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Assessment of cytokine profile in rheumatoid arthritis patients

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Abstract--Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily affects small joints, characterized by inflammation and cellular proliferation in the synovial lining of joints that can ultimately result in cartilage and bone destruction. This study aims to detect the IL-6 and TNF- α in addition to assess some diagnostic parameters in 105 Rheumatoid arthritis patients and compared with healthy individuals as control. The mean level of ESR and CRP in RA patients were increase significantly ($P < 0.05$) in (81.25 ± 14.35 and $224 \pm$ mg/dl), respectively than control. The mean IL-6 and TNF- α serum level were significantly higher ($p \leq 0.05$) in RA patients (197 & 308) pg/ml, respectively compared to the control (5 & 57) pg./ml. There was no significant correlation between anti-CCP with RF, IL-6, TNF- α ($p \geq 0.05$) and only significant with RA33.

Keywords---Rheumatoid arthritis, IL-6, TNF- α , CRP, ESR, anti-ccp.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that primarily affect small joints, characterized by inflammation and cellular proliferation in the synovial lining of joints that can ultimately result in cartilage and bone destruction (Al-Mughales ,2015). The inflammatory process of Rheumatoid arthritis is convoluted by many factors genetic, environmental and others. The synovial joint is infiltrated with T cells, B cells, macrophages, plasma cells along with cytokines, fibroblasts, growth factors, chemokines, adhesion molecules and matrix metalloproteinase. (Lee *et al.*, 2012). Several studies were conducted for evaluation the role of inflammatory cytokines such as IL1- α and

TNF- α in rheumatologic disorders to find new treatment methods base to pathogenesis. They described successful treatment of refractory arthritis in patients with RA by infusion of antibodies against tumor necrosis factor – alpha (TNF- α), suggesting a key role for this cytokine in the pathogenesis of chronic arthritis (Alm *et al.*, 2018). TNF- α levels are raised at prime sites of inflammation in convinced autoimmune diseases, including the synovial fluid of patients with rheumatoid arthritis and the synovium and sacroiliac joints of patients with ankylosing spondylitis (Grine *et al.* . 2015). Interleukin-6 (IL-6), released by T cells, fibroblasts, monocytes and macrophages, promotes B cell differentiation and maturation, causing proliferations in the production of rheumatoid factor (RF). Moreover, IL-6 enhances bone resorption, induces the acute phase response (erythrocyte sedimentation rate ESR, C-reactive protein CRP), and stimulates the proliferation of synovial fibroblasts that cause tissue and cartilage destruction by releasing matrix metallo proteinases ((Straub *et al.*, 2006). This study aims to detect cytokines profile (IL-6, TNF- α , CRP) in RA patients.

Materials and Methods

This case control study was carried out on 105 patients that were attending the Rheumatology out patient’s clinic in Al-Sadder Medical City and other hospitals in Najaf/Iraq, during the period between December, 2021 to August, 2022. All patients diagnosed according to 2010 American college of Rheumatology/ European league Against Rheumatism (ACR/EULAR) .Forty five (45) age and gender matched healthy subjects taken as control .Patients with other inflammatory autoimmune disease were excluded from the study. All patients were subjected to full history taking, thorough clinical examination and laboratory investigations including erythrocyte sedimentation rate (ESR) , C-reactive protein (CRP), rheumatoid factor (RF) by nephelometry method, using automated analyzer (Genius 120). Measurement of serum interleukin-6level and TNF - α were performed by a commercial ELISA kit for RA patients and control subjects. According to the instruction of the manufacturer by Solar bio company, China. From each subject 5ml of venous blood was aspirated ,sera were separated by centrifugation and were stored at -20 centigrade and tested. serum samples were collected from patients on the same day of examination.

Results and Discussion

The mean level of ESR were increase significantly ($P \leq 0.05$) when compared RA patients(79.3 ± 16.3) than control group (5.3 ± 2.1) as show in Figure (1) . These results were agreement with (Abbas *et al.*, 2014) and Chiad (2015) who appears RA patients have higher value of ESR than that for healthy control group. (Birrell, *et al.*, 2000) and Cock *et al.* (2014) reported that ESR is increased in nearly all patients with active RA. The higher rate of sedimentation resulted from the presence of large symmetric molecules in plasma which accelerates the Rouleau formation and setting of RBC. The most important of these molecules are fibrinogen. ESR is the cheapest test, but can easily be influenced by anemia and hyperglobulinemia which frequently present in RA.

