IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 7 Ver. I (July. 2017), PP 105-109
www.iosrjournals.org

Evaluation of Albuminand Uric Acid Levels, Catalaseactivity andtotal Antioxidant Statusin Pulmonary Tuberculosis Patientsin Osogbo, Nigeria

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Abstract: *Previous reports showed that tuberculosis is associated with increase free radical load and oxidative stress thereby worsening the disease state. An understanding of the antioxidant defense system may be helpful in management and care of the disease. Albumin, Uric acid, catalase activity and total antioxidant status (TAS) were determined in blood samples ofthirty five (35) pulmonary tuberculosis (TB) patients (28 TB and 7 TB+HIV) on drug treatment and thirty (30) apparently healthy controls (Ziehl Neelsen test negative) by standard spectrophotometric methods. Results showed that the means of albumin (30.66mmol/L), catalase activity (50.60 IU/ml) and TAS (2.49 mmol/L) of TB patients were significantly lower than those of the control group (42.50mmol/L, 69.80 IU/ml and 4.86 mmol/L respectively). Mean uric acid (0.76mmol/L) of TB patients was significantly higher than that of (0.58mmol/L) of corresponding control. In addition, means of albumin (31.29mmol/L),uric acid (0.77 mmol/L), catalase activity (50.50 IU/ml) and TAS (2.40mmol/l) of TBgroup did not differ from the respective means ofTB+HIV patients (albumin =28.40mmol/L, uric acid =0.71mmol/L, catalase activity=51.00 IU/ml and TAS =2.81 mmol/L).Means of TAS,albumin and catalase activity of TB+HIV patients were significantly lower than respective means of control but the uric acid of TB+HIV patients (0.71 mmol/L) was higher than that of control (0.58 mmol/L).Significantly low level of plasma albumin, catalase activity and total antioxidant status observed in this study might be due to increased utilization of antioxidants to combat oxidative stress seen in TB and the increase plasma uric acid due to excessive breakdown of cells in pulmonary tuberculosis. Increased antioxidant intake may be essential in the management of TB patients.*

Keywords:*Oxidative stress, Total antioxidant status, Catalase, Tuberculosis, HIV*

I. Introduction

Concerning tuberculosis (TB), Nigeria ranked 4th among the 22 high burden countries for TB in the world and the 1st in Africa with a 2014 estimate of 570,000 new cases occurring per year. A total 86, 464 of all forms of TB cases were notified from the 37 States in 2014 [1].The TB burden is further compounded by the high human immunodeficiency virus (HIV) prevalence of 4.4% in the country. The recorded HIV prevalence among TB patients increased from 2.2% in 1991 to about 27% in 2008. HIV is the most powerful risk factor for developing TB disease [2].

The prevalence of HIV among TB patients increased from 2.2% in 1991 to 19.1% in 2001 and 25% in 2010. This indicates that the TB situation in the country is HIV-driven. The proportion of TB patients tested for HIV was 79% in 2010, with a 25% TB-HIV co-infection rate. 59% of these patients were started on cotrimoxazole (CPT) prophylaxis and 1.8% provided with isoniazid (IPT) prophylaxis. The proportion of TB/HIV co-infected patients on anti-retro viral (ARV) therapy was 33% in 2010. The proportion of HIV-registered cases screened for TB was 57% in 2010. The proportion of HIV cases that developed TB was 4% in 2010 and 3% in 2011 [3].While a treatment short-course program has been initiated in Nigeria, the detection of new smear-positive cases remain low, estimated at 12% in 2007[4].

HIVinfection and TB are so closely connected that they are often referred to as co-epidemics or dual epidemics. These epidemics drive and reinforce one another: HIV activates dormant TB in a person, who then becomes infectious and able to spread the TB bacillus to others. HIV infection has contributed to a significant increase in the worldwide incidence of TB by producing a progressive decline in cell-mediated immunity [5, 6]. Mycobacteriumtuberculosis in the immune cells of an infected patient can induce the production of reactive oxygen species (ROS) especially hydrogen peroxide which serves as a ROS intermediate providing a steady pool for the more potent generation of hydroxyl (OH*) species [6, 7].Furthermore, during pulmonary inflammation, increased amounts of ROS and reactive nitrogen intermediates (RNI) are produced as a

consequence of phagocytic respiratory burst. Phagocytosis is a physiological response but increased free radical load could result in oxidative stress leading toan increased utilization of the body's antioxidant defences [8, 9]. In addition, the inner surface of the lung is covered by a thin film of fluid that contains a broad array of proteins, which contribute to antioxidant capacity[10]. TAS is a function of dietary, enzymatic and other systemic antioxidants and it is therefore an indicator of the free radical load. In addition,TAS alsomeasures the low molecular weight and chain breaking antioxidants such as albumin and uricacid [11]. TB and HIV infections have been associated with decreased immunity and lowered total antioxidant capacity [8]. Uric acid has a potential therapeutic role as an antioxidant and over half of the antioxidant capacity of blood plasma comes from uric acid. In addition to these chain breaking antioxidants, enzymes such as catalase, superoxide dismutase (SOD) and glutathione peroxidase (GSHPx) play important roles as primary antioxidants that prevents the initiation phase of free radical mediated reactions. Catalase in particular is useful in the conversion of hydrogen peroxide into water and oxygen, thus preventing the formation of the OH^* radical [11, 12]. This study was designed to evaluate the albuminand uric acid levels, catalase activity and total antioxidant status in pulmonary tuberculosis patients undergoing treatment.

