Original Article

Detection and Role of Some Interleukins and Tumor Necrotic Factor Alpha among Patients with Tuberculosis

Wael Rasheed Obaead Alfatlawi, Marwa Kadhim Khudhair[1], Jwan Ahmed Ali

Department of Medical Microbiology, College of Medicine, University of Babylon, Babylon, Iraq, [1]Department of Pharmacy, Al-Mustaqbal University, Babylon, Iraq

Abstract

Background: The bacterium Mycobacterium tuberculosis causes tuberculosis (TB), a contagious illness. Primarily, it affects the respiratory system, although it may also influence other parts of the body (known as extrapulmonary TB). **Objective:** This study aims to measure the levels of IL-2, IL-10, IL-17, and TNF-α in patients infected with TB and determine the influence of these cytokines on the confirmed infection. **Materials and Methods:** This study is limited to 40 collected samples from individuals diagnosed with TB. The selected samples ranged between (20–70) years of age, in addition to the other 40 who are apparently healthy as a control group within the same age range. The studied samples were collected between February 2020 and February 2021 from the Babylon Center for Tuberculosis and Chest Disease. Serum was used to estimate the levels of IL-2, IL-10, IL-17, and TNF-α using a sandwich ELISA experiment. **Results:** The results revealed a highly significant increase in IL-2 levels 83.88 ± 10.62 ng/L in TB patients compared to healthy individuals 58.22 ± 3.12 ng/L, The IL-10 levels showed highly significant differences between the tested subjects ($P > 0.05$). The mean IL-17 level was increased in TB patients to 115.14 ± 7.99 ng/L, whereas it decreased to 80.00 ± 7.07 ng/L in healthy individuals, and the serum TNF-α concentration was increased in TB patients to 1.33 ± 0.28 ng/L compared to healthy individuals at 0.515 ± 0.07 ng/L. **Conclusions:** IL-2, IL-10, and IL-17 were significant components of the immune response to TB; their distinct profiles, obtained from easily accessible kits, might be used to diagnose TB cases. TNF-α is a significant contributor to both the prevention and progression of TB.

Keywords: Interleukin-17, interleukins10, tuberculosis, tumor necrosis factor

Introduction

The bacterium *Mycobacterium tuberculosis* (MTB) causes the infectious disease tuberculosis (TB). TB mostly impacts the respiratory system, specifically the lungs; however, it can also manifest in other areas of the body.[1] The majority of infections remain undetected, and this condition is known as latent TB.[2] Airborne transmission of TB occurs when individuals with active pulmonary TB release respiratory droplets when they sneeze, speak, spit, or cough.[3] Individuals with inactive TB will not transfer the disease.[4] Active TB infection is more prevalent in individuals with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and in smokers.[5] The confirmation of active TB involves the use of chest X-rays, along with microscopic examination and culture of body fluids.[6] Latent TB may be diagnosed using either blood tests or a tuberculin skin test (TST).[7,8] MTB has a distinctive hydrophobic due to the existing of mycolic acid. MTB can exhibit characteristics of both Gram-negative and Gram-positive bacteria due to its unique cell wall composition.[9] MTB requires a significant amount of oxygen to survive.[10,11] The main diagnostic procedures for TB include the TST, acid-fast staining, culture, and polymerase chain reaction.[12] Cytokines are bioactive molecules synthesized by several cellular components of the immune system, primarily serving as mediators for intercellular communication.[13] Cytokines

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Address for correspondence: Dr. Wael Rasheed Obaead Alfatlawi, Department of Medical Microbiology, College of Medicine, University of Babylon, Hilla 51002, Babylon, Iraq.
E-mail: wael.alfatlawi6@uobabylon.edu.iq

