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Original Research Article

Assessment of Oxidative Stress Markers and Antioxidants Status of Pulmonary Tuberculosis Patients on First- And Second-Line Drugs in a Nigerian Tertiary Institution

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Abstract: ***Introduction*:** Pulmonary tuberculosis remains a major global health concern, particularly in resource-limited settings like Nigeria. Oxidative stress has been implicated in the pathogenesis and complications of various diseases, including infectious diseases such as Tuberculosis. This study explored the impact of Pulmonary Tuberculosis infection on the antioxidant mechanisms and the resulting redox imbalance in general. The specific objective was to determine the changes in oxidative stress marker/antioxidant level by comparing the serum levels of Glutathione peroxidase, Vitamin C, Vitamin E and Malondialdehyde between PTB patients and control group. ***Method*:** A comparative cross-sectional study was conducted involving 214 pulmonary tuberculosis patients and 214 control group at AKTH. Blood samples was collected from both groups for the measurement of Malondialdehyde, Glutathione peroxidase, vitamins C and E. Clinical and demographic data was obtained through structured questionnaires. Results were presented as mean and standard deviation. Mean serum levels were compared using T-test while Mann Whitney u-rank test was used to determine correlation between Malondialdehyde and antioxidants. ***Results*:** Both PTB patients and the control group were largely composed of individuals between the ages of 21 and 40 years with a mean age of 34 years and 31 years respectively. The investigation demonstrated that individuals with PTB exhibited a notably higher Malondialdehyde level (1201+323µmol/L, $p<0.05$), in comparison to the control group (433+313µmol/L). Additionally, the average serum concentrations of Glutathione peroxidase, Vitamin C, and Vitamin E were significantly lower in the PTB patients (glutathione peroxidase: 218.4 ± 166.6 ng/ml, Vitamin C: 6.4 ± 2.5 µg/mL, and Vitamin E: 8.1 ± 1.6 µg/mL) compared to the control group (glutathione peroxidase: 653.2 ± 368.6 ng/ml, Vitamin C: 8.3 ± 3.8 µg/mL, and Vitamin E: 12.7 ± 2.2 µg/mL). Moreover, all three antioxidants level exhibited a negative linear correlation [glutathione peroxidase r=-0.53, Vitamin C r=-0.27, and Vitamin C r=-0.62] with Malondialdehyde. Notably, there was no statistically significant disparity in antioxidants and Malondialdehyde between PTB patients undergoing first line and second-line treatment regimen. ***Conclusion*:** In conclusion, the findings of this research underscore a significant elevation in Malondialdehyde levels among PTB patient compared to the control group, indicative of heightened oxidative stress. Concurrently, PTB patients

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exhibited lower serum levels of Glutathione peroxidase, Vitamin C, and Vitamin E, suggesting a compromised antioxidant defense mechanism. The observed negative linear correlations between these antioxidants and Malondialdehyde emphasize their potential role in mitigating oxidative damage. Treatment regimen does not appear to exert a discernable impact on the oxidative stress and antioxidants status in individuals with pulmonary tuberculosis. These insights contribute to our understanding of the oxidative stress dynamics in PTB and highlight the importance of comprehensive care strategies in managing the condition.

Keywords: Oxidative Stress, Antioxidants, First- And Second-Line Drugs and Pulmonary Tuberculosis.

INTRODUCTION

Pulmonary tuberculosis (PTB) is an infectious disease caused by mycobacterium tuberculosis (MTB) [1]. MTB generally affects the lungs, but can also affect other parts of the body. Most infections show no symptoms, in which case it is known as latent tuberculosis [1]. Typical symptoms of active tuberculosis (TB) are chronic cough with blood-staining mucous, fever, night sweats, and weight loss [1].

Globally, TB persist as a leading cause of death by a single pathogen, an estimated 10.0 million people developed TB disease in 2019, out of which about 1.2 million TB deaths were recorded [2]. About 33% of the world populations infected with Mycobacterium tuberculosis reside in developing countries including Nigeria [3]. About one-third of world population have latent TB infections where most patients show no symptoms [1], if left untreated, 10% of latent infections progress to active disease which kills about half of those affected [1]. In 2019, approximately 1.4 million people were diagnosed with TB in the Africa, but epidemiologists estimated that 1 million more had TB but were neither diagnosed nor treated [4]. Nigeria is among the high TB and drug resistant tuberculosis (DR-TB) countries globally, the country ranks 7th among the 30 high TB burden countries globally and 2nd in Africa, accounting for 4% of the estimated incidence cases globally [2], significant efforts are still needed to reduce the burden of the disease in Nigeria [3]. Kano State being the most populous state in Nigeria and one of the fifth (5th) highest TB burden states is estimated to have TB burden of 32,376 in year 2019 [5].

