EVALUATION OF IL1-α AND TNF-α SERUM LEVELS IN RHEUMATOID ARTHRITIS PATIONTS WITH ACTIVE AND INACTIVE, WITH OR WITHOUT BONE EROSION

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Abstract- Rheumatoid arthritis is the most common inflammatory joint disease with 1 percent prevalence in community which presents with symmetrical polyarthritis of hands with inflammatory behavior. Several studies in recent years were conducted for evaluation of inflammatory cytokines such as IL1-α (Interleukin 1α) and TNF- α (Tumor necrosis factor) in rheumatologic disorders including rheumatoid arthritis to find new treatment methods base to pathogenesis. In this study different serum levels of IL1-α and TNF- α in 160 rheumatoid arthritis patients with active and inactive disease and also disease with or without bone erosion are assessed. 4% of our patients had rheumatoid nodule and 70% of all patients had positive RF, IL1-α, and TNF- α levels. Active with bone erosion patients had IL1-α and TNF- α serum levels higher than active without bone erosion patients; it was not significant in T-test but it was significant in Mann-Whitney Test. The results was the same as expected; IL1-α, and TNF- α serum levels were higher in active with bone erosion in comparison with inactive without bone erosion patients.

INTRODUCTION

Rheumatoid arthritis is the most common inflammatory joint disease which presents with symmetrical polyarthritis of hands with inflammatory behavior, and extra articular manifestations. The disease initially involves synovium membrane of joints.

The disease prevalence is about 1 percent so 700000 of 70000000 population in Iran have rheumatoid arthritis and severe disability will result with delay in diagnosis and treatment. Despite of effects on life quality, rheumatoid arthritis has direct and indirect effects on patients and their society.

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Statistics of other countries consider rheumatologic disorders as second most common causes of disability and disablement.

Several studies in recent years were conducted for evaluation of inflammatory cytokines such as IL1-α and TNF- α in rheumatologic disorders including rheumatoid arthritis to find new treatment methods base to pathogenesis. These studies reveal disequilibrium between stimulatory and inhibitory mechanisms in inflammatory disorders such as rheumatoid arthritis and cytokines (IL1-α, & TNF-α) have a leading role in pathogenesis (1-5).

According to improper treated rheumatoid arthritis as a prevalent and disable disease, recognition of pathogenesis and suitable treatment base to pathogenesis is a necessity for prevention of disease adverse effects. Diversity in epidemiological factors such as sex, age, prevalence, pathogenesis, clinical and laboratory findings related to genetics and environmental conditions makes regional and ecological studies a fundamental approach to this

disease. In this study different serum levels of IL1-α and TNF- α in rheumatoid arthritis patients with active and inactive disease and also disease with or without bone erosion are assessed. Moreover, patient's history and physical examination besides their radiologic pictures, take in account in our study. Our study would be a unique in its field. TNF-α has synergism in stimulation of other cytokines. IL-1α and TNF-α stimulate each other too. Moreover IL-1α stimulates itself (6, 7).

Fiege *et al.* show that: Continuous infusion of 200 ng/day hrIL-1 alpha for 14 days into knee-joints of rabbits leads to a severe arthritis of low aggressivity and these results indicate that IL-1 might play an important role in the induction and maintenance of arthritis (8).

Graudal *et al.* try to investigate the possible association of interleukin 1 auto antibodies (IL1 aAb) with the long term course of joint erosion in patients with rheumatoid arthritis (RA). Serum samples from 176 patients with RA included in a prospective study over 30 years were analyzed for IL-1α Ab by binding to human [125I] IL1. Patients who seroconvert more than two years after the onset of RA showed the most aggressive development of joint erosion, with a relative risk of at least 40% of maximum radiographic joint destruction of 2.56 (p=0.048) The progression of radiographic joint destruction in patients with RA is associated with, and perhaps modified by, circulating IL-1α Ab, suggesting that IL1 or IL-1α Ab, or both, have a role in the erosive processes. IL-1α Ab appear to be of prognostic significance in RA (9).

Eastgate JA (1991), Chikaza IC (1995), and Suzuki (1989) revealed less inflammatory disorders in which IL-1α Antibody was positive. Moreover in Eastgate JA study; IL-1α and TNFα had direct relation with ESR (10). F Cominelli et al tried to show that Interleukin 1 (IL-1) was a key mediator of inflammation and tissue damage in inflammatory bowel disease (IBD) in an experimental study conducted on rabbits (11). Early cartilage and bone erosion is associated with the accumulation of several cell populations in the synovial membrane (SM) and the formation of a proliferating pannus relating to IL-1α. The interface between pannus and cartilage is occupied predominantly by activated macrophage populations and synoviocytes capable of secreting destructive proteases in abundance. There was also a relation between bone destruction and IL-1α; however TNF has a more prominent association than IL-1α (12).

