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Article

Comparison of interleukin 17A and interleukin -18 cytokines during active and latent TB infection in Iraqi patients

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Abstract
Despite international control programs, tuberculosis remains a public health issue. People with latent TB infection (LTBI) significantly increase the number of active tuberculosis (TB) cases and carry a lifelong risk of developing the disease. Therefore, the present study aims to determine the changes in cytokine production at two phases during the development of active pulmonary and latent tuberculosis infection and to evaluate their role as predictive markers in active and latent infections. Blood specimens were collected from 60 patients with active pulmonary TB, 60 cases with latent TB infection and 40 healthy controls to obtain serum. ELISA kit for IL-17A and IL18 was used to determine the concentrations of IL-17A and IL18 according to the manufacturer's instructions (Elabscience / China). The current study found that the mean serum concentration of interleukin-18 was significantly higher in cases with Active pulmonary tuberculosis compared to cases with latent TB infection and healthy control, respectively (P<0.001). Also, the mean serum concentration of IL-18 was significantly higher in subjects with latent TB infection compared to healthy controls (P<0.001). Also, The present study found that the mean serum concentration of IL-17A showed an insignificant variation in cases with Active pulmonary TB compared to healthy control (P< 0.069). In contrast, the mean serum concentration of IL-17A was significantly higher in subjects with latent TB infection as compared to healthy control(P<0.002) and Active pulmonary TB (P<0.001). A comparison of latent and active tuberculosis cases may provide insight into factors that shield them from disease development and new insights into the roles of interleukin -17A and interleukin -18 at two critical stages of the M. tuberculosis infection. These findings suggest that IL-17A and IL18 play distinct roles in two phases of tuberculosis infection and can potentially be used to develop novel diagnostics. The IL-18 ELISA results revealed a highly significant difference between the three groups. This information allows us to distinguish TB patients and LTBI from healthy controls. Furthermore, the current findings indicated that IL-17A could be an alternative biomarker for LTBI diagnosis.

Keywords: Interleukin 17A , Interleukin 18 , ELISA, Active TB, Latent TB.

Introduction

Despite international control programs, tuberculosis remains a public health issue.

According to the World Health Organization, approximately 10 million cases occur worldwide, with about 2-3 million deaths yearly. In 2020, it was estimated that nearly one-quarter of the world's population was infected with Mycobacterium tuberculosis (Mtb). However, only 5-15 % of those people with latent TB infection would develop the disease in the near or distant future (a process known as "TB reactivation") (WHO,2020). Latent tuberculosis infection (LTBI) is when the host immune system responds to Mtb antigen stimulation without clinically manifested active TB. TST or interferon-release assays (IGRA) can diagnose latent tuberculosis (LTBI). In contrast, clinically suspected TB disease is evaluated using a chest radiograph, diagnostic microbiology for acid-fast bacilli, culture, and the GeneXpert assay [40].In the case of tuberculosis infection, the cellular immune response is essential. Th17 cells are critically important in the fight against Mycobacterium tuberculosis [5]. IL-17 is a key cytokine involved in acquired immunity, and IL17A is primarily secreted by TH17 cells. It can increase the levels of chemokines such as CXCL9, 10, and 11, which attract interferon-producing cells to the site of inflammation [1,4]. According to [3], the interleukin 17 cytokine is a proinflammatory cytokine that primarily mediates resistance to extracellular bacteria and fungi. However, these cytokines have also been linked to host immunity to tuberculosis and the production of autoimmune and inflammatory disorders. IL-17A plays a role in the formation and maintenance of granulomas by stimulating the production of chemokines, which in turn assists in the recruitment of inflammatory cells that are migrating to Mtb-infected sites [2].

Interleukin-18 has been shown to play a significant part in M. tuberculosis infection. It stimulates Natural killer cell cytotoxicity and the development of Th1 cell responses. This mechanism is connected with the production of interferon (IFN)-γ, an essential component in protecting against mycobacteria [8]. Interleukin-18 was first identified as a factor capable of inducing robust production of interferon-γ from Th1 cells, particularly in the presence of IL-12. [7] found that when naive T cells are stimulated with antigen and IL-12, they develop into Th1 cells that express the IL-18 receptor (IL-18R). These cells increase their production of IFN-γ in response to IL-18 stimulation. The present study aims to determine the changes in cytokine production at two phases during the development of active and latent tuberculosis infection and to evaluate their role as predictive markers in active and latent infections.

