Influence of Sex, Age, and Menopausal State on the Course of Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate the influences of the menopausal state, sex, and age on the course and outcome of rheumatoid arthritis (RA).

Methods. A cohort of patients with early RA (209 female, 123 male) was studied. Sex, age, and menopausal state at baseline, and disease activity, radiographic joint destruction, and physical disability during 6 years of followup were assessed.

Results. The Disease Activity Score (DAS) was significantly higher in female compared to male patients at any time point except at the time of inclusion. This was mainly due to postmenopausal patients. Radiographic joint destruction (RJD) was significantly worse in female patients compared to males at the time of inclusion. Postmenopausal patients had significantly higher RJD than premenopausal patients at the time of inclusion and 3 years thereafter. Older male patients showed worse RJD than younger male patients at all time points measured. Physical disability was significantly worse in female compared to male patients, as well as in postmenopausal compared to premenopausal patients, and older male compared to younger male patients. Stepwise regression analysis revealed that at 3 years higher age and female sex were the best predictors for a worse DAS. Higher age and the interaction term between menopausal state and age best predicted higher RJD. Higher age and the interaction term between menopausal state and age best predicted Health Assessment Questionnaire (HAQ) score.

Conclusion. Higher age at presentation of RA leads to a more severe disease course in terms of DAS, RJD, and HAQ. Although female sex has a deteriorating effect on the DAS, the menopausal state is responsible for the major part of the differences in outcome between men and women. Postmenopausal state in early RA influences future disability and damage, especially in older patients. (J Rheumatol 2001;28:1809–16)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE ACTIVITY MENOPAUSE AGE SEX

Rheumatoid arthritis (RA) is a chronic systemic disorder of unknown etiology characterized by symmetric synovitis with a prevalence at present of less than 1% of the Caucasian adult population[1]. Within this population, women are more frequently afflicted with RA than men, with a ratio of 2–3:1[2,3]. In most patients the disease course is fluctuating, which often results in a progressive destruction of the joints.

Many factors have been described to influence the disease course and outcome[4,5]. However, due to conflicting results, agreement only exists about a few of these, such as IgM rheumatoid factor (IgM-RF), disease activity, and female sex[6-9]. It is becoming more accepted that there are gender differences in the susceptibility and the response to several illnesses[10]. There is agreement that there are differences between women and men in terms of RA progression. There is, however, no agreement in whether women or men have a more severe disease course. Several authors have shown that men tend to have a better prognosis in terms of radiographic joint damage[6] and functional capacity as measured by the Health Assessment Questionnaire (HAQ)[7–9]. On the other hand, Weyand, *et al*[11] have shown that men have a more aggressive disease course in terms of nodules and rheumatoid lung disease. In animal models sex differences were seen in experiments on cartilage, where female rats and mice experienced degraded cartilage faster than males[12,13]. Compared to their male counterparts, female mice were more susceptible to proteoglycan induced polyarthritis[14] and female rats to chronic polyarthritis induced with streptococcal cell wall preparation.

An explanation for the different opinions regarding the role of sex in disease progression might be the changes in the hormonal state of women in certain periods of life. The use of oral contraceptive (OC) hormones, pregnancy, or the menopause and whether hormone replacement therapy (HRT) has been used in this period might have an influence on disease course. Studies concerning the effect of female

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Submitted September 13, 2000; revision accepted February 12, 2001.

hormones in humans have shown that OC use may reduce the severity of disease[15,16]. HRT in postmenopausal women improved aspects of disease activity[17,18] and of daily functioning[18,19]. The same phenomenon is seen in animal models of arthritis. The severity of streptococcal cell wall arthritis is enhanced by female sex hormones, while the relative resistance of male Lewis LEW/N rats can be abolished by castration[20]. However, it is also shown that female sex hormones have beneficial effects in a number of T cell dependent diseases such as collagen induced arthritis[21,22] and adjuvant arthritis[23].