MATERIALS AND METHODS

This study is a cross sectional study conducted on rheumatoid arthritis patients who were admitted in rheumatology clinic of Shariati hospital (2003). First we choose 160 patients randomly considering inclusion and exclusion criteria; and then they divided to four groups by physical examination and radiographic findings.

The groups including: active or inactive disease with bone erosion and active or inactive disease without bone erosion. In each group 5 cc blood sample was taken and serum levels of IL-1α and TNF-α were measured by laboratory kits and Elisa method. Other hematological factors such as hemoglobin, platelet, rheumatoid factor, erythrocyte sedimentation rate, and CRP were evaluated in routine laboratory techniques. Data gathered in questionnaires and entered in SPSS soft ware and analyzed by statistical methods including t-test, Mann-Whitney considering parametric and nonparametric variables.

Inclusion criteria including: joint rheumatism disease as defined in ACR diagnostic criteria, disease duration more than 1 year, prednisolone less than 15 mg per day, no usage of cytotoxic drugs; otherwise patients were excluded.

American College of Rheumatology (ACR) diagnostic criteria including: morning stiffness more than one hour, arthritis of more than 3 joint groups, arthritis of hand, symmetrical joint involvement, rheumatoid nodules, positive rheumatoid factor, radiographic changes(erosions and local decalcifications). Patients with 5 criteria for 2 months were considered active, otherwise they considered inactive. Disease remission defined as: morning stiffness less than 15 minutes, no pain in joints, no tenderness during joint motion, no fatigue, no swelling, ESR less than 20 in male and 30 in female.

RESULTS

In our study from 126 patients, 84 were female and 16 were male. Age average was 48.02 years old. follow up duration was exceed up to 25 years (average=90 months).

Physical examination of patients showed 4% rheumatoid nodule, 10.3% ulnar deviation, 2.4% hammer toe, 7.1% swan neck, and 10.3% butonier (Fig. 1).

Laboratory findings showed 70% positive rheumatoid factor, higher levels of CRP in active patients with bone erosion in comparison with inactive and those without bone erosion (Fig. 2).

Hemoglobin was lower in active patients in comparison with inactive ones but it was not statistically significant. Platelet was higher in active patients in contrast to inactive ones but the difference was not significant. ESR in active patients had a significant rise in comparison with inactive patients. Majority of patients had joint erosions in radiographs (90%).

Active patients had higher serum levels of IL-1α and TNF-α in comparison with inactive patients. Serum level of TNF-α in active patients was 93.471 and in inactive patients was 91.616, but the difference was not statistically significant (P= 0.821).

Serum level of IL-1α in active patients was 85.416 and in inactive patients was 81.368, but the difference was not statistically significant (P= 0.766) (Fig. 4). Patients with bone erosion (97) had higher serum levels of IL-1α and TNF-α in comparison with patients without bone erosion (63).
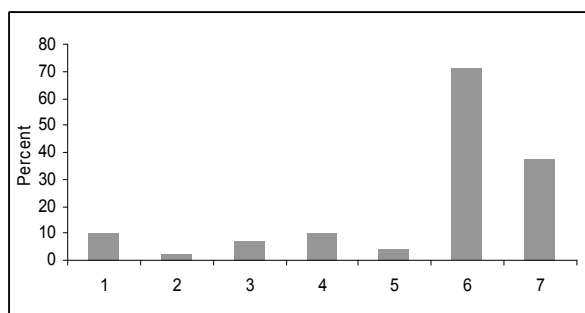

Fig. 1. Physical examination and laboratory findings in patients. 1, Butonnier; 2, Hammer Toe; 3, Swan Neck; 4, Ulnar Deviation; 5, Rheumatoid Nodule; 6, RF+; 7, CRP+.
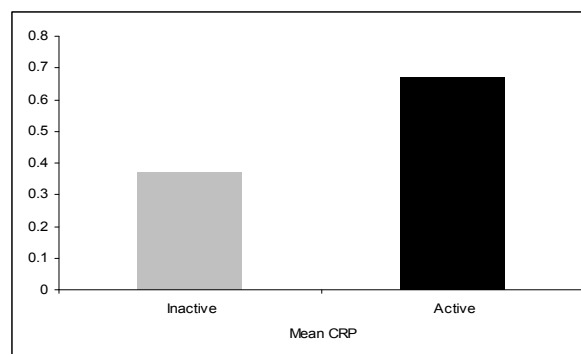

Fig. 2. Comparison of CRP in active patients with bone erosion and those without bone erosion.

