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THE ROLE OF DIABETES MELLITUS IN MODIFYING THE INLAMATORY PROFILE IN PACIENTS WITH PULMONARY TUBERCULOSIS

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The coexistence of diabetes mellitus (DM) and tuberculosis (TB) represents a significant global burden. DM recognized as a major risk factor for TB. This study comprehensively reviews the immunological aspects of TB/DM comorbidity, reflecting the impact of DM on TB pathogenesis and immune responses. It reveals that high blood glucose levels in TB patients contribute to a reduction in innate immune cells, compromised phagocytic function, and delayed antigen presentation. These factors ultimately impair the clearance of Mycobacterium tuberculosis (MTB) and delay adaptive immune responses.

***Keywords:** BAAR, cytokines, C reactive protein, diabetes mellitus, pulmonary tuberculosis, Xpert MBT/Rif.*

INTRODUCTION

According to the 2025 Global Tuberculosis Report of the World Health Organization, 8.3 million people were newly diagnosed with tuberculosis in 2024. Of these, 54% were initially tested with a rapid diagnostic test, showing an increase compared to 48% in 2023. Among the risk factors contributing to the persistence of the pulmonary tuberculosis epidemic are malnutrition, HIV infection, harmful alcohol consumption, smoking, and diabetes mellitus [1].

The bidirectional relationship between tuberculosis (TB) and diabetes mellitus (DM) is well documented, with each condition negatively influencing the course of the other. Recent studies have shown that the overall risk of TB in patients with DM is three times higher than in the population without TB pathology [2,3], while the prevalence of diabetes mellitus among patients with tuberculosis ranges from 1.9% to 35% [4]. Similarly, TB can induce "stress hyperglycemia," which may complicate the management of diabetes mellitus [5].

TB/DM is associated with an increased number of positive sputum smears at the time of diagnosis, the presence of fever, cough, hemoptysis, and false-negative results of the tuberculin skin test [6]. There is also some evidence that diabetes mellitus prolongs smear and culture positivity at the end of the intensive phase of TB treatment [7].

Upon inhalation, the bacilli interact with bronchial epithelial cells, leading to an interaction between *Mycobacterium tuberculosis* (MTB) and the host's innate immune system [8]. Alveolar macrophages, activated by interferon-gamma, are likely the first antigen-presenting cells to encounter the pathogen, along with other cells such as dendritic cells. Following the encounter between MTB and macrophages, phagocytosis occurs, resulting in the engulfment of bacilli into phagosomes, which subsequently fuse with lysosomes to form phagolysosomes [9]. The phagolysosome plays a crucial role in destroying the bacilli through acidification and through the action of reactive oxygen and nitrogen species [9].

Infected myeloid dendritic cells migrate to the lymph nodes and, with the assistance of neutrophils, differentiate into mature dendritic cells. Mature dendritic cells activate lymphocytes through antigen presentation and induce adaptive immune responses [11]. T cells then migrate to the lungs, targeting MTB-infected macrophages through the release of interferon-gamma (IFN-γ) and cytotoxic T cells, thereby stimulating an effective bactericidal response [11].

Other factors may contribute to the increased risk of developing TB among patients with diabetes mellitus, including: (1) hyperglycemia induces M2 macrophage polarization instead of the classical M1 polarization [8,9]. M2 macrophages function in regulating host inflammation and generally support MTB growth by expressing high levels of anti-inflammatory cytokines, such as IL-4 and IL-10.

This also weakens the phagocytic capacity of macrophages, leading to immune evasion. (2) Studies have shown that hyperglycemia increases the number of neutrophils; however, neutrophil migration to infected sites is reduced due to glycated collagen resulting from the advanced glycation end-products of neutrophil receptors [10].

Diabetes mellitus is associated with reduced levels of cytokines essential for controlling MTB growth, such as IFN-γ and TNF-β [11,12]. Macrophages in diabetic individuals exhibit decreased secretion of pro-inflammatory cytokines, including IL-1β and TNF-β. The coexistence of diabetes mellitus and TB is associated with systemically low levels of pro-inflammatory cytokines, including IL-1β, IL-6, and IL-18, along with anti-inflammatory cytokines such as IL-10 [13,14].

