Comparison of Clinical Course, Manifestations and Symptoms of Rheumatoid Arthritis Between Men and Women Referred to Two Medical Centers in Tehran

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Rheumatoid arthritis (RA) is a chronic disease with diffuse involvement of the body systems with unknown cause. The disease is characterized by continuous and persistent inflammatory synovitis with symmetric distribution in peripheral joints. The disease is more common in women than men and uneven sexual distribution is evident in different clinical classifications. Therefore, it is more likely that sexual factor, along with other aspects of the pathogenesis, affects the disease course and manifestations. The study aimed to examine gender differences in Iranian men and women. RA patients referred to two medical centers in 2005-2010 were studied. Demographic data was obtained by a questionnaire form. Data was analyzed by SPSS 16. The number of total patients referred was 438, 314 females and 124 males, with the mean age of 40.5 for women and 40 for men at the onset of study. The mean duration of illness before admission was 3.5 years for men and 4.2 years for women. The rate of swollen and involved joints was more in men than women. Joint deformity was not significantly different between male and female patients, but joint erosion was more in men than women. The average number of positive ACR criteria was almost equal between women (4.08) and men (4.17), but extra-extra-articular involvement was significantly higher in women than men. Rheumatoid factor was approximately the same and about 64% positive in both sexes and Anti-CCP was equal and approximately 43.5% positive. Drug and non-drug therapy had no significant difference between male and female patients. Given that rheumatoid arthritis is 2-4 times more common in women than in men sex hormones and factors associated with fertility have been proposed as a potential etiology of the disease. Gender involves in disease complexity by affecting the quality and quantity of disease inflammatory and functional consequences.

Key words: Rheumatoid arthritis, Gender, Autoimmune .

Rheumatoid arthritis (RA) is an autoimmune disease and affects the whole body organs, but its predominant manifestation is peripheral arthritis with symmetrical distribution. The first symptom of the disease is joint inflammation that involves the different joints of hands and feet and even the joints of cervical spine, shoulder, elbow, hip and knee. Over time, rheumatoid arthritis causes joint destruction and deformity and bone and cartilage inside the joint are gradually corroded. The deformation along the tendon sheath inflammation can cause other side effects. The clinical course and severity of the disease differs in different patients. Some people have mild disease with slow progression and in contrast, some others have a rapidly progressing disease. The most common age of disease incidence is 20 to 50 years old[1-3]. Although some significant steps have been taken to understand the disease cause and its consequences, the cause is still

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unknown. Although the prevalence of rheumatoid arthritis is 1% of general population in Western and African countries[1]; it is less common in Asian populations. The development of autoimmune diseases such as rheumatoid arthritis depends on the interaction of genetic and environmental factors. 50 percent of rheumatoid arthritis causes associate with genetics[4]. Environmental factors are known to cause the disease in other cases. It is an autoimmune disease in many cases, unless an additional event increases the expression of susceptibility to disease, such as environmental factors[5]. The prevalence of disease is being reduced in various parts of the world from 1960 (1), while its increased incidence was observed in women between 1995 and 2007 in a review[6]. Differences in increased or decreased incidence and heterogeneity among sexes in different studies need for further studies on the role of gender[7]. Rheumatoid arthritis may not be a single disease, but a syndrome characterized by a number of clear diseases and different etiology[8]. So, it seems to be necessary to study various factors on the onset and course of disease. The relationship between infection and vaccination[5, 9, 10], smoking[8, 11-15], factors associated with fertility[15-18], education[12, 14], asthma and allergies[4, 12] and urbanization[4] with the occurrence of the disease has been introduced In previous studies. No study has been yet published in order to identify the role of gender in rheumatoid arthritis in Iran. The aim of this study is to examine the relationship between gender and the occurrence of rheumatoid arthritis.

MATERIALS AND METHODS

This study was an observational – descriptive, cross sectional survey on 438 patients with rheumatoid arthritis for five years. Patients and controls consisted of patients referred to a hospital and a private center in Tehran during the years 2005-2010 with rheumatoid arthritis previously diagnosed by a rheumatologist based on ACR 1987 criteria (19). Secrecy was extremely held in files accessibility and filling in order to consider medical ethics. A questionnaire was completed by a trained person with demographic data (age, gender, the mean duration of illness before admission, the amount of swollen joints involved, joint deformity, extra-articular involvement, rheumatoid factor, anti-CCP, and drug and non-drug therapy). After completing the questionnaires, qualitative variables were analyzed by chi-square test and quantitative variables with t-test and SPSS software version 16. The level of p<0.05 was considered significant. Odds Ratio (OR) with 95% confidence interval was used to calculate the *odds* of exposure. It was then analyzed using the chi-square test and t- test by applying gender.

