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Concise report

The impact of menopause on functional status in women with rheumatoid arthritis

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Abstract

Objective. The aim of this study was to investigate the association of menopause with functional status outcomes in women with RA.

Methods. Participants were women in a US-wide observational cohort who developed RA before menopause. The HAQ measured functional status. We controlled for confounding variables and used univariate and multivariable generalized estimating equation methods with the sandwich estimator of variance. Best models were selected using the quasi-likelihood under the independence model criterion. A sensitivity analysis was performed using linear mixed effects regression models.

Results. A total of 8189 women were eligible. Of these, 2005 (24.5%) were pre-menopausal, 611 (7.5%) transitioned through menopause during the study, and 5573 (68.1%) were post-menopausal. Within each respective group, the mean (S.D.) ages were 39.7 (7.8), 50.7 (3.4) and 62.3 (9.3) years. Our results showed that women who were pre-menopausal had less functional decline as measured by the HAQ compared with women who were post-menopausal; these results were robust and strong even after adjustment for other significant factors. The ever-use of hormonal replacement therapy, ever having a pregnancy, and longer length of reproductive life were associated with less functional decline. After menopause, the trajectory of functional decline worsened and accelerated in women with RA.

Conclusion. The results suggest that menopausal status is associated with functional decline in women with RA. Furthermore, menopause is associated with a worsening progression of functional decline. These data indicate that menopause has a significant impact on the level and rate of functional decline in women with RA.

Key words: rheumatoid arthritis, menopause, women's health, functional status

CLINICAL SCIENCE

Rheumatology key messages

- Women with RA have better functional status prior to menopause, even after controlling for covariates.
- After menopause, the trajectory of functional decline worsens in women with RA.
- Pregnancy, HRT and more reproductive years are associated with less functional decline in women with RA.

Introduction

Physical function is an important outcome in RA that determines a patient's ability to complete activities of daily living, as well as their quality of life (QoL). Women, who experience RA at a rate three times greater than men [1], also experience more severe functional decline and increased disability compared with men who have RA [2]. The sex-based differences in RA development and progression have long been identified, but remain poorly understood.

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Several differences in prevalence, incidence and phenotypic characteristics highlight the disparity between men and women with RA. Women with RA do worse than men with RA as measured through patient-reported outcomes (PROs). Women with RA report greater rates of pain [3], higher rates of disease-related fatigue [4], more persistent disease [5] and a lower QoL [6] compared with men with RA. Some variability may be related to differences in muscular anatomy, allowing men to compensate better for RA-related dysfunction [7]. Women may have more activated immune systems, exhibiting more powerful cellular and humoral immune responses than men [8], thus making their disease experience more pronounced. Additionally, disease experience, pain perception and coping strategies vary between sexes [9].

Women experience shifts in their disease surrounding reproductive and hormonal life events. RA hormonal involvement in women is most pronounced surrounding childbirth. Women with RA have a decreased incidence of RA during pregnancy, yet an increased incidence of disease development and flare during the postpartum period [10]. Women who experience early menopause are more likely to develop RA compared with women who experience a normal or late menopause [11]. Development of RA and disease-related activity have been associated with use of oral contraception (OC) and hormone replacement therapy (HRT), with inconsistent results [12].

Given that women have changes in disease development and progression surrounding reproductive and hormonal events, we wondered how menopause would affect a woman's PRO of functional status. The purpose of this study was to explore the relationship between menopause and functional status in women who have RA.

Methods

Design

This was a longitudinal study using data from the National Data Bank for Rheumatic Diseases (NDB). The NDB has Institutional Review Board (IRB) approval from the Via Christi IRB, and informed patient consent to be included in the NDB was obtained. The analysis of deidentified NDB data for this study was approved by the University of Nebraska Medical Center IRB. The HAQ measured functional status. NDB participants complete a questionnaire every 6 months that includes the HAQ. Demographic characteristics and reproductive items, such as date of last menstrual period, are included in each questionnaire.

Inclusion criteria for this study were women participating in the NDB who had an RA diagnosis before menopause, with at least two completed questionnaires between 2003 and 2017. Women were excluded if they had a hysterectomy, were currently pregnant, had menopause before the age of 40 years, or if they were over the age of 55 years and did not report a menstruation cessation date.

