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Assessment of Glutathione and Malondialdehyde in Pulmonary Tuberculosis Patients in Edo State, Nigeria

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ABSTRACT

Background and Objective: Tuberculosis is a major global health problem ranking as the eighth leading cause of death in low and middle-income countries. This study aimed to assess the body mass index, malondialdehyde and glutathione of patients with pulmonary tuberculosis in Edo State, Nigeria. **Materials and Methods:** A total of 200 samples were recruited for this study comprising 150 test subjects and 50 healthy control subjects. Malondialdehyde and glutathione were determined using ELISA (Elabscience Biotechnology Inc., United States of America). Statistical analysis was done using One-way Analysis of Variance (ANOVA) and the student's t-test. **Results:** Significant difference was accepted at $p<0.05$. The results obtained showed that BMI and GSH significantly increased, while MDA significantly decreased in test subjects compared with a control group ($p<0.05$). The BMI, MDA and GSH were significantly higher in female test subjects compared with their male counterparts ($p<0.05$). The MDA significantly increased, while GSH significantly decreased with age ($p>0.05$). There was a significant decrease ($p<0.05$) in MDA and a significant increase in GSH of test subjects on therapy for 6 and 2 months, respectively compared with treatment naive test subjects (new case). **Conclusion:** The pulmonary tuberculosis patients had a significant increase in oxidative stress marker (MDA) with a corresponding reduction in antioxidant marker (GSH). This is an indication that tuberculosis patients do not have enough antioxidants to ward off free radicals generated by the infection.

KEYWORDS

Pulmonary tuberculosis, antioxidant, oxidative stress, malondialdehyde, glutathione

INTRODUCTION

Tuberculosis (TB) is a chronic, infectious-contagious and difficult-to-control disease caused by *Mycobacterium tuberculosis*. Pulmonary tuberculosis affects the lungs, while extrapulmonary tuberculosis affects other parts of the body[1]. Tuberculosis as a major global health issue

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ranks eighth primary cause of death in low and middle-income countries, particularly in adults aged 15-59 years. After HIV/AIDS and ischemic heart disease, TB ranks the third highest cause of death globally[2]. *Mycobacterium tuberculosis* is spread to other people by droplet nuclei that are aerosolized through speaking, sneezing, or coughing in patients with infectious pulmonary tuberculosis[3]. Major risk factors for tuberculosis include poor working conditions, inadequate access to healthcare, HIV infection, diabetes mellitus, smoking, alcoholism and drug misuse. These risks are particularly high in low-income nations where tuberculosis infections and deaths are common[4].

Oxidative stress may be defined as a situation whereby the concentration of free radicals is higher than antioxidants. These radicals usually attack delicate structures such as DNA-forming adducts and Polyunsaturated Fatty Acid (PUFA) in the cell membrane a process called lipid peroxidation[5]. Malondialdehyde (MDA), a three-carbon molecular weight aldehyde is one of the by-products of lipid peroxidation and is the most widely studied marker of oxidative stress. As a crucial marker of lipid peroxidation for a variety of medical conditions, measuring MDA levels in diverse biological systems can be done both *in vitro* and *in vivo*[6]. The MDA-DNA adducts are produced when endogenous MDA is formed during intracellular oxidative stress and this makes MDA a crucial diagnostic of endogenous DNA damage. One helpful technique to estimate the levels of oxidative stress is to measure the amount of MDA in blood plasma or tissue homogenates[7].

Glutathione (GSH) is a unique molecule that is involved in several metabolic activities, transport and detoxification. It is a significant antioxidant that keeps cells' redox states in balance and is crucial for preserving all cells' physiological functioning *in vivo*[8]. Glutathione, apart from being an antioxidant, is the main low-molecular-weight thiol-containing peptide with its cysteine residue present in most living cells. Intracellular glutathione has two different forms; reduced Glutathione (GSH) and oxidized glutathione (GSSG). The capacity of the cell to cope with oxidative stress depends on the proportion between both species[9]. The GSH has peculiar characteristics which facilitate its involvement in numerous biological activities such as transferring amino acids into the cell, conjugation of toxic metabolites and compounds, cellular signaling, regulation of protein synthesis, modifying enzymatic activity and protection against oxidative damage[10].

