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ORIGINAL PAPER

CYTOKINE-MEDIATED INFLAMATORY RESPONSE IN PATIENTS WITH PULMONARY TUBERCULOSIS AND DIABETES MELLITUS

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Abstract

Introduction. The coexistence of pulmonary tuberculosis (TB) and diabetes mellitus (DM) is associated with altered immune responses and poorer treatment outcomes.

The objective of the study was to evaluate the changes in inflammatory cytokines levels and bacteriological indicators in patients with pulmonary TB and type 2 DM during anti-tuberculosis treatment.

Material and methods. A prospective observational study included 118 patients divided into two groups: TB/DM and TB without DM. Serum levels of interleukin (IL)-1β, IL-6, IL-8, and tumour necrosis factor (TNF)-β were measured using enzyme-linked immunosorbent assay (ELISA) before and after treatment. Bacteriological monitoring was performed using acid-fast bacilli (AFB) smear microscopy and molecular method Xpert Mycobacterium tuberculosis/Rifampicin (Xpert MTB/RIF) assay.

Results. Patients with TB/DM demonstrated greater reductions in TNF-β (52.9%) and IL-6 (30.4%) compared with patients without DM (14.2% and 2.28%, respectively). IL-8 decreased by 42.6% in the TB/DM group, but increased by 5.58% in the control group.

Résumé

Réponse inflammatoire à médiation des cytokines chez les patients atteints de tuberculose pulmonaire et de diabète sucré

Introduction. La coexistence de la tuberculose pulmonaire (TB) et du diabète sucré (DS) est associée à des altérations de la réponse immunitaire et à des résultats thérapeutiques moins favorables.

L'objectif de l'étude a été d'évaluer les modifications des taux de cytokines inflammatoires et des indicateurs bactériologiques chez les patients atteints de tuberculose pulmonaire associée au diabète sucré de type 2 au cours du traitement antituberculeux.

Matériels et méthodes. Cette étude observationnelle prospective a inclus 118 patients répartis en deux groupes: patients atteints de TB associée au DS (TB/DS) et patients atteints de TB sans DS. Les concentrations sériques d'IL-1β, IL-6, IL-8 et de TNF-β ont été déterminées per la méthode ELISA avant et après le traitement. Le suivi bactériologique a été réalisé par microscopie des bacilles acido-alcoolo-résistants (BAAR) et par le test Xpert MTB/RIF.

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Positive AFB smear results remained significantly more frequent in the TB/DM group after treatment.
Conclusions. Diabetes mellitus significantly modifies the inflammatory response and may negatively affect treatment outcomes in pulmonary tuberculosis.

Keywords: pulmonary tuberculosis, diabetes mellitus, cytokines, TNF-β, Xpert MTB/RIF.

List of abbreviations:
TB – tuberculosis
DM – diabetes mellitus
AFB – acid-fast bacilli
IL – interleukin
TNF – tumour necrosis factor
ELISA – enzyme-linked immunosorbent assay
SD – standard deviation
CI – confidence interval
Xpert MTB/RIF – Xpert Mycobacterium tuberculosis/Rifampicin assay

Résultats. Les patients atteints de TB/DS ont présenté des diminutions plus marquées du TNF-β (52,9%) et de l'IL-6 (30,4%) que les patients sans diabète (14,2% et 2,28%, respectivement). Le taux d'IL-8 a diminué de 42,6% dans le groupe TB/DS, alors qu'il a augmenté de 5,58% dans le groupe témoin. Après le traitement, les résultats positifs de la microscopie BAAR sont demeurés significativement plus fréquents chez les patients atteints de TB/DS.
Conclusions. Le diabète sucré modifie significativement la réponse inflammatoire et peut affecter négativement les résultats du traitement de la TB.

Mots-clés: tuberculose pulmonaire, diabète sucré, cytokines, TNF-β, Xpert MTB/RIF.

Introduction

The global burden of pulmonary tuberculosis (TB) and diabetes mellitus (DM) is substantial, disproportionately affecting vulnerable populations, including individuals living in poverty, those who are malnourished, and the elderly. Despite sustained efforts in prevention, detection, and treatment, TB remains a major global health challenge[1]. The bidirectional association between pulmonary TB and DM is well established, with each condition negatively influencing the clinical course of the other. Studies have shown that the overall risk of TB in patients with DM is approximately three times higher than in the non-diabetic population[2,3], while the prevalence of DM among patients with TB ranges from 1.9% to 35%[4].

