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Oxidative stress and inflammation biomarkers in pulmonary tuberculosis

Lesnic Evelina, MD, PhD, Associate Professor

Department of Pneumophtysiology, Nicolae Testemitsanu State University of Medicine and Pharmacy
Chisinau, the Republic of Moldova

Corresponding author: evelinalesnic@yahoo.com. Received November 04, 2017; accepted December 08, 2017

Abstract

Background: Tuberculosis outcome and clinical features of the infection are influenced by the degree of the multiplication of mycobacterias, host's defense mechanisms and the organism's capacity to fight through the antioxidant mechanisms against the aggression of the oxidative stress. The aim of the study was to assess the oxidative stress and inflammatory biomarkers in pulmonary tuberculosis.
Material and methods: A prospective study, which included 46 patients with pulmonary tuberculosis and 36 healthy persons determined according to the clinical and biochemical criteria, was performed. The oxidative stress was assessed through the level of the advanced oxidation protein products, advanced glycation end-products, fibrinogen, amino acid catabolic products, activity of N-acetyl-β-D-glucosaminidase. The determination of the total antioxidant activity of plasma was performed through ABTS and CUPRAC methods. IL-8 and TNF-α were assessed using analysis kits of BOSTER (USA) producer.
Results: Was established high level of the oxidative stress following the assessment of the concentration of the advanced oxidation protein products, advanced glycation end-products, fibrinogen, N-acetyl-β-D-glucosaminidase, urea and creatinine. High concentration of amino acid catabolic products was attributed to the nephrotoxic properties of the medication. Was identified high level of the plasma total antioxidant activity and antioxidant compounds. Cytokines concentration IL-8 and TNF-α was several times higher than in the control group and they were assessed as specific biomarkers.
Conclusions: High level of the protein peroxidation, advanced glycation end-products, fibrinogen, protein catabolism compounds, pro-inflammatory cytokines – IL-8 and TNF-α confirmed the boosting of the oxidative stress. The elevated total antioxidant activity and antioxidant proteins demonstrated the organism's capacity to redress the oxidative aggression.

Key words: tuberculosis, oxidative stress, IL-8, TNF-α.

Introduction

Tuberculosis (TB) represents a multifactorial disease with an evolution and treatment response determined by the continuous interaction between *Mycobacterial tuberculosis* (MBT) and human genotype. Natural history and morphological features of the tuberculous infection are influenced by the degree of the multiplication and dissemination of MBT and host's defense mechanisms [5]. The resistance against micobacterial infection is performed by macrophages through phagocitosis of MBT and by CD4 lymphocytes through interleukin production. If at least 5 MBT achieve the lung of a previously non-infected host there are two possibilities of outcome: 1) alveolar macrophages destroy MBT through their phagocytosis, 10% of cases; 2) surviving and intracellular division of the MBT [1]. The host response against mycobacterial infection consists of two phases: a 3rd type hypersensitivity reaction induced by the immune circulating complexes (antibody mediated) which is developing in 2-3 weeks after the infection and a 4th type hypersensitivity (cell-mediated) developed in 8-12 weeks. The 3rd type immune response is morphopathologically characterized by exudative lesions rich in active MBT and the 4th type represents nodular-proliferative granulomas which contain the latent forms of MBT [1].

The nonspecific resistance of the organism against infection, including TB is based on the recognizing of the specific antigens as well as of the common antigenic groups called pathogen associated molecular patterns (PAMPs) [1]. The typical PAMPs are constituted from different substances such as: lipopolisaharides, endotoxins, peptidoglicans, viral nucleic acids, fungus β-glicans, flagelines, lipoteichoic acid, etc. The recognizing of the PAMPs is realised by the specific membrane receptors, defined as pattern-recognition receptors (PRR). The most important representatives of the PRR implicated in the TB immunity are: Toll-like receptors (TLRs), C-type lecithin receptors (CLRs) and Nod-like receptors (NLRs) [1]. The specified receptors are a family of the transmembranes proteins identified in many immune cells (macrophages, neutrophyles, dendritic cells, lymphocytes, mastocytes) and non-immune cells (enterocytes, astrocytes, hepatocytes, epithelial cells, etc.). Their stimulation will activate the gene response by the production and releasing of the different types of the immune inductors: interleukins (IL), interferons (IFN), hematopoetic growth factors, tumor necrosis factors (TNF) and chemokines [1, 5, 9,]. Interleukins regulate the systemic inflammatory response before the development of the adaptive immunity. Pro-inflammatory cytokines are IL-1, IL-6, IL-8, IL-12 and are secreted as a specific response to specific molecules PAMPs that bind to pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) [1]. IL-1 is a mitogenic protein, a lymphocyte B activating factor and a lymphocyte B differentiation factor [1]. IL-2 are secreted by the lectin stimulated T lymphocytes and B lymphocytes. It induces the differentiation of the T lymphocytes and activates B lymphocytes as a growth factor, being the antibody secretion