Serum level of TNF-α in patients with bone erosion was 96.130 and in patients without bone erosion was 82.449, but the difference was not statistically significant ($P = 0.347$).

Serum level of IL-1α in patients with bone erosion was 86.210 and in patients without bone erosion was 77.471, but the difference was not statistically significant ($P = 0.655$) (Fig. 5).

Active patients with bone erosion (39) had higher serum levels of IL-1α and TNF-α in comparison with active patients without bone erosion (34).

Serum level of TNF-α, in active patients with bone erosion was 102.261 and in active patients without bone erosion was 59.557; the difference was not statistically significant by *t* test method, whereas it was significant by Man-Whitney method.

Serum level of IL-1α in active patients with bone erosion was 35.65 and in active patients without bone erosion was 19.89; the difference was statistically significant by Man-Whitney method (Fig. 6 and 7).
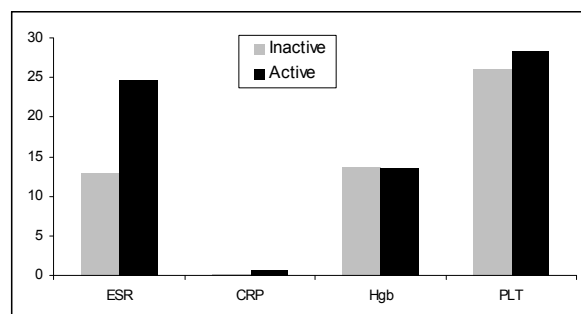

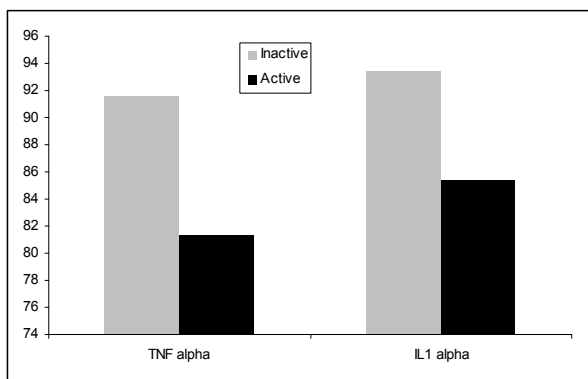**Fig. 3.** Mean of ESR (mm/houer), CRP, Hgb (mg/dl), and Platelet (×1000) in active and inactive disease.

Fig. 4. Serum levels of IL-1α and TNF-α in active and inactive patients.

Fig. 6. Serum levels of IL-1α and TNF-α in Active patients with bone erosion and those without bone erosion (T-test).

Inactive patients without bone erosion (29) had higher serum levels of IL-1α and TNF-α in comparison with inactive patients with bone erosion (58). Serum level of TNF-α in inactive patients without bone erosion was 103.051 and in inactive patients with bone erosion was 88.576, but the difference was not statistically significant ($P= 0.445$). Serum level of IL-1α in inactive patients without bone erosion was 85.067 and in inactive patients with bone erosion was 82.070, but the difference was not statistically significant ($P= 0.883$) (Fig. 8).

In this study we measure serum levels of IL-1α and TNF-α in rheumatoid arthritis patients with active or inactive disease and with or without bone erosion. Our results showed the same outcomes as other studies except that of higher levels of IL-1α and TNF-α in inactive patients without bone erosion in comparison with inactive patients, however the difference was not statistically significant (1-4, 9). Sex and age range of rheumatoid arthritis in our study was the same as textbooks (female= 84%, male=16%, age average= 48).