DM is associated with reduced levels of key cytokines essential for controlling TB growth, such as interleukin (IL)-1β and tumour necrosis factor (TNF)-β[5,6]. Macrophages from diabetic individuals exhibit diminished secretion of inflammatory cytokines, including IL-1β and TNF-β. The coexistence of DM and TB is linked to elevated systemic levels of pro-inflammatory cytokines, including IL-1β, as well as anti-inflammatory cytokines, such as IL-6 and IL-8. Prolonged exposure to high glucose levels sensitizes macrophage responses to cytokine stimuli while simultaneously reducing their phagocytic activity, potentially due to alterations in metabolic pathways[7]. Impaired immune responses and reduced intracellular bacterial killing in patients with DM may increase bacterial burden, sustain chronic inflammation, and facilitate bacterial dissemination and severe forms of TB. These findings highlight the importance of understanding the immunological and biochemical mechanisms underlying TB susceptibility in diabetic patients in order to develop rational strategies aimed at reducing the dual burden of these diseases.

The objective of the study was to evaluate the dynamics of pro-inflammatory and anti-inflammatory cytokines (IL-1β, IL-6, IL-8, and TNF-β) in patients with pulmonary TB associated with type 2 DM and to assess their relationship with bacteriological treatment outcomes.

Material and methods

The prospective observational study was conducted between 2019 and 2024 at the "Chiril Draganiuc" Institute of Pneumology in Chisinau, Republic of Moldova, and was approved by decision no. 31 dated 18th of May 2019, issued by the Research Ethics Committee of the "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau.

A total of 118 patients were included in the study, comprising newly diagnosed cases of pulmonary TB with DM, assessed before and after hospital treatment. The participants received standardized anti-TB treatment, in accordance with the National Clinical Protocol for Tuberculosis Management[8]. The study population included 31 women (26.3%) and 87 men (73.7%). Participants were divided into two groups: group L_1 – patients with TB/DM evaluated before and after treatment, and group L_2 – patients with pulmonary TB without DM assessed before

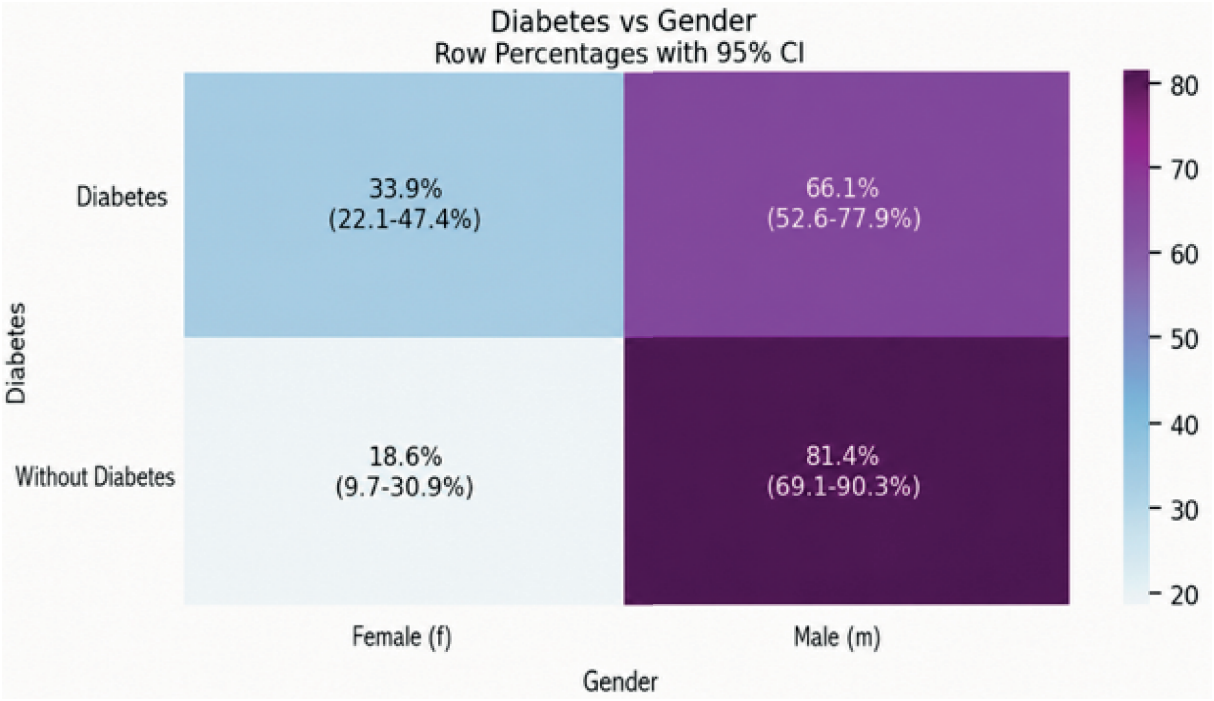


Fig. 1. Sex distribution of patients with pulmonary TB with and without diabetes mellitus (DM).

and after the treatment. The patients were evaluated monthly during hospitalization.

