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Impact of serum chitotriosidase activity on tuberculosis treatment response: single center study from Serbia

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Abstract

Background The aim of our study was to investigate serum chitotriosidase level in tuberculosis patients, its relationship with microbiological and clinical parameters, and response to treatment.

Materials and methods This longitudinal panel study included 149 patients with confirmed TB disease. Serum chitotriosidase activity was measured at the beginning and the end of treatment. Factors associated with chitotriosidase activity were explored using univariate and multivariable logistic regression analysis.

Results Out of 149 study participants, 71(47.7%) were female. The mean age was 53.0 (SD = 18.2). Majority of cases were new 118(79.2), predominantly 145 (97.3%) having pulmonary tuberculosis. More than half of the patients were sputum smear positive 91 (61.1%) while culture positive in 146 (98%) of them. According to radiological findings, cavitary lesions were found in 92 (63.4%) patients. Anti TB treatment was associated with significant decrease in serum chitotriosidase level (< 0.001). New TB treatment (OR = 4.41%;95% CI = 1.20–9.89), and cavitary lesions (OR = 3.86;95%CI = 0,59-26.57) were found to be significantly associated with decrease of chitotriosidase activity.

Conclusions The results of our study showed that serum chitotriosidase values are strong biomarkers for starting anti TB treatment and for treatment monitoring, since decrease in serum chitotriosidase level can predict favorable treatment response in patients with tuberculosis. Further studies are needed to explore these, and other factors associated with chitotriosidase activity among tuberculosis patients.

Keywords Tuberculosis, Chitotriosidase, Serum, Biomarker, Decrease, Treatment response

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Introduction

Tuberculosis (TB) presents global public health problem with more than 10.6 million people affected with the TB disease globally in 2022 and 1.3 million deaths [1]. Approximately, one third of the world's population is infected with *Mycobacterium tuberculosis*, out of whom 5–10% will progress to active TB during their lifetime. Prevalence of smear negative TB has been increasing among patients co-infected with human immunodeficiency virus (HIV), patients using biological therapy with anti-tumor necrosis factor agents, (TNF) and other immunosuppressed conditions like cancer chemotherapy or hemodialysis [2]. During the past COVID-19 pandemic, serious lung damage happened due to severe acute respiratory coronavirus 2 (SARS CoV-2) or because of used immunomodulatory therapy like corticosteroids or anti-interleukin 6 agents (IL-6) which both seem to predispose patients for different superinfections including tuberculosis [3]. TB treatment monitoring using serum biomarkers by non-sputum-based assays could play an important role in future TB control [4]. Chitotriosidase (CHT) presents glycosylated hydrolytic enzyme that catalyze the degradation of chitin in N-acetylglucosamine in order to supply carbon and nitrogen as an important energy source for many microorganisms such are fungi and bacteria [5, 6]. Although humans do not have chitin itself, they express chitinase and chitinase-like proteins both elevated in numerous diseases like lysosomal storage disease (Gaucher, Niemann-Pick), infectious diseases (tuberculosis, systemic fungal infection, malaria, filariasis, brucellosis, leprosy, Crimean-Congo hemorrhagic fever), respiratory diseases (asthma, chronic obstructive pulmonary disease, interstitial lung disease), cardiovascular disease (atherosclerosis, coronary artery disease), neurological diseases (amyotrophic lateral sclerosis, Alzheimer's disease, multiple sclerosis), endocrinological disease (diabetes) gynecological and obstetrical diseases (polycystic ovarian syndrome, endometriosis, preeclampsia) and miscellaneous (sarcoidosis, acute appendicitis, juvenile idiopathic arthritis, prostate cancer) [7–9]. Serum or plasma chitotriosidase value could be used for screening, therapeutic monitoring or marker of severity and prognosis in many diagnoses including tuberculosis. Thus, chitotriosidase activity might be helpful while waiting for conventional Lowenstein-Jensen culture results for 6 or 8 weeks. The aim of our study is to investigate serum CHT level in tuberculosis patients, its relationship with microbiological and clinical parameters and response to treatment.