A point of discussion concerning the hormonal state is the possible interaction with age. This may indicate that age is of importance in RA. There is, however, no agreement on the precise contribution of age. Some authors have shown that patients who are first diagnosed with RA at an older age develop a more severe disease in terms of disease activity and radiographic joint damage than patients diagnosed with RA at a younger age[6,24]. Others claim that patients who develop RA at an older age have a more slowly progressive disease course relative to younger patients[25-28]. Experiments in antigen induced arthritis in C57Bl/10 mice have shown that old female mice developed a more chronic arthritis and more often severe joint damage compared to young female mice, or male mice of both age groups[29]. This indicates that both age and sex play a role in the severity of experimental arthritis.

In a cohort that was prospectively followed since 1985, we investigated whether the menopausal state, sex, or age affects the disease course of RA in terms of disease activity, radiographic joint damage, and physical disability.

MATERIALS AND METHODS

Patients. For this study all patients participating in the Nijmegen inception cohort study were selected. This cohort started in 1985 at the Department of Rheumatology of University Hospital Nijmegen (University Medical Center) and is continuing. All consecutive patients meeting the inclusion criteria are asked to participate in a prospective followup. The inclusion criteria are: RA according to the revised 1987 American Rheumatology Association criteria (patients included in the early years were retrospectively checked), disease duration < 1 year, and no history of slow acting antirheumatic drugs.

By June 1997, 332 patients were included in the cohort, 209 women and 123 men. All female patients received a questionnaire regarding their gynecological history. Based on these questionnaires patients were defined as post or premenopausal, according to the 1981 WHO guidelines. From the 209 female patients, 109 were postmenopausal and 64 were premenopausal at the time of inclusion. A total of 36 female patients were excluded. Thirteen were excluded because they were perimenopausal at the time of RA diagnosis; one patient was excluded because she had had amenorrhea since the age of 17. Twenty-two patients had an unknown menopausal state, because they did not return their questionnaire (n = 17) or because they underwent a hysterectomy (n = 4), or both a hysterectomy and ovariectomy (n = 1) in the same period that the RA diagnosis was made. The age range of the postmenopausal patients at the time of RA diagnosis was 43 to 83 years, while the age of the premenopausal patients ranged from 17 to 53 years.

To make comparisons between the sexes possible, male patients were stratified for age in the same way as female patients. From the 123 male patients, those who were above 53 years of age (n = 72) were classified as "older" men (age matched with postmenopausal women). Patients who were below 43 years of age (n = 25) were classified as "younger" men (age matched with premenopausal women). Male patients between 43 and 53 years of age (n = 26) were randomly divided between both groups. The age range of the male patients was 23 to 88 years at the time of RA diagnosis.

Methods. All patients were tested for the presence of IgM-RF (by ELISA, < 5 IU/ml negative)[30]. To evaluate the course and severity of RA, several disease activity variables, radiographic joint damage (RJD), and physical disability were assessed. At entry and every 3 months thereafter clinical and laboratory measurements — Ritchie Articular Index, number of swollen joints (range 0–44), erythrocyte sedimentation rate (ESR, Westergren, mm/h), and general health (100 mm visual analog scale, VAS) — were collected. With these measurements the mean Disease Activity Score (DAS) was calculated[31] for every year of investigation. Physical disability was assessed with the Dutch version of the HAQ[32]. Patients were asked to complete a HAQ every 6 months. To be able to compare the different groups, we calculated yearly median values. Radiographs of hands and feet were taken at the time of RA diagnosis and then every 3 years. The radiographs were used to score RJD according to the modified method of Sharp[33]. Mean differences in RJD were calculated after square-root transformation.

Statistical analysis. Univariate analyses using Student's t tests were performed with sex, age, and menopausal state as independent variables, and mean annual DAS values or square-root transformed RJD values as dependent variables. The association between the independent variables and the median annual HAQ scores was studied using Wilcoxon rank sum tests. All tests were 2 sided with $\alpha = 0.05$ as the level of significance. To investigate the contribution and relevance of the variables menopause, age, and sex together, a stepwise regression analysis procedure for the dependent variables DAS, RJD, and HAQ was used. All selected variables were assessed for their suitability for multivariate statistical analysis. If necessary, transformation to a reasonably normal distribution was performed. All statistical analyses were performed with SAS®[34].

