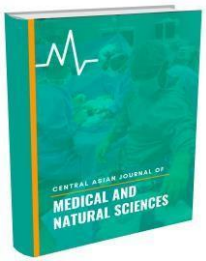

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Article

Evaluating the Role of Interleukin IL-38 Level in Tonsillitis Patients and Relationship with Rheumatoid Arthritis in Diyala Province

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Abstract: Rheumatoid arthritis (RA) is an autoimmune inflammatory disease linked to Streptococcus pyogenes infection, often initiated by tonsillitis or rheumatic fever. This study investigates the relationship between IL-38 levels and the presence of tonsillitis and RA. Conducted from October 2023 to May 2024 in Diyala Governorate, Iraq, 88 participants were categorized into four groups: RA patients, tonsillitis patients, patients with both conditions, and healthy controls. ELISA tests revealed significantly decreased IL-38 levels in RA (63.63 ± 14.45 Pg/ML), tonsillitis (46.97 ± 12.76 Pg/ML), and dual-condition patients (15.18 ± 5.64 Pg/ML) compared to controls (17.16 ± 10.66 Pg/ML). The study highlights IL-38's dual role in disease pathogenesis, suggesting its potential as a biomarker for RA and tonsillitis.

Keywords: Rheumatoid arthritis, IL-38, Tonsillitis, Autoimmune Disease, Biomarker

1. Introduction

Tonsillitis results in irritation and inflammation of the membranes lining the pharynx after they are exposed to a bacterial infection. Streptococcus pyogenes affects all age groups, and the infection is usually active in late fall and early spring [1]. The tonsils are the first line of defense against pathogens and are also the site of recurrent chronic inflammatory processes, as acute recurrent tonsillitis is a common chronic inflammation of the palatine tonsils that often requires surgical removal [2]. Rheumatoid arthritis is one of the most widespread diseases in the world resulting from tonsillitis resulting from infection with the bacterium S. pyogenes. It is an inflammatory disorder resulting from an autoimmune response that develops into a chronic condition that affects different joint parts of the body. Rheumatoid arthritis is characterized by with persistent synovitis, which leads to appearance of autoantibodies (especially rheumatoid factor) [3].

Cytokines play a major role in modulating the innate and adaptive immune response, and when they fail to regulate the response, it leads to a wide range of autoimmune and inflammatory diseases, including Pathogenesis rheumatoid arthritis [4]. Interleukin-38 is a new member of the IL-1 family. It has the ability to bind to many receptors, and regulates the function of inflammatory cytokines through downstream signaling pathways. IL-38 is expressed in many tissues, such as placenta, heart, and brain. It may be involved in a wide range of diseases, both inflammatory and chronic and especially its role in rheumatic autoimmune diseases such as rheumatoid arthritis. It is

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important for inflammation and host defenses, as it plays a prominent role in inflammation and immune responses. It represents the first line of defense against microorganisms that cause invasive diseases and provides protection against long-term persistent infections in addition to autoimmune diseases [5].

IL-38 is an antagonist of IL-36 signaling similar to IL-36Ra, and may play an important role in the pathogenesis of autoimmune disease. Peripheral blood mononuclear cells activated with IL-36γ in the presence of IL-38 showed reduced expression of IL-8. Likewise, PBMCs were activated with IL-36γ upon anti-IL-36Ra treatment from IL-8 generation, supporting the hypothesis that IL-38 suppresses IL-36γ-induced IL-36γ. (Mora et al., 2016). Elevated IL-38 in ACM inhibits the production of IL-17 by T cells, confirming that IL-38 is a suppressor of macrophage-dependent Th17 cell production. Through its regulatory role on the T helper 17 cell axis, dendritic cells, T regulatory cells, and macrophages [6], IL-38 could have anti-inflammatory properties in RA and perhaps It can be used in a therapeutic strategy [7]. During recent years, the cytokine IL-38 has aroused increasing interest, as it has been found to have a role in various diseases, including rheumatoid arthritis [8].

2. Materials and Methods

Samples

This study was conducted in Diyala Governorate for the duration from the first of October October 2023 until the end of May 2024. 88 blood samples were collected and divided into four groups, Their ages ranged between) 10-80)years, where the first group included 22 samples from patients with rheumatoid arthritis, and the second group included 22 samples from patients with acute and chronic tonsillitis. As for the third group, it included 22 samples from patients with tonsillitis and rheumatoid arthritis. The samples were taken after the clinical diagnosis of the disease cases by the specialist doctor from the ear, nose and throat division as well as the joint diseases division in the consulting clinic at Baquba Teaching Hospital in Diyala Governorate. The fourth group, the control group, included 22 samples from apparently healthy people Clinically. Their ages from (21-60)years.

