Scholars Academic Journal of Biosciences
Abbreviated Key Title: Sch Acad J Biosci
ISSN 2347-9515 (Print) | ISSN 2321-6883 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pathology

Evaluation of Antioxidant Levels in Pulmonary Tuberculosis Patients in a Tertiary Hospital in Kano, North Western Nigeria

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DOI: https://doi.org/10.36347/sajb.2024.v12i11.004 | **Received:** 14.11.2024 | **Accepted:** 20.12.2024 | **Published:** 24.12.2024

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Abstract **Original Research Article**

***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 antioxidant level by comparing the serum levels of Glutathione peroxidase, Vitamin C and Vitamin E 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 were collected from both groups for the measurement of 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. ***Results*:** Both PTB patients and the control group were largely composed of individuals between the ages of 21 and 30 years with a mean age of 34 years and 31 years respectively. The average serum concentrations of Glutathione peroxidase, Vitamin C, and Vitamin E were significantly lower in the PTB patients (glutathione peroxidase: 218.4 ± 166.6ng/ml, Vitamin C: 6.4 ± 2.5µg/mL, and Vitamin E: 8.1 ± 1.6µg/mL) compared to the control group (glutathione peroxidase: 653.2 ± 368.6ng/ml, Vitamin C: 8.3 ± 3.8µg/mL, and Vitamin E: 12.7 ± 2.2µg/mL). ***Conclusion*:** In conclusion, the PTB patients exhibited lower serum levels of Glutathione peroxidase, Vitamin C, and Vitamin E, suggesting a compromised antioxidant defense mechanism. 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: Glutathione peroxidase; vitamin C; vitamin E 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 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 [14, 15]. 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 [14, 15].

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 [16], 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 GPX, vitamins C and vitamin E of the study participants.

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

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 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.

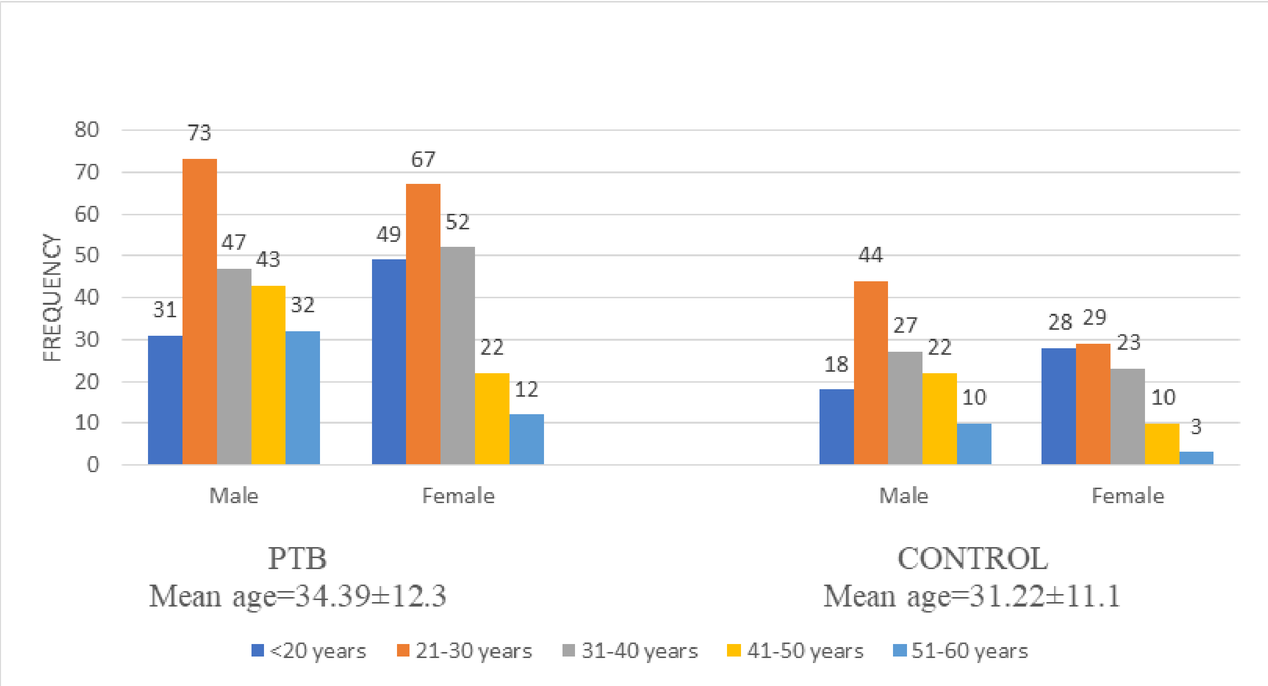

Figure 1: Showing Age (years) and Gender distribution of PTB patients and Control group

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.