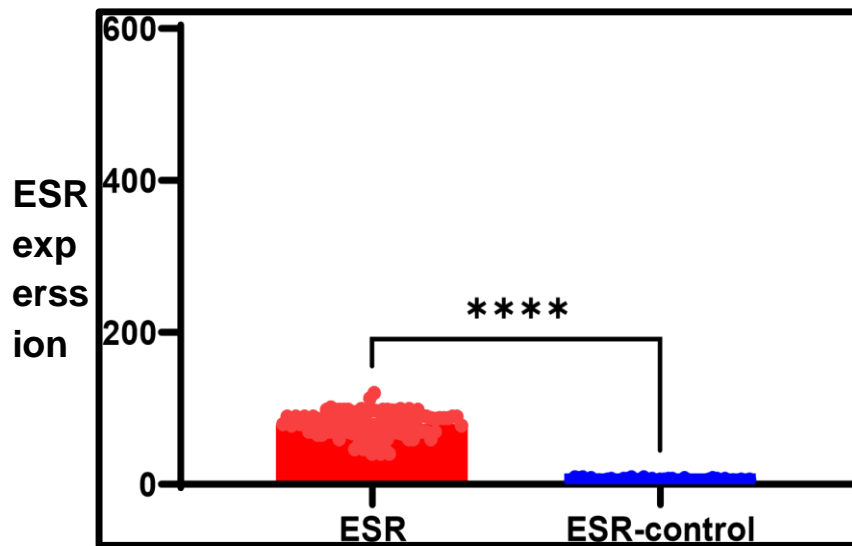


Figure 1: The mean serum concentration level of ESR (mm/h) in RA patients & control

Detection of CRP in RA patients

The results in the figure (2) appear that the mean level of CRP in case group was increase (67.9 mg/dl) significantly than control. It is an important acute phase protein and is a prominent indicator of disease activity in RA as well as other conditions. The increased levels of it indicate uncontrolled disease or a flare, while the reduced levels indicate disease remission or chronicity (Chiad ,2015). The statistical results of this study refers to the high frequency of positive serum CRP test which was significantly found among RA patients 66.7% compared with 36.1% in control group (P value = 0.004) and OR (3.54). This result was nearly compatible with Al Kurdi,*et al.*(2014)who reported that 72.4% of RA patients were positive for CRP compared with 8.0% for control group . While, results of (Akeel, 2014).showed that 90% of RA patients were positive for CRP compared with 5.0% CRP positivity in control group. Chiad (2015) appear that the mean level of CRP in control group was (4.20 ± 0.09 mg/dl) whereas the mean titer of control group This differences demonstrated in CRP positivity rate among RA patients may be due to the variable stages of the disease (Al-Obeidy et al 2011).

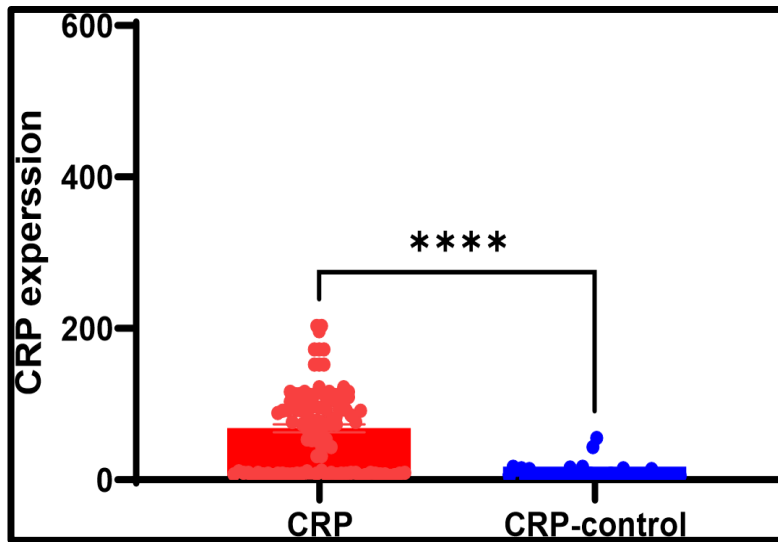
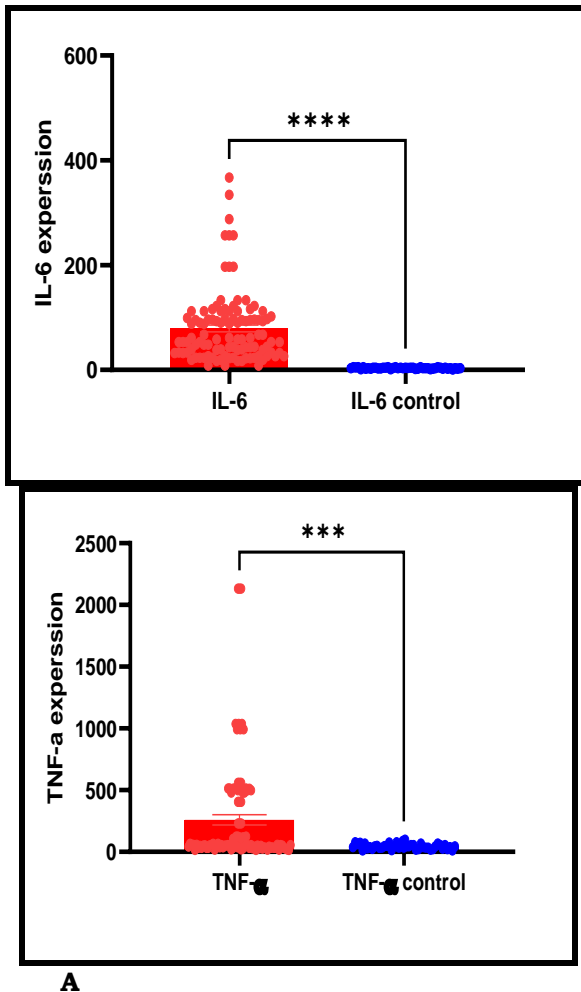