stimulant [1]. IL-6 is secreted by the T lymphocytes and macrophages during infection, inflammation, trauma as a specific response to PAMPs. It mediates the acute phase response, the production of neutrophils and the maturation of B lymphocytes. IL-6 is the major regulator of the lymphocytes B transformation into plasmocytes [1]. IL-8 is released by phagocytes and mesenchymal cells induced by the IL-1 and TNF-α. It activates neutrophil chemotaxis and their accumulation, lysosomal exocytosis and the OS at the site of the infection, inflammation, tissues ischemia or traumatism [4, 8, 9]. IL-12 is produced by the macrophages, neutrophils, dendritic cells, B-lymphoblastoid cells as a response to antigenic stimulation. The main function represents the differentiation of T lymphocytes into T helper 1 lymphocytes. It stimulates the production of IFN-γ and TNF-α from lymphocytes T and natural killer cells. TNF superfamily is a family of cytokines that cause the cell apoptosis [14]. The first described was TNF- α (also named cachectin) known as monocyte-derived cytotoxin involved in the cytolysis of certain cell lines, induces cachexia, fever (by IL-1 secretion) and cell differentiation [5]. The clinical expression of the cytokines is various, but the most of them cause the endogenous intoxication syndrome. Besides the immune response, the disease outcome depends on the organism's capacity to fight through the antioxidant mechanisms against the aggression of the oxidative stress (OS) determined by the released mycobacterial exotoxins and antituberculosis drugs [8]. OS is caused by the imbalance between the production of the free oxygen radicals and the capacity of the biological system to detoxify the peroxides and free radicals [12]. OS is manifested through the peroxidation of the cellular DNA, proteins, lipids, carbohydrates and other biological macromolecules. OS and protein peroxidation determine chronic metabolic disturbances with extensive fibrosis and collagen accumulation in the tissues, in consequence developing the multisystemic organ failure. The advanced oxidation protein products (AOPP) are important biomarkers of the OS. Those are constituted from uremic toxins which result from the interaction between the chlorine oxidants (chloramines and hypochlorus acid) with plasmatic proteins. The kidneys, spleen and the liver are major organs responsible for the isolation and excretion of the AOPP [16]. The increased blood concentration of AOPP is established in chronic inflammatory systemic diseases (systemic sclerosis), chronic kidney disease, hyperparathyroidism, atherosclerosis, diabetes mellitus, and during the treatment with calcium and vitamin D [16]. AOPP are structurally similar to advanced glycation end-products (AGEs) [15]. Elevated blood concentration of the AGEs can indicate the glucide metabolism disorders. The highest concentration of the AGEs is identified in diabetes mellitus patients and is determined by the non enzymatic glycosilation of the proteins and excessive activation of the polyol way during the hyperglycemia. The AGEs are heterogenous substances which result from the non-enzymatic glycation of the proteins, lipids and nucleic acid during a chain of reaction, defined Maillard reaction [11, 15]. Fibrinogen is an acute phase protein and rises in response to systemic inflammation, infections, trauma, cancer and thrombosis. Fibronogen is the biomarker of OS and inflammation, that demonstrates the functional effects on the fibrin clotting [1]. The antioxidant system is composed by the hydrophilic antioxidant compounds identified in the cytoplasm, blood serum and by the hydrophobic molecules localized in the biological membranes. Enzymatic antioxidants from the blood and cellular cytoplasm are: superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GPO) and gluthatione-S-transferase (GST) [1].