Materials and Methods

Ethical approval and consent

All subjects involved in this work were informed, and the agreement was obtained verbally from each one before collecting samples. The committee approved this study of publication ethics at the College of Medicine, Babylon University, Iraq.

Study design and settings

The current study was designed as a case-control study, and this study was performed from February 2021 – to September 2021 at the National Tuberculosis Institute (NTI) / National Reference Laboratory (NRL) for Tuberculosis in Baghdad. A total of 160 subjects were enrolled in this study. All participants were classified into three groups: 60 patients with active TB (ATB) were included (39 males and 21 females) with ages ranging from 16 -to 68 years and diagnosed by specialist doctors who were based on clinical symptoms and signs, chest radiography (CXR) suggestive of tubercle bacilli (TB) and a positive results from at least one form of microbiological evidence; AFB smear microscopy, MTB culture or from Xpert MTB/RIF. At the time of recruitment, 60 subjects who tested positive for QFT-Plus were considered to be latent tuberculosis, consisting of (37 males and 23 females) aged 18 – 66 years. The diagnosis of latent tuberculosis was made based

on a positive QFT-Plus test and the absence of any microbiological, clinical, or radiological characteristics that would indicate active tuberculosis. A 40 healthy control individual was asymptomatic with a normal chest x-ray, and a QFT- Plus negative result was included in this study. Healthy controls (HC) showed no evidence of TB exposure (individuals with no TB infection or disease), including 22 males and 18 females aged 15 to 70.

Inclusion& Exclusion criteria

The inclusion criteria in the present study included all active pulmonary tuberculosis cases with no record of prior anti-TB treatment (ATT) and newly diagnosed patients. The exclusion criteria included patients with autoimmune diseases, diabetes mellitus, nephropathy, Follow-up patients and extrapulmonary TB. Subjects had close contact with TB with an indeterminate IGRA result or with IGRA negative. Also, the subjects who refused to participate in this study.

Serum specimens collection

A 3 ml of blood was drawn from each subject via vein puncture, placed in gel tubes and allowed to clot at room temperature for 30 minutes, then centrifuged at 3000g for 10 minutes to collect the serum. The serum specimens were kept at -20 C˚ until the ELISA assay was performed.

IL17A and IL18 Cytokines measurement

Assessment of Human IL-17A and IL18 serum levels by ELISA assay. This was done by the method recommended by the manufacturer company (Elabscience /China).

Statistical analysis:

The Statistical Package for Social Sciences (SPSS) version 23 was used to analyze and present the data. After performing the Kolmogorov-Smirnov normality test and making decisions about normally and non-normally distributed variables, numerical data were presented as mean and standard deviation. The one-way ANOVA test was used to investigate the difference in mean between more than two groups when the variable was normally distributed. A P-value of less than 0.05 was used to determine significance.

Results

The present study enrolled 60 cases with active pulmonary TB (ATB) and latent TB infection (LTBI) subjects in 40 healthy controls (HC). Table 1 shows the demographic characteristics of the studied groups.

	Number	Gender		Age (years)	
Group	Total	Male (%)	Female (%)	Mean ± SD	Range
HC	40	22(55.0%)	18 (45.0 %)	38.46 ±14.59	15- 70
ATB	60	39 (65.0%)	21 (35.0%)	36.16 ±14.16	16 - 68
LTBI	60	37 (61.7 %)	23(38.3 %)	42.45±13.62	18 – 66

Abbreviations: HC, healthy controls; LTBI, latent TB infection; ATB, Active pulmonary TB.

Measurement of Serum IL-18 level in studied groups by ELISA

Table 1. Demographic characteristics of TB patients, LTBI cases, and healthy controls in this study.

The present study found that the mean serum concentration of IL-18 was significantly higher in cases with Active pulmonary TB, 412.74 ± 74.54 pg /ml compared to cases with latent tuberculosis and healthy control, respectively, 346.39 ± 70.55 pg/ml and 269.02± 55.14 pg /ml ($p<0.001$) as shown in the figure 1 and the table 2, table 4, also the mean serum concentration of IL-18 were significantly higher

than in cases with latent TB infection 346.39 ± 70.55 pg/ml as compared to healthy control 269.02± 55.14 pg/ml, (p<0.001) as shown in the figure 1 and table 5.