Menopausal stage

Menopausal stage was determined based on survey response. Women were classified as menopausal if they responded that they were menopausal or responded that they had not experienced a menstrual period for 1 year and were not on a hormonal contraceptive. Women were divided into three groups for comparison: pre-menopausal, post-menopausal and transitioning through menopause. Women were included as transitioning through menopause if they had completed at least two questionnaires, were not using hormonal contraceptives, and had at least one questionnaire indicating menstruating and at least one indicating not menstruating or menopausal.

We compared HAQ scores between the three groups and measured the changes in HAQ for these women. This was calculated by computing consecutive differences on HAQ disability divided by the difference in time (in years) between two observations for each patient.

Other variables

The following confounding variables were included: income; age; length of reproductive life (for post-menopausal women this was age from menarche to menopause, whereas for pre-menopausal women this was years from menarche to current age); education level; RA duration; rheumatic disease co-morbidity index; ever smoked; biologic therapy current use; biologic therapy ever-use; HRT ever-use; OC ever-use; and ever pregnant. The search for best model was conducted using this set of variables.

Other variables characterizing RA severity, such as patient activity scale, rheumatoid arthritis disease activity index, the short form (36) health survey physical component summary and mental component summary, global severity and pain, were included in the baseline characterization but not in the models because they were highly correlated with the HAQ. The variables characterizing menstrual status, such as age at menarche and age at menopause, were used indirectly by entering length of reproductive life into the models. HRT, OC or pregnancies were used as ever-variables owing to lack of variation between groups.

Statistical analyses

We analysed the data with univariate and multivariable generalized estimating equations (GEEs). GEEs are helpful in longitudinal samples where the subjects respond to the same questions over time and the researcher wishes to determine and power for both within-subject and between-subject correlations. To estimate the entire distribution with accurate predictability, we used the identity link function and the Gaussian family distribution for the HAQ. For parameter estimation, we applied the robust covariance matrix estimator (sandwich estimator) in order to provide consistent estimates of the variance–covariance matrix. We performed a sensitivity analysis using mixed effect regression models (MRMs).

The way in which NDB addresses missing data is explained elsewhere [13]. Missing covariate data on completed questionnaires were handled using multiple imputation by chained equations (7% missing in total income is the worst case variable). For reproductive

variables, such as age at menarche or menopausal status, the last observation was carried forward. When more than one value of age was given longitudinally by the patient, the most frequent value was assumed. Results were considered using the average, but no differences were found.

To account for the likelihood that the relationship between age and HAQ would be non-linear, a cubic spline with three knots (at ages 42, 58 and 74 years) and an interaction term between age and menopausal status were used. Best models were selected using the quasi-likelihood under the independence model criterion (QICu). This criterion was used in a forward selection approach. The relationship of age and HAQ was assessed by comparing several models: linear, polynomial and by cubic splines exploring several knot values. The introduction of the interaction with menstrual status was also explored with the QICu selection. Analyses were conducted using Stata v. 14 by StataCorp (College Station, TX, USA).

Results

A total of 8189 women participating in our study developed RA before menopause. Of these, 2005 were pre-menopausal (24.5%) at enrolment, 611 transitioned through menopause during the study (7.5%), and 5573 were post-menopausal (68.1%). Within each respective group, the mean (S.D.) ages were 39.7 (7.8), 50.7 (3.4) and 61.8 (9.8) years. Table 1 includes the distribution of the completed follow-up questionnaires, with median values of 2, 7.5 and 4 years, respectively. It also shows demographic and clinical characteristics of women according to menopausal status (pre- and post-menopausal at a random observation, and menopause transition group measured at the first observation without menstrual cycles). Groups differed in demographic and clinical characteristics, which was expected because of the interaction between age and menopausal status.