II. Materials And Methods

Thirty five (35) pulmonary tuberculosis patients (28 TB and 7 TB+HIV) on drug treatment from Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital, and 30 healthy control subjects were recruited for the study.The control subjects wereTB and HIV, negative. TB patients were on treatment with Anti-TB drugs (Directly Observed Treatment–Short course (DOTS) according to the protocol described by the National Guidelines on Treatment of TB and TB and HIV co-infection [13] under the supervision of a consulting physician.Ethical approval for the study was obtained from the LAUTECH/ LAUTECH Teaching Hospital Ethical Committee. Consent was obtained from participants before the commencement of the study.

Blood Sample Collection and Storage

10 ml of blood was drawn from the median cubital vein of each participant into a bottle containing lithium heparin as anticoagulant bottle. Plasma was separated from each blood sample after spinning in a centrifuge at 4000revolutions/minute for 10 minutes into a plain bottle and stored at -20°C until used for the estimation of albumin, uric acid, catalase activityand TAS. Sputum was obtained from each control subject and was used for Ziehl-Neelsen staining.

Biochemical Analysis

Determination of total antioxidant status was determined by the spectrophotometric method described by Koracevicet al, [14]. Estimation of plasma albumin by the spectrophotometric method of Doumaset al,[15] and while uric acid was estimated by the method described byFossatiet al,[16].Measurement of catalase activity was by spectrophotometric method described by Beers et al, [17].

Statistical analysis

Results of the biochemical parameters were reported as mean (±SD). The Student's t-test was used for the comparison of means. Results were regarded as significant at $p<0.05$

III. Results

Results from the study showed that mean albumin concentration was significantly lower in TB patients than in corresponding control group ($p<0.001$). However, uric acid level was significantly higher in TB patients than the value of controls ($p < 0.001$). The mean catalase activity was significantly lower in TB patients than the mean activity of catalase in controls ($p < 0.001$). The TAS level was also significantly lower in the TB patients than means of the corresponding controls ($p < 0.001$) (Table 1)

When the TB patients were classified based on HIV status, the mean albumin concentration of TB only patients was not significantly higher than the mean plasma value of TB+HIV patients ($p = 0.33$). The uric acid level and catalase activity did not differ significantly in the two groups ($p = 0.39$ and $p = 0.92$ respectively).Mean plasma value of TAS of TB only subjects was not significantly higher ($p = 0.55$) than the value of TB+HIV subjects (Table 2).Whenthe means of parameters in TB only and control subjects were compared, results showed that means of albumin, catalase activity and TAS were significantly lower in TB only subjects when compared with the corresponding control group ($p < 0.001$, $p < 0.001$, $p < 0.001$ respectively). On the other hand, uric acid level was significantly higher in TB only subjects than control group ($p < 0.001$) (Table 3)Tuberculosis+HIV subjects had significantly higher level of uric acid than corresponding controls ($p = 0.03$). However, TB+HIV subjects had lower means of albumin, catalase activity and TAS than controls ($p < 0.001$, $p < 0.001$ and $p = 0.005$ respectively) (Table 4).

Table 1. Mean (±SD), t-value and p-value of plasma albumin, uric acid, catalase activity and TASin alltuberculosis patients and controls

Parameter	TB n=35	Control n= 30	t value	p-value
Albumin (mmol/L)	30.66(±6.92)	42.50 (±4.65)	7.95	< 0.001
Uric Acid (mmol/L)	0.76 (±0.17)	0.58 (±0.13)	4.73	< 0.001
Catalase (IU/ml)	50.60(±11.05)	69.80(±7.04)	8.19	<0.001
TAS (mmol/L)	2.49 (±0.99)	4.86 (±1.69)	7.02	< 0.001

TB= tuberculosis (TB only and TB+HIV), TAS= total antioxidant status

Table 2. Mean (±SD), t-value and p-value of plasma albumin, uric acid, catalase activity and TASin TB patients and TB+HIVSubjects

Parameter	TB only n=28	TB+HIV n=7	t-value	p-value
Albumin (mmol/L)	31.29 (±6.54)	28.40(±8.36)	0.99	0.33
Uric Acid (mmol/L)	0.77 (±0.16)	0.71 (±0.17)	0.88	0.39
Catalase (IU/ml)	50.50(±12.07)	51.00(±6.06)	0.11	0.92
TAS (mmol/L)	2.40 (±1.69)	2.81 (±1.19)	0.60	0.55

TB = tuberculosis, TAS= total antioxidant status

Table 3. Mean (±SD), t-value and p-value of plasma albumin, uric acid, catalase activity and TASinTB only and control subjects