RESULTS

A total of 438 subjects were included in the study that 22.6% were hospital-referred and 77.4% clinic-referred, including 314 (81.7%) females and 124 (28.3%) males, approximately equivalent to 2.5: 1. The mean age of patients at the time of admission was 44.96 years for females and 47.34 years for males and the mean age of patients at the onset of study was calculated 40.5 and 40 years for females and males, respectively. The mean duration of illness before admission was 3.5 and 4.2 in males and females, respectively . The rate of swollen, involved and limited joints in male patients implies that these variables are more in men (Fig. 1). Statistical tests showed no significant differences in association with joint deformity between females (9.6%) and males (10.5%), but joint erosion was observed 33.1% and 3.09% in males and females, respectively, representing an increase in male patients than in females . The average number of positive ACR criteria was almost equal in women (4.08) and men (4.17), but extra-articular involvement was significantly higher in females than in males(Fig.2). Among patients with rheumatoid arthritis, test was registered for 418 patients, 281 (67%) subjects were seropositive and 137 (33%) seronegative that 192 (68%) patients in seropositive group and 105 (76.6%) patients in seronegative group were female (P=0.09), however, there was no significant differences in relation to the number and percentage of patients with rheumatoid factor and rheumatoid factor was approximately equal in both sexes and about 64% positive and no difference was observed between two sexes (Fig. 3). Reactive protein C (CRP) was positive in 126 of 321 patients and calculated 62.1% for men and 47.5% for women (PV=0.006). Anti-CCP was positive in 48.4% of males and 41.4% of females and no significant difference was observed
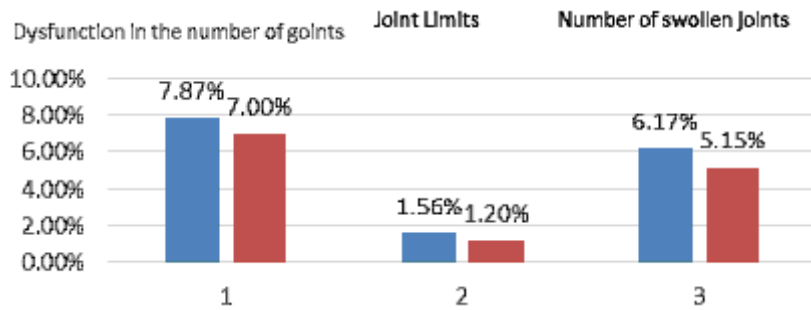
Fig. 1. The rate of swollen, involved and limited joints and joint erosion(Blue: male, Red: female)
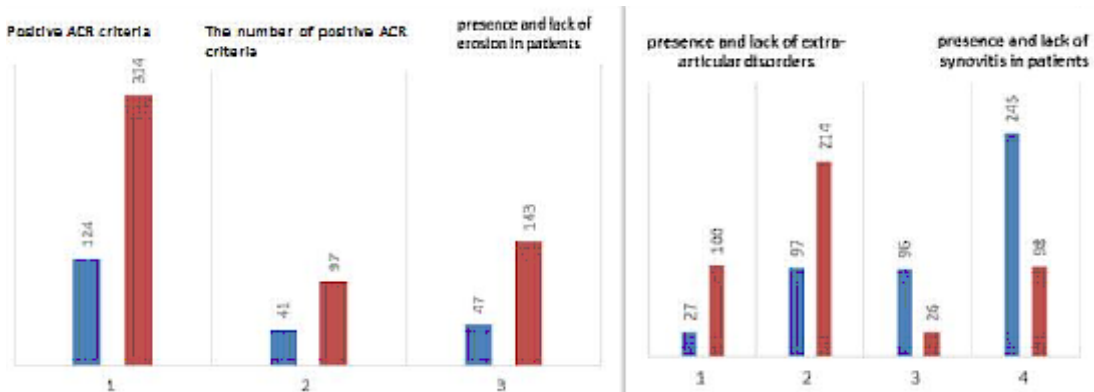