MTB invades and replicate within the host macrophages, as an immune response, the infected macrophage initiates a respiratory burst and produces high levels of reactive oxygen species (ROS) to counteract and kill the mycobacteria [6]. Oxidative stress (OS) arises due to an imbalance between the ROS and the antioxidant mechanism [7]. Excess formation of ROS can initiate series of chemical reactions and cause damage to cellular components as well as proteins, lipids and nucleic acids [7]. Furthermore, enzyme reaction pathways, such as nicotinamide adenine dinucleotide phosphate oxidases, myeloperoxidase, xanthine oxidase, and eosinophil peroxidase are activated to produce endogenous ROS including hydroxyl radical and superoxide radical [8]. Body has several mechanism to counteract OS by producing antioxidants. Together, these antioxidant mechanisms (enzymatic & non-enzymatic) buffer oxidants and maintain the oxidative balance in the lung. However, it is important to note that such complex mechanism can be overwhelmed if the production of ROS is greater than the capacity of cells to scavenge it, leading to OS [8]. OS is mediated by activated macrophages and results in a chronic granulomatous response with central area of caseation necrosis [9]. These activated macrophages release a variety of chemicals including oxygen free radicals (OFRs) which may damage cells and tissues in the body, the ongoing inflammation can lead to a remodeling of the lung architecture, which manifest as extensive fibrosis, cavitation, traction bronchiectasis, broncho stenosis, or parenchymal lung destruction [10]. Although ROS can damage the host cells, it also kills infectious agents, including invading pathogens within the host [11]. ROS is highly toxic to bacteria as it can either directly destroy DNA, protein, and lipids or indirectly damage the nucleic acid via oxidation of the nucleotide pool [12]. Recent research suggest that in pulmonary tuberculosis there is increase in several circulating markers of free radical activity, indicating ongoing oxidative stress and decrease in the antioxidant activity which may contribute to development of lung function abnormalities [13].

Patients with mycobacterium tuberculosis illness have higher serum levels of malondialdehyde (MDA), which is a sign of oxidative stress and an indicative of lipid peroxidation, than the control group.14 Patients with MTB have lower serum levels of glutathione peroxidase (GPX), a selenoprotein enzyme that oxidizes reduced glutathione to remove hydroxyl radicals, vitamin C, and vitamin E, which are vital nutrients involved in tissue repair, collagen formation, the enzymatic production of certain neurotransmitters, the function of multiple enzymes, and antioxidant activity.15, 16 Furthermore, a decrease in antioxidant vitamin levels and an increase in MDA are linked to a

rise in oxygen-derived free radical count. Because they may contribute electrons and have a variety of impacts on the immune system, GPX, vitamins C, and E scavenge ROS and singlet oxygen, which lowers the quantity of OS produced [15, 16].

METHODS

Study Area

The study was undertaken at the DOT Clinic of Aminu Kano Teaching Hospital (AKTH), Kano. Kano State lies between latitude 11^0 30North and longitude 8^0 30East [17], located in the North-Western Geo-Political Zone of Nigeria. It is the most populous and the second largest city in Nigeria. AKTH is a 700-bed tertiary health institution serving Jigawa, Katsina, Zamfara, Kebbi, Kaduna and Sokoto states in Northwestern Geo-political zone of Nigeria. It also provides training facilities for medical & dental students, nurses, post basic nursing courses, laboratory scientist & technologist, radiotherapist, pharmacist, physiotherapist, optometrist, and post graduate trainings.

Study Design

The study is a comparative cross-sectional study involving male and female adults with PTB attending DOT clinic of AKTH, Kano, as cases and apparently non-PTB healthy volunteers (staffs, students and vendors of AKTH) as control group.

Data was collected from eligible consenting patients/control group on a pretested structurally designed questionnaire. The questionnaire contains sociodemographic& clinical characteristics, PTB status, as well as serum levels of MDA of the study participants.

Subjects were counseled on the protocols of the study and samples of whole blood were collected under aseptic measures into serum separator gel vacutainer tubes for the analysis of MDA, GPX, vitamin C and vitamin E.