The N-acetyl-beta-D-glucosaminidase (NAG) is a high molecular-weight hydrolytic lysosomal enzyme identified in different tissues (liver, kidneys, lungs, lymph, tears, urine, blood, etc.). It hydrolyses chemical chains of glycosides and amino carbohydrates that form structural components of the cell membrane and lysosomal membrane [17]. In the lungs this enzyme is secreted by alveolar macrophages in response to phagocytosis. Its role in the control of infection consists in the sterilizing activity within the intracellular compartment of the macrophages [17]. Deficiency of the enzyme determines the susceptibility for reactivation of latent TB infection, dissemination and poor treatment outcome. High activity of NAG in the bronchoalveolar lavage indicates acute or chronic pulmonary injury, fibrosis, exposure to fibrogenic and nonfibrogenic dusts. The highest concentration of NAG is established in the proximal tubular cells of the kidneys. High activity in the urine provides information about the impairment of the tubular functions resulting from a disease, nephrotoxicity of the anti-TB drugs and associated OS [17]. The anti-TB treatment is an important risk factor for the metabolic disorders and elevation of OS [12]. The treatment for the drug susceptible TB consists in an association of the 1st line antituberculosis drugs (isoniazid, rifampicin, pyrazinamide, ethambutol and/or streptomycin) during 6 months and for the drug-resistant TB an association of the 2nd line antituberculosis drugs for 18-24 months. Adverse drug reactions are important clinical signs of the OS. The most frequent anti-TB drug reactions associated with the OS are the hepatotoxicity and nephrotoxicity [12]. This study reflects a comparison of the OS indices, antioxidative activity and some inflammatory biomarkers in patients with pulmonary tuberculosis during the intensive phase of the treatment compared with a representative sample of healthy persons. The aim of the study was the assessment of the oxidative stress, antioxidative activity and inflammatory biomarkers in pulmonary TB.

Material and methods

It was realised a prospective study which included 46 patients with pulmonary tuberculosis (study group) diagnosed in the municipal specialized institutions of Chisinau during the period 01.01.2016-31.08.2016 and 36 healthy persons determined according to the clinical and biochemical criteria (control group). Including criteria in the study

group were: age more than 18 years old, patient diagnosed with pulmonary TB, patient type "new case", the diagnosis confirmed through the conventional microbiological methods, patients treated in the intensive phase in the frame of the Municipal Hospital of Phtisiopneumology in Chisinau and signed informed consent. The study schedule included information about the sex, age, clinical radiological diagnosis, case type, patient's microbiological status and results of the drug susceptibility test, treatment regimen and adverse drug reactions. All patients included in the study were treated according to the national clinical protocol "Tuberculosis at adults". The including criteria in the control group were: age more than 18 years old, healthy individual according to the clinical criteria and laboratory findings (complete blood count, biochemical tests; liver transaminases, blood electrolytes and signed informed consent. The assessment of the immune biochemical indices in the serum was performed using the methods with microquantities of the blood serum and work reagents. The dosage was performed in micro plates with 96 wells, but the filling with the samples and reagents was performed with the automatic multichannel pipettes. The measure was performed using the chemical reagents and assessing the absorbance with the spectrophotometer in the maximum standardization of conditions. The total proteins were assessed according to the modified Lowry method [7]. The OS was assessed through the determination of the AOPP according to the modified method of Witko-Sarsat V. [7, 16] and AGEs according to the modified method of Sero L. [7, 13]. It included the spectrophotometric measure of the two main types of the AGEs: *pentosidine-like* and *vesperlysines-like.* The micromethod was based on the fluorescence measure of the intensity of the studied samples diluted in the phosphate tampon at λexc 335 nm, λem 385 nm (quuantification of the *pentosidine-like* AGEs) and at λexc 370 nm, λem 440 nm (quantification of the *vesperlysines-like* AGEs) [7, 11]. The concentration of the urea and serum creatinine was assessed through the spectrophotometric analysis using the kits of the producer Eliteh (France) according to the attached instructions [6]. The concentration of fibrinogen was assessed using the kits of the producer Eliteh (France) according to the attached instructions [6].