Fig. 2. Positive ACR criteria, and the presence of erosion and the rate
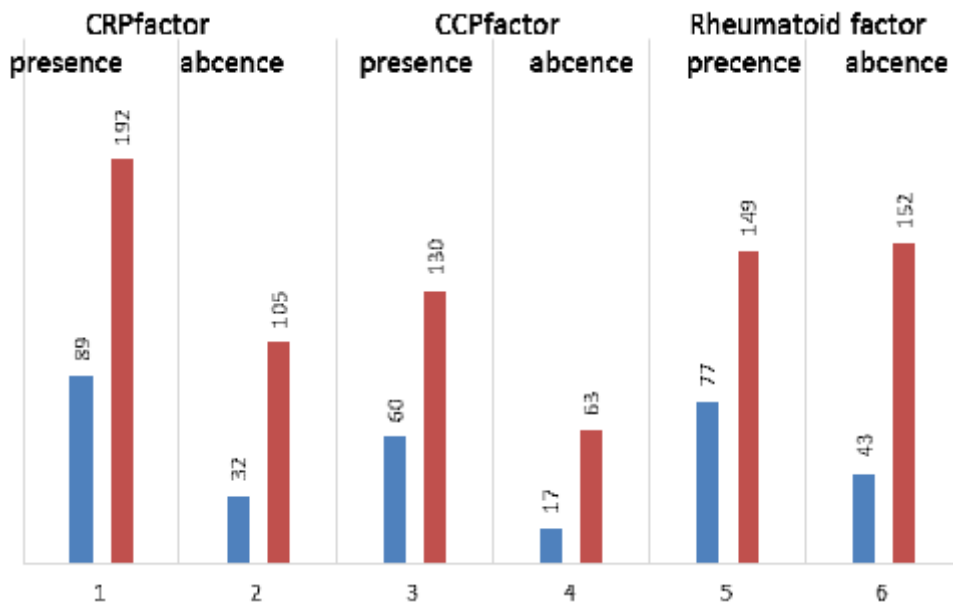of extra articular disorders in patients. (Blue: male, Red: female)

Fig. 3. The presence of rheumatoid factor, C-reactive protein (CRP) and Anti-CCP. (Blue: male, Red: female)
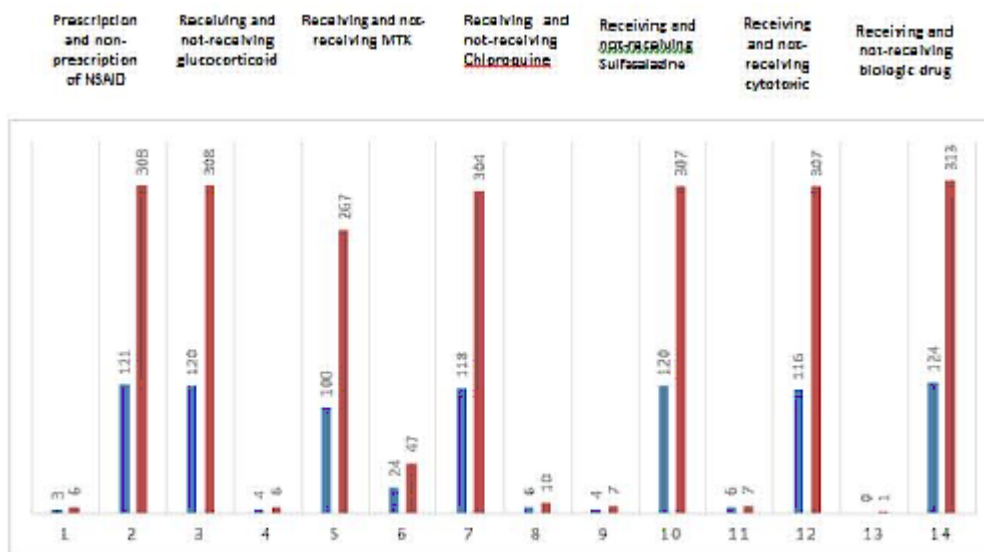
Fig. 4. Positive ACR criteria, and the presence of erosion and the rate of extra
articular disorders and synovitis in patients. (Blue: male, Red: female)

among men and women affected and was equal (about 43.5%) in both genders, including those not registered . Drug and non-drug therapy didn't significantly differ among men and women patients and was evaluated similar in both groups (Fig. 4). 200 patients were followed up regularly and 145 were not. No follow-up was recorded for 93 patients.