Figure 2: The mean serum concentration level of CRP (mg / L) in RA patients & control

IL-6 and TNF- α serum level

The mean IL-6 and TNF- α serum level were significantly higher in RA patients (197 & 308) pg/ml, respectively compared to the control (5 & 57 pg/ml) ($p \leq 0.05$) (Fig.3(A&B)). According to age group there were a higher significant difference ($p \leq 0.001$) in the mean level of IL-6 in group 1,2,3 patients with group 4 as in figure (4 A), while there was no significant difference between all age groups in TNF- α (figure 4B).



A **B**
Figure 3: The mean serum concentration level of TNFα (A) and IL-6 (B) in RA patients & control

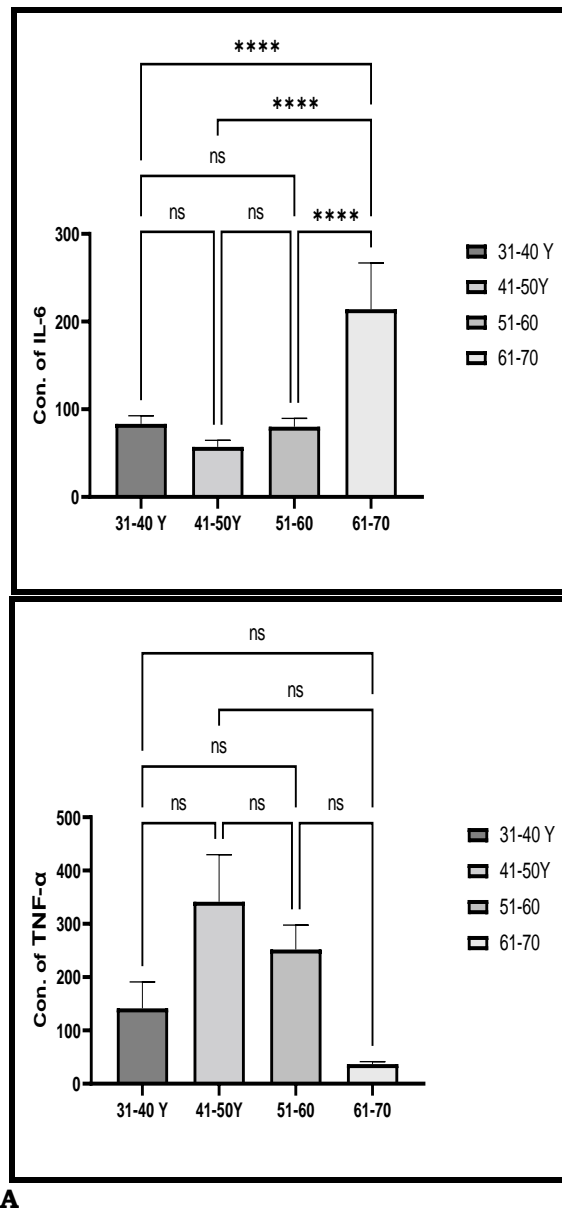


Figure 4: The mean serum concentration level of TNF α (A) and IL-6 (B) at different ages in RA patients & control

The previous studies mentioned that inflammatory cytokines, such as interleukin 1(IL-1 α) have been implicated as important mediators in inflammatory diseases for instance, in patients with RA beside other cytokines can be elevated productions in RA sera such as IL-2R Alessandri et al.(2004). In another previous study Alsheikh *et al.* (2019) reported IL-23 could be a useful marker for disease activity in RA. Its correlation with RASS suggested that IL-23 might be a therapeutic target for prevention of disability.

