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ORIGINAL ARTICLE

Gender Differences in Clinical Characteristics of Rheumatoid Arthritis

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ABSTRAK

Artritis reumatoid (RA) adalah bentuk arthritis radang autoimun yang paling lazim. Hormon seks sangat dikaitkan dengan patogenesis dan perkembangan RA. Oleh itu, tujuan kajian ini adalah untuk membandingkan ciri klinikal RA di kalangan lelaki dan wanita. Kami merekrut 23 orang lelaki dan 23 orang wanita secara berturut-turut mengikut padanan umur dengan RA dari klinik reumatologi. Semua subjek dinilai untuk aktiviti penyakit mereka berdasarkan kriteria DAS-28, kerosakan sendi radiografi berdasarkan Modified Sharp Score (MSS), kapasiti fungsional berdasarkan Soal Selidik Penilaian Kesihatan – Indeks Kecacatan (HAQ-DI) dan responsif rawatan menggunakan kriteria tindak balas Liga Eropah Menentang Rheumatisme (EULAR). Purata umur bagi pesakit lelaki dan wanita masing-masing ialah 60.87 ± 12.5 dan 60.70 ± 11.73. Kami mendapati bahawa subjek wanita mempunyai tahap "c-reactive protein" (CRP) yang jauh lebih tinggi ($p = 0.05$). Skor HAQ-DI ($p<0.02$) dan MSS ($p<0.001$) wanita jauh lebih tinggi daripada lelaki. HAQ-DI dan MSS kekal dikaitkan secara bebas dengan jantina wanita dalam analisis multivariat, dengan nilai p masing-masing ialah 0.017 dan 0.014. Hasil kajian ini menunjukkan bahawa wanita mengalami kerosakan sendi dan kecacatan fungsi yang lebih teruk dengan penyakit arthritis berbanding lelaki.

Kata kunci: Aktiviti penyakit; arthritis reumatoid; hormon seks; jantina

ABSTRACT

The most prevalent type of autoimmune inflammatory arthritis is rheumatoid arthritis (RA). Sex hormones are strongly associated in the pathogenesis and progression of RA. Hence, the core objective of this study was to compare the clinical features

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of RA among men and women. We consecutively recruited 23 men and 23 age-matched women with RA from our rheumatology clinic. Subjects were evaluated for their disease activities, radiographic joint damages and functional capacities. The above assessment was performed using DAS-28, Modified Sharp Score (MSS) and European League Against Rheumatism (EULAR) response criteria; respectively. The mean age for the male and female patients were 60.87 ± 12.5 and 60.70 ± 11.73, respectively. We found that the female subjects had significantly higher c-reactive protein (CRP) levels (p=0.05). The HAQ-DI(p<0.02) and MSS scores (p<0.001) of women were substantially higher than those of males. HAQ-DI and MSS remained to be independently associated with female gender in multivariate analysis, with p values of 0.017 and 0.014, respectively. The findings of this study suggested that in RA, compared to men, women had more severe joint damage and functional disability.

Keywords: Disease activity; gender, rheumatoid arthritis, sex hormones

INTRODUCTION

Rheumatoid arthritis (RA) is the most prevalent form of autoimmune inflammatory arthritis. RA is a debilitating disease resulting from a complex interplay of various epigenetic, ecological, immune and hormonal factor (Barragan-Martinez et al. 2012). This chronic inflammatory condition predominantly damages the synovial membrane, which damages the joints and causes functional impairment (Voulgari et al. 2003).

RA affects 0.5-1% of the general population, with women outnumbering men in a ratio of 3:1. Amongst women under 50, it is 4 to 5 times higher, but beyond 60, the ratio drops to about 2 to 1 (Barragan-Martinez et al. 2012). There is an extensive amount of evidence involving sex hormones in the pathogenesis of RA. However, the findings are contradictory and equivocal. Large-scale cohort investigations and meta-analyses have frequently contradictory findings. This might due to the immune system is influenced in a pleiotropic manner by the immunomodulatory features of sex hormones.

