

Influence of gender on the symptoms and severity of rheumatoid arthritis: do women suffer more?

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When limited treatment options were available, the natural history of rheumatoid arthritis (RA) involved severe outcomes in both genders over 5–20 years [1]. Severe long-term outcomes of RA [2–7] were reported equally in women and men [6], including clinical disease activity, structural damage and deformities. However, several reports indicate that women describe more severe symptoms [8], greater disability [9] and higher work disability rates [10] compared with men. Indeed, women have higher scores for all seven RA core dataset measures, three from the physician (swollen joint count, tender joint count, physician global estimate of status), one laboratory test (erythrocyte sedimentation rate [ESR]) and three from the patient on a self-report questionnaire (health assessment questionnaire [HAQ] physical function, pain and patient global estimate of status). Nonetheless, as in the general population, men with RA have considerably higher mortality rates than women [11].

Occasional reports of differences in the course and outcomes of RA according to gender, which include unexpected results or interpretations, appear to have gained more attention than reports of no differences according to gender. 10 years ago, a study from the Mayo Clinic (MN, USA) [12] compared 55 male patients to 110 female controls with similar disease duration of at least 10 years with an observation that erosive disease was more prevalent and developed earlier in men than in women [12]. The investigators suggested that this and other findings of the study might help 'assess the prognosis and tailor the treatment of the individual patient.' This suggestion was seen by the rheumatology community as a reflection that the old-fashioned treatment approach of 'go low, go slow' [13] should be abandoned. A modern treatment strategy with early and aggressive therapies was suggested to apply equally to both genders [13].

At this time, the clinical status of RA patients is improved compared with previous decades, according to disease activity [14,15], function and structural outcomes [15–21], work disability [22]

and mortality rates [23,24], with no gender preference. However, some recent studies suggest that it is more favorable to be a man than a woman with RA. Males were shown to have better responses to biologic agents than females [25–27]. Two reports suggested that male gender is a predictor of remission in early RA [28,29].

There are obvious differences between genders concerning prevalence, age at onset and auto-antibody production of RA [30]. The prevalence of RA differs between genders, although primarily among menstruating women. Although the majority of patients with RA are middle-aged women, generally more than 70% in any RA cohort, RA can nonetheless occur at any age in both genders. Furthermore, gender differences are seen in biologic (hormones) [31] or behavioral factors (smoking) [32], which influence susceptibility and phenotype of RA. Most rheumatologists have a clinical impression that RA has an overall similar severity and course in females and males.

More information concerning possible influence of gender on the clinical status and course of RA appeared to be of value, and was analyzed in a large clinical multinational RA database [33].

The quantitative standard monitoring of patients with RA (QUEST-RA) program was established in 2005 to promote quantitative assessment in usual clinical care at multiple sites, and to develop a database of RA patients seen outside of clinical trials in usual care in many countries [7]. Data collection began in January 2005 and by April 2008, the program had expanded to include 6004 patients from 70 sites in 25 countries.

Rheumatologists performed a clinical review of each patient and patients completed a 4-page self report questionnaire. Gender differences were analyzed for the measures of disease activity according to the RA core dataset measures, disease activity score (DAS28) and fatigue, for clinical characteristics, such as the presence of rheumatoid factor, nodules and erosions, and for the current use of disease-modifying drugs, including prednisone, methotrexate and biologic agents.



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Results of QUEST-RA confirmed other reports that women had poorer scores than men [34] in all core dataset measures including the number of swollen joints 4.5 versus 3.8, number of tender joints 6.9 versus 5.4 (both on a 28 joint count), erythrocyte sedimentation rate 30 versus 26, functional status on the HAQ 1.1 versus 0.8, visual analog scales for physician global estimate 3.0 versus 2.5, pain 4.3 versus 3.6, patient global status 4.2 versus 3.7, DAS28 4.3 versus 3.8 and fatigue 4.6 versus 3.7 ($p < 0.001$). However, despite statistically significant differences in the values between genders, effect sizes of these measures were small to medium and smallest for the swollen joint count, which was then used as an objective surrogate of inflammation. Among patients who had no swollen joints or only one, women had statistically significant higher mean values compared with men in all other disease activity measures ($p < 0.001$) and met DAS28 remission less often than men [35]. Rheumatoid factor was equally prevalent among genders. Men had nodules more often than women. Women had erosions more often than men, but the statistical significance was marginal. Similar proportions of females and males were taking different therapies.

The QUEST-RA data indicate that currently used disease activity measures are higher in women than in men. The higher likelihood of remission in men versus women according to DAS28 can be explained in large part by the observation that higher values for all DAS28 components are seen in women [34]. As disease severity was similar between genders concerning the proportion of women and men with

an erosive disease, it appears that most of the gender differences in RA disease activity may result from characteristics of the measures of disease activity, rather than from RA disease activity itself.

“Among patients who had no swollen joints or only one, women had statistically significant higher mean values compared with men in all other disease activity measures.”

It is of special interest that gender differences for DAS28, fatigue and RA core dataset measures were most pronounced in patients with low swollen joint counts. This can be interpreted to suggest that even at minor disease activity levels the burden of the disease is greater for women than for men. A clinical implication might be that special attention should be directed to the treatment of women with RA, to relieve signs and symptoms of RA as completely as possible.

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