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Serum Matrix Metalloproteinase-3 Levelin Iraqi Patients With Ankylosing Spondylitis And Its Relationship With Treatment.

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ABSTRACT

Ninety (90) subjects were included in this study, sixty (60) of them (patient group) were diagnosed as established AS patients who were attending the rheumatology outpatient clinic of Baghdad teaching hospital, thirty (30) patients of them were on conventional treatment (steroid and/or cytotoxic drugs), while the other thirty (30) patients were on biological treatment (infliximab infusion) and other thirty (30) were apparently healthy control group.Mean serum level of matrix metalloproteinase-3 was statistically higher in patient group (4.42 ± 3.05 ng/ml) than control group (2.69 ± 2.57 ng/ml), and also was statistically higherin patients on conventional treatment (5.31 ± 3.16 ng/ml) than those on biological treatment (3.54 ± 2.70 ng/ml). The study shown that matrix metalloproteinase-3 was higher in patient group than control group and also was higher in patients on conventional treatment than in patients on biological treatment.

Keyword: Ankylosing spondylitis, Matrix Metalloproteinase-3.

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INTRODUCTION

Ankylosing spondylitis is one of the members of the spondyloarthritis, a family of disorders that are characterized by inflammation around the enthesis (the site of ligament insertion into bone) and an association with the human leukocyte antigen HLA-B27 (1).

The immunopathogenesis of AS is suspected to involve up regulation of proinflammatory cytokines. The dramatic response of AS patients to TNF blocking agent indicate that there is important contribution of TNF-α in the pathogenesis of AS (2).

Immunohistology shows T cells, B cells, bone marrow macrophages, and cells involved in neoangiogenesis (3). The classical site is at the Achilles tendon. Here, the ligaments and tendons interdigitate into cancellous bones through fibrocartilage connections. The enthesis at the Achilles tendon suffers repeated damage and repair even in normal subjects, but, in AS, the process becomes clinically significant (4). In addition to enthesitis, peripheral synovitis is also present in some patients with AS. The synovitis is characterized by hypervascularity and infiltration by macrophages, T cells, and B cells (5).

Matrix metalloproteinases (MMPs) play an important role in the degradation and remodelling of the extracellular matrix (ECM) as a pathological feature of chronic arthritis (6). MMPs are zinc-dependent endopeptidases, essential in normal biological functions, and participate in many pathological conditions (7). MMPs are produced by fibroblasts, macrophages, synovial cells, endothelial cells, neutrophils and chondrocytes in response to proinflammatory cytokines such as interleukin-1 and tumour necrosis factor-α (TNF-α) (8). Of the MMP family, MMP-1 (interstitial collagenase 1) is important in the degradation of articular cartilage. MMP-3 (stromelysin 1) hydrolyses a number of ECM components, including aggrecan, fibronectin, laminin and collagens and also activates several pro-MMPs, such as pro-MMP-1 and pro-MMP-9 (7).

MATERIALS AND METHODS

Kits and reagents: Human matrix metalloproteinase-3 ELISA kit (SHANGHAI YEHUA, China).

Patients: Sixty patients (55 males and 5 females) were attended to medical city, Baghdad teaching hospital, Department of Rheumatology outpatient clinic and biological therapy unit included in this study during period from beginning of October 2016 till end of October 2017, their mean age ± Standard deviation (SD) was (40.05 ± 8.02 years), thirty (30) patients of them treated with biological agent (intravenous infusion of Infliximab of 5mg/kg), and other thirty (30) patients treated with conventional treatment (steroid and/or cytotoxic drugs). The patients were comparedto thirty (30) apparently healthy individualsfrom central blood bank who were randomly selected as control group, written informed consents for the research were obtained from all the enrolled patients and controls.

Methods: From each individual three (3) ml of venous blood was aspirated and let clot at room temperature, then centrifuged to separate the serum which was collected in aliquots to store in(- 20 ºC) until needed for investigation of serum matrix metalloproteinase-3.

Statistical analysis: statistical analysis in this study was done using SPSS version computer software 20. T test was used to analyze the data, and calculation of mean difference, Fisher exact and Chi-square test for comparison of proportion, P-value of less than 0.05 was considered as statistically significant, P-value < 0.01 as highly significant and P-value < 0.001 as extremely significant.

RESULTS

This study was included sixty (60) patients with AS, fifty five 55 (91.6%) males & five 5 (8.4%) females, the male to female ratio was 11:1 as shown in figure-1.

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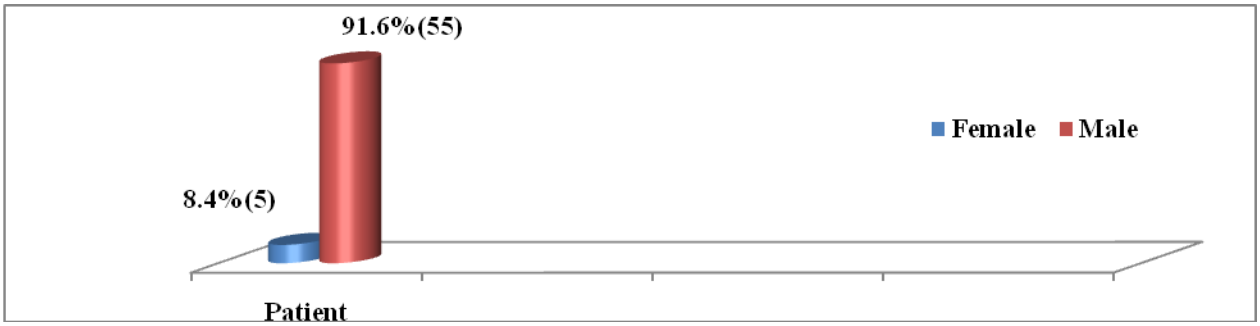

Figure 1: Distribution of patients according to their gender.