DISCUSSION

Several studies in recent years were conducted to confirm the role of inflammatory cytokines (IL-1α and TNF-α) in the pathogenesis of rheumatoid arthritis. Disequilibrium between stimulatory and inhibitory factors has a fundamental role in pathogenesis (1-5).
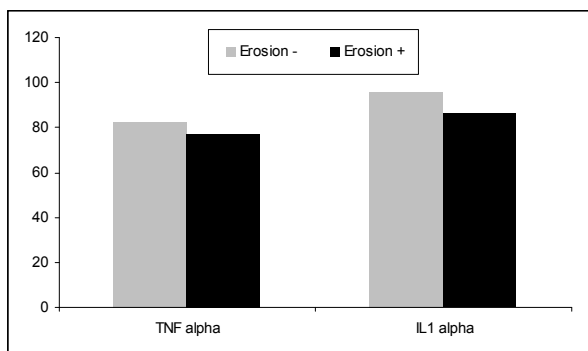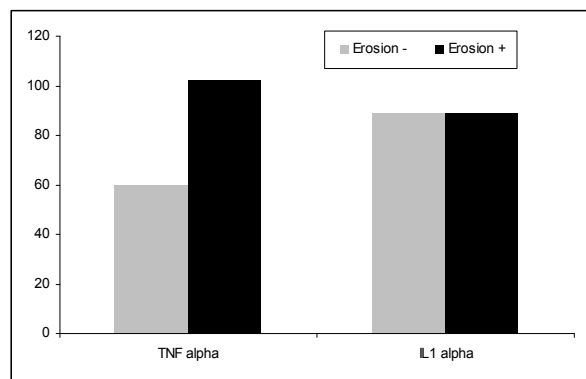
Follow up interval as indicated in rheumatology textbooks can exceeds up to 20 years and it was25 years in our study (Follow up interval average= 90 months) (1, 2). Just 5 patients (4%) had rheumatoid nodules which are in contrast with other statistics (30%), however the less prevalence of rheumatoid nodules in Asian race was previously reported.
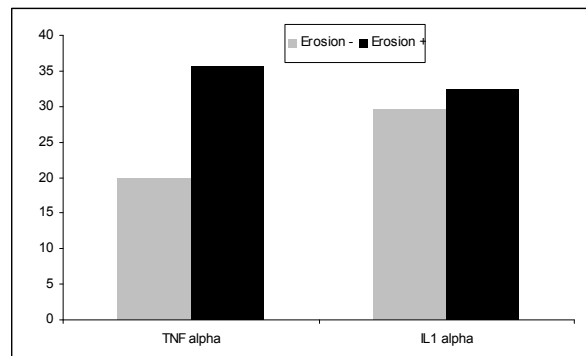

Fig. 5. Serum levels of IL-1α and TNF-α in patients with bone erosion and those without bone erosion.

Fig. 7. Serum levels of IL-1α and TNF-α in active patients with bone erosion and those without bone erosion (Mann-Whitney).
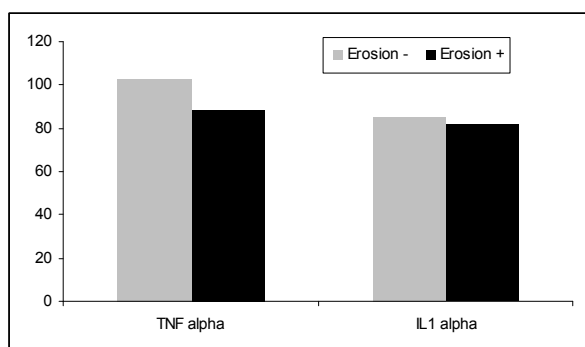
Fig. 8. Serum levels of IL-1α and TNF-α in inactive patients without bone erosion and those with bone erosion.

Rheumatoid factor was positive in 70% of patients which was the same as other references (85%). ESR was higher in active patients in comparison with inactive patients and it was statistically significant. (Active= 24.71, inactive= 12.85, *P*= 0.000). ESR may be in normal range in active patients but it relates to disease activity and it was confirmed in our study too (10). CRP had high levels in 37.4% of patients and it was higher in active patients in comparison with inactive patients and it was statistically significant (Active= 0.54, inactive = 0.11, *P*= 0.000). Radiographs in majority of patients had erosions (84%) and 90% had decalcification. Juxta-articular osteopenia and bone erosion especially in RF+ patients were reported in several textbooks and it was the same in our study. In conclusion, however in many items which were evaluated in our study the differences were not statistically significant but they were the same as predicted, it means that serum levels of IL-1α and TNF-α in active patients with bone erosion was higher than that in other groups but it was not statistically significant. So as indicated in other international results, serum levels of inflammatory factors such as IL-1α and TNF-α could be in association with rheumatoid arthritis pathogenesis. As a result, anti inflammatory drugs against IL-1α and TNF-α would be a useful treatment mode and this hypothesis needs more clinical trials for confirmation.

Conflict of interests

The authors declare that they have no competing interests.

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