Cases control comparison			P- value
IL-18 pg/ml	Active pulmonary TB N= 60	Healthy controls N=40	
Mean	412.74±74.54	269.02±55.14	**< 0.001 † HS**
SD	74.54	55.14	
Range	302.55- 710.75	191.0–358.39	

N: number of cases; SD: standard deviation; †: one-way ANOVA; HS: highly significant at P≤ 0.001.

Table 2. Comparison of Serum levels of *Interleukin-18* in Active TB patients and healthy controls.

Cases control comparison			P value
IL-18 pg/ml	Latent TB infection N= 60	Healthy controls N=40	
Mean	346.39±70.55	269.02±55.14	***< 0.001 † HS***
SD	70.55	55.14	
Range	206.04 – 482.9	191.0–358.39	

N: number of cases; SD: standard deviation; †: one-way ANOVA; HS: highly significant at P≤ 0.001.

Table 3. Comparison of Serum levels of *Interleukin-18* in LTBI cases and healthy controls.

Cases control comparison			*P value*
IL-18 *pg/ml*	*Active pulmonary TB* N= 60	*Latent TB infection* N= 60	
Mean	412.74±74.54	346.39±70.55	**< 0.001 † HS**
SD	74.54	70.55	
Range	302.55- 710.75	206.04 – 482.9	

N: number of cases; SD: standard deviation; †: one-way ANOVA; HS: highly significant at P≤ 0.001.

Table 4. Comparison of Serum levels of Interleukin-18 in Active TB patients and latent TB infection cases.

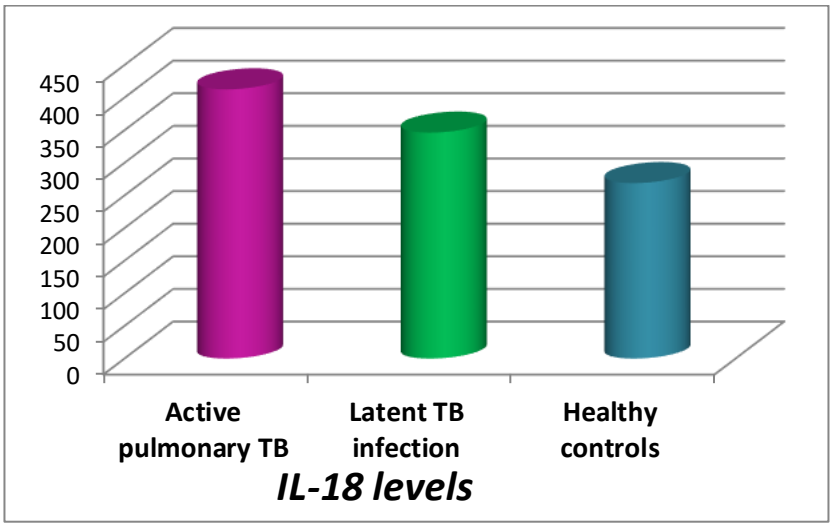

Figure 1. Distribution of Active pulmonary TB, Latent TB infection cases and healthy control groups according to the mean level of *serum IL-18*.

Measurement of Serum IL-17A level in studied groups by ELISA

The present study found that the mean serum concentration of IL-17A showed an insignificant variation in cases with Active pulmonary TB 107.95±41.18 pg/ml as compared to healthy control 122.14 ±39.80pg/ml, (p=0.069) as shown in table 5,

while the mean serum concentration of IL-17A was significantly higher in cases with latent TB infection 147.14±43.99 pg/ml as compared to healthy control 122.14 ±39.80 pg/ml, (p=0.002) shown in the table 6. Also, the mean concentration level of IL-17A was significantly higher with latent TB infection, 147.14±43.99 pg/ml (p<0.001), as compared to Active pulmonary TB, 107.95±41.18 pg/ml, as shown in Table 7 and Figure 2.

