The Influence of Sex on Patients with Rheumatoid Arthritis in a Large Observational Cohort

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ABSTRACT. ***Objective.*** To compare the sex differences of various components of rheumatoid arthritis (RA).

Methods. Data of 4823 patients from a large observational cohort study were analyzed. Remarkable differences were noted between the sexes, and overall, women had significantly higher disease activity.

Results. When variables were adjusted using sex, age, and duration, Health Assessment Questionnaire, rather than Disease Activity Score, contributed most to sex difference. Further analysis showed evidence that progression of disability was approximately 3 times more rapid in female patients compared to male patients.

Conclusion. Women overall have higher RA disease activity and are prone to greater and faster progression of disability over time. (J Rheumatol First Release Feb 1 2009; doi:10.3899/jrheum.080724)

Key Indexing Terms:
RHEUMATOID ARTHRITIS EPIDEMIOLOGY SEX

The development and the course of rheumatoid arthritis (RA) are due to numerous underlying factors. Sex is one feature that seems to play a role in the prevalence of RA since it is widely accepted that women are more prone to the disease than men, although the sex distribution varies by age as well as clinical stages of RA. For example, RA incidence increases in women as they age, while in men it stabilizes over the third through fifth decades and increases thereafter, and there is an evident predominance of women with mild to moderate disease[1].

Regarding severity of RA, women have been reported to have a greater risk, severe symptoms and disease course, and female sex is associated with poor outcome[2-4]. Even though both sexes have similar disease activity before treatment, women have a much lower early RA remission rate than men, and male sex is a major independent predictor of remission[5]. In addition, female sex is one of several independent predictors of radiographic progression[6].

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If the sexes do present essential differences in the presentation of the disease, it is imperative to recognize these variations for evaluation and treatment of the disease. The purpose of our study is to examine and assess the sex difference in a large cohort, and to analyze the variables that are affected by sex in RA.

MATERIALS AND METHODS

The noninterventional observational cohort study (Institute of Rheumatology RA, IORRA cohort), approved by the university's ethics committee, comprises a validated questionnaire given every 6 months to all patients with RA visiting the outpatient clinic of the Tokyo Women's Medical University. The study assesses disability level, pain, disease activity, medication, adverse events, healthcare utilization, satisfaction with care, physician's assessments, patient-reported data, and laboratory data. A response rate of over 97% from about 5000 patients with RA per study allows for practical, high quality epidemiological data on rheumatic diseases in Japan.

In total, 4823 patients with RA (83.5% women, average age men 60.6 ± 12.8, women 57.8 ± 12.8 yrs, disease duration men 10.2 ± 8.2, women 11.8 ± 9.0 yrs) from the IORRA cohort phase 9 study (October and November, 2004), falling under the diagnostic criteria according to the American College of Rheumatology, were evaluated for this cross-sectional study[7].

Univariate analysis. Bivariate data for the 2 sexes included methotrexate (MTX), disease modifying antirheumatic drugs (DMARD), and prednisolone use. Differences between the 2 groups for the following were considered continuous variables: Disease Activity Score 28-joint count (DAS28), DAS 28 C-reactive protein (DAS 28-CRP), tender joint count (TJC) 45, swollen joint count (SJC) 45, Health Assessment Questionnaire (HAQ), patient's assessment of pain on a visual analog scale (patient's pain VAS), patient's global assessment of disease activity (patient's global VAS), physician's global VAS, CRP, erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF). Statistical analysis was performed using Fisher's exact test, and Mann-Whitney U-test was used to analyze the continuous variables.

Multivariate analysis. Sex differences were adjusted according to age, RA

disease duration, body mass index (BMI), and the use of DMARD, MTX and prednisolone. Statistical analysis was performed using logistic regression, stepwise method for variable selection, and contribution of each variable was evaluated using analysis of deviance.

Next, HAQ was analyzed in relation to RA disease duration adjusted by age, MTX use, DMARD use, and prednisolone use. The slopes for each sex are reported as a scatter plot.

RESULTS

Women were significantly older at the time of study and had longer disease duration (Table 1). DMARD and corticosteroids were taken equally by men and women, but more women were taking oral MTX. All variables coinciding with disease activity besides CRP and RF were significantly higher in women (Table 1). Although not significant, both RF and CRP were higher in men.