MATERIALS AND METHODS

The prospective observational study was conducted at the Chiril Draganiuc Institute of Pneumology during the period 2019–2024 and included 118 patients. The study group was divided into two subgroups: group L_1, consisting of 59 patients with pulmonary tuberculosis and diabetes mellitus, and group L_2, comprising 59 patients with pulmonary tuberculosis without diabetes mellitus.

All participants were assessed both before and after the in-hospital treatment. Diagnosis was based on acid-fast bacilli (AFB) smear microscopy, the molecular-genetic Xpert MTB/RIF method, C-reactive protein levels, and

pro-inflammatory cytokine levels. All patients were treated according to the national clinical protocol and were evaluated at one-month intervals during hospitalization.

The study was approved by decision no. 31 of 18.05.2019, issued by the Research Ethics Committee of Nicolae Testemițanu State University of Medicine and Pharmacy. The representative sample size was calculated using Epi-Info version 7.2.2.6, in the "Stat Calc – Sample Size and Power" module. The mean, median, and standard deviation (SD) were determined. To compare the two groups, the Student's t-test was applied, and the statistical significance of differences was assessed using the p -value, with $p < 0.05$ considered significant.

Table 1. Changes in serum levels (M±SD) of inflammatory markers in patients with TB and DM over a one-month treatment period

Marker	Pacients TB/DM study group (n=59)		± (%)	p
	Before treamtent	After treatment		
Il-1β, pg/ml Median	11,5±4,07 11,2	9,7±3,85 9,1	-15,6%	<0.000
IL-6, pg/ml Median	16,1±21,8 10,9	11,2±11,6 14,7	-30,4%	0,12864
IL-8, pg/ml Median	22,5±44 13,1	12,9±10 10	-42,6%	0,09666
TNF-β, pg/ml Median	39,5±101 10,5	18,6±32,7 9.5	-52,9%	0,1413
PCR, mg/L Median	32,1±43 12	23,3±51 12	-47,8%	0,1172

Note: *p – significance value comparing after treatment vs. before treatment; ± (%) – relative changes of the marker during the treatment period.*

Table 2. Changes in serum levels (M±SD) of inflammatory markers in patients with TB over a one-month treatment perio

Marker	Pacients TB control gpoup (n=59)		± (%)	p
	Până la tratament	După tratament		
Il-1β, pg/ml Median	12,8±4,29 12,5	9,4±4,11 9,5	-26,5%	<0.000
IL-6, pg/ml Median	21,9±16,49 15,4	21,4±20,35 14,7	-2,28%	0,852
IL-8, pg/ml Median	21,5±17,29 14,9	22,7±20,48 15,3	+5,58%	0,587
TNF-β, pg/ml Median	59±101 14,7	50,6±93,5 14,7	-14,24%	0,637
PCR, mg/L Median	27,4±45,9 12	14,3±13,9 14,7	-47,8%	0,006

Note: *p – significance value comparing after treatment vs. before treatment; ± (%) – relative changes of the marker during the treatment period.*

RESULTS

Based on the analyzed demographic characteristics, a comparable distribution of male and female participants was observed between patients with pulmonary tuberculosis associated with diabetes mellitus, assessed before and after treatment, and those with pulmonary tuberculosis without diabetes mellitus. In both groups, a predominance of male participants was noted, with 87 males (73.7%) compared to 31 females (26.3%).

To conclusively detect the impact of diabetes mellitus on the course of TB and, in particular, on the effectiveness of applied therapy, it is informative to analyze markers showing significant discrepancies between groups (DM vs. non-DM) both at before and after treatment.

To highlight the specific features of the inflammatory response in patients with TB associated with diabetes mellitus, circulating levels of the same markers (IL-1β, IL-6, IL -8, TNF-β, and C-reactive protein) were measured in group 1 (TB/DM) at the beginning and at the end of anti-TB treatment (Table 1).

