Role of Some Immunological Markers in Iraqi Patients with Rheumatoid Arthritis and Salmonella Typhoid

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Abstract:

The study aimed to investigate the role of some immune indicators in Iraqi patients with rheumatoid arthritis and Salmonella typhi. The current study was conducted on a sample of Iraqi patients with rheumatoid arthritis and Salmonella typhi, as blood samples were collected from 60 patients with rheumatoid arthritis and infected with Salmonella typhi bacteria with ages ranging between 21-70 years, the number of females was more than the number of males with a significant difference of P<0.001 where the number of females was 55 and by 91.7% while the number of males was 5 and by 8.3%. For the purpose of comparison, 28 other blood samples were collected from healthy people (healthy control) ranging from Between 21-60 years, the number of males was 5, by 17.9%, and the number of females was 23, by 82.1%. The association between several immune markers and rheumatoid arthritis and Salmonella typhi was also studied, includingcyclic citrullinated peptides antibody anti, alpha 1 alpha, alpha albineoplasmosis 33, alpha albicanosis 36 alpha, IgG immunoglobulin and IgM immunoglobulin. The results indicated a statistically significant increase (P<0.001) in the concentration of Cyclic citrullinated peptides antibody in blood samples of rheumatoid arthritis patients and Salmonella typhi patients compared to healthy control sample, where the average blood protein in a patient sample was 406.62 mg/L compared to 66.07 mg/L in a healthy control sample. And that there was a significant increase (P<0.001) in the level of interneuloidal 1 thousand in the blood sera of the patient sample compared to its level in the blood serum of the healthy control sample. The concentration of these antibodies in the blood sera of the healthy control sample was 1.36 U/ml compared to 2.87 U/ml in a sample of patients with rheumatoid arthritis and Salmonella typhi. The results also indicated a high significance (P<0.001) in the concentration of interleukid-33 in the blood serum of a sample of rheumatoid arthritis patients and Salmonella typhi patients compared to healthy control, where the average concentration was 19.09 mg/dL in the patient sample and 8.18 mg/dL in the healthy control sample<.) in the interneoplasmic rate of 36 thousand in blood serum of samples of rheumatoid arthritis patients and Salmonella typhi patients, which is 284.65 compared to the healthy control sample, which is 238.59 ng/l. The results indicated a statistically significant increase (P<0.001) in the serum rate of IgG immunoglobulin in the blood serum of samples of rheumatoid arthritis patients and Salmonella typhi, which is 3.39 (ug/ml).) compared to the healthy control sample of 0.72 (ug/ml). This indicates that these immune indicators above can be considered very important immunological indicators for the diagnosis of rheumatoid arthritis.

Keywords: rheumatoid arthritis, Iraqi, Markers, Immunity.

1. Introduction:

Rheumatoid arthritis is one of the most widespread and oldest rheumatic diseases described by the French doctorBeauvais Landré- in 1800, it is a long-term chronic inflammatory autoimmune disorder that mainly affects the synovial joints and contributes to recurrent inflammation of the synovial membrane, most of which are concentrated at the level of the joints of the hand, foot and knee as well as many other joints, which ultimately leads to joint destruction and deformity. Disability, this disease affects almost all countries of the world in varying proportions (Karami et al., 2019). Rheumatoid arthritis is a systemic disease, in addition to mainly joint injuries, which can cause obvious effects of extra-articular manifestations such as the eye, skin, heart, lung and nerves. It is also an autoimmune disease, where when injured, imbalances occur in the immune system, which attacks the joints of the body, causing erosion of cartilage and bone, with the appearance of many external manifestations of articulation, as the actual mechanism causes the

invasion of the joints by the immune system. These immune system responses cause inflammation and proliferation of the joint capsule and also affect cartilage and bone (Gioia et al., 2020). Although the etiology of rheumatoid arthritis has not yet been fully identified, a combination of genetic and environmental factors as well as many other autoimmune related factors are thought to be a major cause of the disease (Lin et al., 2020).