The imbalance between free radical production and cellular defence mechanisms has been described in degenerative lung diseases like tuberculosis[11]. The intracellular pathogen that causes pulmonary tuberculosis develops and multiplies within the host macrophages. It is commonly known that upon coming into contact with this microbe, macrophages experience respiratory bursts. Large amounts of reactive oxygen species (ROS) can be produced by these cells and ROS can cause lipid peroxidation, a chain reaction that affects unsaturated fatty acids primarily found in cell membranes and produces malondialdehyde as its by product[12]. Critical immunological functions like inflammation are regulated by reduced GSH. Alterations in GSH and MDA levels have been reported in various inflammatory conditions, including idiopathic pulmonary fibrosis, acute respiratory distress syndrome, cystic fibrosis and human immunodeficiency virus[13]. Therefore, this study was aimed at assessing the GSH and MDA levels of pulmonary tuberculosis subjects in Benin City, Edo State.

MATERIALS AND METHODS

Study area: This study was carried out in Central Hospital, Benin City, Edo State. Edo State is an inland state in Western Nigeria. It is bounded in the North and East by Kogi State, in the South by Delta State and the West by Ondo State. Benin City is the capital of Edo State with a population of 2,147,188. It is a city approximately 25 miles (40 km) North of the Benin River. It is situated 200 miles (320 km) by road east of Lagos. The study was carried out from December, 2022 to July, 2023.

Ethical approval: Ethical approval for the collection of samples was obtained from the Ministry of Health, Benin City and from Ambrose Alli University, Ekpoma, both in Edo State. Informed consent was also obtained from each subject who participated in the study before the collection of blood samples.

Sample size: The sample size shall be calculated using the Cochrane formula for sample size determination[12]:

$$n = \frac{z^2pq}{d^2} \; n = \frac{z^2pq}{d^2}$$

Where:

n = Minimum sample size
z = Standard normal deviation (1.96)
p = 11% = 0.11
q = 1-p = 0.89
d = Degree of precision at the confidence level of 95% = 0.05

Substituting into the formula above:

$$n = \frac{1.96^2 \times 0.11 \times 0.89}{0.05^2}$$

$$n = 150$$

A total of 200 samples were used in this study, comprising 150 patients with pulmonary tuberculosis (test subjects) attending Central Hospital Benin City, Edo State and 50 healthy individuals (control) in Benin City, Edo State.

Inclusion criteria: Selection of test subjects was based on the following criteria: Age 20-65 years, sputum specimens positive for acid-fast bacilli by microscopy and clinical and radiographic abnormalities consistent with pulmonary tuberculosis.

Exclusion criteria: Patients diagnosed with pulmonary tuberculosis but complicated with other disease conditions such as diabetes mellitus, HIV, cardiovascular diseases etc. were excluded from the study. Tobacco smokers, alcohol users, pregnant and lactating women, those using immunosuppressive drugs and participants who did not give their consent were excluded from the study.

Sample collection: The 5.0 mL of blood samples were collected from fasting subjects via venipuncture and dispensed into a plain bottle. It was allowed to stand for one hour to clot. It was then centrifuged at 3000 g for 10 min to separate blood cells and suspended particles from serum. The serum was aliquoted and stored at -20°C until required for analysis.

Sample analysis: The MDA and GSH levels were determined using an Enzyme-Linked Immunosorbent Assay (ELISA) (Elabscience Biotechnology Inc., United States of America) according to the manufacturer's instructions.

Statistical analysis: The results obtained were presented in tables. Data was presented as Mean±SD (Standard Deviation). Comparison was made between subjects and control groups using One-way Analysis of Variance (ANOVA) and the student's t-test. A Significant difference was accepted at $p<0.05$.