RESULTS

Patient characteristics. The demographic characteristics of all patients with RA at onset are summarized in Table 1. No difference was found in the presence of IgM-RF. The mean age of menopause in the postmenopausal group was 48 (30–57) years, which is comparable to the Dutch population (mean 50, SD 4)[35]. During followup the disease modifying antirheumatic drug (DMARD) prescription policy was the same for all patients. Between the 4 groups (pre- and postmenopausal women, older and younger men) no differences were seen in the time from inclusion until first DMARD prescription, nor were differences observed between the groups concerning the use of DMARD or the drug survival.

Menopausal state and disease activity. The data on disease activity are illustrated in Figure 1. At entry, no statistically significant differences in DAS were found in male versus female patients or in post- versus premenopausal women. However, at this time point a significant difference was found between older and younger male patients ($p = 0.04$). The mean DAS was not different between older men and postmenopausal women, or between younger men and premenopausal women.

At any time point thereafter DAS was significantly increased in female patients compared to their male coun-

Table 1. Demographic characteristics of the study population at the start of followup.

	Postmenopausal Women	Premenopausal Women	Older Men	Younger Men
No. of patients	109	64	85	38
Age, mean (range), yrs	66 (43–83)	36 (17–53)	63 (43–88)	41 (23–53)
IgM-RF ≥ 5 IU/ml, %	76	77	84	82

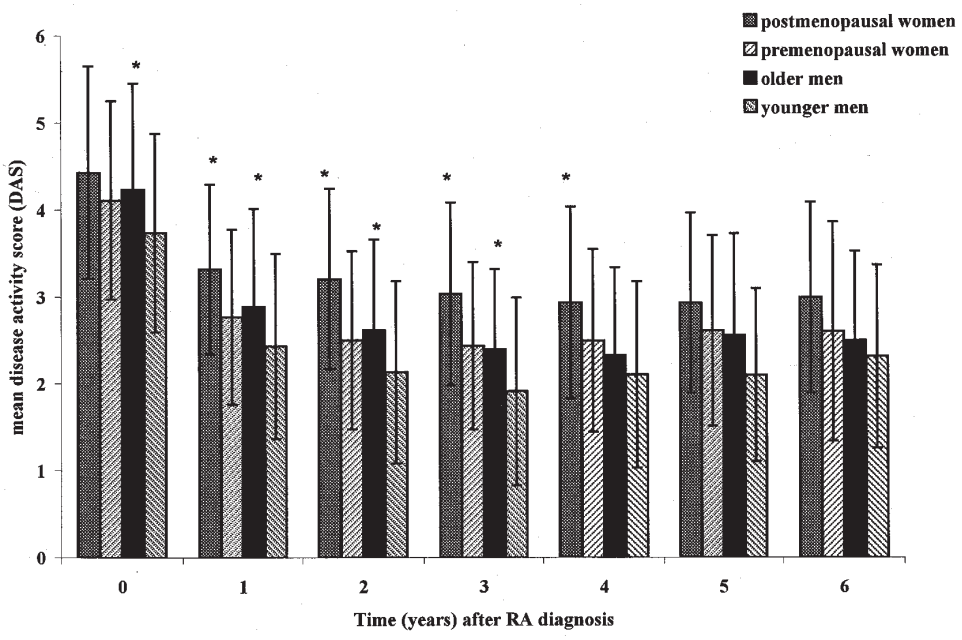

Figure 1. Mean disease activity in post- and premenopausal women and older and younger men, in a 6 year period. * $p < 0.05$.

terparts. Studying the female patients more precisely, it turned out that the increased DAS were mainly caused by postmenopausal patients. At 1, 2, 3, and 4 years, postmenopausal patients showed a significantly more active disease compared to premenopausal patients ($p < 0.01$, $p < 0.01$, $p < 0.01$, $p = 0.02$, respectively). When older men were compared to younger men a significantly higher DAS was seen at 1, 2, and 3 years ($p = 0.04$, $p = 0.02$, $p = 0.02$, respectively). When postmenopausal women were compared to older men a significant difference was seen in DAS at any assessment, except the time of inclusion. In contrast, premenopausal patients were not different from younger men.