It was associated with a 30.4% decrease in IL-6. These cytokines, recognized as important trigger factors for stimulating CRP synthesis, also decreased in $group_1$. Notably, the reduction in serum CRP levels was similar in both groups: 47.8%. In contrast to the positive dynamics of IL-8 in $group_1$, this cytokine, which also has chemokine properties, decreased by 42.6% in the group of patients with tuberculosis and diabetes mellitus. Additionally, it is worth noting that TNF-β levels in TB/DM patients declined more substantially compared to the marker in $group_1$ vs. $group_2$: 52.9% vs. 14.28%.

Thus, the association of diabetes mellitus with pulmonary tuberculosis was marked by a more pronounced reduction in IL-6 and TNF-β compared to $group_1$ during anti-TB treatment, while also leading to a significant decrease in IL-8.

Regarding the algorithm for evaluating the inflammatory response, serum levels of four key pro-inflammatory cytokines—IL-1β, IL-6, IL-8, TNF-β—and C-reactive protein (CRP) were determined both before and after the completion of treatment (Table 2).

Serum IL-1β levels decreased significantly by 26.5%. IL-1β is a trigger cytokine of the inflammatory response, which explains the reduction in other inflammatory markers. Circulating levels of IL-6 and TNF-β decreased non-significantly by 2.28% and 14.24%, respectively. C-reactive protein nearly halved, showing a significant decline of 47.8%. However, IL-8 was observed to increase slightly but non-significantly by 5.58%.

Thus, the inflammatory response remains pronounced in TB patients during treatment, maintaining IL-8 expression which also functions as a neutrophil chemokine while the activity of the genetically programmed inflammatory response triggered by pathogen-derived molecular patterns is attenuated, as reflected by the substantial decrease in IL-1β.

Table 3. Median values of AFB smear and Xpert MTB/RIF indices before and after a one-month treatment period

Index	Before treatment				After treatment			
	Grup$_1$ DZ vs group$_2$ non DZ				Grup$_1$ DZ vs group$_2$ non DZ			
	DZ n (%)	-DZ N (%)	DZ vs -DZ	p	DZ n (%)	-DZ n (%)	DZ vs -DZ	P
AFB pozitiv	37 (62,7%)	27 (45,8%)	+37%	>0,05	16 (27,1%)	5 (8,5%)	+220%	0,014
Xpert MTB/Rif negativ	10 (16,9%)	23 (39%)	-56,5%	0,013	26 (40,7%)	37 (62,7%)	-29,8%	0,026

In our study, we also evaluated the dynamics of laboratory tests, including AFB smear and Xpert MTB/RIF. To conclusively assess the impact of diabetes mellitus on the course of TB and, in particular, on the effectiveness of the applied therapy, it is informative to analyze markers showing significant discrepancies between groups (DM vs. non-DM) both at baseline and after treatment.

Beneficial changes in AFB smear and Xpert MTB/RIF indices were observed in both groups, but their relative restoration was superior in the group without diabetes mellitus (Table 3).

The proportion of AFB-positive smears decreased by 56.8% after treatment in the DM group, while the corresponding reduction in the non-DM group was 81.2%. Thus, the initially non-significant discrepancy became significant after treatment ($p < 0.014$), and the relative incremental gap between DM and non-DM increased from 37% to 220%.

The proportion of negative Xpert MTB/RIF results increased during anti-TB treatment in both groups, indicating the effectiveness of the therapy in the context of this test's ability to detect or rule out the presence of mycobacteria in biological samples. The reduction in AFB-positive smears correlates with the decline in positive Xpert MTB/RIF results. However, although the increase in negative Xpert MTB/RIF results after treatment was higher in the DM group (160% vs. 61%), the final parameter remained significantly higher (+42.3%) in the group without diabetes mellitus.