Materials and methods

Study Design

We performed a longitudinal panel frstudy from September 2018 to September 2019 at the Clinic for Pulmonology, University Clinical Center of Serbia, Belgrade. The first cross-section of the study participants was conducted at the time of TB diagnosis (before treatment initiation) while the second was conducted six months later, at the termination of the TB treatment.

TB diagnosis and measurements

TB diagnosis was based on clinical and radiological findings and was confirmed bacteriologically and/or histologically. Three sputum samples were collected from all the patients who were able to expectorate during 3 consecutive days. Sputum smears for acid-fast bacilli (AFB) were prepared and stained according to the Ziehl-Nielsen (ZN) method. *Mycobacterium tuberculosis* cultures were carried on liquid media (BACTEC TB 460 system, Becton, Dickinson, USA) or solid Lowenstein-Jensen (LJ) media. In cases of negative or insufficient sputum smears, bronchoalveolar lavage or biopsy were taken for further analysis.

On the basis of the chest x ray findings, patients were classified as having: (1) Cavitary lesions; (2) Spotted shadows; (3) TB sequelae; and (4) pleural effusion.

Sample and Procedure

During the study period, we enrolled all patients of any age, diagnosed with active TB and treated at the Clinic for Pulmonology, University Clinical Center of Serbia, who agreed to participate in the study.

Individuals with mental inability to understand the goals and study procedure as well as the one who refused to participate were not included in the study.

Measurements

Data were collected from the patients' medical records related to: socio-demographic characteristics (age, sex, employment), TB characteristics including: anatomical site of the disease, history of previous treatment, laboratory confirmation, chest x-ray findings, concomitant diseases (cardiac diseases, COPD, diabetes, systemic diseases on immunosuppressive therapy, malignant diseases, HIV status) and treatment outcomes.

Measurement of chitotriosidase activity

Blood samples (5 ml) were obtained by venipuncture in an EDTA containing tube. Plasma and packed cells were separated by centrifugation at 1500/10 min and stored at -80 °C until further procedure. 5µL of plasma was incubated with 100 µL of 22 µmol/L 4-methylumbelliferryl-β-D-N-N′-N′- triacetyl chitotriosidase (Sigma M-5369, Sigma –Aldrich Chemie GmBH, Germany) in Mcllvain′s phosphate-citrate buffer. This reaction was finished by the addition of 120 µL 0.5 mol/L Na_2CO_3-$NaHCO_3$. Fluorescence was measured by fluorometer (BIO-TEK Synergy HT; Biotek Instruments, USA) by excitation and

emission waves with approximately 360 nm and 450 nm of lengths respectively. CHT activity was expressed as nanomoles of substrate hydrolyzed per milliliter per hour (nmol/ml/h) [10].

Statistical analysis

Results were presented as frequency (percent), median (range) and mean±standard deviation (SD). The difference in chitotriosidase levels at the start and end of the treatment was calculated using non-parametric test for two dependent samples (Wilcoxon test), due to the absence of normality in the distribution.

Logistic regression was used as the method for analyzing binary outcomes and potential predictors. Independent variables that were significant ($p<0.1$) in univariate logistic regression (ULRA) models were used as the independent variables in the multivariable logistic regression (MLRA) model. All p-values less than 0.05 were considered significant. Statistical data analysis was performed using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA).

Results

Out of 149 study participants, 71 (47.7%) were female. The mean age for all participants was 53,0 (SD=18,2). Comorbidities were noticed in all patients, among non-malignant, cardiac were most frequently found in 40 (28.8%) patients including arterial hypertension and ischemic heart disease. Most cases were diagnosed with TB for the first time 118 (79.2%), predominantly 145 (97.3%) with pulmonary TB. The most common laboratory confirmation method was solid culture in 146 (98.0%) patients. According to chest X-ray findings cavitary lesions were most frequently noticed in 92 (63.4%) patients. Treatment outcome was favorable in almost all the patients 148 (99.3%). Other characteristics of the study participants are described in Table 1.