Menopausal state and joint destruction. Figure 2 shows the course of the RJD outcome variable in the different subgroups. RJD was significantly worse in female patients with RA at entry ($p = 0.048$). During followup no statistically significant differences between female and male patients were seen. Comparing postmenopausal patients to their premenopausal counterparts, RJD was significantly worse in postmenopausal patients at inclusion as well as 3 years thereafter ($p < 0.01$ and $p = 0.02$, respectively). A comparison of older and younger male patients revealed the same results ($p = 0.04$, $p = 0.02$, $p = 0.01$ at 0, 3, and 6 years, respectively). At baseline and at 3 year followup, the postmenopausal women had greater RJD than the older men ($p < 0.01$, $p = 0.03$, respectively), whereas premenopausal women did not differ from younger men.

Menopausal state and physical disability. Figure 3 illustrates the yearly median values of physical disability, as measured by HAQ, in a 6 year period. Female patients had a worse HAQ score than male patients that was statistically significant at all time points ($p < 0.01$ years 0–4, $p < 0.05$ years 5 and 6). When comparing post- and premenopausal patients, postmenopausal patients showed a statistically significantly increased HAQ score compared to their premenopausal counterparts at all time points ($p < 0.01$). Also, older men showed a worse HAQ score than younger men at years 2, 3, 4, and 6 ($p < 0.01$). Postmenopausal patients showed a statistically significant higher HAQ score compared to older men at all years ($p < 0.05$), with an exception at year 6 ($p = 0.08$), while premenopausal women were not different from younger men at any time point including baseline.

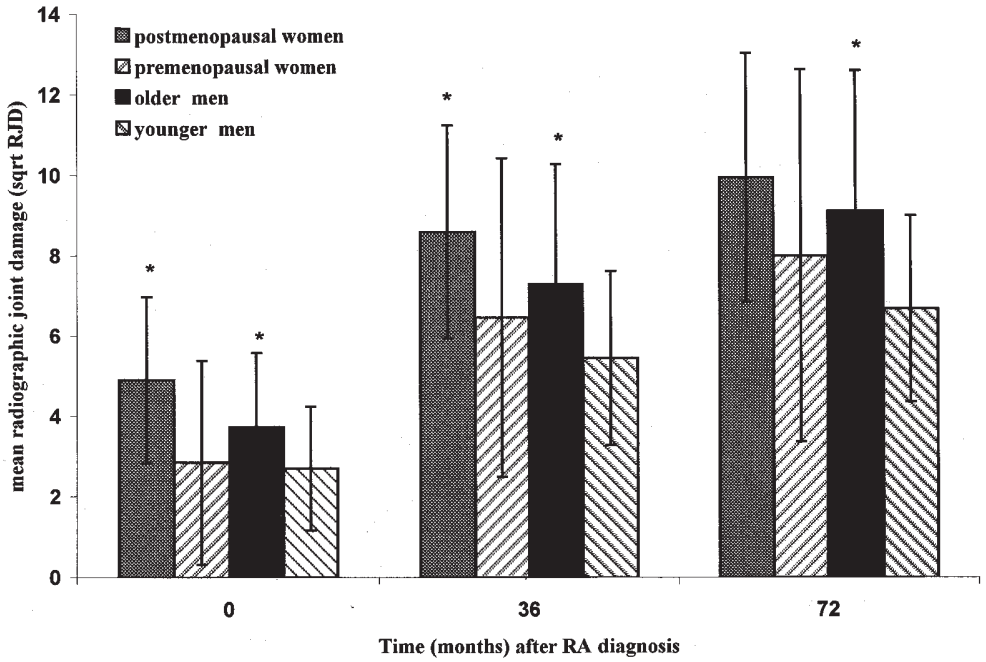

Figure 2. Mean radiographic joint destruction in post- and premenopausal women and older and younger men, in a 6 year period. * $p < 0.05$.