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play a role in the body's defense against pathogens, as well as in inflammatory responses and tissue healing. They have diverse effects and serve as regulators for several biological processes.[14] A bacterial pathogen that lives inside cells is what causes the disease. Its antigens can make the mononuclear phagocyte system make more cytokines.[15] The susceptibility of individuals to the disease varies; not all individuals exposed to this bacterium acquire TB.[16] Tumor necrotic factor alpha (TNF-α), originally found as necrosis inducers in malignancies, representing its earliest discovery in living organisms, is a cytokine that has many pro-inflammatory immune functions.[17] TNF-α is controlled due to the possible deleterious consequences of excessive protein levels, including hypotension, systemic coagulation, and possibly life-threatening hypoglycemia, all of which are indicative of health issues.[18] TNF-α, an inflammatory mediator, is released by various cells, including cells of macrophages and monocytes. TNF is recognized in two distinct forms: transmembrane protein and soluble protein.[19] Polymorphisms occurring in the promoter region of the TNF gene are believed to influence the transcriptional activity associated with susceptibility to TB. The TNF-238 G/A rs361525 gene polymorphisms have been demonstrated to elevate the susceptibility to active TB by significantly impacting the production levels of TNF-α.[20] Patients with active pulmonary TB had elevated levels of TNF-α compared to the control group.[21] The occurrence of the TNF-238A genotype was not ably greater in the TB group compared with the control, as determined by allele frequency studies. The −238A genotype was associated with a higher susceptibility to developing and suffering more severe bouts of TB.[22] The pathophysiology of TB in the lungs begins when the MTB antigenic substance is inhaled in droplets. Activated macrophages play a crucial role in initiating specific immunity against MTB; the primary cells accountable for triggering the non-specific immune response. Antigen MTB will be recognized by macrophages via their surface receptors for antibodies, and when Ag MTB interacts with these receptors, it will trigger inflammatory and immunological processes. APC that has been activated will transform Ag for MTB to peptides, which will subsequently bind to MHC II molecules of the cell in order to activate naive T-helper cells.[23] Phagocytic cells transform Ag MTB, which triggers the activation and creation of cytokines and chemokines, leading to an increase in IL-12 production. Consequently, this stimulates the transformation of T0 cells (naive T) into Thelper1 (Th1). Th1 cells release pro-inflammatory cytokines, including interferon-γ, TNF, and IL-2. Additionally, they enhance the antimicrobial activity of macrophages by attracting monocytes and granulocytes, hence limiting the proliferation of MTB. The antigen of MTB triggers Treg cells to release significant quantities of IL-10 cytokines and promote the conversion of growth factor-β (TGF-β).[23] Induced regulatory T cells possess immunosuppressive capabilities, in contrast to Th1 and Th2 cells. Treg cell activation facilitates the differentiation of T-helper cells into Th2 cells. Th2 lymphocytes will attach to MTB antigen peptides via major histocompatibility complex II (MHC II), leading to the synthesis of IL-4, IL-13, and IL-10 cytokines. Subsequently, these cytokines stimulate an immune response that counteracts inflammation as the infection progresses. MTB bacteria promote the growth of Treg cells, supporting their ongoing reproduction within the respiratory system. Higher elevations of IL-10 and transforming growth factor mediators suppress the function of pro-inflammatory cytokines, leading to a decrease in the immune system's adaptive response.

Consequently, this increases the ability of the infection caused by bacteria to evade the body's defenses. The occurrence of a pro-inflammatory gene variation in the vicinity of the promoter is believed to impact the transcriptional process associated with susceptibility to TB.[24] This study aims to measure the levels of IL-2, IL-10, IL-17, and TNF in patients infected with TB and determine the influence of these cytokines in the confirmed infection.

Materials and Methods

Study design

Forty blood specimens were taken from individuals hospitalized with TB, namely those whose smear and culture findings came back positive. The age range of these patients was from 20 to 70 years. In addition, 40 people who appeared to be in good health were studied as a control group, and their blood was taken. Similarly, those in the control group may be anywhere from 20 to 70 years old. Specimens were obtained from patients between February 2020 and the end of February 2021 at the Babylon Center for Tuberculosis and Chest Disease.

Blood samples

Through the use of a vein puncture, five milliliters of blood were extracted from each subject. To isolate serum, 2 mL of the blood sample was transferred to sodium citrate-containing ethylenediaminetetraacetic acid (EDTA) tubes, while 3 mL was cautiously put into disposable tubes containing separating gel. For future use, the blood collected in EDTA tubes was frozen at −20°C. The blood samples were allowed to coagulate at room temperature for 30 min in disposable tubes with separating gel. After that, they were subjected to centrifugation with a force of 3000 times the acceleration due to gravity for about 3 min. The sera were then collected and stored at −20°C until analysis.

