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ORIGINAL RESEARCH

Impact of early age at menopause on disease outcomes in postmenopausal women with rheumatoid arthritis: a large observational cohort study of Korean patients with rheumatoid arthritis

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ABSTRACT

Objectives To assess the differences in clinical outcomes between patients with rheumatoid arthritis (RA) with early menopause (EM) (<45 years) and usual menopause (UM) (≥45 years) and to identify the impact of EM on longitudinal changes in RA activity and patient-reported outcomes (PROs).

Methods We recruited 2878 postmenopausal women with RA from the Korean Observational Study Network for Arthritis. Patients were examined at baseline and for 5 consecutive years using the Simplified Disease Activity Index (SDAI), Health Assessment Questionnaire–Disability Index (HAQ-DI) and other PROs. Generalised estimating equation (GEE) analyses were performed among patients with a baseline SDAI of >11 to evaluate the impact of EM on longitudinal changes in RA activity and PROs.

Results The EM group (n=437) was younger than the UM group (n=2441), but the RA duration was similar between the two groups. The EM group was more educated and more likely to be seronegative at enrolment. Moreover, the EM group demonstrated higher disease activity and worse PROs for global assessment, fatigue, sleep disturbance and health-related quality of life (HRQoL) (all p<0.05) at baseline. The GEE model revealed that EM significantly influenced the rate of SDAI change (β=1.265, p=0.004) after adjusting for age, RA duration, biologics use and SDAI at baseline. The EM group was also significantly associated with increased HAQ-DI scores and decreased EQ-5D-utility values during the 5-year follow-up period.

Conclusion Patients with RA and EM demonstrate higher disease activity and poorer HRQoL. Furthermore, EM significantly affects the longitudinal changes in disease activity and PROs in patients with RA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clinical outcomes of rheumatoid arthritis (RA) based on age at menopause have been inconsistently reported in previous studies.

⇒ Moreover, no studies have examined the association between age at menopause and longitudinal changes in validated disease activity indices or patient-reported outcomes (PROs) of RA during the follow-up period.

WHAT THIS STUDY ADDS

⇒ Using a large nationwide prospective observational RA cohort in Korea, we identified that patients with RA with early menopause (EM) demonstrated higher disease activity, worse PROs of global assessment, fatigue, sleep disturbance and poorer health-related quality of life (HRQoL) than those with usual menopause.

⇒ In addition, EM was significantly associated with increased disease activity measured by the Simplified Disease Activity Index, Disease Activity Score using 28 joint counts and Clinical Disease Activity Index, and a decline in physical function and HRQoL during the 5-year follow-up period.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Age at menopause should also be considered a major factor in interpreting RA disease outcomes when treating postmenopausal patients with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder that primarily affects synovial joints.[1] RA incidence and prevalence rates are twofold higher in women than in men, and the lifetime risk of developing RA has been reported to be 3.6% and 1.7% for women and men, respectively.[2] The sex difference in RA prevalence has led to studies exploring how female reproductive or hormonal factors affect the development or progression of RA in women.[3–8] Long-term breast feeding has been reported

to significantly reduce the risk of subsequent RA development.[3 4] In contrast, early age at menarche, irregular menstrual cycle and polycystic ovarian syndrome have been reported to increase the risk of RA.[3 5] Furthermore, oral contraceptive use and parity have demonstrated neutral effects on RA development.[3 4] RA disease activity has been shown to decrease during pregnancy and increase during the postpartum period.[6] Among patients with early RA, postmenopausal women reportedly presented with higher disease activity and worse physical disability with more radiographic joint destruction than premenopausal women.[9]

Menopause is defined as the permanent cessation of ovulation with subsequent hypo-oestrogenaemia and high follicle-stimulating hormone levels.[10] It occurs at a median age of 51.4 years,[11] and menopause before 45 years of age is referred to as early menopause (EM).[12 13] The link between EM and adverse health outcomes such as cardiovascular disease, cognitive impairment, dementia, osteoporosis, sexual dysfunction, pain perception, chronic fatigue syndrome and increased overall mortality has been well established in previous studies.[14–16] However, there are conflicting results regarding the effect of age at menopause on the development of RA. Several earlier studies have demonstrated EM as a risk factor for the development of RA.[8 14] Conversely, recent large-scale cohort studies have shown either no association or a significant association between age at menopause and RA risk only among smokers.[17 18]

Regarding the disease characteristics of RA, among 534 postmenopausal women with RA from the Canadian Early Arthritis Cohort, women with EM presented worse patient-reported pain and global assessment scores. Furthermore, they were more likely to be rheumatoid factor (RF) positive than those with the usual age at menopause.[13] In contrast, Pikwer *et al* suggested that EM was associated with a mild seronegative RA phenotype using SPSS TwoStep Cluster Analysis among 127 postmenopausal women with RA.[7] While a few studies have investigated how EM affects the clinical outcomes of RA, these studies had relatively small sample sizes.[7 13] Furthermore, none of these studies has examined the association between age at menopause and longitudinal changes in the validated disease activity indices or patient-reported outcomes (PROs) of RA during the follow-up period.

Therefore, we aimed to assess the differences in clinical outcomes between patients with RA with EM and those with usual menopause (UM) using validated disease activity indices and PROs of RA. Furthermore, we aimed to identify the potential impact of early age at menopause on the clinical course of RA over time using a large nationwide observational RA cohort in Korea.

METHODS

Data source and study population

We selected postmenopausal women from the Korean Observational Study Network for Arthritis (KORONA) cohort, the largest nationwide prospective observational cohort of RA in Korea.[19] The KORONA cohort included 5376 patients aged >18 years who met the 1987 American College of Rheumatology (ACR) classification criteria for RA[20] from 23 university hospitals.[19] They were recruited between July 2009 and December 2011 and were followed up annually until February 2017.