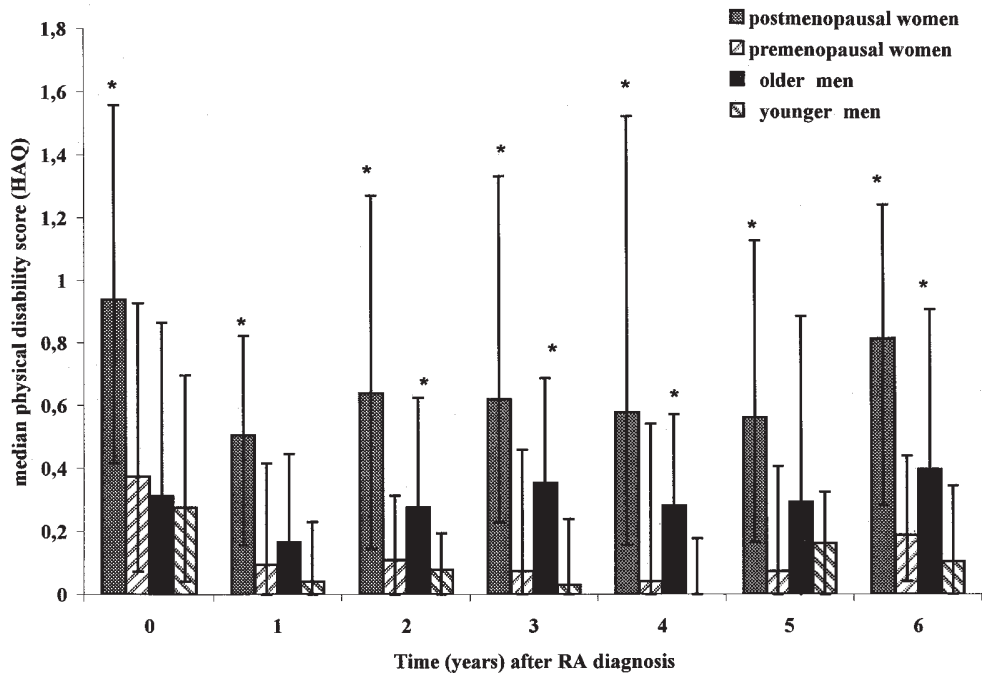

Figure 3. Yearly physical disability in post- and premenopausal women and older and younger men measured by HAQ in a 6 year period. * $p < 0.05$.

The results show that the course of RA varies in the different groups of this investigation. To investigate the contribution and relevance of each of these variables in this explorative study we performed a stepwise regression analysis procedure for the dependent variables DAS, RJD, and HAQ. The entry variables used in this procedure were menopausal state, age, and sex and the interaction terms between age at presentation and the menopausal state and between age and sex. Table 2 shows the results of this analysis at presentation of RA and 3 years thereafter. The model R^2 is a measure of the percentage of variation in the dependent variable, explained by the independent variables in the final model.

For the DAS at baseline the best predictor was age, and

Table 2. Summary of stepwise procedure: variables with a significant contribution to explaining the variance of DAS, RJD, or HAQ at start and after 3 years.

	Menopause	Age	Sex	Menopause × Age	Menopause × Sex	Model R^2
DAS						
Start		0.020* p = 0.005				0.05
Yr 3		0.016 p< 0.001	–0.613 p < 0.001			0.11
RJD						
Start	–4.941 p = 0.018	0.036 p = 0.008		0.095 p = 0.005		0.26
Yr 3		0.043 p = 0.039		0.024 p = 0.013		0.14
HAQ						
Start	–0.965 p = 0.067			0.020 p = 0.014		0.17
Yr 3		0.018 p < 0.001				0.22

*Cells contain the parameter estimates (ß) with p values. Model R^2 is the part of the variance in the dependent variable (DAS, RJD, or HAQ) explained by the independent variables in the model (range 0–1). DAS: Disease Activity Score, RJD: radiographic joint damage, HAQ: Health Assessment Questionnaire.