The determination of the plasma total antioxidant activity was performed through two procedures: method based on the degradation of the 2,2-azino bis (3-ethylbenzotiazoline-6-sulphonic acid (ABTS) radical at the interaction with serum compounds with the antioxidant properties and measure of the decreasing absorbance at 734 nm [7] and CUPRAC method (*Cupric Ion Reducing Antioxidant Capacity*) based on the reducing capacity of the Cu ion through the capture of the hydroxyl radical [2, 7]. The activity of N-acetyl-β-D-glucosaminidase was assessed according to the Gudumac V. method [6]. The concentration of the immune cytokines of the IL-8 and TNF-α was assessed using the ELISA kits of the producer BOSTER (USA) according to the attached instructions.

The study methodology was based on the collection, statistical analysis, graphic representation and analytical assessment. Statistical analysis was realized by comparative assessment of the quantitative and qualitative features of the selected patients using the Microsoft Excel XP programme. Accumulated material was systematized in simple and complex groups. For the assessment of differences between the indices of the compared samples it was performed the statistic non-parametric test "t test" and the significance threshold "p" ($p<0,05$).

Results

Distributing patients, according to the biological characteristics, a similar rate of men and women was set in both groups, with the predomination of men in the same proportion in both groups which ensured the comparability of the results. The same proportion of young persons aged less than 44 years was established in both groups, which was accepted as a condition permitting the comparability of the laboratory data (fig. 1).

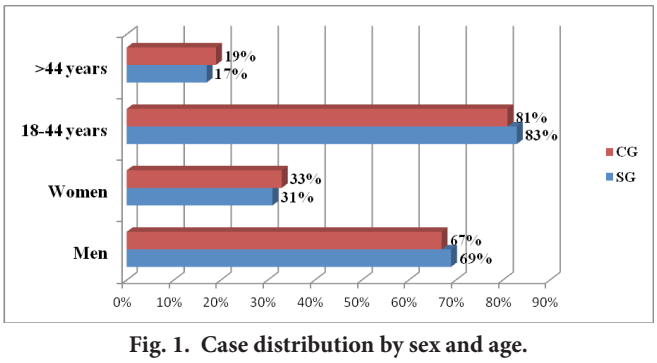

Fig. 1. Case distribution by sex and age.

Detected by passive way were 28 (56.52%) patients in the frame of the symptomatic case examination, 7 (15.21%) through the examination of high risk groups and 16 (34.78%) by direct addressing to the specialized health institution. The majority of patients, 43 (95.65%), were diagnosed with pulmonary infiltrative tuberculosis and 3 (4.35%) with disseminated tuberculosis (fig. 2). At the radiological examination was identified lung destruction in all patients of the study group. Microscopic examination of the smear for acid-fast-bacilli was positive in 30 (65.22%) cases. The conventional cultures revealed MBT colonies in 26 (56.52%) cases. The drug susceptibility test established 20 (43.47%) drug susceptible and 6 (13.04%) drug resistant strains of MBT. Monoresistance to isoniazid was established in 2 (4.34%) cases, but the polyresistance to isoniazid and streptomycin in 3 (6.52%) cases.

Standardized treatment for drug-sensitive TB was administrated in 31 (67.39%) patients, standardized treatment for MDR-TB (DOTS-Plus) in 13 (28.26%) patients and individualised regimen for polyresistant tuberculosis in 2 (4.34%) patients. Immune biochemical indices were analysed at 46 patients with pulmonary tuberculosis (study group) during the intensive phase of the treatment in the hospital performed according to the drug susceptibility test.

The collection (harvesting) of the blood of the control group was performed in ambulatory conditions.

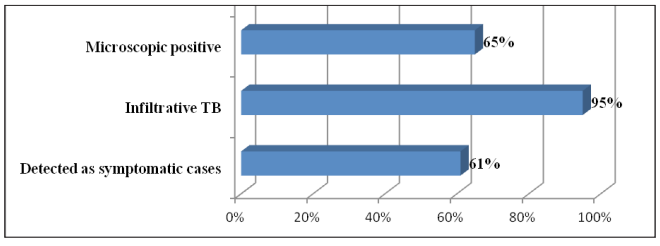

Fig. 2. Clinical, radiological and microbiological characteristics of the tuberculosis patients.

Fibrinogen concentration, as a biomarker of the OS was more elevated in the group of the patients with tuberculosis compared to the control group. During the assessment of the most important products of the amino acid catabolism, was established that the concentration of urea in blood was significantly higher in the group of the patients with tuberculosis compared to the control group. In the same way were established the disturbances of the creatinine concentration, which was significantlty higher in the group of patients with tuberculosis (tab. 1).

