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The Potential Involvement of Interleukin-18 and Interleukin-10 in Rheumatoid Arthritis Patients.

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ABSTRACT: Rheumatoid arthritis, a common chronic disease that may lead to severe obstruction, requires early diagnosis and appropriate treatment, and disruption of regulation in the cytokine network plays a crucial role in the development of this disease. Understanding the role of cytokines can have a significant positive impact on the lives of patients, as technological advances have allowed the introduction of customized treatments targeting cytokines, such as anti-TNF-alpha, IL-1 and IL-6 drugs. In addition, there is increasing interest in the potential participation of interleukin-18 and interleukin-10 in patients with rheumatoid arthritis. This study aimed to measure interleukin-18 and interleukin-10 in the serum of rheumatoid arthritis patients to enhance the detailed understanding of the balance of cytokines in improving the diagnosis and treatment processes and how these cytokines affect the course of the disease and considered potential strong vital indicators of rheumatoid arthritis. The study was conducted with 70 patients of rheumatoid arthritis who reviewing the rheumatoid rheumatic disease unit at Marjan Hospital in Babylon province. All patients were diagnosed with the disease by a rheumatologist, and 40 healthy people as control group in the study. Serum cytokine levels were measured using an ELISA kit. The results of the study showed increased serum levels of Interleukin-18 ($p<0.05$) and Interleukin-10 ($p<0.05$) were significantly higher in patients with rheumatoid arthritis compared to the healthy control group. study's results indicate that patients with rheumatoid arthritis have elevated serum levels of both interleukin-18 and interleukin-10 compared to the healthy group.

KEYWORDS: Rheumatoid arthritis, cytokines, serum.

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disorder whose exact causes are still unknown. This disease is classified as an immune response disorder, which mainly depends on cell activation. Th1 These cells stimulate broad immune responses that contribute to the cause of the disease (Small A,et al.,2023). Recently, a group of additional mediators that play a crucial role in regulating the complex cytokine network associated with rheumatoid arthritis among these mediators, interleukin-18, which is a essential component of many autoimmune diseases, Have existed discovered. IL-18 stimulates Th1 and natural killer cells (NK) cells to produce cytokines responsible for promoting inflammation, and overproduction of these cytokines is thought to exacerbate acute inflammatory diseases (Liew FY& McInnes IB,2002;Song Y et al.,2023). Research has shown that IL-18 is present in the synovial tissue of patients with rheumatoid arthritis as it enhances the surrounding inflammatory environment and contributes to the prolongation of inflammation and the destruction of articular tissue. Rheumatoid arthritis causes chronic inflammation that over time eats the cartilage and bones, leading to poor joint function and worsening pain. Cytokines, which are proteins produced by different immune cells, They serve a vital function in modifying immunological responses (Gracie et al.,1999). In the instance of rheumatoid arthritis, pro-inflammatory cytokines lead to excessive immune responses that increase the severity of chronic inflammation among these interleukine-18 which belongs to the IL-1 superfamily, produced by several types of cells, including monophagocytes, stem cells, cartilage cells and syllial fibroblasts (Dinarello CA,2004). IL-18 is a major factor in promoting inflammation through its interaction with IL-18 and TNF-a, resulting in increased local inflammation in the joints. In addition, IL-18 plays a pivotal role in enhancing the acquired immune response by stimulating T cells, which are key cells in the adaptive immune response. IL-18 is believed to contribute to the continuation of inflammation in the joints by promoting the production