All patients in the KORONA cohort completed an initial questionnaire on demographic profiles, including age, sex, lifestyle features (eg, alcohol consumption and smoking), education level and economic status. We also obtained clinical information regarding comorbidities, RA onset, use of disease-modifying antirheumatic drugs, other drug prescriptions, surgery and bone fractures. In addition, data on female reproductive factors, such as menopausal status, age at menopause, menarche, first pregnancy and delivery, number of previous pregnancies, natural abortion, deliveries, history of total lifetime breast feeding (total duration and number of children with breast feeding), and previous or current use of hormone replacement therapy (HRT), were collected by patient interviews.

Laboratory tests, including erythrocyte sedimentation rate, C reactive protein, and RF and anticitrullinated protein antibodies (ACPAs) tests, and radiographs of the bilateral hands were performed at the baseline and annual follow-ups. RA disease activity was evaluated using the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and Disease Activity Score using 28 joint counts (DAS28). Functional disability and health-related quality of life (HRQoL) were assessed using the Health Assessment Questionnaire–Disability Index (HAQ-DI) and EuroQoL-5D (EQ-5D), respectively. The EQ-5D instruments include a Visual Analogue Scale (VAS, 0–100) and utility-based index values, EQ-5D-3L (hereafter referred to as 'utility values'), which can be converted from answers to five questions, where 0 indicates death and 1 indicates perfect health.[21] All disease activity indices, HAQ-DI, EQ-5D, and patient-reported VAS scores for global assessment, pain, fatigue and sleep disturbance were obtained at enrolment and annual follow-up.

As previously stated, women who had menopause <45 years and ≥45 years were classified into the EM and UM groups, respectively.[12 13] In addition, those who did not report their age at menopause (75 patients, 2.6%) were placed in the UM group to avoid overestimating women with EM.

Statistical analysis

We compared the baseline characteristics and comorbidities between patients with RA in the EM and UM groups. Continuous variables were compared using the Student's t-test or Mann-Whitney test, and categorical variables were compared using the χ^2 test or Fisher's exact test. Differences between baseline and follow-up outcomes were analysed using the Wilcoxon signed-rank test, and multiple comparison corrections were performed using

the Bonferroni method. Data are presented as mean±SD or median (IQR) for continuous variables and number (%) for categorical variables.

A generalised estimating equation (GEE) analysis was performed to assess the differences in the SDAI change between the EM and UM groups during the follow-up period by controlling variances originating from repeated measurements among patients with RA with active disease (moderate to high disease activity: SDAI >11) at baseline. The follow-up time and menopause group were included as the main explanatory variables; age, RA duration, use of biological disease-modifying antirheumatic drugs (bDMARDs), and SDAI at baseline were adjusted. Additionally, the baseline CDAI, DAS28, HAQ-DI and EQ-5D were adjusted for the GEE model analyses of the differences in the CDAI, DAS28, HAQ-DI and EQ-5D changes between the two groups. Cox proportional hazards regression analyses were performed to evaluate the impact of age at menopause on clinical remission among patients with active disease at baseline. Clinical remission was defined as SDAI of ≤3.3,[22] and patients who met the remission criteria at any single year of measurement were classified as being in point remission. In addition, those with an SDAI of ≤3.3 for any two consecutive annual measurements during the follow-up were classified as being in sustained remission. The time of first remission was defined as the event time, and a 1-year interval was maintained for the covariates in the Cox proportional hazards regression analyses. Every isolated missing value was replaced with the measurement following the missing value from the same patient, and participants were censored if more than one consecutive measurement was missing. Potential confounders included age, RA duration, education level, economic status, baseline VAS scores for pain, fatigue, sleep disturbance, seropositivity and baseline SDAI. For the sensitivity analyses, the same procedures using the CDAI (active disease: CDAI >10, remission: CDAI ≤2.8) and DAS28 (active disease: DAS28 ≥3.2, remission DAS28 <2.6) were conducted. We also performed subgroup analyses on those who had never used HRT. Variables with p values of <0.05 in the univariate analysis were analysed together in the multivariate analysis to evaluate the independent effects of covariates.

R language V.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and T&F program V.3.0 (YooJin BioSoft, Korea) were used for all the statistical analyses. Statistical significance was defined at p values of <0.05.

RESULTS

Baseline characteristics and female reproductive factors of the study population

This study included 2878 postmenopausal women from the 5376 patients with RA enrolled in the KORONA cohort. Among them, 437 (23.3%) reported an early age at menopause. The mean age of the study population at study entry was 60.4 years, and the EM group was younger than the UM group (58.0±9.5 vs 60.8±8.0 years, p<0.001) (table 1). However, RA duration did not differ between the two groups (9.2±8.5 vs 8.5±7.6 years, p=0.142). In addition, the EM group had higher education levels than the UM group (p=0.002), but no difference was seen in monthly income or BMI between the two groups (table 1).

While most (91.6%) of the patients in the UM group reached menopause naturally, about half of the patients in the EM group (n=217, 49.7 %) reported natural menopause (p<0.001) (table 1). Among the EM group, 205 (46.9%) and 15 (3.4%) patients had undergone surgically and medically induced (using chemotherapy or hormone therapy) menopause, respectively. The mean±SD age at onset of menopause was 48.6±5.0 years among all the postmenopausal women and 39.7±4.1 and 50.2±3.1 years in the EM and UM groups, respectively (p<0.001) (table 1). The duration since menopause onset was 18.3±9.9 and 10.6±7.9 years in the EM and UM groups, respectively (p<0.001). There were no differences in the mean age at menarche, previous or current use of HRT, or the number of pregnancies or deliveries between the EM and UM groups (table 1). Fewer patients in the EM group had breast fed (356 (81.5%) vs 2130 (87.3%), p=0.001) than those in the UM group had (table 1). However, the total duration of breast feeding was comparable between the two groups (table 1).