Study Population

Adults' patients (214 of age 18 to 60 years) of both sexes who present at the DOT clinic and diagnosed to have PTB based on GeneXpert MTB/RIF were enrolled as cases, and another (214 of age 18 to 60 years) from staffs, students and vendors within the same study area who are apparently non PTB patients as control group.

Ethical Clearance

Ethical clearance was obtained from the research and ethical committee of AKTH. The provisions of HELSINKI declaration were respected at every stage of the study. Informed consent (written) was obtained from all subjects after the study has been thoroughly explained to them, ensuring their confidentiality, stating clearly that they can withdraw at will at any time without any consequences and assure them that their results will be communicated to them. Patients with PTB were managed based on the protocol in the department of community medicine.

Analytical Methods

Quantitative measurements of serum GPX & MDA was conducted using a highly sensitive and specific enzyme-linked immunosorbent assay (ELISA) while vitamin C and vitamin E was conducted using colorimetric methods.

Statistical Analysis of Results

All data obtained from the questionnaire and the laboratory work were entered into excel worksheet and analyzed using Statistical Package for the Social Sciences (SPSS) version 23.0. Data obtained were presented using frequencies and percentages for sociodemographic characteristics and mean and standard deviation for quantitative data. Quantitative data obtained from PTB patients and control group were analyzed using independent t-test and Pearson correlation. A confidence interval of 95% was used and the level of statistical significance was considered to be at p value < 0.05.

RESULTS

The study was conducted from February 2023 to January 2024. A total of 428 study participants were recruited for the study. They were made up of 214 PTB patients and 214 non-PTB apparently healthy control group.

Gender and Age Distribution of PTB Patients and Control Group

Figure 1 demonstrated that, although the gender distribution is roughly 50% for each sex, the control group had a comparatively higher proportion of females (56.5%). This apparent gender proportion disparity was not statistically significant (p=0.052). Figure 1 further illustrated that the mean age of the control group was (31.22±11.1), while the mean age of PTB patients was (34.39±12.3). Both PTB patients (31.3%) and the control group (34.1%) were primarily composed of individuals between the ages of 21 and 30 years.

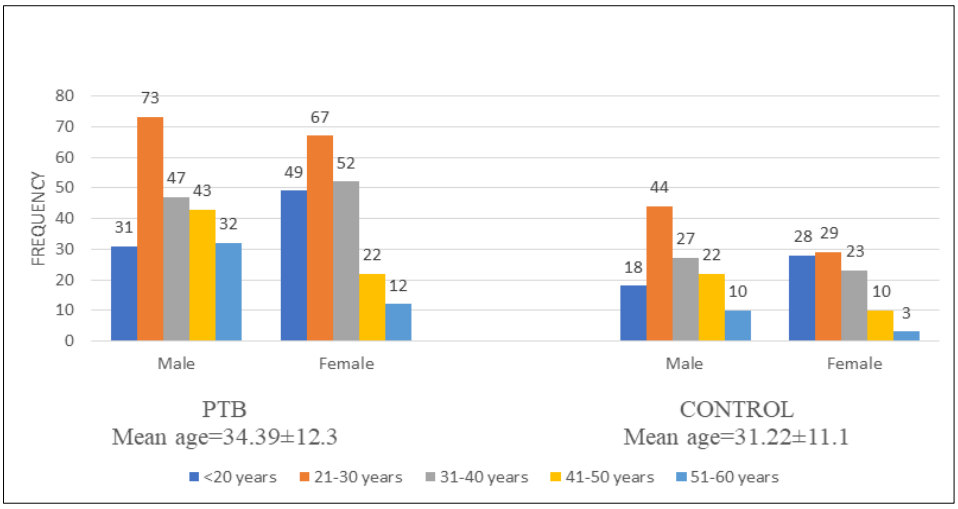

Figure 1: Showing Age (years) and Gender distribution of PTB patients and Control group.

Blood pressure (BP), weight, height, and Body mass index (BMI) of PTB patients and control group are shown in **Table I**. The PTB patients' average weight was 55.46±8.6, but the control group's average weight was significantly higher (P<0.001) at 58.7± 9.3. Similarly, the control group (21.48 ±3.1) had a significantly higher (P<0.001) BMI than the PTB patients (20.24±2.9). Conversely, there is no significant (p=0.638) difference in height between the control group (1.66±0.95) and PTB patients (1.66±0.1). **Table I** also revealed that the BP is not significantly different between the control group (110.9±12.98) and PTB Patients (111.4±11.4). The height (p=0.638), systolic blood pressure (p=0.710) and diastolic blood pressure (p=0.224) were not significantly different between PTB patients and control group.