Analysis of chitotriosidase activity

The initial value of CHT at the beginning of TB treatment was 211.63 (range 5.60-1722.70 or SD=266.56), while the value at the end of TB treatment was 86.76 (range 11,21-567.92, or SD=101.34). During the TB treatment, there was a significant decrease in CHT values (z=10.036; $p<0.001$) .

Serum CHT activity significantly correlated with LDH ($p<0.05$) and hemoglobin ($p<0{\cdot}05$), while no correlations were identified among other parameters (Table 2).

In univariate logistic regression analysis, factors significantly associated with decrease of CHT activity were age 18–44 (OR=0.40; 95% CI=0.16–0.93), employment (OR=0.36; 95% CI=0.15–0.88), diabetes (OR=0.18; 95% CI=0.11–0.30), new TB treatment (OR=2.86; 95% CI=1.09–7.49), and cavity lesions (OR=4.93; 95% CI=1.05–22.95).

In multivariate logistic regression analysis, two variables were found to be significantly independent factors associated with decrease of CHT activity such as: new TB treatment (OR=4.41; 95% CI=1.20–9.89), and cavity lesions (OR=3 ,86; 95% CI=0.59–26.57) - Table 3.

Discussion

Chitotriosidase plays an important role in the innate and acquired immune response and its presence has been reported in many respiratory diseases like interstitial lung diseases, asthma, chronic obstructive lung disease, bronchopulmonary dysplasia, cystic fibrosis and pulmonary infections, including tuberculosis [11, 12]. Pulmonary infections present an emerging problem, with approximately 450 million people affected worldwide, with more than 4 million deaths every year, therefore need for additional tools in solving this problem seems to be reasonable [13]. Moreover, world population is aging, which is a growing risk factor for immunosuppression that can cause tuberculosis [14]. It has been shown that CHT activity is increased and correlates with the disease severity in pulmonary tuberculosis. It is known that chitotriosidase is released in serum from pulmonary granuloma. Activated *M. tuberculosis* and macrophages play an important role in granuloma formation. Macrophage activation brings to interferon delta and tumor necrosis factor alpha (TNFα) production, which both cause increased serum levels of chitotriosidase. Chitotriosidase serum level tends to decline accompanying with inflammation during standard six months treatment regimen as was shown in our results [15]. Among all respiratory diseases, CHT activity was first described in sarcoidosis [16]. In active phase of sarcoidosis, increased levels of CHT were noticed and correlate with the radiological stage of disease. Chitotriosidase level in sarcoidosis is nearly ten times higher than in healthy controls and six times greater than in tuberculosis [17], and was low at the time of remission while enhanced in time of chest X-ray worsening [18, 19]. According to the smear findings, previous papers reported that in patients with active tuberculosis and a negative sputum smear for acid-fast bacillus, plasma chitotriosidase activity seems to be a strong marker for diagnosis of active disease which can be used while awaiting culture results [20]. Our results emphasizes that positive sputum smear for AFB were found in more than a half of our patients (91; 61.1%) which corresponds with positive solid cultures in 146 (98%). Chitotriosidase activity levels of both smear positive and smear negative patients decreased after 6 months treatment and approached normal levels [21] as was shown in our results. Moreover, significantly decrease of CHT activity was shown in treatment of new

Table 1 Characteristics of the study participants ($n = 149$)