Comparisons of RA characteristics and disease activity at baseline according to age at menopause

RA activity at baseline, assessed using SDAI (15.4±11.7 vs 13.9±10.0, p=0.011), CDAI (14.5±11.1 vs 13.1±9.7, p=0.018) and DAS28 (4.1±1.4 vs 3.9±1.3, p=0.018), was significantly higher in the EM group than in the UM group. Additionally, the proportion of patients with RA with moderate to high disease activity (SDAI >11) was also higher in the EM group than in the UM group (244 (58.2%) vs 1202 (51.9%), p=0.017) (table 1). The EM group also showed higher VAS scores for global assessment (46.7±26.9 vs 43.4±26.1, p=0.016), fatigue (50.0±29.9 vs 45.7±29.2, p=0.005), sleep disturbance (34.4±32.6 vs 29.1±29.6, p=0.002) and worse EQ-5D–VAS (59.9±22.2 vs 63.0±19.5, p=0.006) than the UM group did at baseline (table 1). In addition, the proportion of patients with positive RF was significantly lower in the EM group than in the UM group (203/292 (69.5%) vs 1210/1573 (76.9%), p=0.007) (table 1). The incidence of erosive disease was comparable between the two groups (table 1), and there was no significant difference in RA treatment patterns according to age at menopause (online supplemental table S1).

Comorbidities according to age at menopause

Online supplemental table S2 summarises the comorbidities at baseline according to age at menopause. Previous fracture (24.5% vs 19.6%, p=0.024) and neoplastic disease prevalence (17.6% vs 7.9%, p<0.001) rates were

Table 1 Baseline characteristics of the postmenopausal women included in the study

	All n=2878	Early menopause n=437	Usual menopause n=2441	P value
Age at enrolment	60.4±8.3	58.0±9.5	60.8±8.0	<0.001
Age at disease onset	49.5±11.0	46.2±11.9	50.0±10.7	<0.001
Disease duration (year)	8.6±7.7	9.2±8.5	8.5±7.6	0.142
Education, high school or more	1058 (36.8)	187 (42.9)	855 (35.3)	0.002
Monthly income, US$≥1700	1197 (41.6)	187 (42.9)	995 (41.0)	0.492
Current smoker	77 (2.7)	16 (3.7)	61 (2.5)	0.408
Current alcohol drinking	364 (12.7)	69 (15.8)	295 (12.1)	0.081
BMI (kg/m^2)	22.8±3.6	22.9±3.4	23.1±3.2	0.212
Reproductive variables				
Age at menopause (years)	48.6±5.0	39.7±4.1	50.2±3.1	<0.001
Time since menopause (years)	11.8±8.7	18.3±9.9	10.6±7.9	<0.001
Causes of menopause				<0.001
Natural menopause	2452 (85.2)	217 (49.7)	2235 (91.6)	
Surgical menopause	381 (13.2)	205 (46.9)	176 (7.2)	
Medical-induced menopause	45 (1.6)	15 (3.4)	30 (1.2)	
Age at menarche (years)	16.2±2.1	16.0±2.1	16.2±2.1	0.083
Number of pregnancies	4.4±2.2	4.3±2.4	4.4±2.2	0.422
Number of deliveries	2.7±1.4	2.6±1.5	2.7±1.3	0.531
Breast feeding	2486 (86.4)	356 (81.5)	2130 (87.3)	0.001
Duration of breast feeding (months)	39.0±31.6	39.4±31.0	38.9±31.8	0.800
Use of HRT				0.096
Never used	2199 (76.4)	314 (71.9)	1885 (77.2)	
Previous use of HRT	520 (18.1)	96 (22.0)	424 (17.4)	
Current use of HRT	131 (4.6)	23 (5.3)	108 (4.4)	
Patient-reported outcomes				
Morning stiffness >1 hour	2681 (93.2)	412 (94.3)	2269 (93.0)	0.574
Pain VAS	41.5±28.4	43.9±29.2	41.1±28.3	0.055
Global assessment VAS	43.9±26.2	46.7±26.9	43.4±26.1	0.016
Fatigue VAS	46.4±29.4	50.0±29.9	45.7±29.2	0.005
Sleep disturbance VAS	29.9±30.1	34.4±32.6	29.1±29.6	0.002
EQ-5D–VAS	62.5±19.9	59.9±22.2	63.0±19.5	0.006
EQ-5D utility value	0.6±0.3	0.6±0.3	0.6±0.3	0.096
HAQ-DI	0.8±0.7	0.9±0.7	0.8±0.7	0.237
Physician's VAS	27.4±18.8	27.7±19.7	27.4±18.7	0.747
Laboratory findings				
Seropositivity	2188/2301 (95.1)	321/342 (93.9)	1867/1959 (95.3)	0.277
RF-positive	1413/1865 (75.8)	203/292 (69.5)	1210/1573 (76.9)	0.007
RF titre	109.3±209.5	102.4±178.4	110.6±214.9	0.491
ACPA-positive	1759/2117 (61.1)	254/315 (80.6)	1505/1802 (83.5)	0.222
ESR	31.6±24.9	32.2±26.3	31.4±24.7	0.576
CRP	1.1±2.3	1.0±1.9	0.9±1.5	0.160
28-tender joint count	4.4±9.6	4.6±5.8	4.1±5.2	0.046
28-swollen joint count	2.6±11.9	2.4±3.7	2.1±3.2	0.047
SDAI	14.8±19.0	15.4±11.7	13.9±10.0	0.011

