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SERUM ISCHEMIA-MODIFIED ALBUMIN AS AN OXIDATIVE STRESS BIOMARKER IN LUNG TUBERCULOSIS PATIENT

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Aim: The goal of this study was to investigate ischemia-modified albumin (IMA) as a novel marker of oxidative stress in tuberculosis patients.

Materials and methods: Our study included 49 patients with active lung tuberculosis and 45 healthy controls. Serum IMA was measured with automated spectrometric method and results were compared statistically.

Results: We found that IMA levels were significantly higher in pulmonary tuberculosis patients than in the control group. Albumin levels were significantly lower in the patient group than in the control group.

Conclusion: The study showed that we can use this parameter as a new oxidative stress marker in the pathogenesis of pulmonary tuberculosis.

Keywords: Tuberculosis, oxidative stress, ischemia-modified albümin.

INTRODUCTION

Mycobacterium tuberculosis (MTB), the etiological agent of tuberculosis (TB), infects nearly a quarter of the world's population and remains the leading cause of death by a single pathogen (1). The vast majority of this infection settles in the lungs. Transmission occurs from an infected person to another person via droplets or with coughing up blood or contaminated sputum (2).

It derived most of the radicals formed in the human body from oxygen (3). The formation of highly reactive oxygen containing molecular species is a normal consequence of a variety of essential biochemical reactions. In healthy conditions at the cellular level, there is a critical balance exists between the free radical generation and the antioxidant defense (4). Oxidative stress (OS) arises because of an imbalance between the free reactive oxygen species (ROS) and the antioxidant mechanisms (5,6). Lung is the organ most affected by oxidants because it is under the influence of air pollution and blood-borne oxidants. It is also the organ that meets the most oxygen. There is a higher risk of OS in the lung compared to other organs (7,8). Excess formation of ROS can start a series of chemical reactions and cause damage to cellular components, including proteins, lipids, and nucleic acids (5,9). Many studies have linked OS to various lung disorders, including asthma, chronic obstructive pulmonary disease (COPD), acute pulmonary distress syndrome, and TB (10,11). The oxidative environment normally helps to kill pathogenic microorganisms. However, in the intracellular pathogen of

MTB, the opposite can grow well in macrophages in environments with high oxygen concentrations (12). As an immune response, the infected macrophage starts a respiratory burst and produces high levels of ROS to counteract and kill the mycobacteria (13). MTB infection can induce oxidative stres (14).

There are various biochemical markers used to identify OS and inflammation. One of these markers is ischemia-modified albumin. Albumin plays a major role in regulating oncotic pressure with antioxidant, anti-inflammatory, and antithrombotic effects (15). In case of oxidative stress, certain alterations occur in the N terminal portion of albumin, leading to reduced binding to heavy metals such as copper and cobalt. This new chemical structure of albumin is termed as ischemia modified albumin (IMA) (16). The IMA was first identified in the early 1990s and has since been widely studied in patients presenting with myocardial ischemia IMA is one of the earliest predictors of ischemia (17,18). However, new studies have shown that IMA, which is evaluated as a cardiac ischemia marker, may also increase in different pathologies and affect other organs (19). Studies on patients with acute mesenteric ischemia, pulmonary embolism, cardiopulmonary resuscitation, end-stage renal failure cerebrovascular ischemia, systemic sclerosis, arthroscopic knee surgery, post-exercise skeletal ischemia and diabetes mellitus have reported increased serum IMA level (20).

The goal of this study was to evaluate IMA as a novel marker of OS in TB patients and to investigate changes occurring in patients.

MATERIAL AND METHODS

This study was performed regarding the recommendations put forward via the Declaration of Helsinki. The study protocol was approved by the Ethical Committee and each participant gave written, informed consent. 49 patients with active lung tuberculosis referred to the Sanliurfa Tuberculosis Dispensary (28 male, 21 female) and 45 healthy controls (25 male, 20 female) were included in the study. Most of our patients were young adults and had no additional diseases other than tuberculosis.

Venous blood samples from the patients, and healthy controls in the study were collected. Plasma blood samples were centrifuged at 1500 rpm for 10 min and serum was got. The separated serum was immediately placed in eppendorf tubes and these samples were stored at −80°C until used.

For measurement of serum IMA levels, the albumin cobalt binding test was used. This involved the addition of 50 mL 0.1% cobalt (II) chloride (CoClv, 6 H_2O) to the patient serum. After mixing, followed by 10-min incubation for albumin cobalt binding, 50 mL 1.5 mg/mL dithiothreitol was added. After mixing followed by 2 min of incubation, 1.0 mL of 0.9% sodium chloride solution was added in order to reduce the binding capacity. The absorbance of samples was measured at 470 nm using a spectrophotometer. The results were expressed as absorbance units (ABSUs) (18).

Statistical Analysis

Statistical analysis was completed using IBM SPSS 25.0 (SPSS for Windows, SPSS Inc., Chicago, IL, USA). The Shapiro–Wilks test was used for normality testing of IMA and albumin ratios. The groups displayed normal distribution. The independent samples t-test,

among parametric tests, was used to investigate whether there were considerable differences between the groups. P<0.05 was accepted as statistically significant.