In interpreting the HAQ, negative values indicate less functional decline and therefore better functional status, whereas positive values represent more functional decline and worsening functional status. Our results showed that women who were pre-menopausal had a better HAQ score by −0.50 (95% CI: −0.55, −0.19) compared with women who were post-menopausal [with interaction term with age of 0.01 (0.00; 0.01)], indicating that pre-menopausal women had less functional decline than post-menopausal women. This estimate adjusted for age modelled by the three-knot cubic spline and interaction term of age and menstrual status. The change in mean response of HAQ between pre- and post-menopausal women, when all other variables were held constant in the model, was a function of −0.50 + 0.01*age. The difference in HAQ scores indicating less functional decline in pre-menopausal women was robust even after adjustment for other significant factors, including all of the covariates described in Other variables except for OC ever-use. When analysed by menopausal status, the HAQ is a function −0.74 + 0.014*age [β-coefficient of −0.74 (−1.02, −0.45) and interaction term with age 0.014 (0.008, 0.019); Fig. 1]. This translates to a mean difference in HAQ scores between pre- and post-menopausal women of −0.18 for a 40-year-old woman, −0.11 for a 45-year-old woman and −0.04 for a 50-year-old woman, etc. The ever-use of HRT, having had a pregnancy, and longer duration of reproductive life were associated with less functional decline. OC ever-use did not qualify for the multivariable model according to QICu.

When using menopausal status with the three groups for the same multivariate model, HAQ scores of post-menopausal women were increased (worsened) by 0.68 (0.36, 1.00) compared with pre-menopausal women [interaction term with age −0.012 (−0.019, −0.006)]. Women who transitioned through menopause during the study had an increased HAQ of 0.28 (0.002, 0.490) when compared with pre-menopausal women [interaction term with age −0.006 (−0.010, −0.000)].

The results indicate that the annual change of HAQ (a positive value represents worsening and a negative value an improvement) was worsened for post-menopausal women when compared with pre-menopausal women. This was true for age-adjusted analysis [HAQ progression rate/year: −1.38 (−1.98, −0.77) with interaction term 0.01 (0.00, 0.02)] and after adjusting for several confounders: total income, tumour necrosis factor inhibitor use, co-morbidities and baseline HAQ [rates/year: −1.49 (−2.08, −0.91) with interaction term 0.027 (0.02, 0.04)]. This translates into an average annual HAQ change between pre-menopausal and post-menopausal women of −1.49 (−2.07, −0.90). By age, for example, a pre-menopausal 40-year-old woman would have an annual HAQ change of −0.61 (−0.94, −0.28), whereas a post-menopausal woman of the same age would have a change of 0.88 (0.59, 1-16). Similar estimates for women of 50 years old would be −0.88 (−1.28; −0.47) and −0.61 (0.42, 0.80) for pre-menopausal and post-menopausal, respectively.

To confirm results, we performed a sensitivity analysis using MRM. GEE models assume a missing completely at random approach and MRM a missing at random approach. If a missing dropout were not dependent on the available measures, the two models would give similar results [14]. The MRM results were similar and confirmed the conclusions of the GEE. MRMs were estimated including a random slope for menstrual status with an unstructured covariance structure. Average predictions from the GEE model and MRM model for menstrual status were: GEE 0.55 (95% CI: 0.33, 1.35) and MRM 0.50 (0.31, 0.69) for pre-menopausal women; and GEE 1.28 (95% CI: 1.21, 1.35) and MRM 1.29 (1.22, 1.35) for post-menopausal women.

Discussion

We explored how menopause impacts functional status in women with RA. In our study, women who were post-menopausal had worse functional status and a more severe progression of functional decline as measured by the HAQ.

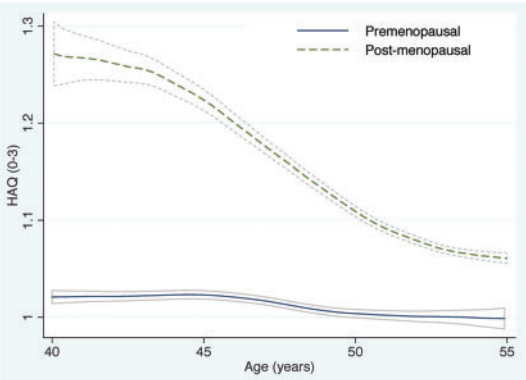
Our results suggest further study on hormonal involvement in functional decline in women with RA. In addition to worsening functional status after menopause, women