Characteristics	*N*	%
Sex		
Male	78	52.3
Female	71	47.7
Age category		
18–44	51	34.2
45–64	50	33.6
65+	48	32.2
Employment		
Employed	56	37.6
Retired	51	34.2
Student/Unemployed	42	28.2
Concomitant diseases		
Cardiac *	40	26.8
COPD **	19	12.8
Diabetes ***	23	15.4
Systemic diseases on immunosuppressive therapy	6	4.0
Malignant ****	13	8.7
HIV positive status	0	0.0
History of previous TB treatment		
New cases	118	79.2
Previously treated cases	29	19.5
Anatomical site of the disease		
PTB*****	145	97.3
EPTB******	4	2.7
TB laboratory confirmation		
Sputum smear	91	61.1
Solid culture	146	98.0
Liquid culture	102	68.5
Radiology findings		
Cavitary lesions	92	63.4
Spotted shadows	28	19.3
TB sequelae	9	6.2
Pleural effusion	16	11.0
Treatment outcomes		
Cured and treatment completed	148	99.3
Died	1	0.7

*Arterial hypertension, ischemic heart disease; ** chronic obstructive pulmonary disease; *** all types of diabetes; **** all localizations, ***** pulmonary TB, ******* extra pulmonary TB.

Table 2 Characteristics of the biochemical parameters of the study participants

Variable	Minimum	Maximum	Mean	Std. Deviation	Spearman's correlation coefficients (rs)	*P* value
ES (mm/h)	2	132	59.8	2.7	-0.02	0.857
CRP (mg/L)	1	251	54.3	51.4	0.01	0.893
WBC (10^9/L)	3,1	34,7	11.4	4.8	0.01	0.919
Hgb g/L	79	167	116.7	13.8	-0.18	0.026
AST (U/L)	1	176	38.2	21.4	0.10	0.251
ALT (U/L)	11	319	41.5	32.7	0.05	0.568
LDH (U/L)	123	795	280.0	111.2	0.18	0.037

ES - erythrocyte sedimentation; CRP - C reactive protein; WBC - white blood cells; Hgb – hemoglobin; AST - aspartate aminotransferase; ALT - alanine aminotransferase; LDH - lactate dehydrogenase

Table 3 Univariate and multivariable analysis of the decrease in chitotriosidase values at the end of TB treatment compared to treatment initiation ($n = 149$)

Characteristics	Univariate		Multivariate	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Sex (ref males)	0.86 (0.44–1.68)	0.665	1.29 (0.56–2.98)	0.543
Age category	1.56 (1.03–2.38)			
18–44 (ref yes)	0.40 (0.16–0.93)	0.035	Ref	
45–64	0.93 (0.42–2.07)	0.931	6.36 (0.78–52.79)	0.087
65 +	0.78 (0.48–1.06)	0.388	2.01 (0.19–20.62)	0.555
Employment	1.65 (1.08–2.53)	0.021		
Employed (ref yes)	0.36 (0.15–0.88)	0.025	Ref	
Retired	1.18 (0.52–2.70)	0.685	0.25 (0.09–0.74)	0.218
Student/unemployed	0.75 (0.35–0.99)	0.356	2.35 (0.28–19.73)	0.430
Concomitant diseases				
Cardiac *	1.66 (0.79–3.48)	0.180		
COPD **	0.78 (0.28–2.21)	0.651		
Diabetes *** (ref yes)	0.18 (0.11–0.30)	<0.001	0.60 (0.19–1.87)	0.380
Systemic diseases on immunosuppressive therapy	0.87 (0.15–4.94)	0.880		
Malignant ****	2.21 (0.70–6.95)	0.175		
History of previous TB treatment				
New case (ref yes)	2.86 (1.09–7.49)	0.033	4.41 (1.20–9.89)	0.049
Previously treated (ref no)	0.31 (0.11–0.94)	0.023	0.95 (0.61–1.18)	0.309
Anatomical site of the disease				
PTB*****	0.11 (0.02–0.36)	0.487		
EPTB******	0.17 (0.01–0.41)	0.511		
TB laboratory confirmation				
Sputum smear	1.61 (0.80–3.26)	0.184		
Solid culture	0.27 (0.02–3.06)	0.292		
Liquid culture	1.52 (0.72–3.19)	0.267		
Radiology findings			ref	
Cavity lesions (ref yes)	4.93 (1.05–22.95)	0.042	3.86(0.59–26.57)	0.069
Spotted shadows (ref yes)	4.53 (0.86–23.93)	0.075	4.55 (0.58–35.79)	0.081
TB sequelae	0.87 (0.07–11.23)	0.918		
Pleural effusion	0.14 (0.01–0.75),	0.855		
Treatment outcomes	0.55 (0.44–0.68)	1.000-		