Cases control comparison			**P value**
IL-17A *pg/ml*	*Active pulmonary TB* *N=60*	Healthy control N=40	
Mean	107.95	122.14	0.069† NS
SD	41.18	39.80	
Range	51.76- 202.46	60.30-215.64	

SD: standard deviation; †: one-way ANOVA; HS: highly significant at P ≤ 0.001 ,
NS: not significant at P ≥ 0.05.
Table 5. Comparison of Serum levels of *Interleukin-17A* in Active TB Patients and healthy controls.

Cases control comparison			**P value**
IL-17A *pg/ml*	Latent TB infection N= 60	Healthy controls N=40	
Mean	147.14	122.14	0.002† S
SD	43.99	39.80	
Range	90.59-300.38	60.30-215.64	

SD: standard deviation; †: one-way ANOVA; HS: highly significant at P ≤ 0.001 ,
NS: not significant at P ≥ 0.05.
Table 6. Comparison of Serum levels of *Interleukin-17A* in LTBI cases and healthy controls.

Cases control comparison			***P value***
IL-17A *pg/ml*	*Latent TB infection* N= 60	*Active pulmonary TB* N= 60	
Mean	147.14	107.95	**< 0.001 † HS**
SD	43.99	41.18	
Range	90.59-300.38	51.76- 202.46	

N: number of cases; SD: standard deviation; †: one-way ANOVA; HS: highly significant at P≤ 0.001.
Table 7. Comparison of Serum levels of *Interleukin-17A* in Active pulmonary TB and LTBI cases.

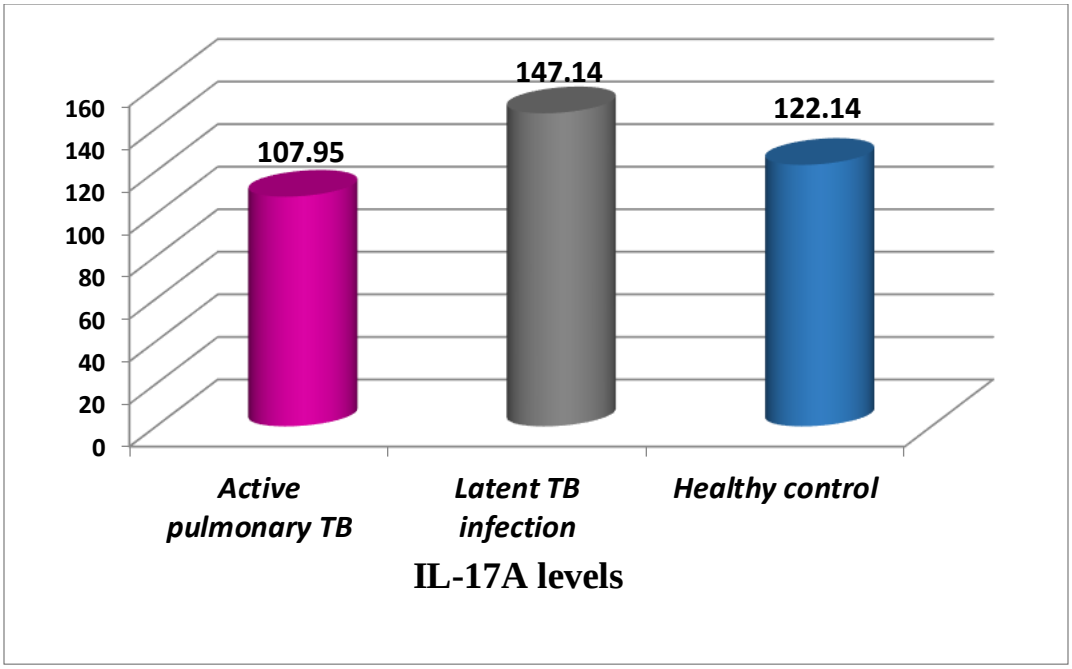

Figure 2. Distribution of Active pulmonary TB, Latent TB infection cases and healthy control groups according to the mean level of Serum IL-17A.

Discussion

The present study found that the mean serum concentration of IL-17A showed an insignificant variation in cases with Active pulmonary TB compared to healthy control. This result is consistent with a local study [23], which showed an insignificant variation between PTB patients and controls in the serum level of IL17A.