Continued

Table 1 Continued

	All n=2878	Early menopause n=437	Usual menopause n=2441	P value
CDAI	14.0±18.5	14.5±11.1	13.1±9.7	0.018
DAS28	4.0±1.3	4.1±1.4	3.9±1.3	0.018
Moderate to high disease activity				
SDAI >11	1448 (52.9)	244 (58.2)	1202 (51.9)	0.017
Erosion on hand X-ray	539/1,197 (45.0)	85 (47.0)	454 (44.7)	0.627

Values are presented as mean (SD) or number (%).
ACPA, anticitrullinated protein antibody; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28, Disease Activity Score using 28 joint counts; DMARD, disease-modifying antirheumatic drug; EQ-5D, EuroQol-5D; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire–Disability Index; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; VAS, visual analogue scale.

significantly higher in the EM group than those in the UM group. Contrastingly, the rate of hypertension prevalence (28.4% vs 35.2%, p=0.006) was lower in the EM group than in the UM group. Regarding the type of neoplastic disease, uterine or cervical neoplasm prevalence was higher (66.2% vs 38.1%, p<0.001), whereas that of colorectal neoplasms (0.0% vs 6.2%, p=0.022) was lower in the EM group than in the UM group. There was no difference in fracture sites between the EM and UM groups (data not shown), and the prevalence of osteoporosis at baseline was comparable between the two groups. In addition, the incidence of newly developed fractures (12.8% (36/281) vs 12.8% (209/1635), p>0.999) during the 5-year follow-up period was comparable between the groups.

Longitudinal changes in RA disease activity and PROs for 5 years

SDAI, CDAI and DAS28 scores among the study population decreased over time during the 5-year follow-up period (figure 1A–C and online supplemental table S3). However, unlike the UM group, in which all the disease activity indices continuously decreased over time, the EM group demonstrated fluctuations in the disease activity indices (figure 1A–C). The EM group had higher baseline SDAI and CDAI scores than the UM group, and the differences in the SDAI and CDAI scores between the two groups remained significant during the 5-year follow-up period, except in the third year (figure 1A,B). Longitudinal changes in functional disability and HRQoL (figure 1D,E) tended to differ from those in the disease activity indices after the third year (figure 1A–C). A subgroup analysis of patients with RA with active disease (SDAI >11 (n=1448), online supplemental figure S1; CDAI >10 (n=1587), online supplemental figure S2; DAS28 ≥3.2 (n=1827), online supplemental figure S3) demonstrated similar trends.

Among patients with RA with active disease at baseline (SDAI >11), the GEE model revealed that the EM group significantly influenced the rate of SDAI change (β=1.265, p=0.004) after adjusting for age, RA duration, use of bDMARDs and SDAI at baseline (table 2). Other significant predictors of SDAI changes over the 5-year follow-up period included RA duration and baseline SDAI. In this subgroup, GEE analyses also showed that EM was significantly associated with an increase in CDAI (β=1.208, p=0.003), DAS28 (β=0.178, p=0.013) and HAQ-DI (β=0.092, p=0.003), and decreased EQ-5D utility values (β=−0.033, p=0.016) during the 5-year follow-up period (table 2). The sensitivity analyses of patients with active RA based on CDAI (online supplemental table S4) and DAS28 (online supplemental table S5) demonstrated overall consistent results, with the primary analyses showing EM as a significant predictor of longitudinal changes in the disease activity indices, HAQ-DI and EQ-5D utility values.

Predictors of clinical remission

Among 1446 patients with active disease (SDAI >11) at baseline, a total of 5003 SDAI measurements were collected during the follow-up, with SDAI of ≤3.3 in 294 measurements (5.9%). Sixty-five patients achieved sustained remission during follow-up, and 201 reached point remission at one or more non-consecutive measurements. We performed univariate and multivariate Cox proportional hazards regression analyses to identify the impact of EM on clinical remission measured by the SDAI. However, after adjusting for confounders during the follow-up, EM was not significantly associated with clinical remission (table 3). Variables significantly associated with clinical remission included RA duration, baseline fatigue VAS score for both sustained and point remission, baseline SDAI score and high monthly income for point remission (table 3). Sensitivity analyses of patients with active RA according to CDAI (online supplemental table S6) and DAS28 (online supplemental table S7) yielded similar results.

Subgroup analyses for patients with RA who had never-used HRT

Since the influence of HRT on pain or inflammation has been reported in previous RA studies, we performed the subgroup analyses excluding patients with previous or current HRT users.[23] We identified 314 patients in the