DISCUSSION

The present study aimed to examine the relationship of gender and rheumatoid arthritis, indicating minor differences between the ages of patients at onset of the disease. The mean age of disease onset was estimated 43.97 years and 43.36 years for men and women, respectively and was consistent with a study by Dr. Soroush and his colleague, but significantly lower as compared to foreign researchers[20]. The difference between men and women in the age of onset was inevitable. The average time of disease onset until referring to doctor was 4.14 years and 3.41 years for women and men, respectively. At least 75% of men had positive ACR criteria and the highest rate was among the groups with 5 positive criteria. However, since the average male and female patients had 4.17 and 4.08 positive criteria, respectively, there were no significant differences between the

genders. Most patients were suffered by morning stiffness for more than one hour, however, morning stiffness had no significant difference between men and women (PV=0.03). The rate of joints involved in all cases was less in women than in men, but only the difference in the number of joints involved was significant (PV=0.03). Deformity of joints showed no significant difference between the sexes (PV=0.7). Involvement of joint erosions was examined in patients with hand radiography reports, but records were not reliable because of defects. However, there was no significant difference between the sexes (P=0.3)[21]. There is evidence indicating that anti-CCP and rheumatoid factor can be found in the serum of patients many years before the outbreak of rheumatoid arthritis[22, 23]. A possible reason for the different results in etiologic investigations may be due to the difference in the role of these factors in rheumatoid arthritis, for example, smoking and low socioeconomic status associate with seropositive rheumatoid arthritis. In this study, the patients had significant difference in term of anti-CCP (PV=0.009). Nodule examination was in 4 cases for male patients and 5 for female patients and was not statistically reliable (PV=0.7). Pulmonary involvement was reported for 4 people and patients difference was not significant in two sexes (PV=0.2). In this study, only 6 women and two men were

studied in terms of Sicca syndrome, although it was small, it is statistically significant, because almost all patients' eyes had been examined at least once (PV=0.7). Based on the criteria determined for anemia, a total of 110 patients had anemia, including 26 men and 84 women and a significant difference was obvious between the sexes (PV=0.006). Cardiac involvement was reported for 3 female and two male patients which was not significant (PV=0.3). In total, no significant difference was observed between the sexes in rheumatoid factors, CRP, synovitis and received drugs. The cause of autoimmune diseases such as rheumatoid arthritis is still unknown[4]. Of 438 patients, 124 were men and 314 were women in this study, which is roughly equivalent to 2.5:1 and in accordance with international studies conducted in this field. The reason maybe due to the concentration on the disease onset, while given that rheumatoid arthritis is 2-4 times more common in men than in women; sex hormones and factors associated with fertility have been proposed as a potential etiology of the disease. The highest incidence of rheumatoid arthritis in women occurs after menopause, when the level of sex hormones decreases. Furthermore, difference in incidence in females compared to males reduces by age that it can be caused by low testosterone in old ages[12]. In another study, menarche age over 15 years was twice associated with an increased risk of rheumatoid arthritis; however the number of children and menopause age was not associated with the occurrence of rheumatoid arthritis[8]. In another study, short period of fertility was associated with an increased incidence of rheumatoid arthritis[12]. However, non-compliance of high percentage of participants in completing the questionnaire and selecting patients with severe disease were reported as study limitations in both studies. By the way, factors affecting the incidence and prevalence of the disease have a high complexity. Involvement of multiple predisposing genes, role of sex hormones and other factors might predispose, perpetuate and create the disease, but be controlled by a complex process. Nonetheless, gender affects the disease incidence. Extra-articular involvement was also reported more in women than in men.

CONCLUSION

In fact, gender involves in disease complexity by affecting the quality and quantity of disease inflammatory and functional consequences. Low penetration in males may be due to a protective mechanism, however, we can not generally say that the disease is merely more severe or has more serious consequences in one gender than in the other. However, men reported more serious consequences in this study, so we can only say that its prevalence and incidence also follows the global pattern in Iranian women. We didn't encounter with a particular drug side effect for patients with rheumatoid arthritis.

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