The synovial membrane of patients with rheumatoid arthritis has a complex network of cellular motility associated with the development of rheumatoid arthritis. B cells in the peripheral blood of rheumatoid arthritis patients can secrete many cellular kinetics including CCL3, TNF-_, IFN-, IL-6, IL-1_, IL-17, and IL-18 (Wu et al., 2021). TNF-_ can increase RANKL expression by B cells in the presence of IL-1 _, thus promoting the formation of osteoclasts. Regulatory B cells (Breg) are a type of B cell that exerts immunosuppressive functions. Breg cells are primarily responsible for the production of anti-inflammatory cellular kinetics (IL-10, TGF-_, and IL-35). Therefore, B reg cells may prevent the progression of rheumatoid arthritis (Luo et al., 2018). Breg cells are enriched Humanity is predominantly in transitional B cells (CD19+CD24hiCD38hi) and memory cells (CD19+CD24hiCD27 +) (Wu et al., 2021). Rheumatoid arthritis patients with disease activity had reduced the number of CD19+CD24hiCD38hi B cells in peripheral blood compared to patients with inactive disease or healthy individuals. These results indicate that CD19 + CD24hiCD38hi B cells The same regulatory function may fail to prevent the development of autoimmune and inflammatory responses in patients with active rheumatoid arthritis (Flores-Borja et al., 2013). In addition, CD19+CD24hiCD38hi B cells can reduce ACPA production while inhibiting the production of inflammatory factors such as IFN- and IL-21 by T cells in rheumatoid arthritis patients (Jang et al., 2022).

The study aimed to investigate the role of some immune indicators in Iraqi patients with rheumatoid arthritis and Salmonella typhi.

2. Materials and Methods:

The current study was conducted on a group of Iraqi patients visiting the consultation clinics for joint diseases at the Baghdad Teaching Hospital of the Medical City in Baghdad Governorate and all governorates of Iraq who are visiting the consulting clinic for the period between December 20 2021. Patients with rheumatoid arthritis and Salmonella typhi by specialist doctors and those undergoing treatment (biological, chemical, mixed). The clinical diagnosis in all cases was made according to the standards approved by the American College of Rheumatology (1997) Yu et al., 2014).

Blood samples were collected from patients and healthy people, by drawing 3 ml of venous blood and placed in plastic gel tubes and left at room temperature (25 ° C) for 5-10 minutes untilthe blood clot formed, then separated by centrifuge at a speed of 4000 cycles / minute for 5 minutes, then the blood serum was withdrawn and the serum samples were divided into three parts in the tubes of Abandand RF (Eppendorf Tubes) at a rate of 500 microliters per test tube and kept in freezing at a temperature of minus 38 °C until serological tests are performed.

Immunological tests

Immunological tests were conducted for the early detection of rheumatoid arthritis as well as to determine the severity and degree of infection in patients undergoing periodic treatment and infected with Salmonella typhi bacteria as well, and these tests were conducted in joint consulting laboratories andeducational laboratories in Baghdad Medical City, and these tests included each of the following:

Widal Test

The WEDAL test was used to investigate typhoid fever in the study group of patients with Salmonella typhi, and the Widal test kit consisted of small test tubes containing Salmonella antigens, which are the type that Salmonella typhi H and Salmonella typhi O, and the principle of action of the test depends on the affinity between *Salmonella* typ hi antigens. And antibodies formed in the serum of patients with typhoid fever and precipitation occurs after mixing drops by 30µl of the examination material with the patient's serum after that two drops of the aforementioned examination material were placed and by 30µl on a glass slide, then30µl of the patient's serum were added to each and mixed by a wooden stick and then moved the slide for two minutes and the agglutination was observed as the occurrence of agglutination is evidence that the test is positive (positive), and the lack of attribution means that the test is negative, Tarique and Haque, 2012).

The IL-1 concentration test α, IL 33, and IL **alpha-36** test using enzyme-linked immunosorpherence (IL-α 1) is a quantitative method for quantitatively

measuring and quantitatively identifying interleukins using the ELISA sandwich test for (60) patients with rheumatoid arthritis with typhoid bacteria and (28) healthy people, according to the instructions in the screening group .

Statistical analysis

Immunomodulatory and hematological parameters were first tested for the normal state (Kolmogorov-Smirnov and Shapiro-Wilk test). All parameters that fit both tests (no significant difference) were given as mean ± standard deviation (SD). The differences between the means were calculated by the test T and F (ANOVA). Other parameters were given as a percentage of frequencies, and statistically significant differences between frequencies were evaluated by Pearson-Chi-square testing. Pearson's binary correlation was used to understand the correlation between certain parameters. A receiver running property (ROC) curve was created for each parameter, thus estimating the area under the curve (AUC), sensitivity and specificity. SPSS v25.0 and Dashboard Prism v6 were used to perform these analyses. The distribution of genotypes and allele frequency was calculated according to the Hardy & Wienberg law.

3. Results and Discussion:

Immunological biomarkers (immunological biomarkers)

anti cyclic citrullinated peptides antibody

This indicator is one of the most important clinical indicators in the diagnosis of rheumatoid arthritis. The concentration of this protein in the blood increases when the disease occurs, and the increase is directly proportional to the severity or activity of the disease (Firooz et al., 2011).