The present findings showed that IL-17A levels were increased in latent tuberculosis cases compared to healthy controls and active pulmonary tuberculosis. This was compatible with [33]. When comparing LTBI groups vs. Active TB., The results of the current study were consistent with a study in Malawi [26] and [25, 6] reported that the primary source of interleukin-17 was CD26+ Th17 cells in latent and active tuberculosis patients, but the levels of interleukin-17 were significantly lower than in latent tuberculosis. In Argentina, [15] documented that CD4 + T cells from active TB produce less IL-17 in response to Mycobacterium antigens than CD4 + T cells from healthy tuberculin reactors. [17] displayed that the frequency of Th17 cells in active tuberculosis patients' blood and pleural fluid was lower than in cases with latent tuberculosis.

Interestingly, [6] reported that Th1 and Th17 were at significantly lower levels in active TB pretreatment compared to latent TB infection; the results of the current study are supported by the results of previous studies, which showed that IL-17 is increased during early Mtb infection before disease progression, in contrast with the present results, a local study by [13] and other studies by [10] and [35]. They reported that IL-17A significantly increased in active TB compared to the healthy group. There were some discrepancies between the results of this study and previous reports, which may be due to several factors, including the Variable immunity of experimental subjects, subjects may be sampled before, after, or during treatment, and the choice of practical methods can also affect results [35].

Subjects with latent TB infection and active TB react differently to mycobacterium. Individuals with latent tuberculosis infection (LTB) and active tuberculosis (TB) have CD4 T cells that produce IL-17, which recognizes different antigens at different stages of the disease. This is one of the possible explanations for this matter [34]. It has also been demonstrated that the depletion of regulatory T cells in

LTB individuals increases the production of IL-17, which suggests that regulatory T cells might be involved in the differences in IL-17 observed between active and LTB subjects. Therefore, the stage of the disease, the number of regulatory T cells, and the production of CTLA-4 and FOXp3 may all contribute to the variations in the levels of IL-17 found in different studies involving Mtb [14]. Differences in Mtb environmental exposure in Iraq should also be considered.

IL-17A is a cytokine that protects the host from getting an infection by mycobacteria; suppressing IL-17A production will increase TB susceptibility [31,20] reported that there is a possibility that a genetic variant causes the down-regulated of IL-17A expression and represents an increased risk of M.tb infection.

The findings of the current study suggest that interleukin-17A (IL-17A) could be an immunological marker that has the potential to help identify subjects who are latently infected with tuberculosis (TB), which is consistent with [33]. According to several reports, IL-17A has been shown to play a protective role during the early stages of Mtb infection. This role includes contributing to recruiting neutrophils and IFN-secreting cells to the site of infection, which is necessary to establish an efficient memory response [22]. These findings imply that IL-17A plays distinct roles at two different stages of the TB infection spectrum. These roles can be utilized in the development of novel diagnostics and treatments.

IL-18 is one of the IL-1 family members and one of the cytokines that have been implicated in both protective and pathological processes associated with M.tb infection, which is produced by a variety of immune cells, including monocytes, macrophages, dendritic cells, epithelial cells, keratinocytes, synovial fibroblasts, and T and B lymphocytes [19]. IL-18 is regarded as a member of the family of Th1 cytokines because of its capacity to stimulate IFN- in T cells and natural killer cells [36].

Interleukin -18 is one of the IL-1 family members produced by various immune cells, including monocytes, macrophages, dendritic cells, epithelial cells, keratinocytes, synovial fibroblasts, and T and B lymphocytes. It has been linked to protective and pathological processes associated with mycobacterium infection 19. Because it can induce IFN-γ in T cells and natural killer cells, IL-18 is regarded as a member of the Th1 cytokine family [36].