The highest prevalence of RA in women is between 50 and 60 years old due to menopause, and the likelihood of RA in men increases in ages above 60 when bioavailable testosterone decreases (Tengstrand et al. 2003). The prevalence and intensity of RA in women are associated with decreased oestrogen and progesterone production throughout menopause and postpartum (Raine & Giles 2022). Hypoandrogenism is related to the pathogenesis of RA in men in which the testosterone levels decreases at the initial stage of the disease and it rises back once the acute symptoms have been alleviated. Younger males are at a lower risk of RA due to their higher levels of testosterone (Bove 2013).

Several studies have also reported that lower levels of testosterone were found in the synovial fluid of male and female patients with active disease (Pikwer et al. 2014).

Throughout the literature, there is a profound lack of data with regard to gender differences of clinical aspects of RA. Hence, the purpose of this study was to evaluate the differences between the disease activity, joint damage and functional capacity between male and female with RA.

MATERIALS AND METHODS

Study Design

This was a cross-sectional study carried out at the Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, from April 2022 to September 2022. The study proposal was approved by the Ethics and Research Committee of the institution (Study Code FRGS/1/2021/SKK08/UKM/02/1).

Study Population

Patients with RA were recruited from the rheumatology outpatient clinics. Patients who met the inclusion and exclusion criteria were approached to take part in this research. The inclusion criterion were patients who fulfilled the American College of Rheumatology 2010 classification criteria of RA. The exclusion criteria were patients with mixed connective tissue disease (MCTD) and overlap syndrome with other connective tissue diseases such as Sjogren Syndrome and Polymyositis.

Study Parameters
(i) DAS 28

The 28-joints based disease activity score (DAS28) is an indicator of the severity of RA disease activity that incorporates data on inflammatory markers, pain score, swollen and tender joints. The DAS 28 scores are based on 4 variables which consist of the number of tender joints, the number of swollen joints , visual analog score, the erythrocyte sedimentation rate (ESR) or the c-reactive protein (CRP) values (Fransen & van Riel 2005). RA patients with a DAS 28 score of 3.2 or higher are considered to have moderate to severe disease activity, while those with a score of less than 3.2 are in remission or have mild disease activity (Dalila et al. 2014).

(ii) Modified Sharp Score

This scoring method was first introduced by SHARP in the year 1971 and was followed by a modified version in the year 1985. In 1996, Van Der Heijde modified this scoring system once again and it has been widely used ever since (Boini & Guillemin 2001). The modified sharp score (MSS) is a method to assess joint erosions and spaces between joints narrowing in RA patients' hands and feet. The MSS comprises 16 sites for joint space erosion in each hand, 15 sites for joint space narrowing in each foot, and 6 areas for joint space erosion in each hand. The maximum MSS is 448 (Dalila et al. 2014).

(iii) HAQ-DI

The HAQ-DI was created to assess the functional status of patients. The HAQ-DI provides information on the respondent's level of functional capacity in performing activities of daily living. According to broad consensus, scores of 0 to 1 denote mild to moderate difficulty, 1 to 2 represent moderate substantial disability, and 2 to 3 represent extreme to exceptionally severe disability (Maska et al. 2011).

(iv) EULAR Treatment Response

Based on the EULAR response criteria, RA patients can be classified as good, moderate or non-responders to treatment. The difference in the DAS 28 scores between disease onset and at the time of follow-up was calculated (DAS 28 at diagnosis- current DAS 28). Patients with DAS 28 ≤3.2 and who had achieved improvement in DAS28 score of more than 1.2 were considered good responders. Moderate responders had moderate disease activity with DAS 28 improvement of between 0.6 and 1.2 from baseline (Fransen & van Riel 2009). The rest were considered non-responders.

Statistical Analysis

All data were analysed using SPSS version 22. Due to the normal distribution of the data, the independent t-test was used for continuous variables, while the chi square test was conducted for categorical variables. A p value of <0.05 was considered significant. Variables which were significant on univariate analysis were further analysed using multivariate analysis.

RESULTS

Clinical Characteristics of RA Patients

A total of 23 males and 23 females were enrolled in the study. Table 1 showed the comparison between male and female RA patients were matched in age and disease duration. Female subjects had a higher percentage of seropositive illness. For both groups, the mean age at onset of disease was above 50 years which was considered middle age. The RA patients were either on disease-modifying antirheumatic drugs (DMARD) monotherapy or combination therapy. The conventional synthetic DMARDs that were prescribed to the subjects included methotrexate, leflunomide, sulfasalazine and hydroxychloroquine. The use of DMARDs did not differ significantly between both groups. Male patients used marginally higher doses of prednisolone and methotrexate but lower percentage of advanced therapies. Advanced therapies in this study consisted of adalimumab and tofacitinib.

