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CHANGES IN THE CYTOKINE PROFILE (IFN-γ, IL-12, TNF-α) IN THE BLOOD OF PATIENTS WITH COMORBID DIABETES MELLITUS AND TUBERCULOSIS

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Abstract

Coordination of immune response reactions against Mycobacterium tuberculosis and the maintenance of intercellular cooperation are directly determined by the functional activity of the cytokine system. Effective protective immunity in tuberculosis infection depends on the balanced synthesis of a Th1-type cytokine profile; the addition of a systemic metabolic disease such as diabetes mellitus causes substantial transformations in the cytokine cascade and disrupts the pathogenetic chain. Therefore, analysis of the dynamics of the main immunopathological markers of comorbidity - interferon-gamma (IFN-γ), interleukin-12 (IL-12), and tumor necrosis factor-alpha (TNF-α) - in patients' blood, as well as their mutual pathogenetic relationships, is highly relevant.

Objective of the study: The aim of this study was to investigate the epidemiology, risk factors, and immunological aspects of diabetes mellitus in patients with tuberculosis, as well as to develop approaches to their treatment and prevention.

To achieve this aim, the following task was set:

To assess changes in the cytokine profile (INF-χ, IL-12, TNF-α) in the blood of patients with tuberculosis comorbid with type 2 diabetes mellitus.

Object of the study: Patients with tuberculosis who had different statuses with respect to diabetes mellitus.

The principal risk factors for tuberculosis in patients with diabetes mellitus are identified, and a system for their stratification is proposed.

Keywords: tuberculosis; type 2 diabetes mellitus; interleukin; tumor necrosis factor; comorbidity.

The number of newly diagnosed cases of diabetes mellitus detected as a result of screening patients with tuberculosis varied across different studies. This difference may be related to variations in screening methods and to differences in the prevalence of diabetes mellitus in the general populations of the respective countries. Nevertheless, the large

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proportion of newly diagnosed diabetes cases indicates the value of identifying patients with diabetes mellitus and emphasizes that screening patients with tuberculosis in TB clinics is an important public-health measure [2]. In this systematic review, the prevalence of tuberculosis among patients with diabetes mellitus, including cases accompanied by comorbid conditions, was relatively lower than the estimates reported in previous systematic reviews [3]. This may be related to the small number of similar studies conducted, the low sensitivity of diagnostic methods used to detect tuberculosis cases, and the extent of tuberculosis prevalence in the countries studied. In addition, the language restrictions applied by us may have reduced the amount of available information. Therefore, this result should be interpreted with caution. In the Asian and African countries included in the study, the prevalence of tuberculosis among patients with diabetes mellitus was higher than in other regions. This may be associated with the fact that countries on these continents are experiencing the most rapid increase in diabetes prevalence while also carrying a high burden of tuberculosis and HIV [1; 4].

It is well known that IL-12, which is produced by antigen-presenting cells (macrophages and dendritic cells), ensures the integration of innate and acquired immune responses. This cytokine induces the synthesis of IFN-γ by T lymphocytes and natural killer (NK) cells; IFN-γ is considered a major effector against mycobacteria. In turn, IFN-γ activates macrophages and thereby increases their phagocytic and bactericidal potential. Under the conditions of chronic hyperglycemia and insulin resistance characteristic of diabetes mellitus, functional suppression of the IL-12/IFN-γ axis is observed, which limits the organism's specific protective capacity.

TNF-α, an important component of immune regulation, has different pathogenetic roles in tuberculosis infection. On the one hand, it participates in macrophage activation and maintains the architecture of specific granulomas that ensure localization of mycobacteria. On the other hand, in the setting of systemic inflammation associated with type 2 diabetes mellitus, hyperproduction of this cytokine promotes tissue damage, the development of caseous necrosis, and the formation of cavitary lesions in the lungs.

The study was conducted among patients with diabetes mellitus who received inpatient treatment in the General Therapy Department of the Andijan Regional Multidisciplinary Clinic during 2024-2025 and among patients of the Regional Tuberculosis Hospital. A total of 350 patients were included in the study. Of these, 100 patients (28.6%) had type 2 diabetes mellitus without tuberculosis, 100 patients (28.6%) had tuberculosis without diabetes mellitus, and 150 patients (42.9%) had concomitant tuberculosis and type 2 diabetes mellitus. All participants provided written consent to participate in the study. The diagnoses of tuberculosis and diabetes mellitus were established on the basis of patients' complaints, medical history, objective examination, and laboratory and instrumental findings, in accordance with clinical protocols approved by Order No. 194 of the Ministry of Health of the Republic of Uzbekistan dated June 14, 2024.

The study participants were divided into three groups. The first group consisted of patients with tuberculosis, the second group consisted of patients with diabetes mellitus, and the third group consisted of patients with both tuberculosis and diabetes mellitus (see Table 1).