Correlation of CCP with RF, RA33, IL-6, and TNF- α

The correlation of anti -ccp with other factors in this study were appeared in figure (4.12 A,b ,c,d).there were no significant difference between anti-ccp with RF ,IL-6, TNF- α ($p \geq 0.05$) and there was significant difference with RA33($P \leq 0.05$), as in figure 5.

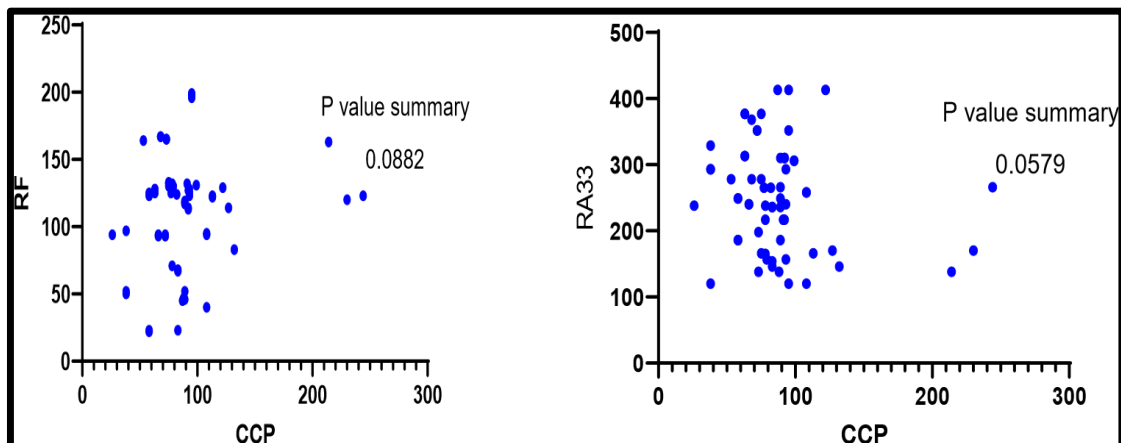
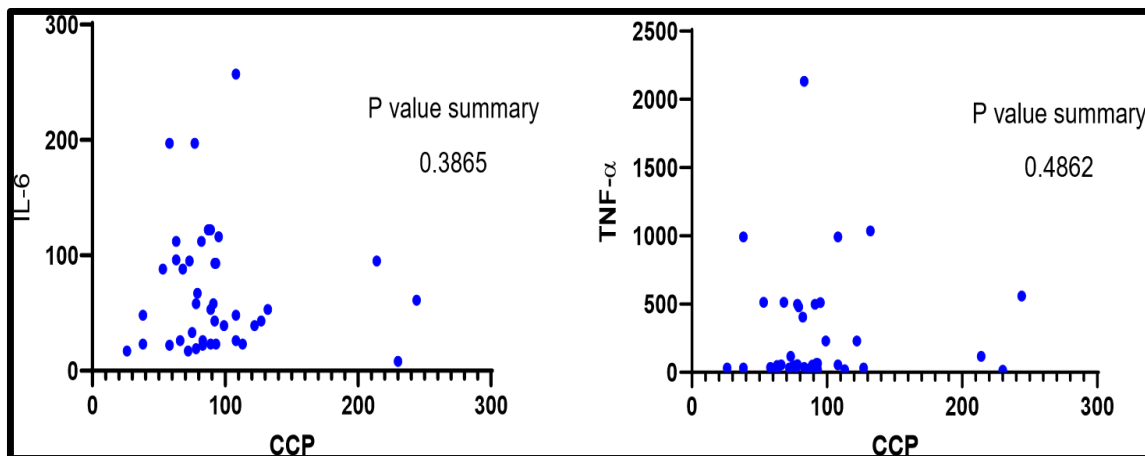


Figure 5: Correlation of Correlation of RA patients RA patients



Figures 6: Correlation between anti-CCP and different markers levels in RA patients: RF, RA33, IL-6 and TNF-a.

Conclusion

There was no significant correlation between anti-CCP with RF, IL-6, TNF- α ($p \geq 0.05$) and only significant with RA33.

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