RESULTS

It included 49 patients with lung tuberculosis and 45 healthy volunteers in the study. 27 patients with lung tuberculosis (55%) were male and 22 patients with lung tuberculosis (45%) were female. 25 control group (56%) were male and 20 control group (44%) were female. The mean age of the patient group diagnosed with lung tuberculosis was 32.95 ± 13.20 years, and the mean age of the control group was 34.18 ± 11.86 years. There was no significant difference between the groups in terms of age. There was no significant difference between the groups in terms of gender.

The evaluation of patient and control group in terms of IMA and albumin levels are shown in Table I. Albumin measurements were 5.14 ± 0.09 in the control group and 4.61 ± 0.41 in the patient group. Albumin level is lower in the patient group when compared to the control group and this difference was statistically significant (p =0.000). IMA level was higher in the patient group than in the control group, and this difference was statistically significant (0.72 ± 0.09, 0.53 ± 0.04, p=0.000).

Table 1. Evaluation of patient (TB) and control group in terms of IMA and Albumin levels.

	Patient (49)	Control (45)	P
IMA (ABSU)	0.72 ± 0.09	0.53 ± 0.04	0.000
Albumin (g/dL)	4.61 ± 0.41	5.14 ± 0.09	0.000

*All parameters are presented as mean ± standard deviation.

DISCUSSION

It is estimated that about a third of the world's population lives with latent TB. Continuing to be one of the most important causes of death until recent years, TB is an important public health problem worldwide (21). Therefore, biomarkers are very important in the diagnosis of tuberculosis disease, in the follow-up of treatment and in determining the outcome effectively and accurately. We need new biomarkers in the prognosis and treatment process of the disease.

Degenerative lung diseases such as tuberculosis are associated with lung oxidant-antioxidant imbalance (22). Mycobacterium tuberculosis is an intracellular pathogen, which grows and replicates in the host macrophages. It is well known that macrophages undergo respiratory burst after contact with this microorganism. Increased amounts of ROS are produced as a result of respiratory burst (23).

Under physiological conditions, antioxidant production also increases to neutralize the harmful effects of increased ROS in tissues. However, the delicate balance between antioxidants and oxidants is key to tissue homeostasis, and when disrupted, it causes irreversible cell damage with pathological consequences (24). There are many studies showing that oxidant

parameters increase and antioxidant parameters decrease in tuberculosis disease. One study showed that thiol/disulfide homeostasis is impaired in TB diseases (25). In other studies, serum SOD activities were significantly reduced and serum MDA levels increased in tuberculosis patients compared to healthy controls (26-28). This result shows that oxidative stress is increased in patients with pulmonary tuberculosis. Most of the thiols in plasma are associated with albumin, and SH groups are oxidized in the presence of oxidative stress, thus causing structural changes in albumin (29).

The production mechanism of ischemia modified albumin is unclear. However with OS, some changes occur in the N-terminal part of albumin, resulting in reduced binding to heavy metals such as copper and cobalt (16). OS may promote an increase in IMA levels as it affects albumin's ability to associate with metals such as cobalt (30). It has been shown that increased IMA concentrations are associated with inflammation, oxidative stress and endothelial dysfunction (18). Elevated IMA levels were detected in patients with COPD (31) and inflammatory bowel disease (32). In another study, significantly higher IMA values were found in pulmonary embolism patients compared to the control group (33). In a study, it was shown that there is an inverse relationship between IMA and albumin levels (34). In another study, serum IMA levels were significantly increased in community-acquired pneumonia patients (35). Albumin, which has an antioxidant effect, constitutes 70% of the total antioxidant capacity of the serum (14). Therefore, albumin modification can be informative about the body's response to OS.

Limited data is available on the relationship between IMA and lung diseases. Determination of IMA levels in diseases where oxidative stress plays a major role in pathogenesis would be important. In our study, IMA levels in the patient group were significantly higher than in the control group. Albumin levels were significantly lower in the patient group than in the control group. In this study, we can say that the increase in ROS released from macrophages in patients with pulmonary tuberculosis disrupts the structure of albumin, which makes up most of the serum proteins, causing an increase in serum IMA levels and a decrease in serum albumin levels.

CONCLUSION

According to the results of our study, it can be clearly said that serum IMA levels increase significantly, while serum albumin levels decrease significantly in pulmonary tuberculosis. This may play a role in the disease's pathogenesis, and measuring these parameters can provide insight into the disease process. To our knowledge, our study is the first to evaluate IMA levels in the serum of patients with pulmonary tuberculosis. The results of our study showed that we can use this parameter as a new oxidative stress marker in the pathogenesis of pulmonary tuberculosis. Evaluation of IMA and albumin parameters in patients with pulmonary tuberculosis may contribute significantly to the evaluation of these patients. We need new and large-scale studies to show the potential effects of oxidative stress on the pathogenesis of pulmonary tuberculosis.

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Declaration of interest

No author has a financial or proprietary interest in any material or method mentioned.

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