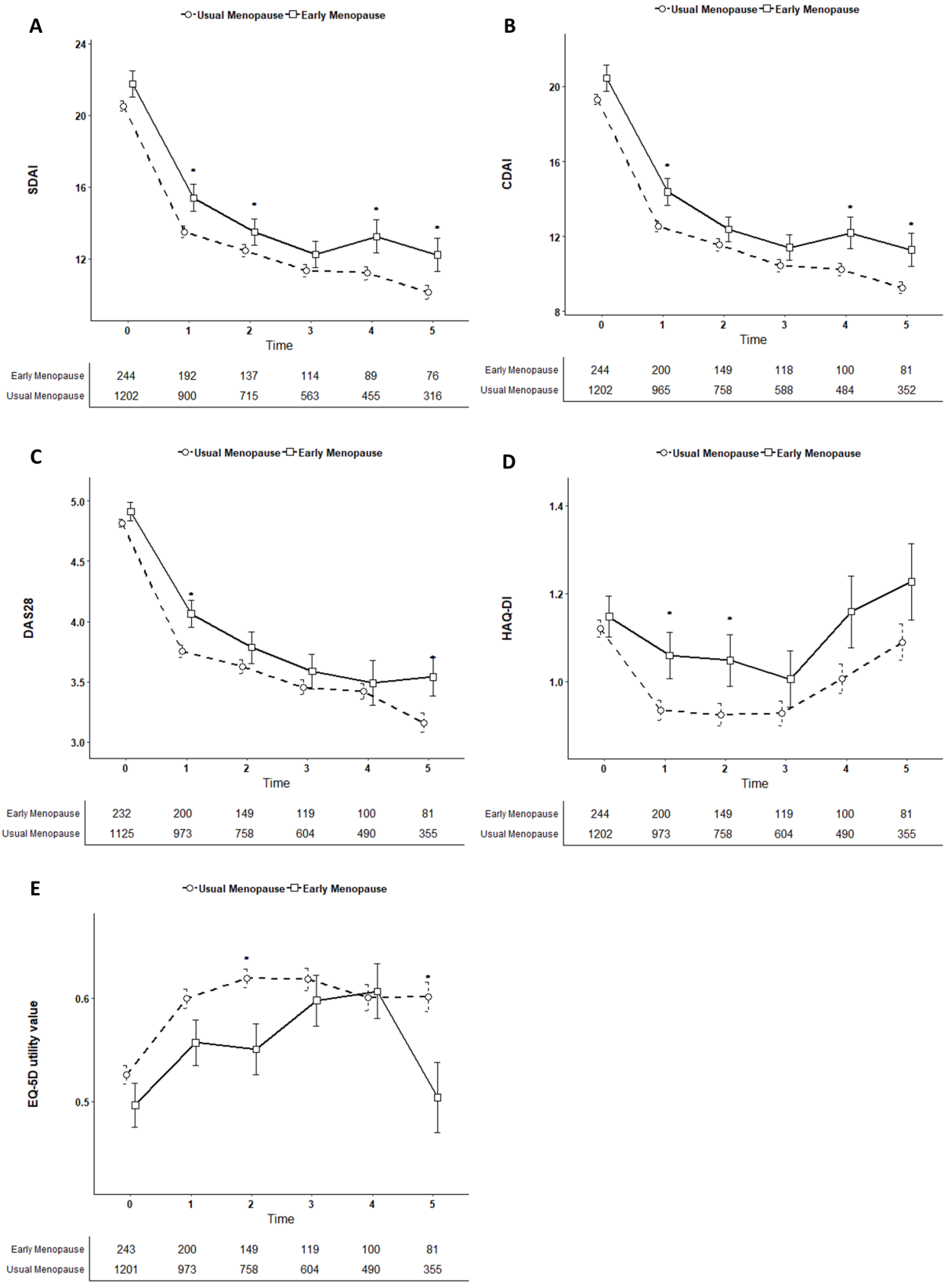

Figure 1 Longitudinal changes in disease activity indices and patient-reported outcomes between the EM and UM groups over the 5-year follow-up period among the entire study population. Time trend graphs of the DAS28, SDAI, CDAI, HAQ-DI, and EQ-5D utility values are shown as mean±SE. The numbers of women in the EM and UM groups with available data at each time point are shown in the bottom table. The mean difference between the two groups was analysed using the Wilcoxon rank-sum test with *p<0.05 at each time point. CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score using 28 joint counts; EM, early menopause; EQ-5D, EuroQol-5D; HAQ-DI, Health Assessment Questionnaire–Disability Index; SDAI, Simplified Disease Activity Index; UM, usual menopause.

Table 2 Longitudinal analysis of predictors of SDAI, CDAI, DAS28, HAQ-DI and EQ-5D utility values over time using a generalised estimating equation model among postmenopausal patients with RA with a baseline SDAI of >11

Outcome variable	Independent variables	Regression coefficient (β) (95% CI)	P value
SDAI	Age	0.013 (−0.024 to 0.049)	0.503
	RA duration	0.084 (0.046 to 0.122)	<0.001
	Baseline SDAI	0.580 (0.531 to 0.630)	<0.001
	Biologic use	0.196 (−0.924 to 1.315)	0.732
	EM	1.265 (0.412 to 2.117)	0.004
	Follow-up time	−1.806 (−1.964 to −1.647)	<0.001
CDAI	Age	0.013 (−0.022 to 0.047)	0.477
	RA duration	0.086 (0.051 to 0.122)	<0.001
	Baseline CDAI	0.567 (0.518 to 0.617)	<0.001
	Biologic use	0.368 (−0.787 to 1.523)	0.532
	EM	1.208 (0.399 to 2.018)	0.003
	Follow-up time	−1.722 (−1.868 to −1.576)	<0.001
DAS28	Age	0.002 (−0.004 to 0.008)	0.477
	RA duration	0.016 (0.010 to 0.023)	<0.001
	Baseline DAS28	0.613 (0.562 to 0.664)	<0.001
	Biologic use	0.195 (0.022 to 0.369)	0.027
	EM	0.178 (0.038 to 0.319)	0.013
	Follow-up time	−0.315 (−0.340 to −0.290)	<0.001
HAQ-DI	Age	0.007 (0.004 to 0.009)	<0.001
	RA duration	0.011 (0.009 to 0.014)	<0.001
	Baseline HAQ-DI	0.674 (0.638 to 0.711)	<0.001
	Biologic use	0.044 (−0.033 to 0.122)	0.264
	EM	0.092 (0.030 to 0.154)	0.003
	Follow-up time	−0.004 (−0.016 to 0.007)	0.457
EQ-5D utility values	Age	−0.002 (−0.003 to −0.000)	0.007
	RA duration	−0.003 (−0.004 to −0.002)	<0.001
	Baseline EQ-5D utility value	0.532 (0.492 to 0.572)	<0.001
	Biologic use	−0.012 (−0.045 to 0.021)	0.489
	EM	−0.033 (−0.059 to −0.006)	0.016
	Follow-up time	0.010 (0.005 to 0.015)	<0.001