Table 1 Descriptive characteristics of women with RA by menopausal status

	Pre-menopausal	At menopause	Post-menopausal	*P*-value
n	2005	611	5573	
Follow-up				
Mean (s.d.)	3.1 (2.7)	7.9 (4.1)	5.3 (4.1)	
Median (interquartile range)	2 (1–4)	7.5 (4.5–12)	4 (2–8)	
Age, years (%)	39.7 (7.8)	50.7 (3.4)	62.3 (9.3)	<0.001
<45	70.8	6.7	1.8	<0.001
45–54	29.2	86.9	21.0	
>55	0.0	6.4	77.2	
RA duration, years	11.6 (9.1)	16.5 (10.4)	25.2 (13.7)	<0.001
Education, years	14.6 (2.3)	14.5 (2.3)	13.8 (2.3)	<0.001
Income, US $1000	62.0 (36.0)	66.3 (34.2)	51.5 (33.8)	<0.001
Smoking ever, %	25.3	34.2	38.2	<0.001
RD co-morbidity index, 0–9	1.3 (1.5)	1.5 (1.5)	2.0 (1.7)	<0.001
HAQ, 0–3	1.1 (0.7)	1.0 (0.7)	1.2 (0.7)	<0.001
PAS, 0–10	3.6 (2.3)	3.5 (2.3)	3.9 (2.2)	<0.001
Pain scale, 0–10	3.8 (2.9)	3.7 (2.8)	4.0 (2.8)	0.004
Global severity, 0–10	3.5 (2.5)	3.3 (2.5)	3.8 (2.5)	<0.001
SF-36 PCS, 0–100	39.9 (11.4)	39.0 (11.5)	35.6 (11.1)	<0.001
SF-36 MCS, 0–100	46.6 (11.6)	48.7 (11.1)	49.0 (11.6)	<0.001
RADAI, 0–10	2.7 (1.7)	2.5 (1.6)	2.7 (1.7)	0.008
Biologic current use, %	58.6	57.2	50.9	<0.001
TNFi current use, %	48.7	50.7	42.0	<0.001
TNFi ever, %	67.1	69.4	63.5	0.001
Menarche age, years	12.7 (1.7)	12.7 (1.7)	12.8 (2.2)	0.078
Menopause age, years	–	49.5 (4.1)	47.6 (6.9)	<0.001
Reproductive years	26.9 (7.9)	36.3 (4.1)	34.4 (7.0)	<0.001
HRT current use, %	2.3	11.7	15.8	<0.001
HRT ever, %	4.4	19.1	25.5	<0.001
OC current use, %	17.5	0.0	0.0	<0.001
OC ever, %	23.3	14.7	0.1	<0.001
Pregnant ever, %	22.3	38.0	36.0	<0.001

Values given as the mean (s.d.) unless otherwise indicated. HRT: hormone replacement therapy; OC: oral contraceptive; PAS: patient activity scale; RADAI: rheumatoid arthritis disease activity index; RD: rheumatic disease; Reproductive years: years from menarche to menopause or last observation; SF-36 PCS: the short form (36) health survey physical component summary; SF-36 MCS: the short form (36) mental component summary; TNFi: tumour necrosis factor inhibitor.

Fig. 1 HAQ functional status prediction by menopausal status



Using multivariable general estimating equation models in women diagnosed with RA before menopause, women who are post-menopausal have worse functional status than pre-menopausal women, with a 95% CI.

who had longer length of reproductive life, were ever pregnant or ever-used HRT, and thus had increased hormonal exposure, had less functional decline. Longitudinal studies with hormonal biomarkers in women surrounding the menopausal and other reproductive transitions are indicated. Studies with matched control cases with comparison in men may elucidate sex-specific hormone-related changes. Additional study on RA symptoms and functional status throughout the menstrual cycle and other hormonal life events are indicated in understanding hormonal involvement in RA disease status.

There were multiple limitations to our study. We did not establish a directional relationship between menopause and functional decline. We may not have accounted for all confounding variables. Although PROs are standard in collecting data about physical function and patient experience, self-reported data are associated with biases and may not correlate with the patient's objective clinical picture. For example, menopause has been associated with depression and decreased QoL and may have changed the patient's perceptual experience of their functional

status. The study participants had a higher socioeconomic status and may have been more compliant than patients with RA in the general population. Some variables, such as ever-pregnancy and ever-use of HRT, have been associated with healthier women in general, thus affecting the interpretation of our results.

In conclusion, the results from this large observational study suggest that menopause is associated with worse functional decline in women with RA. Further study is needed to understand this relationship.

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