Comparison of Disease Activity, Joint Damage and Functional Disability between Male and Female RA Patients

The female group of RA patients had higher CRP levels although ESR and DAS 28 levels showed no difference

Table 1: Sociodemographic and clinical characteristics of subjects

PARAMETER	MALE (n=23)	FEMALE (n=23)	P value
Age	60.87 ± 12.51	60.70 ± 11.73	0.82
Disease duration	7.70 ± 6.14	7.74 ± 5.99	0.91
Age at disease onset	53.17 ± 12.67	52.96 ± 12.26	0.96
Seropositivity	12 (52.17%)	17 (73.91%)	0.13
DAS 28	2.44 ± 1.58	1.52 ± 2.35	0.40
ESR	45.65 ± 24.30	28.74 ± 24.17	0.50
CRP	0.77 ± 0.79	1.14 ± 1.54	**0.05**
Cumulative MTX	2611.30 ± 3633.86	2331.52 ± 3376.72	0.99
DOSE			
PRED DOSAGE	1.74 ± 2.86	1.52 ± 2.35	0.40
Number of DMARDS			0.43
1	12 (52.17%)	8 (34.78)	
2	9 (39.13%)	9 (39.13%)	
3	1 (4.34%)	3 (13.04%)	
Advance Therapies (Biologics and JAK I)	1 (4.34%)	4 (17.39%)	0.16
MSS SCORE	2.22 ± 1.41	13.78 ± 13.40	<0.001*
HAQ DI	0.01 ± 0.32	1.11 ± 0.82	0.02*

DMARDs=disease-modifying antirheumatic drugs; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; DAS 28=28 joint-based Disease Activity Score; MSS=Modified Sharp Score; HAQDI=Health Assessment Questionnaire Disability Index; EULAR=European League against Rheumatism; JAK-I: Janus kinase inhibitors
Data were presented as number (%) or mean ± SD, * p value less than 0.05 is considered statistically significant

statistically. There were more female subjects in the moderate and high disease activity categories (Figure 1). In keeping with this finding, the radiographic joint damage based on MSS was significantly worsened among the women. Besides, the female group of RA patients had worse functional capacity. The mean HAQ-Di score among the women was more than 1 denoting moderate to severe disability whereas for the men was less than 1 indicating mild to moderate disability (Bruce & Fries 2003). HAQ-DI and MSS remained independently associated with female gender with p values of 0.017 and 0.014, respectively; on multivariate analysis.

Treatment Response

The response to treatment based on the EULAR response criteria showed no significant difference between the 2 groups (p=0.254) (Figure 2). Subjects with higher disease activity at disease onset tend to have greater degree of changes in disease activity scores with treatment. Of note, the mean disease activity score for both arms were below 2.6 indicating disease remission. Majority of the subjects were moderate responders. There were more non-responders among females with higher good responders among males.