All covariates adjusted in the model were listed as independent variables.
CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score using 28 joint counts; EM, early menopause; EQ-5D, EuroQol-5D; HAQ-DI, Health Assessment Questionnaire–Disability Index; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index.

EM group and 1885 patients in the UM group among those who had never-used HRT. Consistent with the primary analyses, the baseline RA activity according to SDAI (15.8±12.3 vs 14.1±10.2, p=0.028), CDAI (14.7±11.7 vs 13.3±9.9, p=0.049) and DAS28 (4.1±1.4 vs 3.9±1.3, p=0.047) was significantly higher in the EM group than in the UM group. The EM group also showed significantly higher VAS score for sleep disturbance (33.6±32.5 vs 28.9±29.4, p=0.016) and worse EQ-5D–VAS score (59.3±22.7 vs 63.0±19.4, p=0.007) than the UM group at baseline (online supplemental table S8). In addition, the EM group was significantly associated with increased disease activity measured by the SDAI (β=1.212, p=0.014), CDAI (β=1.105, p=0.013) and DAS28 (β=0.211, p=0.009), and decreased physical function and health-related quality of life during the 5-year follow-up period (table 4).

DISCUSSION

This study is the first to evaluate the impact of age at menopause on longitudinal changes in disease activity and various PROs over time in postmenopausal women with RA. Using a large nationwide prospective observational RA cohort in Korea, we identified that patients with RA with EM demonstrated higher disease activity, worse PROs of global assessment, fatigue and sleep

Table 3 Univariate and multivariate Cox proportional hazard regression analysis of sustained and point clinical remission in postmenopausal women with baseline SDAI of >11 (N=1446)

	Point remission				Sustained remission			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	**HR (95% CIs)**	**P value**	**HR (95% CIs)**	**P value**	**HR (95% CIs)**	**P value**	**HR (95% CIs)**	**P value**
Early menopause	0.806 (0.544 to 1.194)	0.282	–	–	0.988 (0.517 to 1.890)	0.972	–	–
Age	0.992 (0.974 to 1.009)	0.336	–	–	1.007 (0.976 to 1.038)	0.670	–	–
RA duration	0.966 (0.945 to 0.987)	0.002	0.969 (0.948 to 0.990)	0.004	0.913 (0.871 to 0.958)	<0.001	0.921 (0.878 to 0.965)	<0.001
Level of education*	1.303 (0.983 to 1.726)	0.066	–	–	0.886 (0.530 to 1.481)	0.643	–	–
Economic status†	2.020 (1.529 to 2.670)	<0.001	1.677 (1.237 to 2.274)	<0.001	1.809 (1.109 to 2.951)	0.018	1.600 (0.938 to 2.729)	0.084
Baseline pain VAS	0.987 (0.982 to 0.992)	<0.001	0.997 (0.990 to 1.004)	0.456	0.983 (0.974 to 0.992)	<0.001	1.001 (0.989 to 1.013)	0.859
Baseline fatigue VAS	0.988 (0.984 to 0.993)	<0.001	0.993 (0.987 to 0.999)	0.03	0.978 (0.969 to 0.986)	<0.001	0.983 (0.972 to 0.994)	0.003
Baseline sleep disturbance VAS	0.991 (0.986 to 0.995)	<0.001	0.996 (0.990 to 1.002)	0.224	0.986 (0.977 to 0.995)	0.002	0.994 (0.983 to 1.006)	0.313
Baseline SDAI score	0.946 (0.925 to 0.968)	<0.001	0.968 (0.944 to 0.993)	0.011	0.945 (0.906 to 0.986)	0.008	0.981 (0.938 to 1.025)	0.387
Seropositivity	1.211 (0.595 to 2.464)	0.598	–	–	1.023 (0.319 to 3.279)	0.970	–	–

*The reference group received middle school education or less.
†The reference group had a monthly income of <US$1700.
RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; VAS, Visual Analogue Scale.

Table 4 Longitudinal analysis of predictors of SDAI, CDAI, DAS28, HAQ-DI and EQ-5D utility values over time using a generalised estimating equation model among patients with RA who had never-used HRT and with a baseline SDAI>11

