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Markers of Oxidative Stress Evaluation in People Living with Pulmonary Tuberculosis

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ABSTRACT

Pulmonary tuberculosis (TB) is one of the most common infectious diseases globally. This study was done to assess the levels of vitamins C and E, glutathione peroxidase, catalase, superoxide dismutase, and lipid peroxidation product (malondialdehyde) in pulmonary tuberculosis patients in Muzaffarnagar Medical College & Hospital, Muzaffarnagar (MMC). A total of 90 individuals (males and females), comprising 30 newly diagnosed pulmonary tuberculosis patients yet to commence therapy. Thirty old cases on therapy and a control group consisting of 30 healthy individuals of the same age range (35-55 years). The levels of Vitamin C, Vitamin E, glutathione peroxidase, catalase, and superoxide dismutase in pulmonary tuberculosis were determined using the standard method. The results showed that the levels of Vitamin C (1.64±0.41 mg/dl), Vitamin E (1.46±0.38 mg/dl), glutathione peroxidize (0.89±0.07 iu/L), catalase (70.49±2.02 iu/L) and superoxide dismutase (65.45±3.48 iu/L) in pulmonary tuberculosis were significantly decreased when compared with controls (1.91±0.42 mg/dl, 0.84±0.31 mg/ldl, 72.60±2.58 iu/L, 0.94±0.06 iu/L, 68.65±2.83 iu/L) respectively ($p<0.05$). While the level of malondialdehyde (8.7±1.81_mol/ml) was significantly increased ($p<0.05$) in pulmonary tuberculosis when compared with control (4.91±1.90 mol/ml). However, the levels of antioxidants were increased in pulmonary tuberculosis on antituberculosis drugs when compared with those not on therapy. These probably indicate that antioxidant status is significantly reduced in pulmonary tuberculosis patients which may be associated with high levels of free radicals and oxidative stress. Hence, supplementation of pulmonary tuberculosis patients with diet or drugs containing antioxidants can improve their condition.

Keywords: *Pulmonary tuberculosis, antioxidant, oxidative stress*

INTRODUCTION

Mycobacterium tuberculosis is considered as an etiologic agent of tuberculosis (TB) with the identifying feature of the organism being an acidfast property[1] Pulmonary Tuberculosis (PTB) occurs when *M. tuberculosis* primarily attacks the lungs[2]. However, it can spread from there to other organs. Pulmonary TB is curable with an early diagnosis and antibiotic treatment [3]. Tuberculosis is a leading health problem worldwide and remains one of the leading causes of death from infectious diseases [4]. It is a highly infectious disease that is widely distributed throughout the globe [5]. Almost one-third of the world's population is infected with *Mycobacterium tuberculosis* and the majority of these individuals live in less developed countries [6]. It is commonly a disease of the lung where it forms a localized infection after inhalation. Worldwide, TB is responsible for more than 1.5 million deaths every year [7] with an estimated rate of 13.7 million prevalent cases of TB in 2007 (206 per 100.000 populations) [8]. Therefore, despite recent progress, TB remains an important global public health problem [9].

Pulmonary tuberculosis is the commonest form of tuberculosis characterized by general symptoms such as unexplained cough, dehydration, vomiting, unexplained

tiredness, weight loss, high remittent or intermittent pyrexia, and loss of appetite at the prodromal period, and specific respiratory symptoms like hemoptysis, pleural pain, and others depending on the site involved [5]. It can affect extrapulmonary regions like lymph nodes, bones and joints, skin, meninges, eyes, kidneys, and also the gastrointestinal tracts, where it
causes an insidious disease that sometimes develops without any striking clinical evidence. It is a disease of the lungs where it forms a localized infection after inhalation [10]

The pathogenesis of TB is multifactorial and includes the effects of oxidative stress [4]. Reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) are induced by mycobacteria through the activation of phagocytes by respiratory burst mechanism, which is crucial to host defense but may promote tissue injury, and inflammation [1] and may further contribute to immunosuppression. Pulmonary fibrosis and dysfunction in TB are thought to be a consequence of chronic inflammatory events involving pro-inflammatory cytokines, activated macrophages, and ROS that stimulate fibroblast proliferation and mononuclear cell DNA damage [11]

Tuberculosis is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (MTB) [12]. It is a highly infectious disease that is widely distributed throughout the world. The disease is influenced by economic and nutritional factors; although educational background, immunity, and hormonal status have been associated with the prevalence. The economic and nutritional factors account for the highest prevalence in developing countries. The World Health Organization (WHO) reports showed that there were an estimated 9.3 million cases of TB in 2007 [8]. The WHO declared TB a global health emergency in 1993, and the "Stop TB" Partnership developed a Global Plan to Stop Tuberculosis that aims to save 14 million lives between 2006 and 2014 [13]. In 2004, around 14.6 million people had active TB disease with 9 million
new cases [14]. The annual incidence rate varies from 356 per 100,000 in Africa to 41 per 100,000 in the Americas [10]. The rise in human immune virus (HIV) infection and the neglect of TB control programs have enabled a resurgence of TB. The emergence of drug-resistant strains has also contributed to the TB epidemic, with 20% of TB cases from 2000 to 2004 being resistant to standard TB treatments, and 2% resistant to second-line TB drugs. Although *Mycobacterium tuberculosis* is more common, *Mycobacterium bovis* which affects cattle can also be found in man [14]