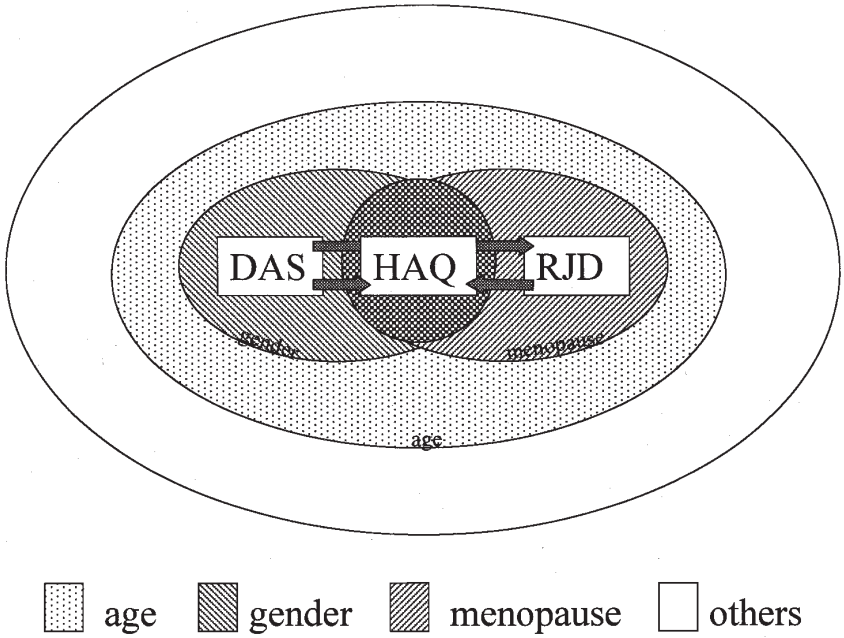

Figure 4. Interaction between disease variables for RA. In the early phase, physical disability is affected by disease activity, but apart from that it is also affected by age, sex, menopausal state, and possibly other unknown factors. Joint destruction is also influenced by disease activity, but as well factors such as age and menopausal state are of importance. In later phases of disease, an effect of joint destruction is seen on physical disability.

for the DAS 3 years thereafter the best predictors were age and sex, which means that higher age and female sex lead to more active disease.

The best predictors for RJD at baseline were menopausal state, age, and the interaction term between menopausal state and age. Three years thereafter age and the interaction term between menopausal state and age were still the best predictors of RJD.

HAQ scores at the start of followup were best predicted by menopausal state and the interaction of menopausal state and age. After 3 years of followup, age was the best predictor for physical disability.

DISCUSSION

To assess future development of RA in an individual patient a physician needs to know which variables have the best predictive value. Although much research has been performed in the field of prognostic factors, authors do not agree on the contribution of some of them. Age and sex are examples of variables on which authors disagree. Some authors have shown that patients who develop RA at an older age have a more severe disease pattern[3,28,29,36]. In contrast, others have shown that patients who develop RA at a younger age have a more progressive disease course[25-28,37]. Finally, there are also authors who find no difference between these 2 groups[38,39]. Such disagreement is also seen with gender, where several authors have shown that women have a worse longterm disease outcome than men, while others suggest that men have a worse disease course[11]. Reviewing the literature it appears that part of the explanation for the different opinions can be found in differences in study design and patient selection.

Another explanation for the different opinions about the role of sex and age in the course of RA might be that it is not just sex or age that could influence the course of disease, but more importantly the hormonal status of female patients. Thus, in studies were age is dichotomized at a cutoff of 60, the younger female patient group consists of a variable proportion of pre- and postmenopausal women, which may mask the effects caused by the hormonal state. It has long been recognized and repeatedly confirmed that during pregnancy, a period in which there is a sharp rise in female sex hormones, disease remission is seen in the majority of cases[40-43]. In addition, the highest incidence of RA in women is seen around the age of menopause[44], where there is a strong decline in the production of female sex hormones. This indicates that female sex hormones may play a role in the incidence and subsequent severity of RA. These observations led to the performance of studies of hormone replacement therapy (HRT). However, these studies also show varying effects concerning the incidence and severity of RA[17-19,45-47].

To study the contribution of female sex hormones we investigated the influence of the menopausal state on the course of RA, expressed with the DAS, the RJD, and the HAQ. Further, we studied the interactive effect of age and the menopausal state as well as the interactive effect of age and sex. At entry, when patients had a disease duration less than 1 year, no statistically significant difference in DAS was seen between female and male patients or between older and younger patients of both sexes. During followup, DAS in postmenopausal patients was statistically significantly increased compared to premenopausal patients, as was DAS in older men compared to their younger male counterparts. As we observed, postmenopausal women not only have higher disease activity than premenopausal women, but they also have significantly more active disease in terms of DAS than older men. These findings confirm that both age and sex play a role in RA[24]. There is some evidence that androgens have a protective effect on the pathophysiology and clinical aspects of RA. Since the androgens produced by the adrenal cortex (DHEA, in women the major source of androgen production) diminish with age, this might explain the more severe RA found especially in older women[48]. In addition, no difference in disease activity was found between premenopausal women and younger men, indicating an effect of female sex hormones, the menopausal state, on the course of RA.