*Arterial hypertension, ischemic heart disease; ** chronic obstructive pulmonary disease; *** all types of diabetes; **** all localizations, ***** pulmonary TB, ******extra-pulmonary TB

TB cases comparing with previously treated patients in line with findings in other published papers [20, 21]. CHT is expressed in various cells including neutrophils, lung macrophages, tissue macrophages and epithelial cells in the lungs and intestine. Neutrophils and macrophages release CHT after toll-like receptor (TLR) stimulation, while macrophages also release CHT after stimulation with interferon (IFNγ), (TNFα), granulocyte macrophage colony-stimulating factor (GM-CSF) [22].

Our results showed that CHT activity is associated with extension of radiographic patterns like cavitary lesions. Majority of our patients manifested bilateral cavitary lesions (85%) conclusive for extensive tuberculosis, as shown before [21]. Although pleural effusion was found in 16 (11%) of our patients with elevated serum CHT level, pleural fluid CHT was not analyzed, but it is investigated in TB and non-TB pleural effusions [23]. Authors demonstrated that pleural fluid CHT level was significantly higher in tuberculosis than in non-TB pleural effusion. Positive correlation was found between pleural fluid CHT and adenosine deaminase (ADA), which was used as diagnostic marker for TB firstly. In other mycobacterial diseases like leprosy significantly higher level of CHT were also noticed [24]. On the contrary to chronic infections like pulmonary tuberculosis, in acute pulmonary infections such as those caused with *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, decrease level of CHT were observed because of neutrophil elastase presence and cleavage of CHT [25]. Recently published papers confirmed that lower level of chitinase protein at the beginning of TB treatment presents biomarker of unfavorable treatment outcome in tuberculosis connected with treatment failure, disease recurrence, adverse events or death which was not shown in our study group [26].

Our study provided important baseline information for clinical management and future improvements of TB prevention and control. However, this study has limitations. It included a limited number of participants due to the funding constraints. Thus, a larger sample size is needed to further explore these, and other factors associated with chitotriosidase activity. In addition, we were not able to explore factors associated with treatment outcomes since outcomes could not been properly dichotomized. Despite its limitations, to the best of our knowledge, the present study is the first investigation of CHT activity in tuberculosis patients in the Serbia and among a few studies worldwide.

Conclusion

The results of our study showed that serum chitotriosidase values are strong biomarkers for starting anti TB treatment and for treatment monitoring, since decrease in serum CHT level can predict favorable outcome in patients with pulmonary tuberculosis. Further studies are needed to explore these, and other factors associated with chitotriosidase activity among tuberculosis patients.

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Author contributions
A: Conceptualization: Tatjana Adzic-Vukicevic, Maja StosicB: Analysis, or interpretation of data for the work: Tatjana Adzic-Vukicevic, Maja StosicC. Writing – original draft: Tatjana Adzic-Vukicevic, Maja StosicD. Writing – review & editing: Zorica Sumarac, Aleksandra Cvetkovic, Ognjen Markovic, Dragana Maric.

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Data availability
The data is not publicly accessible, but it can be obtained from the corresponding author upon a reasonable request.

Declarations

Ethics approval and consent to participate
This study protocol was reviewed and approved by Ethics Committee of the University Clinical Center of Serbia, approval number 92/2018. Personal identifiers of study participants were coded, and patient records were anonymized and de-identified prior to analysis to maintain confidentiality. All participants signed a voluntary informed consent form, providing demographic and clinical data and participation consent.

Consent for publication
Not applicable

Competing interests
The authors declare no competing interests.

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