Parameter	TB only n=28	Control n=30	t-value	p-value
Albumin (mmol/L)	31.29(±6.54)	42.50(±4.62)	7.56	< 0.001
Uric Acid (mmol/L)	0.76(±0.16)	0.58(±0.13)	4.98	< 0.001
Catalase (IU/ml)	50.50(±12.07)	69.84(±7.04)	7.50	< 0.001
TAS (mmol/L)	2.40(±1.69)	4.86(±1.69)	5.54	< 0.001

TB = tuberculosis, TAS= total antioxidant status

Table 4. Mean (±SD), t-value and p-value of plasma albumin, uric acid, catalase activity and TASinTB+HIV and control subjects

Parameter	TB+HIV n=7	Control n=30	t-value	p-value
Albumin (mmol/L)	28.40(±8.36)	42.50(±4.65)	6.14	< 0.001
Uric Acid (mmol/L)	0.70(±0.17)	0.58(±0.13)	2.25	0.03
Catalase (IU/ml)	51.00(±6.06)	69.80(±7.04)	6.51	<0.001
TAS (mmol/L)	2.81(±1.19)	4.85(±1.69)	3.02	0.005

TB = tuberculosis, TAS= total antioxidant status

IV. Discussion

In this study, a decrease in mean plasma albumin value was observed in pulmonary tuberculosis subjects when compared the value of corresponding controls. Decrease in mean plasma albumin was reported in a study by Reddy and co-workers [18]. Tuberculosis is a consumptive disease which may explain in part the decrease in albumin level seen in both TB and HIV+ TB patients in this present study. Albumin is the predominant plasma protein that makes the major contribution to plasma sulfhydrylgroups and the antioxidant role of albumin is related to ligand binding and free radical trapping activity [19]. In pulmonary tuberculosis, albumin could bind and trap the excess free radicals and subsequently transport them to the liver for detoxification [20]. Increased phagocytic activity may arise in TB as a result of the infectious process but albumin is also a powerful scavenger of the phagocytic product hypochlorous acid and provides the main plasma defence against this oxidant [21]. Significant increase in uric level acid was observed in pulmonary tuberculosis subjects when compared with the corresponding control group. However, uric acid and other parameters measured did not differ when means of TB patients were compared with HIV+TB patients. Ina study [22], the authors also observed high level of uric acid in pulmonary tuberculosis compared with the control group. Some other report [23] showed a significant increase in uric acid level in TB patients on pyrazinamide therapy. Generally, free radicals attack onmembrane are cytotoxic and cytoclastic and could result in tissue

necrosis, apoptosis or autophagy [24] and this may explain in part the increased uric acid levels seenin pulmonaryTB subjects in the present study. On the other hand, uric acid is also a powerful antioxidant. It has been demonstrated in previous reports that peroxynitrite which is the main product between superoxide and nitric oxide reaction is a potentially harmful oxidant and uric acid is able to directly scavengeperoxynitrite, resulting in the formation of a stable nitricoxide donor in vitro [25]. Hinkand colleagues [26]demonstrated that uric acid effectively prevents inactivation of extracellular superoxide dismutase (ecSOD)by hydrogen peroxide at concentrations close to physiological level in humans. Urate is aparticularly important antioxidant because, in addition to acting as a free radical scavenger it is able to chelate non-protein bound iron and to subsequently reduce iron induced oxidant activity [27]. A decrease in plasma catalase activity in pulmonary tuberculosis subjects was seen when compared with the value of corresponding control subjects in this study. Catalase functions in the conversion of hydrogen peroxide to water and oxygen. Hydrogen peroxide is reactive oxygen intermediate product and if not properly metabolized, serves as ready source of hydroxyl radical which can cause lipid peroxidation of the cell membrane. Reduction in catalase activity will lead to increased production of OH* radicals resulting in oxidative stress that could worsen the disease.

There was significant decrease in plasma level of total antioxidant status (TAS) in pulmonary tuberculosis patients when compared with TAS level of corresponding controls. The TAS is not a simple sum of the activities of the various antioxidative substances. It isa dynamic equilibrium that is influenced by the interactions between each serum antioxidative constituent. It is thought that the cooperation of antioxidants in human serum provides greater protection against attacks by free radicals than any antioxidant alone. In tuberculosis, there is increased generation of free radicals and the physiologic response to this which also increases the body's antioxidant needed to detoxify, thus, simultaneously reduces the plasma level of circulating antioxidants. A study [28] reported that low food intake and inadequate availability of carrier molecule can lead to reduction inTAS. The decrease level of plasma TAS seen in this study could signify a high generation of free radicals in pulmonary tuberculosis.

In conclusion, the present study showed low levels of albumin, decreased catalase activity and reduction in TAS in pulmonary tuberculosis patients, these may be due to excess free radicals generated in the maintenance of the disease and concomitant consumption of the body's antioxidants. Increased intakeof antioxidants in food and possibly supplementation may represent a novel approach to correcting the observed decreases in antioxidants observed in TB patients in this study.

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Olisekodiaka MJ. "Evaluation of Albumin and Uric Acid Levels, Catalaseactivity And total Antioxidant Status in Pulmonary Tuberculosis Patients in Osogbo, Nigeria." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.7 (2017): 105-09.