The diagnosis of pulmonary TB was based on acid-fast bacilli (AFB) staining and the molecular genetic Xpert Mycobacterium tuberculosis/Rifampicin (Xpert MTB/RIF) assay. Serum levels of pro-inflammatory cytokines (IL-1β, TNF-β) and anti-inflammatory cytokines (IL-6, IL-8) were measured using the enzyme-linked immunosorbent assay (ELISA) method in the Biochemistry laboratory of the "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau.

Sample characteristics

All eligible study participants completed a questionnaire designed to collect demographic information such as age and sex. A volume of 10 mL of venous blood was collected from the antecubital vein of each consenting participant. The collection tubes were labeled with a unique identification code assigned to each participant. After 15 minutes—the time required for blood coagulation—the serum was immediately separated by centrifugation at 3000 rpm for 10 minutes. Subsequently, the obtained serum was transferred into sterile Eppendorf tubes. The serum samples were then preserved by freezing at a temperature of –40°C until the time of analysis. Participants completed a questionnaire that included the following criteria: sex, age, smoking status, alcohol consumption, AFB smear microscopy, and Xpert MTB/RIF results.

Data analysis was performed using R Studio and Python software. For each parameter, the mean, median, standard deviation (SD), and confidence interval (CI) were calculated. To compare the two groups, the non-parametric Mann–Whitney U test was applied, and the statistical significance of differences was assessed using the p-value (considered significant at $p < 0.05$).

Results

According to the demographic distribution, the analyzed samples showed a predominantly male distribution in both groups, more pronounced in the non-DM group. Women were underrepresented compared to men in both the DM and non-DM groups (Fig. 1).

Among patients with pulmonary TB associated with DM, 32.2% were smokers, whereas 67.8% were non-smokers, indicating that most patients with TB/DM in the study population did not have a smoking history. In contrast, the distribution was reversed among patients with pulmonary TB without DM, where 55.9% were smokers and 44.1% were non-smokers. These findings suggest that smoking was more prevalent among patients with pulmonary TB without DM (Fig. 2).

Regarding the algorithm used to evaluate the inflammatory response, the serum levels of four major pro-inflammatory cytokines (IL-1β, IL-6, IL-8, and TNF-β) were determined before and after completion of treatment (Table 1).