The results shown in Table (1) indicate a statistically significant increase ($P<0.001$) in the concentration of cyclic citrullinated peptides antibody protein in the blood samples of rheumatoid arthritis patients and Salmonella typhi compared to the healthy control sample, where the average protein in the blood in the sample of patients was 406.62 mg/L compared to 66.07 mg/L in the healthy control sample.

These results are consistent with those of Cheng et al., (2020) in a study conducted on rheumatoid arthritis patients and those with microbial infections in the mouth, where protein levels were higher compared to healthy control samples. The results were also consistent with the results of this study by Manki et al. (2019) who indicated a significant increase in the concentration of anticyclic citrullinated peptides antibody For a sample of rheumatoid arthritis patients and those with microbial infections in the gums who suffer from severe disease, their study found that the bacteria in the mouth are a cause of high anti cyclic citrullinated peptides antibody and a reason for the exacerbation of the disease. Schwenzer et al. (2017) have also pointed out that rheumatoid arthritis patients have an increased level of anti-citrulline peptide antibodies that are excellent biomarkers of rheumatoid arthritis and are widely used in the diagnosis of the disease where they occur as a result of a breach of immune tolerance, it is still unclear what triggers their production and how it happens. In another study by Akiyama and Kaneko (2022) On rheumatoid arthritis patients in a sample of patients who had the disease progressed to the outside the joint, where it affects the lung and is known as meniscus pneumonia, an increase in the concentration of cyclic citrullinated peptides antibody antibody was found and these studies are consistent with the findings of our study.

Intreleukin- 1 alpha concentration

All members of the interleukin-1 (IL-1) family have vital roles in regulating both adaptive and innate immunity, which is involved in the pathogenesis of autologous, autoimmune and infectious inflammatory disorders. In addition, they systematically mediate inflammatory responses, including rheumatoid arthritis (Wang and Wang, 2021).

The results shown in Table (1) indicate a significant increase ($P<0.001$) in the level of interleukosis 1 thousand in the blood serum of a sample of patients with rheumatoid arthritis sclerosis and patients with Salmonella typhi compared to its level in the blood serum of a healthy control sample. The concentration of these antibodies in the blood sera of the healthy control sample was 1.36 units/ml compared to 2.87 Unit/ml in a sample of patients with rheumatoid arthritis and Salmonella typhi.

These results are consistent with the findings of Ruscitti et al ., (201 8) who indicated a significant elevation in the level of interleukosis 1 in blood serum in rheumatoid arthritis patients, and that the level of these antibodies increases with increasing disease severity, leading to increased secretion of cellular motility, and in a study by Tiao et al. (2016) on Pro-inflammatory markers, including cellular kinetics, such as interneopathy-1, 6, 7, 8 and tumor necrosis factor (TNF-α) are increased in rheumatoid

arthritis patients, and in a study by Selmi et al. (2014) on a group of patients with rheumatoid arthritis it was found that patients with rheumatoid arthritis Those who suffer from exacerbation of rheumatoid arthritis symptoms that there is an increase in the rate of cellular motility secreted as allebenoid 1 and that the high increase in the level of these cellular motility leads to the occurrence of secondary complications such as cardiovascular disease, which is the main cause of death in rheumatoid arthritis, as their study confirmed the need for inhibition of treatment for interneoplasmosis 1, which increases stress resulting from nitrogen oxidation.

Intreleukin-33 Concentration

This cellular motor of the cellular kinetics of the interneolithic family 1 is one of the new indicators that portend in the diagnosis of many autoimmune diseases, including rheumatoid arthritis, (Hueber, 2011).

The results shown in Table (1) indicate a high significant increase (P<0.001) in the concentration of interleukosis 33 in the blood serum of the sample of rheumatoid arthritis patients and Salmonella typhi patients compared to healthy control where the average concentration was 19.09 mg / dL in the sample of patients and 8.18 mg / dL in the control sample of healthy patients.