According to logistic regression, HAQ showed the most contribution to sex difference (Table 2). Between disease duration of 0 to 20 years, HAQ in women worsened in a linear fashion compared to men (Figure 1). The difference in slope inclination is nearly 3-fold in women: the slope for men was 0.0067 and for women 0.0194.

DISCUSSION

Sex differences may differ in specific risk factors, disease severity, disease phenotype, overall prognosis, and response to therapy. In our study, we assessed a large number of patients with RA to evaluate the role of sex, and found that overall RA disease activity was significantly higher in women, and HAQ worsened with longer disease duration. HAQ showed a prominent sex difference, suggesting that women have higher disease activity and a faster progression of functional disability. Past studies support our result of worse HAQ scores in women compared to men[5,8]; however, our study is the first to report HAQ as being the single significant contributor to sex difference in RA. Additionally, a recent study reports that HAQ is the most important predictor of mortality at 5 years and sex becomes more prominent as a predictor of mortality over 20 years[9], a further indication of the importance of HAQ trend and the influence of sex on RA.

Reports on the disease prognostic value of sex in RA are conflicting. Studies have shown that sex was not found to be predictive of poor prognosis[10-13]; however, a recent study suggests female sex as one of the independent predictors of radiographic progression[6], an undeniably important observation since one of the therapeutic goals of RA is to stall disease progression. In addition, women with early RA have a considerably lower remission rate than men, and male sex is a major independent predictor of remission[5]. According to these latter studies, sex does indeed provide a prognostic tool, and therefore, cannot be disregarded when considering outcomes of patients with RA.

Hormones have been suggested as an attribute to sex discrepancies. There may be an involvement of female sex hormones in RA onset, in which androgen plays a suppressive role of the disease[14]. Further, temporary remission of the disease is often observed in pregnant patients with RA, as well as reports that show decreased RA severity with oral contraceptive use[15].

This study, being an observational cohort study, has its

Table 1. Baseline patient characteristics and sex differences.

Variable	Male, median (IQR)	Female, median (IQR)	Mean Difference (95% CI)	p
Age (years)	62 (54–70)	59 (50–67)	2.79 (3.76–1.81)	2.13×10^{-9} †*
Duration, yrs	8 (4–14)	10 (5–16)	1.55 (0.87–2.22)	4.77×10^{-6} †*
DAS28	2.94 (2.11–3.89)	3.45 (2.67–4.30)	0.50 (0.41–0.59)	9.06×10^{-24} †*
DAS28-CRP	2.59 (1.90–3.39)	2.76 (2.02–3.59)	0.17 (0.08–0.25)	2.10×10^{-4} †*
HAQ	0.25 (0–0.875)	0.63 (0.13–1.38)	0.33 (0.27–0.39)	1.04×10^{-33} †*
TJC45	1 (0–2)	1 (0–3)	0.75 (0.39–1.10)	8.00×10^{-8} †*
SJC45	1 (0–2)	1 (0–3)	0.61 (0.35–0.87)	3.49×10^{-9} †*
Patient pain VAS	18 (5–43)	23 (8–51)	4.49 (2.49–6.49)	2.89×10^{-6} †*
Patient global VAS	21 (7–48.5)	25 (9–52)	3.91 (1.98–5.85)	3.62×10^{-5} †*
Physician global VAS	9 (2–19)	10 (3–23)	1.99 (0.81–3.17)	4.22×10^{-4} †*
CRP, mg/dl	0.5 (0.2–1.3)	0.5 (0.2–1.2)	–0.1 (–0.21–0.02)	0.02†
ESR, mm/h	17.9 (8.7–34.8)	27.6 (16.1–45)	7.37 (5.67–9.07)	3.34×10^{-29} †*
RF, IU/ml	70.5 (16–215)	59 (19–148)	–41.27 (–62.73– –19.82)	0.13†
MTX dose, mg/wk	6 (4–8)	6 (4–8)	–0.12 (–0.36–0.12)	0.19†
PSL dose, mg/day	5 (3–6)	4 (3–5)	–0.52 (–0.72– –0.31)	3.2×10^{-3} †*
DMARD, mean use	88.1%	90.2%		0.07††
MTX, mean use	49.4%	56.1%		5.94×10^{-4} ††*
PSL, mean use	51.3%	53.7%		0.23††

IQR: interquartile range; DMARD: disease modifying antirheumatic drug; MTX: methotrexate; PSL: prednisolone; DAS: Disease Activity Score; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; TJC: tender joint count; SJC: swollen joint count; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor. † Mann-Whitney U-test; †† Fisher exact test. * Statistical significance ($p < 0.01$).