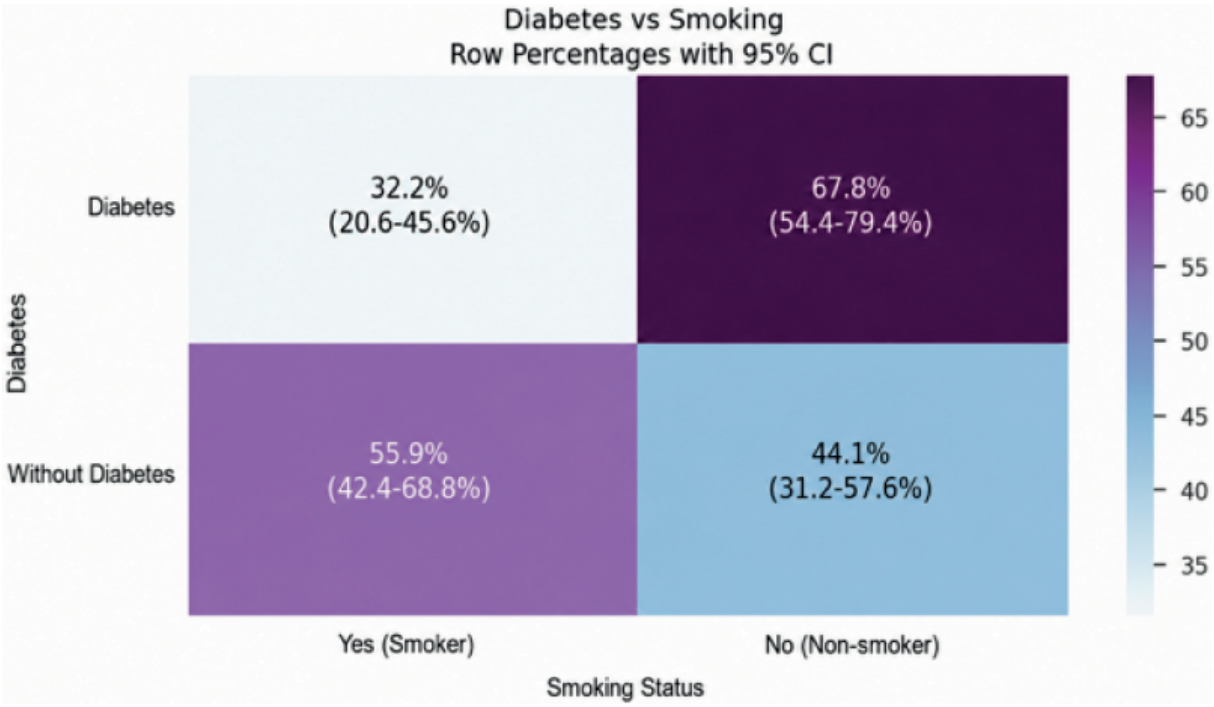


Fig. 2. Distribution of smoking status among patients with pulmonary TB with and without diabetes mellitus (DM).

Table 1. Changes of serum levels (mean±SD) of inflammatory markers in TB patients during the treatment period.

Marker	*Patients with TB control group (n=59)*		± (%)	*p*
	Before treatment	*After treatment*		
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

Note: p –value before treatment vs after treatment; ± (%) – relative changes in the marker during the treatment period

Table 2. Changes in the serum levels (mean±SD) of inflammatory markers in patients with TB and DM during the treatment period

Marker	*Patients with TB/DM research group (n=59)*		± (%)	*p*
	Before treatment	*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

Note: p – value for before treatment vs after treatment; ± (%) – relative changes in the marker during the treatment period

Table 3. Median values of AFB smear and Xpert MTB/RIF indices, before and after treatment

Indices	*Before treatment*				*After treatment*			
	Group TB/DM vs non-DM				*Group TB/DM vs non-DM*			
	TB/DM n (%)	Non-DM N (%)	TB/DM vs non-DM	p	TB/DM n (%)	non-DM n (%)	TB/DM vs non-DM	p-value
BAAR – positive	37 (62.7%)	27 (45.8%)	+37%	>0,05	16 (27.1%)	5 (8.5%)	+220%	0.014
Xpert MTB/Rif negative	10 (16.9%)	23 (39%)	-56.5%	0,013	26 (40.7%)	37 (62.7%)	-29.8%	0.026

Serum IL-1β levels decreased significantly by 26.5%. IL-1β is considered a trigger cytokine of the inflammatory response; therefore, the reduction of other inflammatory markers is understandable. Circulating levels of IL-6 and TNF-β decreased non-significantly by 2.28% and 14.24%, respectively. At the same time, IL-8 showed a non-significant increase of 5.58%. The reduction in inflammatory marker levels suggests a decrease in the systemic inflammatory response, indicating an improvement in the acute inflammatory state. This evolution may reflect the positive effect of therapeutic interventions or the organism's adaptation to the study conditions, highlighting the attenuation of inflammatory processes and the modulation of the immune response. Thus, the inflammatory response in patients with TB during treatment is characterized by the maintenance of IL-8 expression, also recognized as a neutrophil chemokine, in association with the attenuation of the inflammatory genetic program triggered by molecular patterns derived from the mycobacterial pathogen, as evidenced by the considerable decrease in IL-1β. To evaluate the inflammatory profile in patients with pulmonary TB associated with DM, the circulating levels of the same inflammatory markers previously analyzed in Group 1 (patients with TB without DM) were determined, namely IL-1β, IL-6, IL-8, TNF-β. These markers were evaluated both at the initiation of anti-TB therapy and at the end of the treatment period, allowing comparison of the evolution of the immune-inflammatory response in the context of DM comorbidity.

The dynamics of the laboratory tests BAAR and Xpert MTB/RIF are presented in Table 3.

According to the dynamics of BAAR and Xpert MTB/RIF results, it can be concluded that anti-TB treatment demonstrated notable effectiveness. As evidence, it is important to mention the increase in the number of patients with negative BAAR results at the end of treatment, from 31 to 54 cases, which in relative terms represents an increase from 54.2% to 91.5%. At the same time, the number of patients with positive BAAR results decreased from 27 to 5, corresponding to a decline from 45.8% to 8.5%. The results demonstrate that favorable changes in BAAR and Xpert MTB/RIF indices were observed in both groups, indicating a positive response to anti-TB therapy. However, the comparative analysis revealed that the relative bacteriological improvement was more pronounced in the group without DM, suggesting that the presence of DM may delay bacterial clearance and negatively affect the efficacy of anti-TB treatment. The proportion of positive BAAR results decreased after treatment by 56.8% in the DM group, whereas the corresponding decline in the non-DM group reached 81.2%. Thus, the initially non-significant discrepancy became statistically significant after treatment ($p < 0.014$), while the relative incremental gap between the DM and non-DM groups 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 therapy in the context of this test's role in identifying or excluding the presence of mycobacteria in biological material. The reduction in the proportion of positive BAAR results correlated with the decline in positive Xpert MTB/RIF findings.

