared with MDR-TB patients without HIV co-infection. However, serum creatinine in male MDR-TB patients was significantly raised compared with female MDR- TB patients. This might be related to higher muscle mass in males compared with females. Although, this has no clinical implication but this study recommends that creatinine should be frequently monitored in these patients since raised creatinine is a sensitive and specific marker of kidney damage. Besides this, regular biochemical investigations should also be performed essentially to predict when the patients are likely to develop hepatic and renal function derangements. According to Ciba Laboratories, kidney and liver function tests should be carried out before initiating ATT (17) as it has been reported that patients with abnormal baseline transaminases levels are at increased risk of developing hepatic injury eventually (16). It was reported that renal and hepatic profiles should be determined twice weekly for the first two weeks followed by weekly monitoring till the end of two months and then monthly investigations till the end of the treatment (18). This is not affordable in patients in resource poor countries, thus a single sensitive parameter like SGOT may be most useful in this situation.

Conclusion

The results indicate that HIV infection did not significantly alter renal and hepatic profiles in MDR-TB patients prior to treatment. However, since the current recommended treatment anti-tuberculosis

drugs are found to be potentially nephrotoxic and hepatotoxic, continuous monitoring of hepatic and renal functions of MDR-TB patients is necessary.

REFERENCES

1. World Health Organization, 2014 Tuberculosis Global Report, WHO, Geneva.
2. World Health Organization. Nigeria factsheets of Health Statistics, 2012; Regional office for Africa. World Health Organization. TB/HIV in the African Region Status Report. Regional Meeting of National TB Programme Managers, Geneva:
3. WHO treatment of tuberculosis guidelines. 4th edition. 2010. p. 96–7.
4. Eastwood J. B., Corbishley C. M., Grange J. M. Tuberculosis and the kidneyJ Am SocNephrol. 2001;12:1307–14
5. Blumberg H.M., Burman W. J., Chaisson R. E., Daley C. L., et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis Am. J. Respir. Crit Care Med. 2003; 167: 603–662.
6. Parthasarthy R.,Prabakar R.,Somasundaram P. R. A controlled clinical trial of 3 and 5 month regimens in the treatment of sputum-positive pulmonary tuberculosis in south India*Am Rev Respir Dis*.1986; 134: 27–33.
7. Jacobsen J and Wennberg R. P. Modified Powell (1944) Determination of unbound bilirubin in the serum of newbornsClin. Chem. 1974; 20: 783-789.
8. Reinhold J. C. Estimation of serum total proteins by Biuret method, Standard methods in clinical Chemistry edited by Reiner M: Acadamic press, New York; 1953; 1:88.
9. Spencer K and Price C.P. Influence of reagent quality &reaction condition on the determination of serum albumin by bromocresolgreendye binding method. Ann. Clin. Biochem Spencer and Prince1977; 14 (2): 105-115.
10. Varley H.,Gowenlock A. H., Bell M. Non protein nitrogen, urea, urate, creatine and creatinine, in Practical clinical biochemistry, 5'" edition, Vol. 1. (William Heinemann Medical Books Ltd, London) 1980: 459-484.
11. Tietz N. W. Measurement of serum alkaline phosphatase J ClinChemClinBiochem. 1983; 21: 731-748.
12. Bergmeyer H. U., Horder M., Rej R. Approved recommendation (1985) on IFCC methods for the measurement of catalytic concentration of enzymes. Part 2. IFCC method for Aminotransferases J ClinChemClinBiochem.1986; 24: 497-508.
13. Persijn J. P., VanderSilk . A new method for the determination of gamma glutamyltransferase in serum. J ClinChemClinBiochem. 1976; 14:421-7.
14. Varley H; Determination of electrolytes. Practical clinical biochemistry ; Alan H, 6thedition , CBS publishers and distributors, London, 2009: 490-496
15. *Thompson N. P., Caplin M. E.,Hamilton M. I., Gillespie S. H.,et al. Anti-tuberculosis medication and the liver: dangers and recommendations in management.*EurRespir J 1995; 8: 1384–1388.
16. MarrionMerrel Dow Ltd. ABPI Data Sheet Compendium 1994–1995. London, Datapharm Publications Ltd, 1994; pp. 878–883.
17. Ciba Laboratories. ABPI Data Sheet Compendium 1994–1995. London, Datapharm Publications Ltd, 1994; pp. 362–366.
18. Lederle Laboratories. ABPI Data Sheet Compendium 1994–1995. London, Datapharm Publications Ltd, 1994; pp. 749–750.