of IL-18 and TNF-a, thus contributing to the development of rheumatoid arthritis. Furthermore, IL-18 helps differentiate the B cells accountable for the generation of antibodies, which results in the advancement of autoimmunity (Paradowska-Gorycka et al.,2021; Wong et al.,2020). Although Interleukin-10, an anti-inflammatory cytokine, is present the affected joints and in the fluids of patients, its inhibitory effect of the inflammatory response may not be sufficient in some cases to reduce ongoing damage to the joints. Cellular sources of interleukine-10 in the case of Rheumatois synovial mainaly include macrophages, with less contribution of T cells. Extensive studies of the properties of IL-10 have been conducted using in vivo cell cultures that include a combination of synovial cells such as fibroblasts and macytos, as well as lymphocytes (Keffer et al.2015). The results indicate that these cell cultures produce IL-10 along with a group of Cytokines associated with inflammation, like Interleukin-6, GM-CSF,Interleukin-8 and TNF-alpha. Evidence suggests that most of the IL-10 product on these cultures is sourced from Macrophage-like cells. Experiments have shown that Inflammatory cytokines like TNF-α, IL-1 promote the synthesis of IL-10, and IL-10 in turn shows an inhibitory role in the inflammatory response. Studies have shown that neutralization of IL-10 using special antibodies increases The release of Interleukin-1 and TNF-alpha, while GM-CSF and IL-8 inhibits the production of IL-10 (St Clair et al.,2009 ; Udalova et al., 2016). These results demonstrate the existence of an integrated network of cytokines, where IL-10 regulates synovial inflammation by inhibiting certain responses, highlighting IL-10 as an inhibitor in the context of the rheumatoid synovial.Although IL-10 contributes to in reducing the acute inflammatory response, it has double effects, as it may enhance some aspects of the self-immune response that exacerbates arthritis.The balance between Understanding the role of pro and anti-inflammatory cytokines remains critical the development of rheumatoid arthritis, In developing effective therapeutic strategies to control this disease (St Clair et al.,2008).

MATERIALS AND METHODS

This study was conducted over three months from September 2024 to December 2024, in the Rheumatology Unit, Marjan Hospital, Babylon Governorate, and the number of participants were 110 participants for this study divided into two groups of 70 patients with rheumatoid arthritis disease and 40 healthy people. rheumatoid arthritis patients were diagnosed by specialized doctors and people who had a history of other autoimmune diseases and people suffering from chronic infections or receiving immunosuppressive treatments were excluded. The Institute's Ethics Review Board approved the initiative. The approach and techniques of the study were also approved by the ethical committees at the University of Babylon and the Iraqi Ministries of Higher Education and Scientific Research. The ethical consent was provided on September 16, 2024, under the process number (MRT-4302). All participants supplied informed written consent. The patients' ages ranged from 12 to 54 years, while the control group consisted of 40 people and they were free of any diseases based on the examinations. The clinical age was identical to the ages of the patients, and the group of patients was classified by gender and 25 were males and 45 females, while the control group was 15 males and 25 females. Venous blood collection (5 ml) and blood samples were processed to separate the serum and store the serum at -80°C to ensure the stability of cytokine levels. serum cytokine Levels of Interleukin-18 and Interleukin-10 were measured The ELISA kit was utilized following the guidelines outlined by the manufacturer, Abcam Limited, The analysis of the results was conducted using SPSS version 20, specifically utilizing the t-test for statistical evaluation.

RESULT

Table 1 compares serum IL-18 and IL-10 levels by age group and gender. When the data were analyzed by age or gender, there were no significant differences in IL-18 or IL-10 levels between rheumatoid arthritis patients and healthy people. For IL-18, the P values for gender and age were 0.61 and 0.79, respectively, showing no statistically significant differences. Similarly, for IL-10, the P values for age and gender were 0.09 and 0.95, respectively. These findings indicate that neither age nor gender substantially influenced cytokinin levels in the cohort investigated.

Table 2 compares the serum levels of IL-18 and IL-10 between patients with rheumatoid arthritis and a healthy group. The results clearly indicate significantly higher levels of both IL-18 and IL-10 in patients with rheumatoid arthritis compared to controls. Specifically, levels of IL-18 increased significantly in patients with rheumatoid arthritis with an average of (163.94±28.87 pg/ml) compared to controls, where the average was (66.46±17.89 pg/ml), The P value <0.001, indicating a very large difference between the groups. Similarly, levels of IL-10 were significantly higher in patients with rheumatoid arthritis (32.23 ± 9.7 pg/mL) compared to the control group (20.99 ± 9.38 pg/mL), with a P value <0.01. These results indicate that both IL-18 and IL-10 are elevated in rheumatoid arthritis serum.

With regard to the relationship between interleukin-18 and interleukin-10, the analyses showed an absence of moral correlation between them, with a correlation coefficient (r) of 0.671 and a P-value of 0.054, indicating the absence of a statistically significant reactive relationship between the two immunological indicators in this sample Table 3.

Table1. Comparison of IL-18 and IL-10 serum level in a number of case and control parameters.