Table I: Showing Clinical characteristics of the study participants

		PTB			CONTROL		p-value
Variable		**n**	**%**		**n**	**%**	
Weight (kg)							
≤50		57	26.6		28	13.1	
>50		157	73.4		186	86.9	
Total		214	100		214	100	
Mean weight	**55.46±8.6**			**58.74±9.3**			**<0.001**
Height (m)							
≤1.5		5	2.3		4	1.9	
>1.5		209	97.7		210	98.1	
Total		214	100		214	100	
Mean height	**1.66±0.11**			**1.66±0.95**			**0.638**
BMI (kg/m^2)							
Under weight		60	28.0		14	6.5	
Normal weight		151	70.6		182	85.1	
Over weight		1	0.5		15	7.0	
Obesity		2	0.9		3	1.4	
Total		214	100		214	100	
Mean BMI	**20.24±2.9**			**21.48±3.1**			**<0.001**
SBP (mmHg)							
≤120		116	54.2		127	59.3	
>120		98	45.8		87	40.7	
Total		214	100		214	100	
Mean SBP	**110.96±12.98**			**111.4±11.4**			**0.710**
DBP (mmHg)							
≤60		7	3.3		1	0.5	
>60		207	96.7		213	99.5	
Total		214	100		214	100	
Mean DBP	**73.5±9.8**			**74.56±7.96**			**0.638**

Key: n=number examined, %=percentage.

Relationship between Serum level of Malondialdehyde and Glutathione peroxidase, Vitamin C & Vitamin E among PTB patients

To assess the linear relationship between the oxidative stress marker and antioxidants, a bivariate product moment correlation coefficient (r) was calculated. The result observed showed that all the antioxidants; Glutathione peroxidase, Vitamin C and Vitamin E exhibited a negative linear correlation [Glutathione peroxidase r = -0.53; Vitamin C r = -0.27 and Vitamin E r = -0.62] with Malondialdehyde levels as shown in **table II.**

Table II: Showing relationship between Malondialdehyde and Glutathione peroxidase, Vitamin C & Vitamin E among PTB patients

	Malondialdehyde (µmol/L**)**			
	n	**r**	**r^2 (%)**	**p-value**
Glutathione peroxidase (ng/ml**)**	214	-0.53	0.28(28)	0.044
Vitamin C (µg/mL**)**	214	-0.27	0.07(7)	0.069
Vitamin E (µg/mL**)**	214	-0.62	0.38(38)	0.036

Key: n=number examined, r=correlation, %=correlation percentage.

Comparison of Serum Levels of Malondialdehyde, Glutathione Peroxidase, Vitamin C and Vitamin E of PTB Patients on First- And Second-Line Drugs

Mann Whitney-U rank test was used to compare the mean value of malondialdehyde and glutathione peroxidase, vitamin C and vitamin E between PTB patients on first line treatment regimen (n=194) and PTB patients on second line drugs) (n=20). The t-test was not statistically significant for all the parameters compared. The mean level of MDA was not statistically significantly different between PTB patients on first line (Mean =1201) and those on second line (Mean =1198.5). Similarly, the mean levels of Glutathione peroxidase (Mean rank =220.7), Vitamin C (Mean rank =6.5) and Vitamin E (Mean rank =8.2) were all not significantly different between the two groups as shown in **table III.**

Table III: Showing serum levels of Malondialdehyde and Glutathione peroxidase, Vitamin C & Vitamin E between first- and second-line treatment regimen PTB patients

	First line(n=194)	**Second line(n=20)**	
	Mean Rank	**Mean Rank**	**p-value**
Malondialdehyde (µmol/L**)**	1201.3±323.3	1198.5±331.6	0.627
Glutathione peroxidase (ng/ml**)**	220.7±170.1	196.5±128.8	0.406
Vitamin C (µg/mL**)**	6.5±2.5	5.9±2.7	0.968
Vitamin E (µg/mL**)**	8.2±1.7	8.1±1.6	0.405

DISCUSSION

Oxidants and Antioxidants Levels

Imbalance between the ROS and antioxidant mechanism leads to oxidative stress that manifest as increase in oxidative stress markers such as malondialdehyde (MDA) [7]. One of the most significant indicators of oxidative stress is MDA, which can cause cellular dysfunction through lipid peroxidation when elevated owing to oxidative stress [18]. This effect is counteracted by the action of strong antioxidants such as glutathione peroxidase (GPX), which catalyzes the reduction of H_2O_2 to water & oxygen and lipid peroxide radicals to alcohol & oxygen [19]. Another antioxidant, vitamin E, guards against lipid peroxidation in cell membranes [20], and vitamin C complements vitamin E in fighting free radicals by regenerating reduced form of vitamin E [21].