Sample collection

Venous blood samples were collected. (5 ml) of blood using a disposable syringe and kept in gel tubes and left for (30) minutes at room temperature for coagulation. The serums were then separated by centrifuge for 5 minutes at a rate of 3000 rpm. Then it was divided into equal quantities (250 µl) in Eppendorf tubes and stored at a temperature of (-20) until use. The preserved serum is used once to avoid repeated thawing. For the purpose of measuring IL-36 concentration using sandwich ELISA.

ASSAY PROCEDURE

1. prepared standard solutions and samples according to the instructions and opened the measuring plate for the purpose of starting work.
2. 100 µl of standard and samples were added to the holes designated for them, the plate was covered with an adhesive cover equipped with the diagnostic kit, then the plate was incubated in the incubator at a temperature of 37°C for two hours.
3. All liquids were removed from the holes without washing.
4. 100 µl of (1x) Biotin – antibody was added to each hole, then the plate was covered with a new adhesive cover and incubated at a temperature of 37°C for one hour.
5. The plate was washed three times for two minutes each time.

6. 100 µl of HRP – Avidin (1x) was added to each hole, the plate was covered with a new adhesive cover, and it was placed in the incubator at a temperature of 37°C for one hour.
7. The plate was washed five times for two minutes each time.
8. 90 µl of the base material (TMB) (Tetra Methyle Benzinide) was added to each hole, and the plate was incubated at a temperature of 37°C for (15-30) minutes and stored away from light.
9. 50 µL of 2M Sulfuric acid stopping solution was added to all the holes, and the color changed from blue to yellow.
10. The absorbance of the samples was read at a wavelength of (450) nanometers five minutes after adding the stop solution.

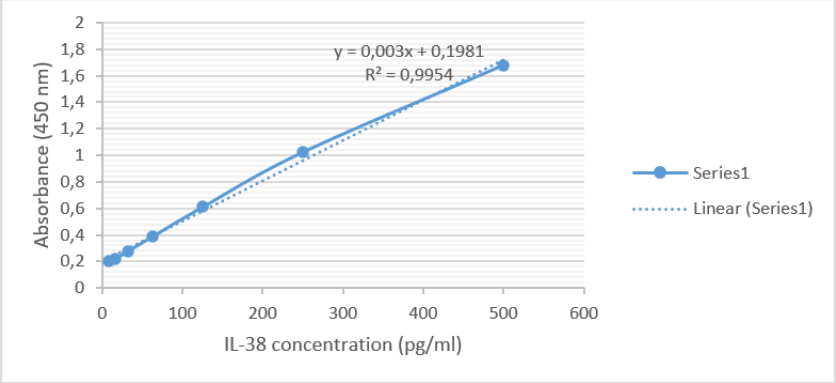

Figure 1. Standard curve for IL38 concentration.

Statistical analysis:

Software: IBM SPSS computer software version V27.0. Tests used: arithmetic mean, SE, ANOVA table (Duncan test), independent t-test, frequency and percentage, and chi-square test.

3. Results and Discussion

The results in Table (1) showed that infection rate among females 18 (82.0%) higher than males 4 (18.0%) among patients with rheumatoid arthritis, where the average age for females (48.24 ± 1.32) years and for males (48.78 ± 2.92) years, as shown in Table (2).The infection rate among females 16 (%73.0) higher than of males 6 (%27.0) among tonsillitis patients, shown in Table (1). The average age for females (37.79 ± 1.59)years and for males (38.81 ± 3.25) years. It shown in Table (2) that infection rate among females 17 (77.0%) higher than males 5 (23.0%) among patients with tonsillitis and rheumatoid arthritis according the average age for females (44.65 ± 3.22) years and for males (43.75 ± 5.22) years as shown. In Table (2).

Compared to control, the infection rate in females 8 (%36.0) is lower than in controls males 14 (% 64.0), and the average age for females (32.35 ± 2.30) years and for males (31.32 ± 1.95) years. The current study found that the percentage ages females infected with disease is greater than percentage of ages of males infected with disease, and there was no statistically significant difference between the study groups, as the p-value was equal to ($p > 0.05$), as shown in the two tables below [9].