RESULTS

The mean values of Body Mass Index (BMI), malondialdehyde (MDA) and Glutathione (GSH) of test subjects and control group. The results obtained showed that the BMI (kg m^{-2}) of the subjects and control was 20.23±3.24 and 24.67±3.59, the MDA (μM mg^{-1}) was 7.59±1.06 and 3.79±0.80, while GSH (μM) was 173.90±17.29 and 434.28±49.25, respectively. The BMI and GSH significantly increased, while MDA significantly decreased in test subjects compared with the control group ($p<0.05$) as shown in Table 1.

Table 2 shows the BMI, MDA and GSH levels of test subjects according to gender. The results obtained showed that the BMI (kg m^{-2}) of the male and female test subjects were 20.08±3.24 and 22.38±3.42, MDA (μM mg^{-1}) were 6.30±1.09 and 6.81±0.98, while GSH (μM) were 242.72±27.68 and 272.96±29.69, respectively. The BMI, MDA and GSH were significantly higher in female test subjects compared with their male counterparts ($p<0.05$).

Table 3 shows the BMI, MDA and GSH levels of test subjects with age. The BMI (kg m^{-2}) of the test subjects in age group 18-30 years, 31-40 years, 41-50 years and >51 years were 22.68±2.91, 21.64±4.12, 21.46±3.40 and 21.34±3.88, MDA (μM mg^{-1}) were 4.37±0.55, 6.02±1.17, 6.78±1.29 and 6.97±0.87, while GSH (μM) were 269.72±35.08, 209.73±43.14, 197.28±40.64 and 182.92±34.91, respectively. The MDA significantly increased, while GSH significantly decreased with age ($p>0.05$). The BMI did not show any statistically significant difference ($p>0.05$).

Table 4 shows the mean values of BMI, MDA and GSH of test subjects in the treatment and treatment naïve group. The results obtained showed that the BMI (kg m^{-2}) of subjects newly diagnosed, subjects on 2 months' therapy, subjects on 6 months' therapy and control group were 20.22±3.24, 22.95±3.37, 23.43±3.49 and 24.67±3.59, MDA (μM mg^{-1}) were 7.58±1.05, 6.78±0.79, 4.79±0.58 and 3.79±0.80, while GSH (μM) were 173.90±17.29, 257.84±32.26, 323.20±32.85 and 434.28±49.25, respectively. There was a significant decrease ($p<0.05$) in MDA of test subjects 6 months' therapy and 2 months' therapy compared with treatment naïve test subjects (new case). Similarly, there was a significant increase ($p<0.05$) in BMI and GSH of test subjects 6 months' therapy and 2 months' therapy compared with treatment naïve test subjects (new case).

Table 1: BMI, malondialdehyde and glutathione levels of test subjects and control

Parameter	Subjects (Mean±SD)	Control (Mean±SD)	t-value	p-value
BMI (kg m^{-2})	20.23±3.24	24.67±3.59	8.304	0.000
MDA (μM mg^{-1})	7.59±1.06	3.79±0.80	11.034	0.000
GSH (μM)	173.90±17.29	434.28±49.25	45.167	0.000

Values are significant at $p<0.05$, MDA: Malondialdehyde, GSH: Glutathione and BMI: Body mass index

Table 2: BMI, malondialdehyde and glutathione levels of test subjects according to gender

Parameter	Male (Mean±SD)	Female (Mean±SD)	t-value	p-value
BMI (kg m^{-2})	20.08±3.24	22.38±3.42	2.219	0.036
MDA (μM mg^{-1})	6.30±1.09	6.81±0.98	2.196	0.043
GSH (μM)	242.72±27.68	272.96±29.69	3.396	0.002

Values are significant at $p<0.05$, MDA: Malondialdehyde, GSH: Glutathione and BMI: Body mass index

Table 3: BMI, malondialdehyde and glutathione levels of test subjects in relation to age

Parameter	18-30 years (Mean±SD)	31-40 years (Mean±SD)	41-50 years (Mean±SD)	>51 years (Mean±SD)	p-value
BMI (kg m^{-2})	22.68±2.91^{a}	21.64±4.12^{a}	21.46±3.40^{a}	21.34±3.88^{a}	0.254
MDA (μM mg^{-1})	4.37±0.55^{a}	6.02±1.17^{b}	6.78±1.29^{c}	6.97±0.87^{d}	0.000
GSH (μM)	269.72±35.08^{a}	209.73±43.14^{b}	197.28±40.64^{c}	182.92±34.91^{d}	0.000