In this study, both the age of PTB patients and control group ranged from 18 to 60 years with mean age for PTB patients and control group of 34.39 and 31.22 years respectively. The majority of PTB patients (31.3%) and control group (34.1%) were in the age group of 21 to 30 years, indicating that this observation is desirable because the groups were well-matched, and the results were comparable. This result agreed with the report of WHO that tuberculosis primarily affects people during their most productive years [2-22], due to a combination of factors including living in cramped quarters, poverty, psychological stress, and disruptions in the healthcare system that cause delays in diagnosis and treatment, this age group is frequently at disproportionately high risk for tuberculosis.

Overall gender distribution showed that there was an equal sex distribution among PTB patients (50, 50%) and a small female preponderance (56.5%) in the control group. The high rate of health seeking behaviour among the female patients, along with the fact that most staff members and students who agreed to participate in the study were female, are the reasons for the increased female ratio seen in this study. Similar distribution was observed in a study conducted at the National Institute of Respiratory Diseases (INER) in Mexico City [13]. However, most studies conducted revealed male preponderance including studies in India, Ethiopia and Edo state of Nigeria [23-25].

Among the study participants, the higher number of PTB cases observed among Hausa/Fulani could be attributed to the ethnicity of the inhabitants of

the study environment which are predominantly Hausa/Fulani.

Low level of western education is also another factor promoting the spread of Mycobacterium tuberculosis infection among the study participants. It was established that individuals with high level of education tends to be more aware of the ways of avoiding contracting the disease and have high health seeking behavior [2]. The highest number of PTB patients were observed to have attended primary level of education whereas the lowest number of PTB patients were demonstrated among those that attended tertiary institution. This is also in agreement with a study conducted in North-eastern Nigeria, Gombe state [26].

Cigarette smoking and ingestion of alcohol were not common in this ethnicity due to cultural and religious prohibition, and this may explain the reason why there are fewer percentages of PTB patients that smoke cigarette and ingest alcohol in this study. Similar findings were found in studies conducted in Cameroon [64], and North-eastern Nigeria, Gombe state [26]. Conversely, marital status and ingestion of traditional concoction were not associated with active Tuberculous infection in the present study.

The average Weight and BMI of PTB patients and control group were significantly different. Cell membranes are also attacked by free radicals resulting to tissue damage and wasting disease in PTB patients [1]. This is in keeping with findings from earlier studies [8-12]. Weight loss in tuberculous (TB) infection is as a result of anorexia and loss of adipose tissues that results from reduced production of leptin induced by chronic inflammation [28]. The observed undernutrition among PTB patients suggests that undernutrition could play a pivotal role in the pathogenesis of active tuberculosis [28]. Another study conducted in Romania revealed that the incapacity of neutralising oxidative stress, due to lower weight and wasting, is one of the most important risk factors in developing active PTB [29].

The height, systolic blood pressure and diastolic blood pressure were not significantly different between PTB patients and control group. This is similar to what was found at the National Institute of Respiratory Diseases (INER) in Mexico City [13]. PTB patients tend to be haemo-dynamically stable, and blood pressure neither contribute to the development of active TB infection nor to the pathogenesis of the disease [2].

In this study, the PTB patients were categorized into drugs susceptible patients which are the majority (90.7%) that are on first line treatment regimen (≤6 months), and drug-resistant patients which are the minority (9.3%) that are on second-line treatment regimen (18 - 24months). This result is consistent with other similar studies conducted in Addis Ababa metropolitan area, Ethiopia [30], and Zambia [31]. This is likely due to the substantial efforts made to lower the disease burden in vulnerable nations like Nigeria, such as by enhancing mass literacy initiatives, raising living standards, and adopting and implementing short-course Directly Observed Treatment (DOTS) [32].