Assessing obtained data it was established a statistical higher concentration of the AOPP in the group of patients with tuberculosis compared to the control group. The serum concentration of the AGEs *pentosidine-like* assessed through the fluorescence at 330 ex/390 em established a nonsignificant lower concentration in the group of patients with tuberculosis compared to the control group, but the concentration of the AGEs *vesperlysines-like* at the fluorescence at 370 ex/440 em demonstrated a significant higher level in the group of the patients with tuberculosis compared to the control group (fig. 3).

Assessing the results of the antioxidant activity of the serum through the method CUPRAC and ABTS it was established a significant increasing of the antioxidant system compounds in the group of patients with tuberculosis compared to the control group. The concentration of the ceruloplasmine, known as an acute phase protein with antioxidant role, was significantly higher in the group of patients with tuberculosis as well. The concentration of the total serum proteins (albumin and globulin α1, α2, β, γ) with antioxidant role was established in a higher concentration in the group of patients with tuberculosis (fig 4).

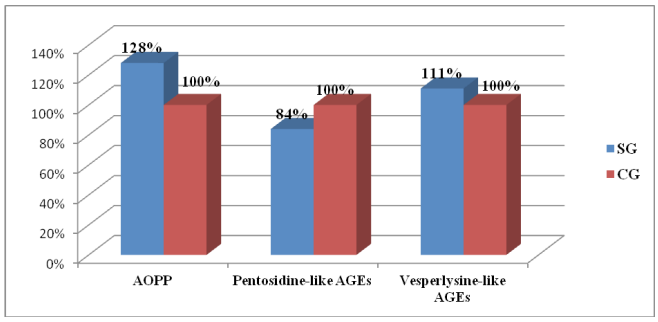

Fig. 3. Oxidative stress biomarkers in the blood.

Note: AOPP – advanced oxidation protein products, AGEs – advanced glycation end-products (AGEs).

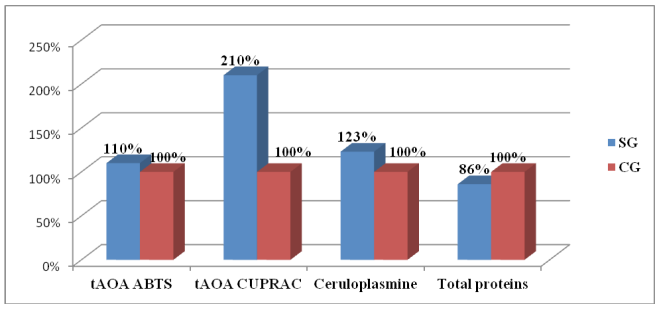

Fig. 4 Comparative assessment of the antioxidant ativity and antioxidant compounds of the blood serum.

Table 1

Some indices of the oxidative stress

Oxidative system	Parameter	SG (N=46)	CG (N=36)	P
		M±SE	M±SE	
Oxidative stress biomarkers	AOPP μMol/l	44,06±2,86 (128%)	34,349±3,58 (100%)	**0,032**
	Pentosidine-like AGEs μg/ml	174,3±15,41 (84%)	208,5±16,27 (100%)	0,13
	Vesperlysines-like AGEs, μg/ml	382,2±25,42 (111%)	343,2±49,63 (100%)	0,45
	Fibrinogen mg/dl	40,90±1,02 (182%)	22,45±0,7 (100%)	**<0,0001**
Amino acid catabolism products	Urea mg/dL	18,92±9,2 (145%)	13,00±2,28 (100%)	**0,02**
	Creatinine mg/dL	79,79±6,84 (173%)	45,87±5,69 (100%)	**0,0003**

Note: AOPP – advanced oxidation protein products, AGEs – advanced glycation end-products (AGEs).

Table 2

Some indices of the antioxidative activity

Antioxidant defense	Parameter	SG (N=46)	CG (N=36)	P
		M±SE	M±SE	
Total antioxidant activity (tAOA)	Method ABTS mMol/l	0,77±0,005 (110%)	0,71±0,004 (100%)	**<0,0001**
	Method CUPRAC mMol/l	1,09±0,18 (210%)	0,517±0,04 (100%)	**0,008**
Proteins with antioxidant role	Ceruloplasmine mg/l	887,2±36,48 (123%)	724,3±27,8 (100%)	**0,0008**
	Serum total protein g/l	59,4±3,61 (114%)	57,1±2,3 (100%)	**0,001**

In terms of the quantitative data the total antioxidant activity determination was more elevated being assessed through the CUPRAC method compared with ABTS. Ceruloplasmine, an acute phase reactant with copper-dependent anti-oxidant activity, was more elevated than the serum total proteins, which include albumin and globulins (α1, α2, β and γ globulins). Data are shown in the table 2.