DISCUSSION

In our study, the impact of diabetes mellitus (DM) on the effectiveness of specific TB therapy was assessed by evaluating AFB smear and Xpert MTB/RIF values before and after treatment. It is noteworthy that in group$_2$, the number of patients with negative AFB smears decreased 2.3-fold during treatment (in group$_1$, the reduction reached 5.4-fold), with the relative decline estimated from 62.7% to 27.1%. Thus, the number of AFB-positive patients among those with TB and DM remained statistically higher compared to group$_1$. At the same time, the reduction in AFB-positive cases was associated with an increase in negative Xpert MTB/RIF results from 16.9% to 40.7%, with the final value still lower than that in group$_1$ (40.7% vs. 62.7%).

Regarding the inflammatory status, it is worth noting the higher serum CRP levels in group$_2$ (TB+DM) compared to group$_1$, both at baseline (by 17.1%) and at the end of treatment (by 62.9%). The degree of elevation of this general inflammation marker reflects the severity of the infectious agent's manifestation and serves as a negative predictor of TB progression [15,16]. In group2, the increased CRP synthesis, determined by the functional activity of *Mycobacterium tuberculosis*, is compounded by the pro-inflammatory effect of type II diabetes mellitus, which also involves extrapulmonary cells, including vascular endothelial cells.

In this context, it is important to highlight the opinion of S. Masafumi et al. (2022), who stated that elevated CRP levels at admission—i.e., before the start of anti-TB treatment—pose a hazard for TB-related complications [17].

To reference to the dynamics of other inflammatory markers in the groups, it is notable that TNF-β and IL-6 decreased more markedly during treatment in group$_2$, along with a 42.6% reduction in IL-8, whereas this marker increased by 5.58% in group$_1$.

In TB, TNF-β is considered not only a marker of inflammation but also an indicator of phagocytic activation, as it is derived from Th1 cells, which also release IFN-γ, a potent activator of macrophages critically involved in the eradication of the infectious agent. The predictive role of TNF-β and IFN-γ has also been emphasized by other authors [18,19].

Furthermore, according to A. Arias et al. (2024), the severity of tuberculosis in individuals with TNF-β and IFN-γ deficiency is significantly increased, with a poor long-term therapeutic prognosis [19]. The decline of TNF-β in patients with diabetes mellitus was 52.9%, well above the 14.24% reduction observed in patients from group1. Thus, the 33% decrease at baseline became more substantial by the end of treatment, reaching 63.2%.

A similar pattern was observed for IL-6: lower baseline levels in group$_2$ and a more considerable reduction in patients with diabetes mellitus (30.4% vs. 2.28%). The pathophysiological significance of IL-6 in TB progression is considered similar to that of TNF-β according to contemporary understanding. Reduced IL-6 levels are associated with increased aggressiveness of *Mycobacterium tuberculosis* and a poorer prognosis, including a higher risk of developing drug resistance in TB patients. F. Hamilton et al. (2025) demonstrated that IL-6 inhibition through anti-cytokine therapy (e.g., tocilizumab) can attenuate the inflammatory response and, as a consequence, exacerbate TB progression [20].

CONCLUSIONS

In conclusion, the association of type II diabetes mellitus with pulmonary tuberculosis is characterized by a pronounced attenuation of the immune-inflammatory status during anti-tuberculosis treatment. This is supported by more marked decreases in serum levels of TNF-β and IL-6 compared to patients without diabetes mellitus, as well as a 42.6% reduction in IL-8, in contrast to a 5.58% increase of this marker in the reference group. These changes reflect diminished macrophage activity and reduced phagocytic capacity against the infectious agent.

Therapeutic efficacy, assessed in both groups during anti-TB treatment through the analysis of AFB smear and Xpert MTB/RIF indices, highlights the unfavorable influence of diabetes mellitus comorbidity on the course of tuberculosis. The proportion of AFB-positive patients was higher in the DM group both at hospital admission and at the end of therapy, likely due to delayed bacillary clearance resulting from an attenuated inflammatory response. In parallel, the rate of negative Xpert MTB/RIF results was lower in patients with diabetes mellitus, both at treatment initiation and at its completion.

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