The present study found that the mean serum concentration of IL-18 was significantly higher in cases with Active pulmonary TB compared to cases with latent TB infection and healthy control, respectively ($P<0.001$). Also, the mean serum concentration of IL-18 was significantly higher in subjects with latent TB infection compared to healthy controls ($P<0.001$). In line with the present findings, A recent study in China by [24] reported that IL-18 was remarkably upregulated in TB patients compared to healthy controls. In addition, IL-18 levels in LTBI were first measured, and it was discovered that these were significantly higher in the LTBI group than in the control group, while these levels were lower than those in the TB group. In Poland, a study by [38] found that ATB patients' serum levels of IL-18 were significantly higher than those of LTBI or healthy controls. This finding suggests that there has been a significant loss of balance in the range of the IL-18 signaling complex in ATB. The current study's findings were partially consistent with those of [37]. They found that LTB subjects had a significantly higher relative level of IL-18 mRNA expression than healthy controls without M.tb infection. The difference in values between the ATB and Control groups was not statistically significant.

Interleukin-18 is a proinflammatory cytokine that is essential in the inflammatory cascade. The production of IL-18 in response to mycobacterial antigens (Ags) is strongly linked to the production of IFN- and mycobacterial defensive immunity [29]. However, IL-18 levels were elevated in patients with active pulmonary TB (ATB), suggesting that IL-18 may play a role in protective immunity and human

TB pathological responses [27]. The role of IL-18 in the pathogenesis of many diseases, including cancer and digestive disorders, has been extensively researched [16]. M. tuberculosis may use the IL-18 signaling complex to expand the clinical manifestation of pulmonary TB, according to [38]. As a result, direct analysis of serum components of the IL-18/IL-37 signaling complex could help develop novel rapid screening tests for pulmonary tuberculosis.

[37] confirmed the role of IL-18 in developing the immune response against mycobacteria by observing an increased level of IL-18 in a group of patients with active pulmonary TB. Furthermore, IL-18 is an essential mediator of macrophage activation in the control of M.tb. Under certain conditions, IL-18 is required to produce IFN-γ from T cells, and its absence can result in increased susceptibility to Mtb. Indeed, [30] discovered a significant positive correlation between serum levels of IL-18 and IFN-γ. Interleukin -18 exhibits a similar tendency to IFN-γ, which has been recognized for a long time as one of the markers that can be used to evaluate the state of tuberculosis infection. In this context, parallel concentrations of IL-18 and IFN-γ were detected in tuberculosis pleurisy.

The levels of interleukin-18 in cases of latent tuberculosis were lower than in Active TB but higher than in healthy control. One explanation of these results is that Interleukin-18 is a T-regulatory cytokine that plays a crucial role during the reactivation phase of pulmonary TB, with increased production possibly being a key factor in promoting TB reactivation [11]. On the other hand, [37] found that the increase in IL-18 gene expression and the decreased expression of the IL-18R gene that occurs in cases of latent tuberculosis infection has the potential to at least partially prevent the development of a pathological inflammatory reaction and promote the maintenance of homeostatic conditions between host immunity and TB infection. Several cytokines have demonstrated promise as stage-specific markers of TB infection. However, there is little agreement between studies, and a great deal of heterogeneity in the changes reported for various cytokines [32,32,24] indicated that It is among a group of cytokines LTBI could be distinguished from healthy controls using IL-18. The results of the ELISA test conducted in this study revealed that there was a statistically significant distinction to be found among the three groups. With the help of all of these data, it may be possible to differentiate between patients with active and latent tuberculosis and healthy controls. Additional verification would contribute to obtaining molecular markers that are more effective in distinguishing among the three groups. The cohorts need to be expanded and diversified to generalize the importance of IL-17A and IL-18 as candidate biomarkers differentiating active TB states and Latent TB from healthy individuals. If these studies confirm some preliminary results, biomarker validation studies involving thousands of clinical samples can be carried out. The end goal is to develop immunological tests that are specific, less expensive, and point-of-care based for the diagnosis of tuberculosis in both symptomatic and asymptomatic stages.

Conclusion

A comparison of latent and active tuberculosis cases may provide insight into factors that shield them from disease development and new insights into the roles of interleukin -17A and interleukin -18 at two critical stages of the M. tuberculosis infection. These findings suggest that IL-17A and IL18 play distinct roles in two phases of tuberculosis infection and can potentially be used to develop novel diagnostics. The IL-18 ELISA results revealed a highly significant difference between the three groups. This information allows us to distinguish TB patients and LTBI from healthy controls. Furthermore, the current findings indicated that IL-17A could be an alternative biomarker for LTBI diagnosis.

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