ARTICOLE ORIGINALE

DOI: 10.5281/zenodo.6510111
UDC: 616.24-002.5-008.9+577.122

THE DISTURBANCES OF THE ANTIOXIDANT DEFENSE AND PROTEIN METABOLISM BIOMARKERS IN THE SERUM OF THE PATIENTS WITH PULMONARY TUBERCULOSIS

Evelina Lesnic, Valentin Gudumac, Valeriana Pantea

State University of Medicine and Pharmacy "Nicolae Testemițanu", Chișinău, Republic of Moldova

Summary

Objectives. Evolution of the infection with *Mycobacterium tuberculosis* and treatment outcome depends on the balances between the adaptive immunity to reduce the bacterial replication and the capacity of the antioxidant defense to prevent the damages following the immune activation and oxidative stress. The purpose of the study was to assess the disturbances of the antioxidant defense and protein metabolism in the serum of the patients with pulmonary tuberculosis.

Material and methods. A prospective, case-control study, which included 137 patients, distributed in 3 groups: 1st study group (N=54 new cases with drug susceptible tuberculosis), 2nd group (N=56 new cases with multidrug-resistant tuberculosis) and 3rd group (N=27 cases with acquired multidrug-resistant tuberculosis) diagnosed between 2017 and 2019, similar distributed according to the sex and age were compared with a control group constituted from 50 healthy persons. The investigations were realized according to the national protocol and biochemical analysis standards. The antioxidant defense was assessed through the total serum antioxidant capacity, the activity of the enzymes and the proteins with antioxidant role: superoxidismutase, catalase, ceruloplasmin and active phase reactants (fibrinogen and C-reactive protein), protein metabolism indicators (total serum proteins, alanine aminotransferase and aspartate aminotransferase).

Results. The depletion of the antioxidant defense was confirmed through the diminished of the total serum antioxidant capacity and superoxidismutase, regardless the drug resistance of mycobacteria, compared with the control group. A higher anti-oxidant protection was demonstrated by the increased activity of catalase in all groups and ceruloplasmin in patients registered as new cases compared with the control group. The acute phase reactants: C-reactive protein and fibrinogen and enzymes of the protein metabolism were increased in all patients, but the concentration was higher in patients who acquired the drug resistance during the treatment.

Conclusions. The depletion of the the antioxidant defense, increased acute phase reactants and enzymes of the protein metabolism should be taken into account for recommending the individualized therapy for metabolic disturbances.

Keywords: tuberculosis, oxidative stress, antioxidant defense

Introduction

Tuberculosis (TB) is one of the priorities of the health system of any state, and prevention and infection control are national strategic objectives [1]. According to the report of the World Health Organization (WHO), the Republic of Moldova (Moldova) is one of the countries in the WHO European region where tuberculosis control is a priority and one of the 30 countries in the world with the highest-burden of multidrug-resistant tuberculosis (MDR-TB) [2]. The global incidence, which included the new cases and relapses of tuberculosis in 2020 was 43.9/100.000 population (1.762 cases), in 2019 was 71.6/100.000 population (2.877 cases); in 2018 – 75.1/100.000 population (3.016 cases); in 2017 – 83.3/100.000 population (3.352 cases); in 2016 – 88.5/100.000 population (3.569 cases) [3, 4]. The causes of maintaining high epidemiological indicators are the low therapeutic success, late detection of patients, predominance of severe forms with lung parenchymal destruction, high rate of MDR-TB, high rate of HIV co-infected patients, associated immuno-metabolic disorders [1-5]. The evolution of the infection with *Mycobacterium tuberculosis (M. tuberculosis)* and treatment outcome depends on the capacity of the innate immunity to reduce the bacterial replication and the ability of the antioxidant system (AOS) to prevent the damages due to immune activation and oxidative stress (OS) [6, 7]. The OS is caused by the imbalance between the systemic manifestation of the reactive oxygen species (ROS) and the biological system's ability to detoxify them and repair the resulting damage. The severe OS determines the depletion of the enzymatic and non-enzymatic antioxidants, which results in the peroxidation of the cellular DNA, proteins, lipids, carbohydrates, and other biological macromolecules. Mild OS causes cell apoptosis and severe OS determined the necrosis and functional impairment [8]. The AOS includes the hydrophilic antioxidant compounds identified in the cytoplasm and blood serum, as well as the hydrophobic compounds, localized in the biological membranes [9, 10]. From the AOS make part the antioxidant enzymes - superoxidismutase (SOD), catalase (CAT), as well as the enzymes of glutathione and thiol-disulfide metabolism: glutathione reductase (GR), glutathione peroxidase (GPO), glutathione-S-transferase (GST), and glutaredoxin [11-13]. Catalase (EC 1.11.1.6; CAT) is an enzyme from the oxidoreductase group, localized in mitochondria and