Recent studies suggest that in pulmonary tuberculosis, there is an increase in several circulating markers of free radical activity, indicating ongoing oxidative stress and a decrease in antioxidant activity which may contribute to the development of lung function abnormalities [15]. Although these are important parts of the host defense against the organism, enhanced reactive oxygen species (ROS) generation may promote tissue injury and inflammation. This further contributes to immune suppression. Moreover, the malnutrition that is commonly associated with patients with TB may further contribute to the impaired antioxidant capacity in these patients which may result in severe oxidative stress that has been reported in TB patients due to malnutrition and poor immunity [16]. To maintain normal lung function, there must be a protective antioxidants balance between toxic ROS and antioxidants which protects the body from the damaging effects of ROS. Antioxidants are physiologic substances that are derived both from endogenous and exogenous sources and act to quench ROS. An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction that can produce free radicals, leading to chain reactions that may cause cellular damage. Antioxidants such as ascorbic acid (vitamin C), terminate these chain reactions (oxidation). Plants and animals maintain

complex systems of overlapping antioxidants such as glutathione, catalase, and superoxide dismutase produced internally or dietary antioxidants such as vitamin A, vitamin C, and vitamin E [17]. Oxidative stress can be considered as either a cause or consequence of some diseases, an area of research stimulating drug development for antioxidant compounds for use as potential therapies. Free radicals are responsible for widespread and indiscriminate oxidation and peroxidation of lipids causing cell death or organ damage. Free radicals oxidative stress has been implicated in the pathogenesis of a variety of human diseases [18]. When a host tissue is challenged by a pathologic insult of either an immunologic or non-immunological nature, an inflammatory reaction may occur, with subsequent clearance of the pathologic stimulus by phagocytic cells. Tissue injury may result from either the direct effects of the pathologic agent or as a consequence of an inflammatory cell influx [15]. Upon recognition of a phagocytic or soluble stimulus, both neutrophils and macrophages experience a "respiratory burst" which is characterized by an
increase in oxygen consumption and increased glucose metabolism via hexose monophosphate shunt. In conjunction with an increase in oxygen consumption, neutrophils and macrophages secrete both superoxide (O2-) and hydrogen peroxide (H_2O_2) as a defense mechanism [19]. The biological effects of these highly reactive compounds are controlled *in vivo* by a whole spectrum of antioxidative defense mechanisms: vitamins E and C, carotenoids, antioxidant enzymes (superoxide dismutase, glutathione peroxidase, and catalase. During pulmonary inflammation increased amounts of reactive oxygen species and reactive nitrogen intermediates are produced as a consequence of phagocytic respiratory burst [13]. Though pulmonary tuberculosis is a disease of most common occurrence and is widely studied, many questions in this field remain unanswered. There is a paucity of local reports on the status of lipid peroxidation and antioxidants in Owerri Imo State Nigeria. The present study was aimed at investigating the status of malondialdehyde and antioxidants to provide information that will enhance the success rate in the treatment and management of patients with TB. Pulmonary tuberculosis infection is associated with mortality and morbidity. Knowing the levels of antioxidant markers may be useful for better management of the patients. This will alleviate the suffering of this group of patients. There is a paucity of data on the levels of antioxidant markers in tuberculosis patients in our environment. Hence, the need to have a data

MATERIALS & METHODS

Subject: A total of 90 individuals (males and females), comprising 30 newly diagnosed pulmonary tuberculosis patients yet to commence therapy. Thirty old cases on therapy and a control group consisting of 30 healthy individuals of the same age range (35-55 years). Informed consent of the participants was obtained and was conducted in line with the ethical approval of the Hospital. Blood sample: Five ml of venous blood was collected from all subjects, into dried test tubes. These were spun in a centrifuge to enable fast separation of serum into a clean dry bijou bottle. The levels of Vitamin C, Vitamin E, glutathione peroxidase, catalase, and superoxide dismutase in pulmonary tuberculosis were determined using the standard method. Data analysis: The results obtained in the study were expressed as mean ± standard deviation. The statistical analysis of data was done by using a student's t-test. The level of significance was calculated at $p<0.05$.

Statistical Analysis Data analysis: The results obtained in the study were expressed as mean ± standard deviation. The statistical analysis of data was done by using a student's t-test. The level of significance was calculated at $p<0.05$.