Comparison of Serum level of Glutathione peroxidase, vitamin C and vitamin E among study participants

An independent sample t-test was used to compare the mean value of glutathione peroxidase, vitamin C and vitamin E between PTB patients (n=214) and control group (n=214). Mean serum levels of Glutathione peroxidase, Vitamin C, and Vitamin E were significantly ($p<0.05$) lower in the PTB patients (glutathione peroxidase: 218.4 ± 166.6, Vitamin C: 6.4 ± 2.5, and Vitamin E: 8.1 ± 1.6) than in the control group (glutathione peroxidase: 653.2 ± 368.6, Vitamin C: 8.3 ± 3.8, and Vitamin E: 12.7 ± 2.2) as shown in Table II.

Table II: Showing serum levels Glutathione peroxidase, Vitamin C and Vitamin E among study participants

	PTB Patients	**Control group**	
	Mean ± SD	**Mean ± SD**	***p*-value**
Glutathione peroxidase (ng/ml)	218.4 ± 166.6	653.2 ± 368.6	0.001
Vitamin C (µg/mL)	6.4 ± 2.5	8.3 ± 3.8	0.001
Vitamin E (µg/mL)	8.1 ± 1.6	12.7 ± 2.2	0.001

Key: SD=standard deviation.

DISCUSSION

Antioxidants levels

Imbalance between the ROS and antioxidant mechanism leads to oxidative stress that manifest as increase in oxidative stress [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 [17]. 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 [18]. Another antioxidant, vitamin E, guards against lipid peroxidation in cell membranes [19], and vitamin C complements vitamin E in fighting free radicals by regenerating reduced form of vitamin E [20].

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, 21] 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 [22-24].

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 [25].

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 [26], and North-eastern Nigeria, Gombe state [25]. 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, 11, 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 [27]. The observed undernutrition among PTB patients suggests that undernutrition could play a pivotal role in the pathogenesis of active tuberculosis [27]. 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 [28].

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].

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, 8, 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 lower concentrations of antioxidants (GPX, vitamins C and E) were observed in PTB patients compared to control group and both GPX. 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 various antioxidants including GPX, vitamins C and vitamin E in PTB patients [17-20]. There is established evidence of lower concentrations of antioxidants (GPX, vitamins C and E) in PTB patients [17-20]. According to a study done in India, higher oxidative stress markers and lower antioxidant capacity are major contributory factors to the pathogenesis of PTB. Another study from Ekpoma and

Irrua, Edo State, Nigeria, have shown that total antioxidants status (vitamin C & E) is significantly reduced in PTB patients [24] 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, this is also in agreement with the study conducted in North-eastern Nigeria, Gombe state [25].

CONCLUSION

According to this study, PTB patients' levels of antioxidants (GPX, vitamin C, and vitamin E) are lower than those of healthy controls who are matched for age and sex. Together, these results point to a disruption of the redox balance in PTB, highlighting the possible role of oxidative stress in the disease's etiology.

RECOMMENDATIONS

During their clinic visit, PTB patients should receive routine nutritional advice to inform them of the risk of antioxidant deficiency and how to avoid it by making sure they consume foods that will supply the essential antioxidants, such as peanuts, fresh leafy vegetables, citrus fruits, tomatoes, and egg yolks. It is also important to encourage physicians who treat PTB patients to actively look for indicators of antioxidant deficiencies and, where practical, evaluate serum antioxidant levels. In a similar vein, supplements like vitamin E capsules and vitamin C pills can be used to treat deficiencies when there is significant evidence of them or when a shortfall is imminent. Prophylactic dosages of micronutrient supplements can be administered to PTB patients.

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