peroxisomes, that catalysis the decomposition of hydrogen peroxide to water and oxygen, protecting the cells from the oxidative damage by ROS [12]. In the cytoplasm, GPO is coupled with superoxidismutase (EC 1.15.1.1; SOD). In this way, by coupling two enzymes and some non-enzymatic anti-oxidants, both the protection of the subcellular structures and the modulation of the oxygen activation process are ensured, avoiding the formation of the hydroxyl radical (OH^-) [11].

Ceruloplasmin is a serum ferroxidase, glycoprotein, member of the multicopper oxidase family that uses copper to couple substrate oxidation with the four-electron reduction of oxygen to water. Even it contains more than 95% of the copper from plasma, plays a non-essential role in the transport or metabolism of cooper. Has both anti-oxidant and pro-oxidant properties. Oxidizing the ferrous iron to nontoxic ferric iron shows an anti-oxidant property. The deficiencies in the ceruloplasmin function determine the iron efflux from cells, which exhibits a pro-oxidant activity. Is a potential biomarker in the prognosis of the evolution of pulmonary TB [14]. The acute phase reactants, biomarkers of acute inflammation are fibrinogen and C-reactive protein (CRP). CRP is synthesized primarily by hepatocytes but can be released also by macrophages, lymphocytes, endothelial cells, smooth muscle cells, and adipocytes in response to the pro-inflammatory cytokines. It has an important role in the innate immune system by activating the complement, binding to Fc receptors, and opsonizing the pathogens [6]. Fibrinogen is one of the major plasma protein coagulation factors, which is synthesized in the hepatocytes. The physiological function is the formation of fibrin that binds together platelets, erythrocytes, leukocytes, and plasma proteins in a hemostatic plug. Both, CRP and fibrinogen are potential biomarkers of the OS [9]. The aspartate transaminase (EC 2.6.1.5.7; AST) catalyzes the reversible transfer of an alpha-amino group between aspartate and glutamate acting as an important enzyme in amino acid metabolism. The alanine transaminase (EC 2.6.1.2; ALT) is involved in the amino acid metabolism and gluconeogenesis. Both AST and ALT are the most widely used clinical biomarkers of liver injury [13]. In the literature, there are no published studies about the changes in the AOS and pro-inflammatory biomarkers in patients with different types of the drug-resistance.

The study was conducted to assess the disturbances of the antioxidant system, the pro-inflammatory biomarkers, and the indicators of the protein metabolism in serum of the patients with drug-susceptible and multidrug-resistant tuberculosis.

Material and methods

It was realized a prospective research which included 137 patients, from which 54 were new cases with drug-susceptible pulmonary tuberculosis included in the 1st study group (1st SG), 56 were new cases with MDR-TB included in the 2nd study group (2nd SG) and 27 cases in which the acquired MDR-TB was confirmed were included in the 3rd study group (3rd SG). The groups were compared between them and were compared with a control group (CG) composed of 50 healthy persons assessed according to the clinical and biochemical criteria. The research reported ethics committee approval (no. 14 from 21/11/2017) and the patient's consent was obtained. Including criteria in the study, groups were: age more than 18 years old; a patient diagnosed with pulmonary tuberculosis, new case type in the 1st and 2nd SG; previously treated for TB in the 3rd study group; the diagnosis and the drug susceptibility was confirmed through the conventional microbiological methods (bacteriological examination of the sputum on Lowenstein-Jensen and BACTEC media). The study investigation schedule included information about sex, age, radiological aspects, microbiological patient status, treatment regimen, the results of the biochemical investigations. The including criteria in the control group were: age more than 18 years old; conditioned healthy persons according to the clinical examination, blood test (complete blood count), and biochemical tests (liver transaminases, bilirubin test, hepatitis virus serological tests, HIV serology).