Outcome variable	Independent variables	Regression coefficient (β) (95% CI)	P value
SDAI	Age	0.011 (−0.029 to 0.050)	0.591
	RA duration	0.092 (0.049 to 0.135)	<0.001
	Baseline SDAI	0.591 (0.535 to 0.646)	<0.001
	Biologic use	0.463 (−0.862 to 1.787)	0.493
	Early menopause	1.212 (0.250 to 2.175)	0.014
	Follow-up time	−1.850 (−2.033 to −1.667)	<0.001
CDAI	Age	0.012 (−0.025 to 0.049)	0.531
	RA duration	0.096 (0.056 to 0.137)	<0.001
	Baseline CDAI	0.577 (0.522 to 0.632)	<0.001
	Biologic use	0.778 (−0.597 to 2.152)	0.267
	Early menopause	1.105 (0.229 to 1.980)	0.013
	Follow-up time	−1.756 (−1.925 to −1.587)	<0.001
DAS28	Age	0.003 (−0.003 to 0.010)	0.335
	RA duration	0.016 (0.009 to 0.023)	<0.001
	Baseline DAS28	0.617 (0.561 to 0.672)	<0.001
	Biologic use	0.236 (0.020 to 0.452)	0.032
	Early menopause	0.211 (0.053 to 0.369)	0.009
	Follow-up time	−0.311 (−0.339 to −0.283)	<0.001
HAQ-DI	Age	0.007 (0.004 to 0.010)	<0.001
	RA duration	0.011 (0.008 to 0.014)	<0.001
	Baseline HAQ-DI	0.682 (0.643 to 0.721)	<0.001
	Biologic use	0.040 (−0.054 to 0.134)	0.400
	Early menopause	0.099 (0.027 to 0.171)	0.007
	Follow-up time	0.000 (−0.014 to 0.014)	0.968
EQ-5D utility values	Age	−0.002 (−0.003 to −0.000)	0.008
	RA duration	−0.004 (−0.005 to −0.002)	<0.001
	Baseline EQ-5D utility value	0.537 (0.491 to 0.584)	<0.001
	Biologic use	−0.016 (−0.054 to 0.022)	0.405
	Early menopause	−0.031 (−0.061 to −0.001)	0.040
	Follow-up time	0.010 (0.005 to 0.016)	<0.001

All covariates adjusted in the model were listed as independent variables.
CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score using 28 joint counts; EQ-5D, EuroQol-5D; HAQ-DI, Health Assessment Questionnaire–Disability Index; SDAI, Simplified Disease Activity Index.

disturbance, and poorer HRQoL than those with UM. In addition, EM was significantly associated with increased disease activity measured using the SDAI, DAS28 and CDAI and decreased physical function and HRQoL during the 5-year follow-up period.

The median and mean ages of menopause in our study population were 50.0 and 48.6 years, respectively. When excluding surgical or medical menopause, our study cohort's median and mean ages of natural menopause were 50.0 and 49.6 years, respectively, similar to that reported in previous studies among Korean women.[24 25] Various studies have explored demographic and female reproductive factors associated with the timing of natural menopause and have reported inconsistent results.[11 26 27] In a cross-sectional study of seven centres in the USA and five racial/ethnic groups, current smoking, lower educational level, not being married, and unemployment were associated with earlier age at natural menopause. Simultaneously, oral contraceptive use and parity were related to later age at menopause.[11] In contrast, another multiethnic cohort study demonstrated that smoking, parity, age at menarche and body mass index (BMI) did not significantly affect the age at natural menopause.[26] In the current study, patients with RA with EM were younger and had higher education levels than those with UM; however, no difference was seen in

smoking history, economic status, BMI, parity and age at menarche between the two groups. Furthermore, breast feeding has been associated with a significantly lower risk of EM in a large population-based cohort study within the Nurses' Health Study II cohort.[28] Consistent with this study, significantly fewer patients with EM had breast fed during their premenopausal years than those with UM in our study cohort. However, there was no significant difference in the total breastfeeding duration among those who had breast fed.

The clinical outcomes of RA according to age at menopause have been inconsistently reported in previous studies.[7 13] Pikwer *et al* reported that EM was associated with a milder disease course based on less use of bDMARDs with less radiographic erosions, more RF negativity and lower HAQ-DI scores in a nested case–control study of 127 postmenopausal women with RA.[7] In contrast, a larger cohort study of 534 postmenopausal women with new-onset early RA demonstrated that women with EM were more likely to be RF positive than those with UM.[13] In the current study, the proportion of RF-positive patients in the EM group was 69.5%, which was lower than that reported by Wong *et al* (71.6%) and higher than that reported by Pikwer *et al* (44.0%). Wong *et al* also included patients with RA who satisfied the 2010 ACR/European League Against Rheumatism classification criteria for RA,[29] in which seropositivity is weighted more highly. In contrast, our study and Pikwer *et al* 's study[7] were based only on the 1987 ACR classification criteria.[20] RF and/or ACPA, especially at high levels, are well-known poor prognostic factors for RA,[30 31] and patients with seropositive RA are reported to have more deformities and bone destruction on radiographs than those with seronegative RA.[32] Although the EM group was less likely to be RF positive than the UM group at baseline, the proportion of ACPA-positive patients was comparable between the two groups, and data on titres of ACPA were unavailable. These might explain why there was no difference in the incidence of erosive disease between the two groups. Further studies in larger cohorts are needed to clarify the association between EM and seropositivity.

We observed significantly higher disease activity indices and PROs at baseline and during the 5-year follow-up in the EM group than those in the UM group. Wong *et al* also reported worse patient-reported pain and global assessment together with higher seropositivity in the EM group than in the UM group, although disease activity of RA according to DAS28 was comparable between the two groups at the time of disease presentation.[13] In contrast, Pikwer *et al* found an association between EM and a mild seronegative RA phenotype; however, they did not use a validated disease activity measure.[7] Compared with previous studies, our study included a larger number of patients with RA, with 2878 postmenopausal women from nationwide hospitals. Additionally, Wong *et al* only measured DAS28 to compare RA disease activity between patients with EM and UM,[13] whereas we used the SDAI, CDAI, and DAS28 as validated disease activity measures. Moreover, none of these studies examined how age at menopause affects the clinical course over time in postmenopausal women with RA.[7 13] In addition, we demonstrated that EM significantly affected the rates of SDAI, CDAI and DAS28 changes over the 5-year follow-up period after adjusting for age, RA duration, bDMARD use and disease activity indices at baseline in the GEE analyses.