The mean age of patient group did not differ significantly from control group (40.05 ± 8.02 years vs 40.07 ± 7.20 years respectively, P > 0.05) as shown in table-1.

Table1: Mean age distribution with ± standard deviation for patient and control groups.

Group	Patients	Controls
Number	60	30
Mean (yr.)	40.05	40.07
Standard deviation	± 8.02	±7.20
P-value=0.99 Not statistically significant		

Serum levels of matrix metalloproteinase-3 (ng/ml) by using ELISA technique; the mean serum level was higher in patient group (4.42±3.05 ng/ml) than control group (2.69±2.57 ng/ml) and this difference was statistically significant (P-value =0.0093) as shown in Table-2.

Table2 : Results of serum levels ofmatrix metalloproteinase-3 (ng/ml) in patients and controls groups

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Group	Patients	Controls
Number	60	30
Mean (ng/ml)	4.42	2.69
Standard deviation	± 3.05	±2.57
P-value=0.0093 Highly statistically significant		

Table-3 showed that serum level of matrix metalloproteinase-3 (ng/ml) was higher in patients treated with conventional treatment(5.31±3.16 ng/ml), than in patients treated with biological treatment (infliximab infusion) (3.54±2.70 ng/ml)and the difference was statistically significant (P-value =0.0235).

Table3: Results of serum levels ofmatrix metalloproteinase-3 (ng/ml) inpatients treated with conventional treatment and other patients treated with biological treatment

Group	Conventional treatment	Biological treatment
Number	30	30
Mean (ng/ml)	5.31	3.54
Standard deviation	± 3.16	±2.70
P-value =0.0235 Statistically significant		

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DISCUSSION

Ankylosing spondylitis (AS) is a potentially disabling chronic inflammatory condition affecting the axial skeleton that is manifested by chronic back pain. The onset is typically before 45 years of age (9).

This study included sixty (60) patients with ASwho attended the rheumatology consultation clinic of Baghdad teaching hospital in the period between October 2016 to October 2017, thirty (30) of them treated with biological treatment and other thirty (30) treated with conventional treatment, and thirty (30) control healthy person.

Regarding the gender variation in the susceptibility to AS patients reported by the present study which showed that the disease is more predominant in males than in females with a ratio of 11:1, this result nearly in agreement with local study done by Rawaaet al who found that male to female ratio 14:1(10) which disagrees with chenet al who showed male: female ratio 3:1 (11) and this inconsistency might be attributed to low sample size of the present study.

Ankylosing spondylitis is a disease which occurs during the third decade of life (12), rarely at the age older than 45 year. About 10 -20 % of patients have the disease between 10 and 20 year of age (13). The mean age of the patients with AS in this study was 40.05 ± 8.02 years as shown in [Table-1], this result was nearly in accordance with previous study done on Iraqi AS patients by Rawaaet al that reported mean age of AS patient of 37.1±8.9 years (10), and other international study of Demirdalet al in AS Turkish patients that reported mean age of participated AS patient of 37.9±12.7 years (14).

This study showed that mean serum level of matrix metalloproteinase-3 (ng/ml) was higher in patient group (4.42±3.05) than control group (2.69±2.57) and this difference was highly statistically significant (P-Value=0.0093)as shown in [Table-2], this is because Matrix metalloproteinase-3 (MMP-3) play an important role in the pathogenesis of chronic arthritis and associated with disease activity, progression of structural damage of AS and these results are in accordance with previous study done by Chenet al(15) who found that MMP-3 had a significantly higher serum level in AS patients than in healthy individuals and disagrees with a study done by Yang et al(16) who showed no significant difference in serum MMP-3 levels between AS patients and healthy individuals. These differences in findings may be due to a difference in study population and also due to the analysis kits used, which measured different MMP-3 components.

With the advance in the treatment of AS with TNF blockers (17), it is imperative to evaluate disease activity and monitor therapeutic efficacy more accurately. Yang et al (16) showed that both serum MMP-3 levels and BASDAI decreased significantly after infliximab infusion. Maksymowychet al(18) also observed a significant correlation between change in BASDAI and change in serum MMP-3 levels in AS patients with 14 weeks of infliximab therapy. Taken together, serum MMP-3 could be of value in assessing AS disease activity both cross-sectionally and longitudinally, and acts as an indicator of response to biological therapies.

These findings are in accordance with our study in which we found that mean serum level of matrix metalloproteinase-3 was higher in patients treated with conventional treatment (5.31±3.16 ng/ml), than patients on biological treatment (infliximab infusion) (3.54±2.70 ng/ml) and this difference was statistically significant (P-value =0.0235) as shown in [Table-3].

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