Table 1. Shows the infection rate for the study group and its comparison with the control group by gender

groups	Males	Females	Total
RA group	4 (18.0)	18 (82.0)	22 (100.0)
Tonsilitis group	6 (27.0)	16 (73.0)	22 (100.0)
RA & tonsilitis group	5 (23.0)	17 (77.0)	22 (100.0)
Control group	14 (64.0)	8 (36.0)	22 (100.0)

Table 2. Distribution of the study groups and comparison with the healthy group according to gender and age

groups	Males Age mean ± SE	Females Age mean ± SE	Total Age mean ± SE	Probability
RA group	48.78 ± 2.92	48.24 ± 1.32	48.39 ± 1.24^{A}	P > 0.05
Tonsilitis group	38.81 ± 3.25	37.79 ± 1.59	38.17 ± 1.56^{B}	P > 0.05
RA & tonsilitis group	43.75 ± 5.22	44.65 ± 3.22	44.48 ± 2.74^{AB}	P > 0.05
Control group	31.32 ± 1.95	32.35 ± 2.30	31.78 ± 1.48^{C}	P > 0.05

The results of this study showed that the rate of infection with tonsillitis and RA in females increased in the rate of infection on males. This can be due to several reasons, including hormonal influence in the case of infection with the disease in women, which is more than in men, genetic predisposition, type of life, environmental factors, and lack of interest in health care [10]. It has been observed that there is an interaction between endogenous sex hormones and the occurrence of inflammation, with an increased risk of contracting the disease. This study found a higher incidence of chronic tonsillitis in females than in males, and it agreed with the results of a study conducted by researchers Khadilkar and Ankle (2016). The study agreed with a study conducted by Haidara et al. (2019). In addition to this, lack of health awareness, lack of regular exercise, and following an unbalanced diet, as the disease is associated with being overweight in females more than males due to eating unhealthy food and lack of movement, which increases the chance of contracting chronic diseases that weaken the efficiency of the immune system, in addition to genetic factors [11].

And the environment plays a complex role in enhancing immunity, which is confirmed by the emergence of autoimmune disease and the fluctuations accompanying the disease when hormonal changes occur, as well as the way males and females deal differently with their chronic diseases [12]. Chronic Tonsillitis is a trigger for the occurrence of autoimmune diseases and may be one of its causes due to the induction of helper T cells, which play a role in the development of inflammation [13]. In addition to the presence of other factors that have a significant impact on the weak efficiency of the immune system, such as aging and a family history of tonsillitis and rheumatoid arthritis [14].

Table 3. Serological evaluation of IL-38 in the study groups and comparison with the control group.

groups	Males	Females	Probability	Total
RA group	74.98 ± 36.11	61.74 ± 16.11	P > 0.05	63.63 ± 14.45^{A}
Tonsilitis group	46.41 ± 27.31	47.30 ± 13.56	P > 0.05	46.97 ± 12.76^{AB}
RA & tonsilitis group	11.10 ± 3.04	16.14 ± 6.96	P > 0.05	15.18 ± 5.64^{B}
Control group	20.96 ± 16.77	10.99 ± 7.70	P > 0.05	17.16 ± 10.66^{B}
Duncan's test: Similar letters indicate that no significant differences when comparing the four groups vertically				

The results showed a higher concentration of IL-38 in patients with rheumatoid arthritis (63.63 ± 14.45) Pg/ML and tonsillitis patients (46.97 ± 12.76) Pg/ML compared to the healthy group (17.16 ± 10.66) Pg/ML, while it decreased in patients with Of tonsillitis and rheumatoid arthritis, it reached (15.18 ± 5.64). The results showed that IL-38 has both a positive and negative effect on disease pathogenesis, as it exhibits pro-inflammatory and anti-inflammatory properties, by inhibiting Production of pro-inflammatory cytokines, which leads to a decrease in Th17, and thus, This makes this cytokine important for the induction of many chronic inflammatory diseases, especially rheumatic ones. And autoimmune diseases. The results of this study were consistent with the results of Gao et al. (2022). It did not agree with the findings of the study conducted by Abdul-Sahib et al. (2024).

4. Conclusion

The present study concludes that IL-38 plays a complex role in the pathogenesis of both rheumatoid arthritis (RA) and tonsillitis, as evidenced by its significantly reduced levels in patients with these conditions compared to healthy controls. The findings suggest that IL-38 could potentially serve as a biomarker for both RA and tonsillitis, offering new insights into their underlying mechanisms. This dual role of IL-38 underscores its importance in modulating inflammatory responses, which could have significant implications for the development of targeted therapeutic strategies. Given the observed variability in IL-38 levels across different patient groups, further research is warranted to explore its precise function in immune regulation and its potential use in clinical practice. Future studies should also investigate the long-term effects of modulating IL-38 levels in patients with autoimmune and inflammatory diseases to better understand its therapeutic potential.

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