Quantification of cytokines

Each participant in this research provided samples of whole blood. Immunological indicators, such as IL-2, IL-10, IL-17, and TNF-α, were identified in serum samples using an enzyme-linked immunosorbent assay (ELISA) kit from Demeditec Diagnostics, Kiel, Germany, following the provided instructions.

Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences program (Version 24.0, IBM Corp., Chicago, IL, USA). Aside from Fisher's Exact Test, the Mann–Whitney *U* test, independent samples *t* test, and Chi-square (χ^2) test were used to compare the means of various groups and provide the data in terms of number (*n*), percentage, mean, and standard deviation. A difference was considered statistically significant if the *P* value was 0.05 or less.

Ethical approval

The study was conducted according to ethical principles derived from the Declaration of Helsinki. It was performed after obtaining verbal consent from patients prior to sample collection. The study protocol and patient informed consent were obtained from the Babylonian Health Authority and the Publication Ethics Committee of the Faculty of Medicine, Babylon University, Iraq, reference number 17 (dated February 15, 2021).

Results

The quantity of IL-2 was measured in this study using an ELISA. The results revealed a significant difference in the average values for the two categories being studied. Based on the data in Table 1, it is evident that the average value of TB patients was noticeably higher than the control group ($P < 0.001$).

The results revealed a significant difference in the average values of IL-10 across the various study groups. Table 2 demonstrates that patients with TB had significantly higher average values compared to the group of healthy individuals ($P < 0.001$).

The concentration of IL-17 was measured by ELISA. The findings revealed a substantial disparity in the average values across the study groups. More precisely, the average value of patients diagnosed with TB was greater than the healthy control group ($P < 0.001$), as shown in Table 3.

The concentration of TNF-α was quantified using the ELISA method. The findings demonstrated a substantial disparity in the mean values across the study groups.

Table 1: The concentration of IL-2 in TB patients compared to a control

Cytokine	Study groups		*P* value
	Case (40)	Control (40)	
	Mean ± SD	Mean ± SD	
IL-2 (ng/L)	83.88 ± 10.62	58.22 ± 3.12	0.001*

*The value of *P* signifies ≤ 0.05

Table 2: The concentration of IL-10 in TB patients compared to a control

Cytokine	Study groups		*P* value
	Case (40)	Control (40)	
	Mean ± SD	Mean ± SD	
IL-10 (ng/L)	53.09 ± 7.02	33.88 ± 2.39	0.001*

*The value of *P* signifies ≤0.05

Table 3: The concentration of IL-17 in TB patients compared to a control

Cytokine	Study groups		*P* value
	Case (40)	Control (40)	
	Mean ± SD	Mean ± SD	
IL-17(ng/L)	115.14 ± 7.99	80.00 ± 7.07	0.001*

*The value of *P* signifies ≤ 0.05

Table 4: The concentration of TNF-α in TB patients compared to a control

Cytokine	Study groups		*P* value
	Case (40)	Control (40)	
	Mean ± SD	Mean ± SD	
TNF-α (ng/L)	1.33 ± 0.28	0.515 ± 0.07	0.001*

*The value of *P* signifies ≤0.05

Table 4 shows that the mean number of TB patients was substantially higher than the healthy control group ($P < 0.001$).

Discussion

The IL-2 concentration showed a significant difference between the research groups, with higher levels observed in individuals with TB.[25] Cytokines have a crucial importance in the advancement of respiratory disease. Interferon and IL-2 play a vital role in defending against MTB infection.[26] This recent data indicates that the development of IL-2 was notably greater in TB patients compared to uninfected individuals. Multiple authors have asserted that the IL-2 test results might be considered as an alternate, or according to the results of