The biochemical investigation of patients from study groups was performed before the treatment in the 1st and 2nd SG and after the determination of the acquired drug resistance in the 3rd SG. The 36 healthy persons from the control group were investigated in ambulatory conditions. Samples of venous blood (5 ml) were collected and centrifuged for 10 minutes with a spin speed of 3500 rpm, with further separation of the serum. All the samples were dispensed into Eppendorf microtubes and frozen at minus 40°C before biochemical determinations. The estimation of the biochemical indices in the serum of blood was performed using the methods with microquantities of the clinical material. Total proteins were determined using the Lowry modified method [12]. The determination of the total antioxidant activity (tAOA) was performed using two procedures: 1) method based on the degradation of the 2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical at the interaction with serum compounds with the antioxidant properties and measure of the decreasing absorbance at 734 nm [12]; 2) method CUPRAC (Cupric Ion Reducing Antioxidant Capacity) based on the reducing capacity of the cupric ion through the captation of the hydroxyl radical [15]. The determination of the activity of the SOD was performed according to the method described by Gudumac V, et al. [12]. The assessment of the activity of the CAT was done according to the method described by Королюк М. А. and modified by Gudumac V, et al [12]. The quantification of the activity of ceruloplasmin was performed through the colorimetric kit. The assay used an oxidase substrate, which gave an intensely colored product upon oxidation [12]. The concentration of fibrinogen was the Clauss fibrinogen (FIB_{Clauss}) assay, which measures the clotting time of plasma after the addition of excess thrombin [12]. For the quantification of CRP in serum was used the latex-enhanced nephelometry according to the attached instruction. The determination of the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) used the colorimetric analysis as a fixed-time method according to the attached instruction.

Statistical analysis was carried out by the comparative assessment of the quantitative and qualitative peculiarities of the selected patients using SPSS 23.0 software. For the testing

of significant differences between the indices of the compared groups was performed the statistic non-parametric Mann-Whitney test. The t-test was applied to test the significant differences of the normally distributed variables. The significance threshold was p<0,05. The study was approved by the Research Ethics Committee of the State University of Medicine and Pharmacy "Nicolae Testemițanu", Chișinau, Republic of Moldova (21.11.2017). Participants signed a written informed consent before enrolment in the study. All procedures performed were following the national law and ethical standards of the Research Ethics Committee.

Results

Distributing patients according to sex established the statistical predomination of men compared with women (p<0,001 in all groups). The patients younger 44 years and older were in the same proportion in all groups. The proportion of persons, younger than 44 years old statistically predominated compared with those older than 45 years (p<0,001 in all groups). All enumerated conditions permitted the comparability of the laboratory data (table 1).

Table 1

Segregating patients into sex and age groups

Biological segregation	Parameters	CG (N=50)	1st SG (N=54)	2nd SG (N=56)	3rd SG (N=27)
		N (%)	N (%)	N (%)	N (%)
Sex stratification	Men	33 (67%)	36 (67%)	31 (55%)	18 (67%)
	Women	17 (33%)	18 (33%)	25 (45%)	9 (33%)
Stratification in age groups	18-44 years	39 (78%)	32 (59%)	34 (61%)	21 (77%)
	≥45 years	11 (22%)	22 (41%)	22 (39%)	5 (23%)

Note: *The applied statistical test: paired Student's t-test. The study groups were compared with the CG.*

**Absolute numbers and percentages per column (in brackets).*

By passive way of the detection of the symptomatic patients, using standard tools for the diagnosis of pulmonary tuberculosis were identified 38 (70%) cases of the 1st SG, 37 (66%) cases of the 2nd SG, and 16 (59%) cases of the 3rd SG. By active way of the detection, using the radiological screening of the high-risk groups were detected 16 (30%) cases of the 1st SG, 18 (34%) cases of the 2nd SG, and 11 (41%) cases of the 3rd SG. All selected patients were diagnosed with pulmonary infiltrative TB with lung parenchymal destruction. Microbiological status was positive in all patients and drug susceptibility testing permitted their distribution in groups according to the obtained results.

M. tuberculosis infection is characterized by an imbalance between the reduction and oxidation systems. The depletion of the AOS contributes to the development of a pro-oxidative environment, the destruction of the lung tissue, and caseous necrosis. The anti-oxidant defense was evaluated through the total antioxidant activity (tAOA) of the serum and antioxidant enzymes. The tAOA of the serum assessed through the ABTS and CUPRAC methods established nonsignificantly lower levels of activity in all study groups compared with the CG, without differences between the