Groups	**Factor**	**Means+sd Case**	**Means+sd Control**
IL-18 (pg/ml) Gender	Male	117.71±130 n=25	28.18±10.81 n=15
	Female	98.7098.38 n=45	29.69±13.05 n=25
P.value		0.61	0.77
Age (years)	12-25	85.27 ± 77 n=10	26.92±8.45 n=8
	26-40	109.83113.0 n=25	32.27±15.85 n=14
	41-54	117.07 ± 124.43 n=35	27.45±10.6 n=18
P.value		0.79	0.87
IL-10 (pg/ml) Gender	Male	18.09±17.92 n=25	12.71 ±12.52 n=15
	Female	17.77±14.38 n=45	10.1947.52 n=25
P.value		0.95	0.46
Age (years)	12-25	22.37±11.2 n=10	9.66±5.82 n=8
	26-40	31.10±9.43 n=25	12.36±11.9 n=14
	41-54	22.14±12.05 n=35	8.63±4.29 n=18
P.value		0.09	0.18

Table 2. Comparison Serum levels of IL-18 and IL-10 for patients and controls.

Cytokines	**Case (no.50) Mean ± SD**	**Control (no.50) Mean ± SD**	***P*.value**
IL-18 (pg/ml)	163.94±28.87	66.46±17.89	0.001**
IL-10 (pg/ml)	32.23 ± 9.7	20.99 ± 9.38	0.01**

Table 3. Correlations between IL-18 and IL-10.

Sample	Links	IL-10 (pg/ml)
IL-18 (pg/ml)	Correlation	0.671
	Sig.	0.054

DISCUSSION

Interleukine-18 and interleukine-10 are cytokines that have been used in the evaluation of autoimmune diseases because they have a prominent effect on the regulation of immune and decisive responses in rheumatoid arthritis patients, and interleukine-18 is considered an inflammatory cytokines, unlike interleukine-10, which acts as an anti-inflammatory response. To understand the complex immune interaction network between these two immune standards, there was a need to study them in rheumatoid arthritis (Sahakian et al.,2019; Nolte et al.,2021).

The results of the study indicate that there are no moral differences in the concentrations of interleukin-18 and interleoquine-10 in the seros of patients between the sexes, This observation is significant because it implies that IL-18 and IL-10 levels in serum are unaffected by demographic characteristics, making them viable biomarkers across a broad range of rheumatoid arthritis patients.

Many studies have shown that the ratio of infection between males and females is equal and that sex has no moral impact on the occurrence and development of the disease. These results agreed with the results provided by (Matzinger, P.,2002;Klein et al.,2016), which showed that the immune responses that occur in rheumatoidic patients depend on the duration and severity of the disease and that the levels of interleukin-18 and interleukin-10 are not regulated based on sex-related biological factors. Other literature that has been emphasized for gender differences in the epidemiological and clinical characteristics of rheumatoid arthritis (RA) have been shown in several studies. Some research has shown that environmental factors, sex hormones and the menstrual cycle may play a role in the sexism associated with this disease (Alamanos et al.,2006), the (Fitzgerald et al.,2000) found that increased estrogen levels and decreased androgen levels in the rheumatoid arthritis synallus contribute to the local inflammatory immune response. On the other hand,(El-Hajj Fuleihan et al.,2015) that although some studies indicate that sex hormones affect multiple mechanisms in the etiology of rheumatoid arthritis, such as immune regulation and interaction with cytokines, while (Salman et al., 2016) showed that female sex hormones may play a protective role in rheumatoid arthritis. According to (López-Olivo et al.,2016) complex changes in sex hormones during a woman's life cannot fully explain the development of rheumatoid arthritis and its clinical characteristics, unless the results of our study agree with it.The results of the study did not show a moral difference between the immunological standards of patients in terms of age, and the results of our study agreed with (Saeed et al., 2019) who showed that the concentrations of cytokines that stimulate autoimmune diseases such as rheumatoid rheumatitis are not affected by age and their levels may rise as a result of being affected by pathological factors specific to the disease and pathogens affecting those cytokines. However, our study did not agree with other studies that confirmed that there is increasing evidence that age may have an effect on the levels of some cytokines in certain cases. Research by (Gollner et al.,2019) showed that IL-18 may increase with age in some inflammatory diseases, indicating increased immune activity in older individuals.