The present study also showed that oxidative stress resulting from overproduction of reactive oxygen species (ROS) is present in PTB patients. The increased serum total oxidant status (TOS) accompanied by the reduction in serum total antioxidant status (TAS) levels in PTB patients is consistent with the increased oxidative stress found in this study. This is supported by the fact that an ongoing oxidative stress triggered by the enhanced generation of reactive oxygen species by activated phagocytes overwhelmed the antioxidant capacity of the PTB patients [8-11]. The response of the macrophages disrupts the balance between oxidant and antioxidant system in favour of the oxidants thereby causing oxidative damage and this may also promote tissue injury and inflammation, and further contribute to immune suppression with impaired antioxidant capacity in PTB patients [7-11]. Cell membranes are also attacked by free radicals resulting to tissue damage and wasting disease in PTB patients [1]. Hence, my findings further contributes to the pathogenesis of active TB disease.

In this study, significantly higher concentration of oxidative stress marker (MDA) and lower concentrations of antioxidants (GPX, vitamins C and E) were observed in PTB patients compared to control group and both GPX, Vitamins C and E exhibited a negative linear correlation with MDA levels. Low concentrations of GPX, vitamins C and E have been associated with high oxidative stress. The finding of lower concentrations of GPX, vitamins C and E in PTB patients suggest that increased production of free radicals and increased depletion of antioxidant reserves as a result of high levels of oxidative stress and lipid peroxidation is a contributory factor to the reduced antioxidant concentrations. Several studies have been done on the status of oxidative stress marker and various antioxidants including GPX, vitamins C and vitamin E in PTB patients [18-22]. There is established evidence of higher concentration of total oxidative stress marker (MDA) and lower concentrations of antioxidants (GPX, vitamins C and E) in PTB patients [18-22]. A similar study conducted at the National Institute of Respiratory Diseases (INER) in Mexico City revealed higher concentration of MDA in PTB patients compared to control groups [13]. According to a study done in India, higher oxidative stress markers and lower antioxidant capacity are major contributory factors to the pathogenesis of PTB [23]. Additionally, a study conducted in Ethiopia showed high concentration of MDA and significantly lower concentration of vitamins C & E in PTB patients compared to control group [24]. A study conducted at Institute for advanced Medical Research & Training, College of Medicine, University of Ibadan, Ibadan, Nigeria showed significantly more MDA

and reduced GPX in PTB patients compared with the control group [18]. Another study from Ekpoma and Irrua, Edo State, Nigeria, have shown that total antioxidants status (vitamin C & E) is significantly reduced in PTB patients [25], which may be associated with high levels of free radicals and oxidative stress. Similar study in Owerri, Imo State, Nigeria, demonstrated significant decreased in serum vitamins C & E and significant increase in MDA in PTB patients compared to control group at <0.05 [33], this is also in agreement with the study conducted in North-eastern Nigeria, Gombe state [26].

This study also has showed that the mean level of MDA is higher among PTB patients on first line drugs than PTB patients on second line drugs though this finding is not statistically significant. This pattern is probably because the patients on second line drugs have been on treatment for longer duration than the first line drug users. Similarly, that the mean level of GPX, vitamins C & E are slightly higher among PTB patients on first line drugs than PTB patients on second line drugs, though not statistically significant. Studies conducted in Oman[43] demonstrated non-statistically significant similar findings in the mean levels of GPX, Vitamin C and Vitamin E among patients on first line drugs and the patients on second line drugs. This is probably due to the resistant nature of the mycobacterium tuberculosis that warrants the patient to be on second line anti-tuberculous drugs. Conversely, a study conducted in Imo state Nigeria, showed serum levels of vitamins C & E were significantly increased in PTB patients on therapy when compared to control group [33].

CONCLUSION

This study showed that PTB patients have lower levels of antioxidants (GPX, vitamin C & vitamin E) and higher cellular oxidative stress compared to age and sex matched healthy controls. There is a negative linear correlation between antioxidant levels and oxidative stress in PTB patients. Similarly PTB patients on first line and those on second line treatment have similar oxidative stress profile and antioxidant status. These findings collectively suggest a dysregulation in the redox balance in PTB, emphasizing the potential contribution of oxidative stress to the pathophysiology of the disease.

Recommendations

To examine the clinical ramifications of these findings and evaluate the potential of antioxidant-based treatment approaches as supplemental measures in the treatment of pulmonary tuberculosis, more investigation is necessary.

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