Values in a row with different superscript alphabets are significant at $p<0.05$, MDA: Malondialdehyde, GSH: Glutathione and BMI: Body mass index

Table 4: BMI, malondialdehyde and glutathione levels of test subjects on treatment and treatment naïve group

Parameter	TB (New case) (Mean±SD)	TB (2 month) (Mean±SD)	TB (6 months) (Mean±SD)	Control	p-value
BMI (kg m^{-2})	20.22±3.24[a]	22.95±3.37	23.43±3.49	24.67±3.59	0.000
MDA (µM mg^{-1})	7.58±1.05	6.78±0.79	4.79±0.58	3.79±0.80	0.000
GSH (µM)	173.90±17.29	257.84±32.26	323.20±32.85	434.28±49.25	0.000

Values in a row with different superscript alphabets are significant at p<0.05, MDA: Malondialdehyde, GSH: Glutathione and BMI: Body mass index

Table 5: Relationship between BMI, malondialdehyde and glutathione of pulmonary tuberculosis subjects using pearson correlation

		MDA	GSH	BMI
MDA	Pearson correlation		-0.460**	0.066
	Significant (2-tailed)		0.001	0.651
GSH	Pearson correlation	-0.460**		0.230
	Significant (2-tailed)	0.001		0.108
BMI	Pearson correlation	0.066	0.230	
	Significant (2-tailed)	0.651	0.108	

**Correlation is significant at the 0.01 level (2-tailed)

Table 5 shows the relationship between BMI, MDA and GSH in pulmonary tuberculosis subjects using Pearson correlation. The results obtained showed that MDA had a significant negative correlation with GSH (r = -0.460, p = 0.001) and a non-significant positive correlation with BMI (r = 0.066, p = 0.651). The GSH had a non-significant positive correlation with BMI (r = 0.230, p = 0.108).

DISCUSSION

Oxidative stress caused by free radicals results from an imbalance between the generation of reactive oxygen and protective mechanisms. The oxidative stress is known to be a component of molecular and cellular tissue damage mechanisms in a wide spectrum of human diseases. This study was therefore aimed at evaluating the BMI, GSH and MDA levels of pulmonary tuberculosis subjects in the current study area. The result of this study showed that Body Mass Index (BMI) was significantly lower in test subjects compared with a control group. This finding was in agreement with previous studies[14-16]. The fact that poor nutritional status has detrimental effects on a cell-mediated immune system helps to explain the potential mechanistic relationship between tuberculosis incidence and underweight[14]. Low BMI can suppress lymphocyte stimulation and reduce Th1 cytokine secretions (the Th1 cytokines interleukin-2, interferon-γ and tumor necrosis factor-α), which could cause the higher burden of TB infection and increase the severity of TB disease in underweight patients[15]. Malnutrition has also been linked to immune system impairment (reduction of reactive nitrogen intermediates) in response to mycobacterium infection[16]. Tuberculosis (TB) is associated with poverty, which in turn drives malnutrition resulting in low BMI.

In this study, MDA was significantly higher (p<0.05) in pulmonary tuberculosis subjects compared with the control group. This finding was consistent with reports from previous studies[17-19]. Increased production of ROS during pulmonary inflammation results from the phagocyte respiratory burst. Lipid peroxidation and redox homeostasis dysfunction are two manifestations of these free radical-mediated processes that lead to elevated MDA levels[17]. Reducing antioxidant effectors and increasing ROS production through the respiratory burst are the two main causes of oxidative stress[18]. Because of the incapacity to appropriately eliminate the oxidative burden, this condition impairs normal lung function and the host immune responses that contribute to the pathogenesis of the disease, ultimately leading to pulmonary dysfunction[19]. The oxidative environment is crucial for the survival of *Mycobacterium tuberculosis* (MTB), therefore, MTB may alter the host physiology biasing towards a pro-oxidative environment. Such an adaptation of the host by the bacteria would be beneficial for the survival and proliferation of the pathogen. Since high oxidative stress is also favorable for other pathogens like HIV, it is possible that modulation of the host oxidative stress machinery might further aid in developing co-infections[20].