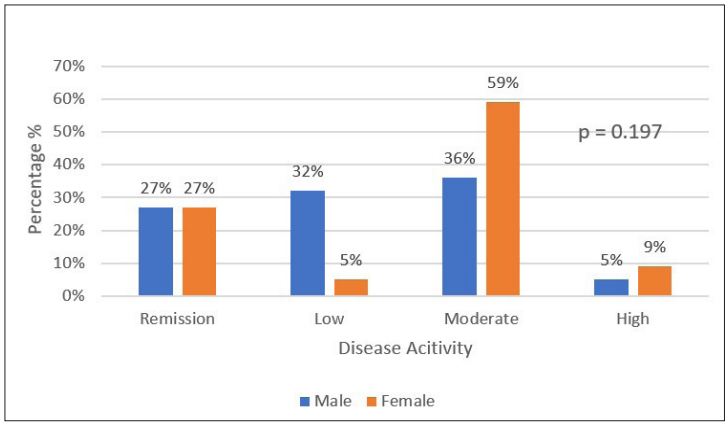

FIGURE 1: Categories of disease activity according to gender

DISCUSSION

The key finding of this study was the more severe disease among female RA subjects based on radiographic joint damage and functional disability. Women had more joint erosions and joint space narrowing in their hands and feet. Kuiper et al. (2001) reported similar findings. Apart from hormonal influence, it had been postulated that women had narrower joint space compared to men due to thinner articular cartilage (Dacre et al. 1991). Majority of our female subjects were postmenopausal. The age-related mismatch in bone resorption and formation is more pronounced in elderly women compared to elderly men. Estrogen deficiency which occurs after menopause; is known to increase bone remodeling and resorption. Experiments in arthritic mice models had shown that old female mice developed more often severe joint damage compared male

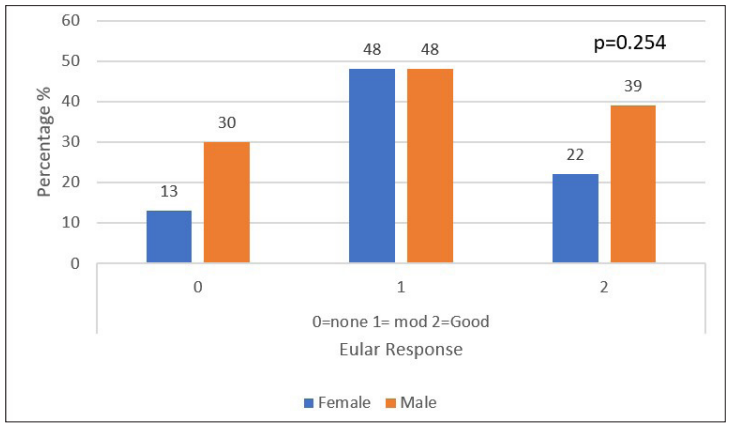

FIGURE 2: Categories of EULAR treatment response according to gender

mice (van Beuningen et al. 1989). D'Elia et al. (2003) reported that hormone replacement therapy (HRT) had significant ameliorating effects on progression of radiological joint destruction.

Expression of estrogen receptors has been identified in both human osteoblastic cells and osteoclastic cells. Estrogen decreases osteoclast formation and activity while increasing the apoptosis of osteoclasts. Besides, it has a stimulatory effect on bone formation by the osteoblasts. Estrogens are indirectly involved in the regulation of growth factors especially insulin-like growth factor-1 and 2; and cytokines (interleukin-6 and tumour necrosis factor [TNF] α) in osteoblasts, which in turn regulate bone remodelling (Spelsberg et al. 1999).

Female gender was independently associated with higher HAQ-DI scores after adjusting for radiographic joint damage which was a confounder. Functional disability in RA is multifactorial. Many studies have consistently pointed out toward worsened functional capacity in female patients (Kuiper et al. 2001; Tengstrand et al. 2004). Tengstrand et al. (2004) in a prospective study with 844 subjects revealed higher HAQ scores among women. Apart from disease related variables, non-disease related variables such as demographic, psychological, social and behavioural factors may predict disability scores (Baruth et al. 2013).

Our female subjects had more active disease based on the significantly higher CRP level and greater numbers than men in the moderate and high disease activity categories. This can be partially due to the higher incidence of seropositivity among women. Seropositive disease tends to run a more aggressive course in RA (Nordberg et al. 2018). Despite contradictory evidence relating sex hormones and RA pathogenesis, decreased oestrogen levels in elderly women are consistently linked to a higher likelihood and severity of RA (Raine & Giles 2022). It has been discovered that estrogens directly inhibit inflammation in T cells. The expression of inflammatory cytokines like interleukin 17 and TNF were demonstrated to be decreased by silibinin, a naturally occurring estrogen-receptor β. This effect was facilitated through the downregulation of the of the epigenetic modifier microRNA-155 (Correale et al. 1998).

We acknowledged the limitations of our study. The small sample size increased the likelihood of type 1 error, making it to be difficult in making precise estimates or drawing strong conclusions. Our subjects comprised mainly of older patients i.e middle aged to elderly. The applicability of our findings to younger RA patients might be questionable.

CONCLUSION

In conclusion, among older RA patients, female was associated with more severe joint damage and functional disability. The reasons for the above discrepancies merit further investigation including measurement of sex hormone levels.

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