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The first group - the main group - included 150 patients with tuberculosis and type 2 diabetes mellitus.

The second group - the control group - consisted of 100 patients with type 2 diabetes mellitus.

The third group - the control group - included 100 patients with tuberculosis.

Thus, an imbalance in the IFN-γ, IL-12, and TNF-α profile serves as an important pathogenetic factor in the worsening of the clinical course, prolonged bacterial shedding, and progressive destructive processes in lung tissue in patients with comorbid tuberculosis and type 2 diabetes mellitus. The quantitative values of these cytokines in the study groups and their comparative statistical analysis are presented below.

Table 1

Main correlations between immunological parameters

No.	Groups	Parameters	ρ	P
1	DM2	IL-6 - TNF-α	0.242	0.015
		IL-6 - CD4+	-0.277	0.005
		IFN-γ - CD4+	0.229	0.022
		IFN-γ - CD16/NK	0.205	0.041
2	TB	IL-6 - TNF-α	0.225	0.024
3	TB+DM2	IL-6 - CD4+	-0.172	0.035
		IL-6 - CD8+	0.198	0.015
		IL-6 - CD16/NK	-0.176	0.031
		IFN-γ - CD4+	0.213	0.009

Note: These are the results of Spearman's rank correlation analysis. Here, ρ (rho) is the correlation coefficient (strength and direction of association), while P is the level of statistical significance. In all presented pairs, $P < 0.05$; therefore, the associations are statistically significant.

The table presents the results of correlation analysis using Spearman's method in order to identify patterns of functional relationships between the pathogenetic chains and markers shown. The obtained results demonstrated that the characteristics of interaction among immune-system indicators differed between the groups.

During the study, several statistically significant correlations were identified between the intensity of systemic inflammation and indicators of cellular immunity in the blood of patients in the group with type 2 diabetes mellitus only. A weak positive relationship was recorded between IL-6 and TNF-α ($\rho = 0.242$; $P = 0.015$). This indicates simultaneous activation of the cytokine cascade during the chronic low-grade inflammatory process characteristic of diabetes mellitus. An inverse correlation was

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observed between IL-6 and CD4+ (ρ = -0.277; P = 0.005). It was found that an increase in the level of the cytokine IL-6 during systemic inflammation was accompanied by suppression of T-helper cells (CD4+) (see Table 1).

Positive correlations were recorded between IFN-γ and CD4+ (ρ = 0.229; P = 0.022) and between IFN-γ and CD16/NK (ρ = 0.205; P = 0.041). This reflects the functional proportionality of T-helper cells and natural killer cells as sources of IFN-γ (see Table 1).

In the second group, which consisted only of patients with tuberculosis, a weak positive correlation between IL-6 and TNF-α was identified in the blood cytokine profile (ρ = 0.225; P = 0.024). This association can be explained by increased activity of the macrophage system in response to mycobacterial infection (see Table 5.2.1).

In the third main comorbidity group of tuberculosis and type 2 diabetes mellitus (DM2+TB), the combined course of the diseases fundamentally altered the architecture of correlations among immunological markers. Although the inverse relationship between IL-6 and CD4+ remained (ρ = -0.172; P = 0.035), its strength was somewhat lower than in monopathology. A positive relationship developed between IL-6 and CD8+ (ρ = 0.198; P = 0.015). This indicates that, in the comorbid state, the increase in systemic inflammation occurs in parallel with compensatory or pathogenetic hyperproduction of cytotoxic T lymphocytes. An inverse correlation was identified between IL-6 and CD16/NK (ρ = -0.176; P = 0.031). As the intensity of inflammation increased, the number of natural killer cells, an element of innate immunity, decreased significantly, indicating immunosuppression (see Table 1).

In the comorbid group, a significant positive relationship was also recorded between IFN-γ and CD4+ (ρ = 0.213; P = 0.009). Against the background of comorbidity, a decrease in the T-helper-cell population was considered a systemic pathophysiological pattern directly leading to a deficiency of gamma-interferon, the main factor in antimycobacterial defense (see Table 1).

Thus, the results of the correlation analysis confirm that, in tuberculosis-diabetes comorbidity, the systemic inflammatory cytokine IL-6 has a direct negative effect on the cellular immune system, manifested by depression of CD4+ and NK cells and activation of CD8+ cells. The direct correlation between effector lymphocytes (CD4+) and IFN-γ is considered a major pathogenetic factor in impairment of the T-cell component in comorbid patients.

In summary, the correlation analysis revealed predominantly weak associations among the immunological markers. In the TB+DM2 group, an increase in IL-6 showed an association with decreases in CD4+ and CD16+/NK indicators and with an increase in the proportion of CD8+ lymphocytes.

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