A significant decrease in the GSH level of pulmonary tuberculosis subjects compared with healthy control indicates oxidative stress. The reduction in the circulating levels of antioxidant molecules such as GSH and others has been reported in tuberculosis patients in previous studies[19,21-22]. The GSH play an important role in the progression of tuberculosis. It has been demonstrated that reduced GSH levels activate NFκB, which in turn triggers a sequence of downstream signal transduction events that promote TB growth and survival[23]. The pathogen may use the low GSH levels in the serum of TB patients as a survival strategy. Since circulating antioxidant effectors are insufficient to combat the oxidative stress associated with tuberculosis, free radicals will likely build up in lung tissue and attack membrane lipids, resulting in lipid peroxidation[22].

In this study, there was a statistically significant decrease ($p<0.05$) in MDA and a significant increase in GSH levels of pulmonary tuberculosis subjects on therapy for 6 and 2 months, respectively compared with the treatment naive group (new case). This finding was in agreement with the previous studies[24-26]. This is most likely an ameliorative effect of the anti-tuberculosis drugs used by the patients. It is supposed that treatment in combination with other antioxidant supplementation used by the subjects on therapy could have decreased the level of oxidative parameters, down-regulate the lipid peroxidation (MDA) levels and up-regulated GSH levels[24]. Glutathione supplementation has been reported to increase cell proliferation in vitro and increase GPX and GSH levels of pulmonary tuberculosis-infected subjects on therapy over time[26].

A significant decrease ($p<0.05$) in MDA and GSH of male test subjects compared with female test subjects was reported in this study. Previous studies have shown sex-specific differences in antioxidant capacities in various tissues[27-28]. Higher levels of GSH and GPX activities have been reported in female mitochondrion which is postulated to confer protection from ROS-mediated damage[27]. Furthermore, significant biochemical changes are linked to menopause, such as a notable decrease in the levels of sex hormones in plasma and an increase in gonadotrophin and other hormone concentrations[29]. At high concentrations, oestrogen inhibits DNA oxidation, which has antioxidant effects; however, because of its catechol structure, oestrogen acts as a pro-oxidant at low concentrations[30] which could have contributed to the results of this study as most of our female subjects were in menopause. In this study, MDA negatively correlated with GSH. Several antioxidants correlate negatively with MDA, as expected for antioxidants, which was also observed in this study[27]. In this study, MDA significantly increased, while GSH significantly decreased with age. Aging is associated with changes in different biomarkers of (per) oxidation[28].

The finding of this study is important to clinicians and healthcare providers in the management of patients with pulmonary tuberculosis. Therefore, it is recommended that the treatment of tuberculosis patients through nutrition and anti-oxidant supplementation be taken into consideration in the management of tuberculosis patients. One limitation of this study was a small sample size which in no way had any significant impact on the outcome and results of this study. However, it does not underscore the importance of future studies with larger sample sizes.

CONCLUSION

In conclusion, pulmonary tuberculosis patients had a significant increase in oxidative stress marker (MDA) with a corresponding reduction in antioxidant marker (GSH). This is an indication that tuberculosis patients did not have enough antioxidants to ward off free radicals generated by the infection which consequently provoked the oxidation of membrane lipids leading to the production of high MDA as a marker of oxidative stress.

SIGNIFICANCE STATEMENT

The imbalance between free radical production and cellular defence mechanisms has been described in degenerative lung diseases like tuberculosis. Alterations in GSH and MDA levels have been reported in

various inflammatory conditions, but poorly reported in subjects with pulmonary tuberculosis. Therefore, this study was carried out to assess the GSH and MDA levels of pulmonary tuberculosis subjects in our study area. Our findings revealed a significant increase in MDA and a significant decrease in GSH of pulmonary tuberculosis patients compared with healthy control which indicates that patients with pulmonary tuberculosis lack enough antioxidants to ward off free radicals generated by the infection. Treatment regimens for tuberculosis patients should take into consideration nutrition and anti-oxidant supplements.

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