the current investigation, an extra diagnostic technique has been identified for investigating MTB infections. However, it was emphasized that IL-2 is not a useful diagnostic tool.[27] A prospective engagement of IL-2 in the detection of active TB suggests the identification of a novel biomarker.[28] This could be attributed to the differential expression of IL-2 in individuals suffering from active TB.[29] Furthermore, IL-10 exhibited a notable disparity concentration between the study teams, with an increase observed in TB patients.[30] Multiple data indicate that during TB infection, a diverse range of pro-inflammatory and anti-inflammatory cytokines are formed and delivered into the stream of blood at the locations of the disease.[31] IL-10 is a cytokine with anti-inflammatory properties that has been demonstrated to impact several types of cells, like macrophages, monocytes, dendritic cells, CD4 T cells, and CD8 T cells.[32] The immune response and the damage of tissue are decreased through the function of IL-10. An increasing amount of this cytokine prevents the CD4+ T cell proper response which will result to inability to control infections.[33] IL-10 is found in plasma, serum, and alveolar lavage fluid in those who are diagnosed with active TB. Its presence leads to lack of immunity and inhabits the response to MTB.[34,35] A continuous drop in IL-10 levels among TB cases as a result of their treatment procedure. In other words, those who have high levels of IL-10 after therapy are likely to recurrence TB.[36,37] The levels of antigens mycobacterial motivate immunity cells producing this cytokine. In addition, this cytokine supports the natural immune system highly responding to the pro-inflammatory which is caused by TNF.[38] A positive impact on patients with TB will be reflected by the simultaneous presence of IL-10 and TNF-α.[39] The IL-10 plays a vital role in governing the pro-inflammatory effects in both those who are patients and healthy individuals.[40] In comparison with the other study groups, the level of IL-17 was significantly elevated in cases with TB.[41] One of the important cytokines in acquired immunity is IL-17 which is has a vital role and produced by Th17 cells.[42] Th17 cells are a subset of CD4+ T cells that may be differentiated from Th1 and Th2 cells based on their production of the cytokines IL-17A and IL-17F. Th17 cells have a notable pro-inflammatory function due to their production of cytokines.[40,43] Th 17 cells have been linked to the development of autoimmune and inflammatory illnesses, among other conditions.[44] Additionally, it provides defense against intracellular infections. IL-17 can enhance the levels of chemokine including CXCL9, 10, and 11, which can recruit cells that produce IFN to the site of inflammation.[45] CD4+ T cells derived from individuals with TB demonstrate less IL-17 production when exposed to MTB antigens, compared to CD4+ T cells from stable controls and healthy individuals who have reacted positively to tuberculin.[46] Moreover, there was a notable disparity in the TNF-α levels throughout the research groups, with a noticeable increase among those who were diagnosed with TB. Patients with pulmonary TB displayed increased levels of TNF-α.[47] The researchers looked at the levels of TNF-α in the serum of individuals with TB. Their results, which were consistent with the current investigation, showed a notable elevation in TNF-αlevels in the cases compared to the control.[48] Other investigations have demonstrated how TNF-α plays a crucial function in individuals with TB.[49] Patients with MTB infection exhibited elevated TNF-α production compared to the control group. Cytokines play a critical role in the immunological response of the host to Mycobacterium infections.[50] TNF-α is crucial in both defending against TB and causing negative reactions to the disease among these cytokines. TNF-blocking has a substantial effect on the progression of TB in laboratory animals. TNF-neutralization exacerbates or reactivates TB in mouse models.[51] Insufficiency of the TNF-α receptor hampers the immunological response to acute TB, causing the development of granulomas or severe TB.[52] MTB-infected tissues express TNF-α and other cytokines, including IFN-α throughout the latent infection phase. This suggests that TNF-α, similar to IFN-α, regulates the proliferation of the bacillus.[53] Macrophages commence the process of engulfing and destroying MTB and also control immunological responses through the release of pro-inflammatory cytokines, including TNF-α, IL-1, IL-6, IL-12, and IL-18. In pulmonary TB infection, the key regulator and anti-inflammatory cytokine is IL-10.[21] The function of cytokines generated by Th1/Th2 cells is intricate as a result of the influence of both pro-inflammatory and IL-10 as an example for anti-inflammatory cytokines. Numerous facets of this intricate connection have been thoroughly examined.[20] TNF-α is involved in the creation and upkeep of granulomas by restricting the exponential growth of the mold MTB inside macrophages and the inhibition granuloma necrosis. The response of the immunological system is highly influenced by TNF in those who are diagnosed with TB.[21]

Conclusion

Making use of the four essential immunological factors (IL-2, IL-10, IL-17, and TNF), TB can be diagnosed in various cases that are gathered from low-cost kits. TNF plays a vital role in disease progression and TB prevention.

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Conflicts of interest

There are no conflicts of interest.

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