# Assessment of Oxidative stress markers and Antioxidants status in Pulmonary Tuberculosis patients in a Nigerian Tertiary Institution

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## ABSTRACT

**Background:** 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 controls at AKTH. Blood samples were 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 Mann Whitney u-rank test, while Spearman correlation 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 30 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 E r=-0.62] with malondialdehyde. **Conclusion**: In conclusion, the findings of this research showed a significant elevation in malondialdehyde levels among PTB patients compared to the control group, indicative of heightened oxidative stress. Concurrently, PTB patients 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. These insights may contribute to our understanding of the oxidative stress dynamics in PTB and highlight the importance of comprehensive care strategies in managing the condition.

**Keywords:** Malondialdehyde; Glutathione peroxidase, Vitamin C; Vitamin E and Pulmonary tuberculosis

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## 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-stained mucus, fever, night sweats, and weight loss.[1]

Globally, TB persist as the 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 population 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 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 five (5th position) highest TB burden states was 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] The body has several mechanisms 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, and the ongoing inflammation can lead to a remodeling of the lung architecture, which manifest as extensive fibrosis, cavitation, traction bronchiectasis, bronchial 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] Upregulated serum levels of malondialdehyde (MDA) [as an indicator for lipid peroxidation, therefore as a marker of oxidative stress] are observed in patients with *Mycobacterium tuberculosis* disease compared to control group.[14] Downregulated serum levels of glutathione peroxidase [(GPX), a seleno-protein enzyme that removes hydroxyl radicals by oxidizing reduced glutathione], vitamin C and vitamin E (are an essential nutrient involved in the repair of tissue, the formation of collagen, the enzymatic production of certain neurotransmitters, functioning of several enzymes and as an antioxidant) are observed in patients with MTB.[15,16] Additionally an increased in the level of oxygen derived free radicals is associated with reduction in the levels of antioxidant vitamins and increased level of MDA. GPX, vitamins C & E because of their ability to donate electrons as well as their multiple effects on the immune system, scavenge ROS as well as singlet oxygen thereby reducing the amount of OS generated.[15,16]

## Methods

### Study Area

The study was undertaken at the DOT (Directly observed therapy) Clinic of Aminu

Kano Teaching Hospital (AKTH), Kano. AKTH is a 700-bed tertiary health institution serving Jigawa, Katsina, Zamfara, Kebbi, Kaduna and Sokoto states in Northwestern Geo-political zone of Nigeria.

## 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 containedsociodemographic& 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

Adult patients (214 of age 18 to 60 years) of both sexes who presented 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 were apparently non-PTB patients as control group.

## Ethical Clearance

Ethical clearance was obtained from the research and ethics 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 had been thoroughly explained to them, their confidentiality was ensured.It was clearly stated that participants could withdraw at will at any time without any consequences and their results were 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 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 ± 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, data obtained during the period was analyzed. 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 illustrates that the mean age of the control group was (31.22 ± 11.1 years), while the mean age of PTB patients was (34.39 ± 12.3 years). Both PTB patients (31.3%) and the control group (34.1%) were primarily composed of individuals between the ages of 21 and 30 years.
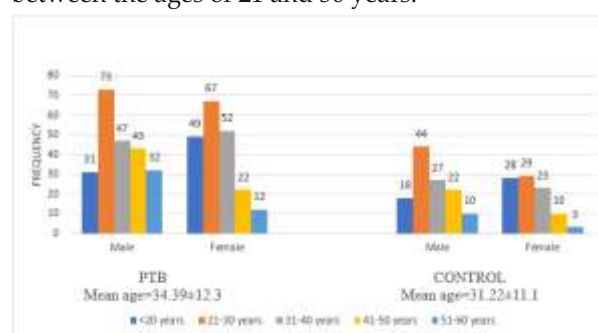


**Figure 1**: Age (years) and Gender distribution of PTB patients and Control group.

Some clinical characteristics of the PTB patients and control group are shown in **Table I**. The PTB patients' average weight was 55.46±8.6 kg, but the control group's average weight was significantly higher (P<0.001) at 58.7±9.3 kg. 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 was no significant difference in height between the control group (1.66±0.95) and PTB patients (1.66±0.1), p=0.638. **Table I** also revealed that the BP (SBP & DBP) was 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 Clinical characteristics of the study participants

| Variable | PTB | | CONTROL | | *p*-value |
|---|---|---|---|---|---|
| | 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 (kg)** 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/m²)** | | | | | |
| Under weight | 60 | 28.0 | 14 | 6.5 | |
| Normal weight | 151 | 70.6 | 182 | 85.1 | |
| Overweight | 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.

### 4.7: 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:** The relationship of malondialdehyde with glutathione peroxidase, vitamin C &vitamin E among PTB patients

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

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

## 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.[23,24,25]

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 behaviour.[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,[27] 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.[8,11,12] 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.[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 haemodynamically 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 shortcourse 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.[7,8,11] Cell membranes are also attacked by free radicals resulting in tissue damage and wasting disease among 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.[18-19,20-21] 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.[18-19,20-21] 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.[62] 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.[63] 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.[15] 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 decrease 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.[26]

**Conclusion:**

This study showed that PTB patients have lower levels of antioxidants (GPX, vitamin C & vitamin E) compared to age- and sex-matched healthy controls and also have higher cellular oxidative stress compared to age- and sex-matched healthy controls. Similarly there is a negative linear correlation between antioxidant levels and oxidative stress in PTB patients.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**

PTB patients should receive routine nutritional advice during their clinic visit 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. Additionally, physicians who treat PTB patients should be encouraged to aggressively look for indicators of antioxidant deficiencies and, where practical, evaluate serum antioxidant levels. Supplements like vitamin E capsules and vitamin C pills can also be used to correct deficiencies when there is strong evidence of them, as well as when there is strong evidence of an approaching deficit. Micronutrient supplements can be administered prophylactically to PTB patients. Additionally, therapeutic lifestyle changes should be routinely advocated for PTB patients to reduce oxidative stress burden associated with cigarette smoking and comorbid conditions such as coronary vascular disease (CVDx) that has the potential to increase disease burden in these patients.

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