Assessed inflammatory biomarkers constituted the activity of the N-acetyl-β-D-glucosaminidase (NAG), the concentration of IL-8 and TNF-α. The NAG activity was higher in the group of patients with tuberculosis in comparison with the control group. The concentration of the pro-inflammatory cytokine IL-8 was 10 times higher in the serum of the patients with tuberculosis in comparison with the control group. The concentration of the TNF-α was three times higher than in the control group (tab. 3).

Table 3

Pro-inflammatory biomarkers

Parameters	SG (N=46)	CG (N=36)	P
	M±SE	M±SE	
NAG	80,48±5,315 (122%)	65,88±3,06 (100%)	**0,027**
IL-8 ng/ml	15,595±8,411 (1134,05%)	1,163±1,685 (100%)	**<0,0001**
TNF-α pg/ml	212,41±195,5 (323%)	65,78±12,09 (100%)	<0,0001

NG N-acetyl-β-D-glucosaminidase.

Discussion

Distribution of patients in sex and age groups determined the predomination of the men and economic reproductive age in both selected samples, which allowed the comparability of the results. Diagnosed through at least one microbiological conventional method the patients with a wrong diagnosis were excluded. The diagnosis of the pulmonary infiltrative tuberculosis and lung destruction in a high propotion demonstrated the similarity of the selected group with the national cohorts [10].

Estimation of the level of the oxidative stress markers through the serum concentration of the advanced oxidation protein products, fibrinogen and products of the protein catabolism demonstrated the presence of a higher peroxidative stress in the group of patients with tuberculosis. Studies evaluating advanced oxidation protein products and advanced glycation end-products in patients with tuberculosis in the specialised literature have not been identified. High values of urea and creatinine are comparable to the results of international studies, being attributed to the nephrotoxic properties of medications of the aminoglycoside group included in the regimen of every patient, but also can be explained by the exacerbation of the catabolism [8].

The concentration of the *pentosidine-like* advanced glycation end-products at a lower level in patients with tuberculosis, demonstrated the metabolic changes during starvation. The concentration of the *vesperlysine-like* advanced glycation end-products was insignificantly higher in the group of tuberculosis patients. The level was lower than in comorbid diabetic patients associated with tuberculosis reported in international studies [11].

The markers of the serum antioxidant system underwent elevated changes in the group of the tuberculosis patients. The similar results from the specialised literature demonstrated the hyperactivity of the defensive mechanisms against mycobacterial exotoxins as well as the increased metabolic detoxification of the antituberculosis medication [8]. The intensification of the blood antioxidant activity in patients with pulmonary tuberculosis was demonstrated also by the high concentration of the ceruloplasmine and total serum proteins. The same results were identified in other scientific papers [3].

The elevated activity of NAG in the blood of patients with pulmonary tuberculosis indicated pulmonary injury due to infectious aggresion of MBT. No similar studies were reported in the specialized literature. The quantitative immunoassay revealed that IL-8 was significantly elevated in the patients with tuberculosis. Considering the fact that IL-8 is a chamotactic factor for neutrophils, lymphocytes T and basophils its pivotal role in the modulation of acute and chronic inflammation can be deducted by obtained results also [4, 9]. Assessment of TNF-α established it as one of the most important mediator of the inflammation in the antimycobacterial cytokine cascade that suggests acute pulmonary inflammation and apoptosis in pulmonary tuberculosis [14].

Conclusions

In conclusion, in tuberculosis the increased level of the protein peroxidation, advanced glycation end products, fibrinogen, protein catabolism compounds and pro-inflammatory cytokines: IL-8 and TNF-α confirmed the boosting of the oxidative stress. The increased total antioxidant activity, elevated concentration of the proteins with the antioxidant role in pulmonary tuberculosis demonstrated the organism's capacity to redress the oxidative aggression.

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