This research also showed that the general immune response may become more aggressive or inflammatory with age, which is known as the concept of inflammation. As a result, we expect to see an increase in the level of inflammatory cytokines such as IL-18 as we age. In the same vein, other studies have been suggested, such as (Franceschi et al.,2019; Kearney et al.,2020; O'Connor et al.,2021) that with age, the response to cytokines in general may change, as the body becomes less able to regulate the response to inflammation, and this leads to higher levels of IL-18 in elderly individuals. If this theory is correct, the absence of this effect in our study may be attributed to the structure of the sample or the characteristics of the disease itself that make it difficult to distinguish between the effects of age and the chronic inflammation present, and this disease also hides any age differences.

The results of the study showed a moral increase in the concentration of interleukine-18 and interleukin-10 levels in the serum of rheumatoid patients compared to the healthy control group,emphasizing their potential significance in the inflammatory processes associated with rheumatoid arthritis, and this is consistent with previous results and research (Aletaha et al., 2018) that showed that rheumatoid arthritis is a chronic autoimmune disease characterized by the accumulation of inflammatory cells in the synovial and the destruction of the joints. Some cytokines play a role in promoting inflammation and degrading cartilage such as interleukin-18, while other cytokines play an anti-inflammatory role such as interleukin-10. The imbalance between pro- and anti-inflammatory cytokines is attributed to chronic joint damage in rheumatoid arthritis, as well as rheumatoid factor levels and

autoantibodies are formed, especially those directed against By over-production of tumor necrosis factor (TNF) by T and B cells and synovial-like fibroblasts and macrophages, which contributes to the persistence of inflammation and destruction of joints, and also promotes inflammatory cytokines such as IL-6 and IL-18 (McInnes et al.,2011).

on the other hand, elevated levels of IL-10 are observed in the serums and fluids of RA patients, and this cytokine may have a role in reducing the severity of the disease. However, due to its effect on stimulating B cells, it is thought that a rise in IL-10 levels may contribute to the promotion of autoantibody production in RA, while at the same time reducing levels of IL-6 and some acute reactions. IL-10 plays a dual role in RA as it suppresses pro-inflammatory cytokines on the one hand, while at the same time enhancing the autoimmune response. This discrepancy is reflected in the results of clinical trials conducted to evaluate its effectiveness as a treatment for RA disease (Rao SK & Cummings JR.,2020).

In one study, an individual dose of IL-10 (25 µg/kg) was safe, but higher sequential doses led to complications such as neutropenia and lymphocyticy. Another study also showed limited effectiveness when administering IL-10 under the skin for 28 days without serious complications.

The result of the study was in terms of the correlation relationship between immune standards. The association was non-moral in the serum of rheumatoid patients. This result is reflected in that these cytokines work separately from each other in the formation of a complex reaction within the inflammatory environment itself (Davis MM et., 2017).

This result was agreed with (Harris AR et al.,2020) which shows that the pathogenesis of rheumatoid rheumatism includes a complex network of associations and immune reactions between cytokines, including polypotent cytokines produced by activated T cells and works to cause damage and damage to cartilage and synovial cells such as interleuine-18, including anti-inflammatory cytokines, where they can inhibit excessive inflammatory response and face harmful effects. Pro-inflammatory cytokines such as interleoquine-10, and these cytokines may be active in independent pathways. Or it may reflect the lack of association in this study due to the study sample or other factors that were not examined.

CONCLUSION

The study indicates variations in the levels of certain cytokines,IL-18 and IL-10, in the serum of rheumatoid arthritis are not affected by age or gender, which means that these demographic factors are not associated with changes in the levels of these cytokines. The study also showed that patients with rheumatoid arthritis have high levels of these two cytokines compared to healthy people, highlighting their role in the inflammatory process associated with this disease. Despite the joint rise in the concentrations of interleukin-18 and interleukin-10, there was no strong or moral association between them, suggesting that these cytokines may function independently in the disease. These findings could guide future research towards a deeper understanding of the role of these cytokines in causing disease and the development of therapies that target multiple pathways to control inflammation, especially in the absence of a relationship between interleukin-18 and interleukin-10.

CONFLICTS OF INTEREST

The authors assert no conflict of interest

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