In addition to composite disease activity indices, patient assessments of global health, pain, fatigue and physical function are also important for meticulously assessing patients with RA.[33] In this study, patients with RA with EM reported higher VAS scores for global assessment, fatigue, sleep disturbance and poorer HRQoL than those with UM at baseline. Although longitudinal changes in PROs tended to differ from those of the composite disease activity indices after the third year (figure 1), EM was also significantly associated with aggravation of patient-reported physical function (HAQ-DI) and HRQoL (EQ-5D–VAS) over time. The discrepancy between the changes in the composite disease activity indices and PROs after the third year can be partly explained by the relatively high rate of follow-up loss during that period.

The poor disease activity and PROs in the EM group can be partly explained by the low lifetime exposure to female hormones. Although the immunomodulatory roles of female hormones are complex and multifaceted, it has been reported that oestrogen and progesterone can suppress T helper (Th) 1 and Th17 cell differentiation. A rapid decline in Th1 and Th17 circulating levels during menopause could augment the production of proinflammatory cytokines such as interleukin (IL)-6, IL-1β and tumour necrosis factor-alpha.[34] In addition, considerable evidence suggests that female hormonal changes associated with EM could heighten pain hypersensitivity and central sensitisation in patients with chronic pain.[35 36] Because the coexistence of fibromyalgia may influence the self-reported PROs of RA, we investigated its prevalence and found no difference between the EM and UM groups (6 (2.5%) vs 20 (1.5%), p=0.273). Accordingly, when treating postmenopausal patients with RA, age at menopause should also be considered a major factor in interpreting RA disease outcomes.

The current study noted differences in the prevalence and distribution of comorbidities among patients with RA with EM and UM. EM is a well-known risk factor for both osteoporosis and bone fracture.[37–39] A systematic review and meta-analysis of age at menopause and fracture risk demonstrated that EM increased fracture risk (OR 1.36, 95% CI 1.11 to 1.66, p<0.002, I^2 81.5%) compared with those with UM.[39] Similar to previous studies, the prevalence of bone fractures in the current study was significantly higher among patients with RA with EM. However, osteoporosis prevalence was comparable in the EM and UM groups. Osteoporosis was defined based on the results of bone mineral density measurement by dual-energy X-ray absorptiometry (DEXA) performed within

1 year of enrolment (T-score ≤−2.5, SD at the spine or hip) or based on the prescriptions of bisphosphonate or selective oestrogen receptor modulators (SERMs). However, osteoporosis prevalence might have been underestimated in both groups because DEXA results were available only in 1352 (47.0%) patients. Furthermore, not all patients diagnosed with osteoporosis may have been prescribed bisphosphonates or SERMs. We also found that hypertension and colorectal cancer prevalence was significantly lower in women with EM than in those with UM. These differences may be attributable to the age difference between the two groups because old age is a well-recognised risk factor for hypertension and colorectal cancer.[40–42] As expected, the prevalence of uterine or cervical neoplasms was significantly higher in the EM group (66.0% vs 38.1%), and more patients in the EM group had undergone surgical menopause (46.9% vs 7.2%) than those in the UM group.

To identify the impact of EM on the disease course of RA, we conducted a Cox regression analysis on achieving remission in the subgroup with active disease at baseline. Achieving remission was associated with short disease duration and low baseline scores for disease activity indices and PROs, which is consistent with the results of previous studies.[43] However, EM was not associated with point or sustained remission. In our cohort, the proportion of patients achieving remission was low, and the rate of follow-up loss was high, making it difficult to analyse factors related to remission. Additionally, since the reimbursement criteria for bDMARDs prescriptions in Korea were stringent at the time of enrolment, the low use of bDMARDs may have influenced the low rate of achieving remission. Further similar analyses in a large, well-controlled RA cohort may better elucidate the impact of EM on the disease process of RA.

Our study had several limitations. First, a high percentage of participants were lost during the follow-up, which may have led to a bias. Second, the 1-year follow-up interval may not have captured a brief flare-up of RA activity. Third, information on age at menopause was retrospectively collected by self-reports; therefore, possible recall bias should be considered. Fourth, the EM group had higher prevalence of neoplastic disease than the UM group, which may have negatively affected various PROs and, furthermore, the disease activity of RA. Nevertheless, there are strengths to this study that deserve consideration. First, we analysed 2878 postmenopausal women diagnosed with RA from nationwide hospitals, making our study one of the largest ever to identify the impact of age at menopause on clinical outcomes of RA. Second, our study population provided a good representation of all Korean postmenopausal women with RA in real-world clinical care. However, additional multiethnic or multinational prospective cohort studies are warranted to generalise our results. Third, we used validated disease activity scores, including the SDAI, DAS28 and CDAI, to assess the disease activity of RA at enrolment and annual follow-up. To the best of our knowledge, this is the first study to analyse how age at menopause affects longitudinal changes in disease activity and PROs of RA over time. We have also presented comprehensive data regarding the differences in the prevalence and distribution of comorbidities and demographic and female reproductive characteristics between patients with RA with EM and UM.

CONCLUSIONS

Using data from a large nationwide prospective observational RA cohort in Korea, we identified that EM was significantly associated with increased disease activity and a decline in physical function and HRQoL during the 5-year follow-up period. Our findings support the notion that reduced lifetime exposure to ovarian hormones contributes to disease outcomes and comorbidities in postmenopausal women with RA. Moreover, menopausal state and age at menopause should be carefully considered in the assessment and management of female patients with RA. However, further studies are required to understand the role of female hormones in RA pathogenesis.

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