Discussion

The present study evaluated the influence of type 2 DM on the inflammatory response and bacteriological outcomes in patients undergoing anti-TB treatment. Our findings indicate that DM may adversely affect both immune regulation and treatment response in pulmonary TB.

The assessment of treatment efficacy through bacteriological monitoring demonstrated a less favorable evolution among patients with TB/DM. Although both study groups showed improvements in AFB smear microscopy and Xpert MTB/RIF results following treatment, bacterial clearance was slower in patients with DM. The proportion of positive AFB smears decreased from 62.7% to 27.1% in the TB/DM group, whereas a more pronounced reduction was observed in patients without DM. Furthermore,

the proportion of negative Xpert MTB/RIF results increased during treatment in both groups but remained significantly lower in patients with TB/DM at treatment completion. These findings support previous evidence suggesting that DM impairs host defense mechanisms and delays microbiological recovery during anti-TB therapy. The analysis of cytokine dynamics revealed substantial differences between the study groups. Patients with TB/DM exhibited a markedly greater decline in TNF-β and IL-6 concentrations during treatment compared with patients without DM. In addition, IL-8 levels decreased by 42.6% in the TB/DM group, whereas a slight increase was observed in the control group. These findings suggest a more pronounced attenuation of the immune-inflammatory response in the presence of DM comorbidity. TNF-β plays a central role in the immune response against *Mycobacterium tuberculosis*, by promoting macrophage activation and granuloma maintenance. As a cytokine predominantly produced by Th1 lymphocytes, TNF-β acts synergistically with IFN-γ, which is essential for intracellular mycobacterial killing. Therefore, the substantial reduction in TNF-β observed among patients with TB/DM may reflect impaired cellular immunity and reduced phagocytic activity during treatment. Similar observations have been reported in previous studies, highlighting the prognostic significance of TNF-β and IFN-γ in TB progression and treatment response[9,10]. The findings of Arias et al. (2024) further support the biological relevance of these observations, demonstrating that deficiencies in TNF-β and IFN-γ are associated with increased disease severity and poorer long-term outcomes in TB patients[11,12]. In our study, the reduction in TNF-β levels reached 52.9% in the TB/DM group, substantially exceeding the 14.2% decrease observed in patients without DM. This divergence became more pronounced by the end of treatment, suggesting that DM may contribute to persistent dysregulation of cytokine-mediated immune mechanisms.

Our results indicate that DM significantly modifies the inflammatory profile of patients with pulmonary TB and may negatively influence bacteriological conversion during anti-TB treatment. These findings emphasize the importance of closer monitoring of inflammatory biomarkers and treatment response in patients with TB/DM and support the need for integrated management strategies targeting both conditions.

Conclusions

The association of type 2 DM in patients with pulmonary TB is characterized by a pronounced attenuation of the immune-inflammatory status during anti-TB treatment with rifampicin. Patients with TB/DM exhibited more pronounced reductions in serum TNF-β, IL-6, and IL-8 levels compared with patients without DM, suggesting altered cytokine regulation and impaired macrophage-mediated immune activity.

In addition, bacteriological monitoring demonstrated less favorable treatment outcomes in the TB/DM group, as reflected by the persistently higher proportion of positive AFB smear results and lower rates of negative Xpert MTB/RIF findings throughout the treatment period. These observations indicate that DM may delay bacterial clearance and negatively affect the response to anti-TB therapy.

The findings highlight the importance of integrated management of TB and DM and support the potential utility of inflammatory cytokines as biomarkers for monitoring disease progression and treatment response in patients with TB/DM comorbidity.

Author Contributions:

Conceptualization, M.R. and A.V.; Methodology, M.R.; Software, M.R.; Validation, M.R. and A.V.; Formal Analysis, A.V.; Investigation, M.R.; Resources, M.R. and A.V.; Data Curation, M.R.; Writing–Original Draft Preparation, M.R.; Writing–Review and Editing, M.R. and A.V.; Visualization, M.R.; Supervision, A.V.; Project Administration, M.R. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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