Table 2

Indices of the antioxidant defense

Type	Indices	CG (N=50)	1st SG (N=54)	2nd SG (N=56)	3rd SG (N=27)
		M±SD (%)	M±SD (%)	M±SD (%)	M±SD (%)
Total antioxidant activity	ABTS μM/L	394,1±88,13 (100%)	357,9±26,47 (90%)	352,3±26,87 (90%)	356,9±31,29 (90%)
	CUPRAC μM/L	16,3±2,04 (100%)	14,3±3,44 (90%)	15,1±3,38 (90%)	14,8±4,01 (90%)
Antioxidant enzymes	Superoxide dismutase CU/L	631,6±134,85 (100%)	560,1±114,98 (90%)	610,3±151,14 (95%)	610,8±144,02 (95%)
	Catalase μM/L	9,53±3,01 (100%)	11,3±2,94 (120%)*	11,1±3,66 (120%)*	11,5±3,73 (120%)*

Note: *The applied statistical test: Mann-Whitney U Test; The percentage was assessed by comparing the study groups with the reference value of the control group (100%). CU - Conventional Units.*

** – The statistically significant difference with the control group, p<0,05.*

study groups. The essential representative of the antioxidant enzyme – superoxidismutase (SOD) showed reduced activity in the 2nd and 3rd SG, compared with the CG and the 1st SG, without achieving the statistical threshold. The activity of catalase was statistically increased at the same level in all study groups compared with the CG (z=3,9; p<0,01 for the 1st SG, z=4,2; p<0,01 for the 2nd SG and z=4,4; p<0,01 for the 3rd SG) without differences among study groups, which demonstrates a similar level of the pro-oxidative environment despite the drug-resistance. So, the depletion of the AOS, confirmed through the tAO and blood SOD activity was insignificantly diminished at a similar level in all study groups despite the drug resistance. However, the blood CAT activity was significantly increased in all study groups, which marked the excess of ROS production and high oxidative stress in patients with pulmonary TB despite the drug resistance (table 2).

The activity of serum ceruloplasmin, known as a protein of the acute phase, with pro- and anti-oxidant properties was significantly higher in the 1st SG (z=3,4; p<0,01), slightly increased in the 2nd SG compared with the CG and considerable decreased in the 3rd SG compared with the CG and study groups (z=4,4; p<0,01 compared with CG, z=6,4; p<0,001 compared with 1st SG and z=3,1; p<0,01 compared with 2nd SG).

The concentration of fibrinogen, an acute-phase protein, was two times higher in the study groups compared with the CG with the highest level in the 3rd SG (z=10,9; p<0,001 for the 1st SG, z=10,2; p<0,001 for the 2nd SG, and z=11,4; p<0,001 for the 3rd SG).

The C-reactive protein (CRP), the pro-inflammatory biomarker was not found in the CG. The concentration of the CRP was higher in the 1st SG compared with the 3rd SG (z=3,2; p<0,01) and insignificantly higher compared with the 2nd SG.

The quantitative and qualitative evaluation of the disturbances of the protein metabolism was done through the determination of the concentration of the total serum proteins (which comprises albumin, α1, α2, β and γ globulins) and the activity of alanine and aspartate aminotransferase (ALT, AST). The concentration of the total serum proteins was slightly reduced in the 1st SG and 3rd SG compared with the CG. The activity of AST was 2 times higher in all study groups compared with the CG (z=12,5; p<0,001 for the 1st SG, z=9,7; p<0,001 for the 2nd SG and z=11,9; p<0,001 for the 3rd SG). As well the activity of ALT was statistically increased in all study groups with the highest level in the 1st and 3rd SG compared with the CG (z=7,5; p<0,001 for the 1st SG, z=4,5; p<0,001 for the 2nd SG and z=12,1; p<0,001 for the 3rd SG). ALT activity was higher in the 3rd SG compared with the 1st and 2nd SG (z=4,7; p<0,01 for the 1st SG, z=5,8; p<0,001 for the 2nd SG). Due to inclusion criteria, in the 3rd group were enrolled patients who acquired the drug resistance during the anti-TB treatment, which explained a higher activity of the liver enzymes due to the hepatotoxicity of the anti-TB drugs (table 3).