In contrast to the DAS, a statistically significant difference in RJD between female and male patients was already seen at inclusion, which may indicate a gender difference. During followup this difference between male and female patients was not present. On the other hand postmenopausal women showed a statistically significantly higher RJD than premenopausal women, and RJD in older men was significantly higher than in younger men, indicating that age is also a factor that influences RJD. However, the difference between female and male patients as well as between post- and premenopausal women seems to be mainly caused by the menopausal state. There are 2 possible explanations for the difference in RJD between men and women at inclusion. First, it has been suggested that women have, independent of body height or weight, a smaller joint space visible on radiographs than men, which means that they have a smaller amount of articular cartilage[49,50]. We examined this phenomenon in our patient group and found a statistically significant difference in joint space narrowing between women and men. Second, in the elderly there is an imbalance between bone resorption and formation. In postmenopausal women this imbalance is more pronounced than in older men. It has been shown that as a result of hormonal changes after the menopause, bone resorption increases[51-54]. Both the smaller amount of cartilage in all women and the increased bone resorption in postmenopausal women may lead to advanced bone fragility that makes postmenopausal bone and cartilage more sensitive to mechanical and inflammatory stress[12].

Physical disability measured with HAQ was significantly worse in older patients of both sexes compared to younger patients. This confirms that physical disability in RA, as in the general population, can partly be explained by age. In addition, female patients showed higher HAQ scores than male patients. However, on dividing the groups into post- and premenopausal women and older and younger men, it turned out that the difference between women and men was mainly caused by postmenopausal women, again indicating a role for the menopausal state.

To investigate the contribution and relevance of the variables menopause, age, and sex together, a stepwise regression analysis procedure for the dependent variables DAS, RJD, and HAQ was conducted. The above variables explain

(separately or combined) a relatively small part of the variance in the 3 dependent variables. The larger part of the variance is explained by other variables that are not within the scope of this study. The stepwise regression analysis procedure showed that higher age was a statistically significant predictor for DAS at entry. Three years later both higher age and female sex were the best predictors for DAS. The R^2 value of age and sex was then roughly 10%. This is in agreement with the univariate analysis. The sign of the parameter estimate shows that male sex is predictive for less severe disease in terms of the DAS. Although postmenopausal state seemed to be of no importance in disease activity, it was predictive for joint destruction and physical disability. At the start of followup the menopausal state predicted some of the variation in RJD and in HAQ. Interactively with age it explained some of the variation in RJD and in HAQ at the start, and some of the variation in RJD after 3 years. This indicates that menopausal state has a significant effect on RJD and HAQ, increasingly so with higher ages at the beginning of the disease.

It is generally thought that physical disability in the early phase of RA is mainly determined by disease activity and in later stages by joint destruction[55]. We recently found that up to 3 years after the start about 20% of HAQ score is predicted by disease activity and not by joint destruction, while after 6 years HAQ is determined mostly by joint destruction and to a lesser extent by disease activity[56]. Figure 4 illustrates the interaction between disease activity, joint destruction, and physical disability and the influence of menopausal state, sex, and age on these, as found in our study population.

In summary, stepwise regression analysis suggests that disease severity in older patients is worse than in younger patients, but in addition to this, older patients who are at the same time postmenopausal have even more severe disease in terms of joint destruction and physical disability. In future research menopausal state and the interaction term between age and menopausal state should be taken into account when explaining RA outcome variables.

ACKNOWLEDGMENT

We thank all the patients who participated in our study. We also thank Erik Brummelkamp for his assistance in preparing data sets, and our rheumatology research nurses Jacqueline Deenen, Leny Theunisse, and Dorothé Kampschreur for data collection.

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