RESULT

Subject: A total of 90 individuals (males and females), comprising 30 newly diagnosed pulmonary tuberculosis patients yet to commence therapy. Thirty old cases on therapy and a control group consisting of 30 healthy individuals of the same age range (35-55 years). Informed consent of the participants was obtained and was conducted in line with the ethical approval of the Hospital. Blood sample: Five ml of venous blood was collected from all subjects, into dried test tubes. These were spun in a centrifuge to enable fast separation of serum into a clean dry bijou bottle. The levels of Vitamin C, Vitamin E, glutathione peroxidase, catalase, and superoxide dismutase in pulmonary tuberculosis were determined using the standard method. Data analysis: The results obtained in the study were expressed as mean ± standard deviation. The statistical analysis of data was done by using a student's t-test. The level of significance was calculated at $p<0.05$.

DISCUSSION

In this present study, it was observed that the antioxidants vitamins C and E were significantly depleted in tuberculosis patients when compared with healthy individuals. This is in line with the work of Madhab *et al.,* [20] which stated that the lower levels of vitamin C and E levels were associated with excessive ROS production and oxidative stress in tuberculosis This finding also correlates with the work of Reddy *et al* [16] which stated that the reduced levels of vitamin C and E were linked with the increased radical formation in tuberculosis. Several factors such as low food intake, nutrient malabsorption, inadequate nutrient release from the liver, acute phase response to infection, and inadequate availability of carrier protein may influence circulating antioxidant concentrations [21] Several factors such as low food intake, nutrient malabsorption and inadequate nutrient release from the liver, acute infections and an inadequate availability of carrier molecules may influence circulating antioxidant concentrations. Vitamin C is the most aqueous phase chain breaking antioxidants which directly scavenges radicals present in the aqueous compartment. While vitamin E the most important lipid phase chain-breaking antioxidant scavenges radicals in membranes and lipoprotein particles and is central to the prevention of lipid peroxidation Both vitamin C and E have a protective role against oxidative membrane attack [22] Indeed free radicals released from *mycobacteria tuberculosis* patient initiate lipid peroxidation by attacking polyunsaturated fatty acids in cell membranes, converting them to lipid peroxides and a variety of secondary metabolites. The uncontrolled peroxidation alters membrane fluidity and permeability. Hence, the lipid peroxides and their secondary metabolites such as malondialdehydes are then transported through the circulation by lipoproteins causing damage to distant tissues [15]. Furthermore, it was observed that there was a higher level of MDA in the *Mycobacterium tuberculosis* patients than the healthy individuals. However, the level of MDA significantly decreased among those on antituberculosis therapy, hence there is a significant decrease in ROS generation, and the extent of lipid peroxidation is decreased by chemotherapeutic destruction of Mycobacteria. This is in line with the work of Reddy *et al.,*[16]. Madhab *et al.,* [20] reported low concentration of MDA level in tuberculosis on therapy. The decrease is mainly due to decreased disease progression due to antituberculosis drugs. Hence, this reduced free radical production and reduced MDA. High MDA production is linked with increased production of ROS and is also a marker of the extent of oxidative stress elicited by the immune system. Guler *et al* [23] and Turgut *et al* [24] reported that tuberculosis stimulates cellular activation which decreased when treatment was effective. Also, it was observed in this study

that superoxide dismutase (SOD) and glutathione peroxidase (GPX) were significantly decreased when compared with the control. Also, catalase (CAT) was significantly decreased when compared with the control. The generation of reactive oxygen species is a steady-state cellular event in respiring cells. Their production can be grossly amplified in response to a variety of pathological conditions such as inflammation, immunological disorders, hypoxia, metabolism of drugs or alcohol, exposure to therapeutic radiation and deficiency of antioxidant enzymes. Uncontrol production of reactive oxygen species often leads to damage of cellular macromolecules. Several major cellular defense mechanisms exist to neutralize and combat the damaging effects of these reactive substances. Enzymatic systems function to directly remove reactive oxygen species thereby terminating their activities [25]. The low level of SOD and GPX may be associated with their bid to mop up the free radicals produced. This is consistent with the work of Akiibinu *et al* [21]. In this study, it was observed that SOD, GPX and catalase were significantly low in pulmonary tuberculosis patients when compared with the control. This may be due to the consumption of these substances by pro-oxidants in pulmonary tuberculosis patients. This hence places pulmonary tuberculosis patients at increased risk of oxidative stress and injury. However, patients on antituberculosis therapy had increased antioxidant levels

CONCLUSION

The results of this study have shown that antioxidant status is significantly reduced in pulmonary tuberculosis patients which may be associated with high levels of free radicals and oxidative stress. This could probably imply that supplementation with diet food or drugs containing antioxidants could improve therapy**.**

Declaration by Authors

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