Table 2. Adjusted sex difference variables and their contributions to the differences in the 2 groups.

Variable	Relation Coefficient	OR	SE	Confidence Interval	p	% Contribution
HAQ	0.992	2.697	0.085	2.284, 3.183	1.06×10^{-31}	36.36
BMI	–0.117	0.890	0.014	0.866, 0.915	8.63×10^{-17}	26.34
Age	–0.026	0.974	0.004	0.967, 0.981	3.42×10^{-12}	12.83
CRP	–0.132	0.877	0.029	0.828, 0.927	4.85×10^{-6}	7.51
PSL dose	–0.056	0.946	0.014	0.920, 0.972	5.57×10^{-5}	4.94
RF	–0.001	0.999	0.000	0.999, 1.000	1.20×10^{-4}	3.49
Patient global VAS	–0.007	0.993	0.002	0.989, 0.997	3.30×10^{-4}	3.00
SJC	0.054	1.056	0.017	1.021, 1.092	1.52×10^{-3}	3.55
Disease duration	0.014	1.014	0.005	1.003, 1.024	0.01	1.97

SE: standard error; HAQ: Health Assessment Questionnaire; BMI: body mass index; CRP: C-reactive protein; PSL: prednisolone; RF: rheumatoid factor; VAS: visual analog scale; SJC: swollen joint count.

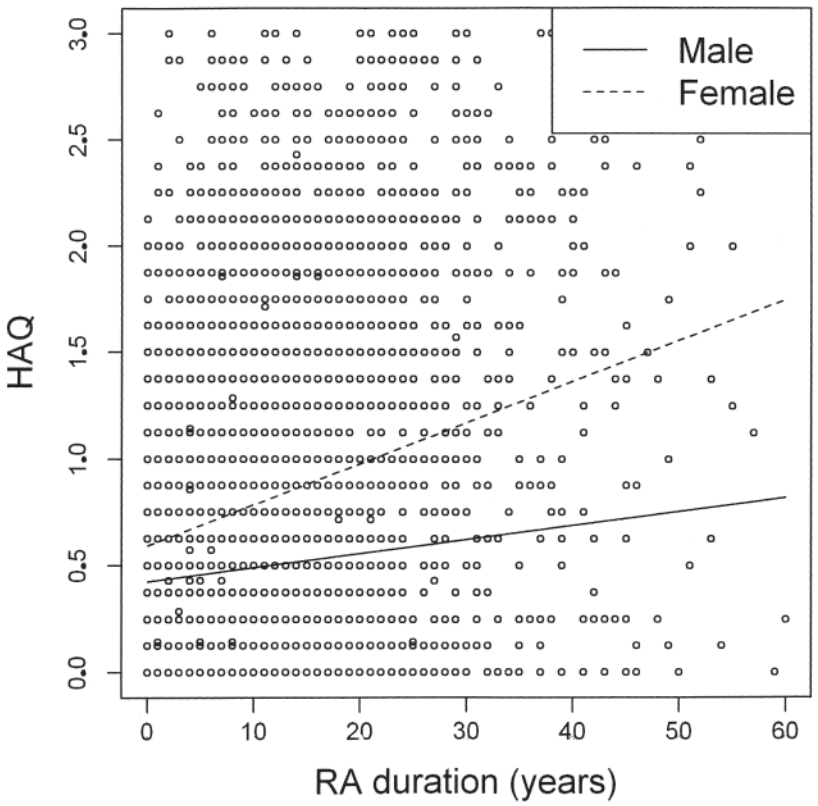

Figure 1. The relation between Health Assessment Questionnaire (HAQ) results and disease duration. Fitted lines were adjusted by age and medications using mean values for each sex.

limitations, however, and data can only be derived from investigations done within clinical visits. There may be other confounding factors that cannot be derived from this type of study that may further define the difference between male and female patients. Under this limitation, we can conclude that in our observational cohort, women present with overall higher disease activity and longer disease duration, which in turn, leads to worsening of HAQ, which was revealed to be the principal contributing factor to sex difference. Greater understanding of sex differences may provide a better insight into underlying disease mechanisms, and comprehension of these differences in daily clinical practice is vital in deciding therapeutic strategies, determining RA prognosis, and preventing disabilities.

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