These results are consistent with those of Palmer, (2009). In a study he conducted on the effect of interovalosis 33 on arthritis, he found an increase in its concentration in patients, which causes damage and destruction. In another study by Kondo et al., (2021) on the effect of some cellular motility, including interneoplasmosis 33 and its increased incidence in rheumatoid arthritis patients. Various studies have shown the importance of IL-33 in inflammatory arthritis, which usually studies mouse models of the disease, showing that IL-33 can exacerbate rheumatoid arthritis, depending on the mast cells present in patients. The use of an antibody-induced arthritis model provided further evidence that mast cells are necessary for inflammation mediated by interneoplasmosis 33 in arthritis. This cellular motor is present in the synovial membrane in rheumatoid arthritis patients (Choi et al. 2009). In a study conducted by Matsuyama et al. (2010) on 59 samples of rheumatoid arthritis patients, it was found that interneoplasmosis 33 Blood is significantly higher in rheumatoid arthritis patients, especially in the high disease activity group compared to the moderate or low activity group, and the study also confirmed that the production of interneoplasmosis 33 is mainly in inflamed joints; and its high concentration has an important role in human rheumatoid arthritis. This is identical to the results of our study, but there is no previous study that linked the effect of interneoplasmosis 33 on patients with rheumatoid arthritis and Salmonella typhi, so our study is the first of its kind. While the results were contrary to their findings (Wu et al., 2021) that showed a large number of rheumatoid arthritis patients have low levels of IL-33 in blood serum but still show high activity of the disease, the reason for the high levels of leukothemia in the blood serum and synovial fluid of rheumatoid arthritis patients is due to the fact that it induces the activation of mast cells neutrophil migration and the production of pro-inflammatory cellular kinetics by Macrophages, which are considered a serious indicator of the disease (Zhu et al., 2018). There are no previous studies that have studied rheumatoid arthritis and people with Salmonella typhi with this indicator, so our study is the first of its kind.

Interleuken-36 Alpha concentration

This interleutoid is a component of the 1 alpha interneukomotor family and a high expression of 36 alpha interneubicans is found particularly in epithelial tissues and keratinocytes. In addition, preliminary studies have shown that IL-36α mRNA is expressed in leukocytes (Frey et al. 2013). Interleukosis 36 is found mainly in leukocyte infiltration as well as the endothelial layer, and in synovial tissue in rheumatoid arthritis

The results shown in Table (1) indicate a statistically significant increase (P<0.001) in the interneoplasmosis rate of 36 thousand in the blood serum of rheumatoid arthritis patients and Salmonella typhi patients, which is 284.65 compared to the healthy control sample, which is 238.59 ng/l.

These results are consistent with the findings of Frey et al. 201 3 where it was found that there was an elevation of intraleukosis levels 36 in the blood serum of rheumatoid arthritis patients, which is regulated in the synovial tissue of patients. In a 2019 study by Yuan et al. on the effect of interneoplasmosis 36 on a group of systemic inflammatory diseases , including rheumatoid arthritis, where interneoplasmosis 36 thousand and its receptors were detected in synovial tissues. In rheumatoid arthritis patients, the expression of interneoplasmosis in synovial tissue was higher in

rheumatoid arthritis patients than in arthritis patients with osteoporosis, and in the same study carried out by (Frey et al. 2013) it was found that the increase in interneoplasmic production associated with synovial cells increases the production of interneoplasmosis 6 and interneoplasmosis 8. et al., (2013) were highly expressed in the joints of mice with collagen-induced arthritis, where limited data indicated that interneoplasmosis 36 may be associated with rheumatoid arthritis in a range of chronic systemic inflammatory joint disease and psoriatic arthritis, 36,000 interneoplasmosis expression could be detected in the synovial endothelial layer and in cell leaks of patients. The expression of white interval was 36 thousand higher in patients with psoriatic arthritis compared to patients with osteoporosis. The presence of synovial plasma cells is believed to be the main source of expression of interneudistaneous in rheumatoid arthritis. , as well as for markers specific to the cell. Since 36,000-positive interleukemia cells were closely associated with leukocyte infiltration while it was also found to be shared with plasma cells in the synovial membrane (Frey et al. 2013). Note that all previous studies have dealt with the disease without typhoid, making our study the first of its kind that brought together patients with rheumatoid arthritis and those with Salmonella typhoid and interneoplasmosis 36.

Table 1: Rates of measurement of some immune indicators among study groups using the T test **compared to healthy control***

Groups		N	Mean	SD	P value
Anti-CCP antibody (U/ml)	patients	60	406.62	178.28	P<0.001***
	healthy	28	66.07	12.06	
IL-1 alpha (ng/l)	patients	60	2.87	0.96	P<0.001***
	healthy	28	1.36	0.49	
IL-33 (ng/l)	patients	60	19.09	6.69	P<0.001***
	healthy	28	8.18	2.58	
IL-36 alpha (ng/l)	patients	60	284.65	66.19	P<0.001***
	healthy	28	238.59	64.98	

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