Table 3

Pro-inflammatory biomarkers and protein metabolism indicators

Type	Indices	CG (N=50)	1st SG (N=54)	2nd SG (N=56)	3rd SG (N=27)
		M±SD (%)	M±SD (%)	M±SD (%)	M±SD (%)
Pro-inflammatory biomarkers	Cerulopslamine mg/L	724,3±27,8 (100%)	911,3± 210,71 (125%)*	852,1± 256,11 (117%)	517,7±172,24 (71%)*
	Fibrinogen mg/L	2,4±0,7 (100%)	5,4±1,8* (220%)	4,9±1,4* (200%)	5,9±1,3* (250%)
	CRP mg/L	Non detected	8,4±1,2	7,9±3,9	6,5±1,6
Protein metabolism indicators	Total serum proteins mg/L	76,5±5,45 (100%)	75,1±8,195 (98%)	76,4±8,32 (100%)	74,3±7,92 (97%)
	AST IU/L	17,6±1,5 (100%)	42,5±8,3* (250%)	38,8±7,9* (220%)	45,6±6,8* (270%)
	ALT IU/L	22,5±2,74 (100%)	47,1±2,4* (210%)	39,3±4,2* (170%)	58,4±5,2* (270%)

Note: *the applied statistical test: Mann-Whitney U Test; The percentage was assessed comparing the study groups with the reference value of the control group (100%). IU-international units.*

** – the statistically significant difference with the control group, p<0,05.*

Discussions

Our research was focused on the assessment of the disturbances of the antioxidant defense, associated pro-inflammatory biomarkers, and indices of the protein metabolism in serum of the blood harvested from patients with pulmonary infiltrative tuberculosis. The distribution of the patients in study groups, according to sex and age allowed the comparability of the results. All patients were diagnosed through standard microbiological examinations and chest X-ray investigations. All patients showed positive microbiological results and had available drug susceptibility testing. Standard treatment for the drug-susceptible was

administrated in patients from the 1st group. Second-line anti-TB drugs were used in the treatment of MDR-TB in patients from the 2nd and 3rd SG. The samples of blood were collected before the anti-TB treatment in patients from the 1st and 2nd SG. The collection of blood in patients from the 3rd SG was realized after obtaining the results of the drug resistance during the ongoing treatment. The research results established the mild depletion of the total antioxidant activity of the serum assessed using ABTS and CUPRAC methods, reduced activity of SOD, and the concentration of the total serum proteins in all groups regardless of the drug-susceptibility or resistance. Similar data were obtained in other experimental studies [16, 17]. Concomitantly, the increased OS was marked by the high activity of CAT in all study groups and increased ceruloplasmin level in the 1st and 2nd SG. Discordant results in the assessment of ceruloplasmin could be explained by the increased OS in patients new-cases (1st and 2nd SG), and the deficiencies of the iron and copper metabolism in those who acquired the drug resistance (3rd SG). Arshya B, et al. provided evidence that ceruloplasmin can be considered a biochemical marker in the prognosis of poor evolution in patients with pulmonary TB [14]. The pro-inflammatory biomarkers, such as active phase reactants (C-reactive protein, fibrinogen), confirmed an acute inflammation in all patients, but the level was higher in patients who acquired the drug resistance. The role of the OS and acute phase reactants in the development of diffuse lung diseases was established by Bargagli, et al [18].

The activity of liver transaminases was increased in all patients with superior values obtained in the group who acquired the drug resistance during the treatment [20]. Our study has limitations because changes in AOS levels in the serum of patients with pulmonary tuberculosis cannot be explained solely by the AOC and activity of non-glutathione enzymes. There is a need to expand the research on a higher number of patients and assess other biomarkers marking the efficiency of the AOS.

Conclusions

- This study completes the current information on the possible mechanism of the lung protection against the OS resulting during the infection with *M. tuberculosis* with different types of the drug-resistance and activation of the innate immune response. The depletion of the AOS was confirmed through the similar diminished activity of tAOA of the serum and SOD, regardless the drug resistance. The superior anti-oxidant protection in new cases was demonstrated by the increased activity of CAT and ceruloplasmin.
- The active phase reactants (C-reactive protein, fibrinogen) were increased in all patients, but the level was higher in patients who acquired the drug-resistance, which had low antioxidant protection provided by ceruloplasmin.
- In patients with acquired the drug-resistance the enzymes of the amino acid metabolism were increased, which reflected the liver injury and metabolic disorders.
- The depletion of the AOS, increased acute phase reactants and disturbances in the amino acid metabolism enzymes showed be taken into account for the individualized therapy and improvement of the metabolic disturbances.

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Received – 15.02.2022, accepted for publication – 02.04.2022
Corresponding author: Evelina Lesnic, e-mail: evelina.lesnic@usmf.md
Conflict of interest Statement: The authors reports no conflicts of interest in this work.
Funding Statement: The authors reports no financial support.

Citation: Lesnic E, Gudumac V, Pantea V. The disturbances of the antioxidant defense and protein metabolism biomarkers in the serum of the patients with pulmonary tuberculosis. Arta Medica. 2022;82(1):4-9.