

Impact of sex hormone fluctuations on functional health status and menopause rating scale among postmenopausal RA patients

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Abstract

Introduction: Women with RA have higher grades of disease activity and more declines in health status than men with RA; this recommends a relationship between estrogen and disease activity and severity.

Aim: Our aim was to detect the effect of sex hormone fluctuations and menopause on functional disability and quality of life of postmenopausal RA patients.

Methods: This is an observational cross-sectional study that was carried out on 84 postmenopausal rheumatoid arthritis patients who fulfilled the ACR/EULAR2010 classification criteria of RA attending to Rheumatology and Rehabilitation inpatient and outpatient clinics at Zagazig University Hospitals. All cases were exposed to full history taking, clinical examination, and laboratory investigations; acute phase reactants, rheumatoid factor (RF), anti-cyclic-citrullinated peptide (anti-CCP) antibodies, estrogen (E2) and follicular stimulating hormone (FSH). Functional disability measured by modified health assessment questionnaire (MHAQ). Menopause Rating Scale (MRS) assessed menopausal quality of life.

Results: Our results revealed a significant correlation between menopausal duration and the MHAQ score. Estrogen (E2) levels but not FSH levels in postmenopausal RA patients were positively correlated with MHAQ and MRS scores. In addition, a significant correlation was found between disease activity parameters (SJC, ESR and DAS28) and the MRS scores. Moreover patients with higher MHAQ scores had higher MRS scores. Psychological and somatic domains of the MRS scale were the most affected.

Conclusion: Our findings suggest an increased functional disability and reduced quality of life in postmenopausal RA patients throughout menopause. Postmenopausal RA patients require a closer medical follow-up because of their potentially less favorable functional evolution. Optimal management of the

disease activity is mandatory to minimize functional impairment and improve their postmenopausal quality of life.

Key words: rheumatoid arthritis, menopause, functional disability, quality of life, disease activity, disease severity

1. Introduction:

Rheumatoid arthritis (RA), one of the most widely recognized autoimmune disorders, is characterized by inflammation of the joint with subsequent destruction of articular structures. Patients with active RA also experience systemic inflammation that is related with an assortment of extra-articular manifestations. Pain, fatigue, and disability accompanied with RA causes a remarkable decline in health-related quality of life ^(1, 2).

The peak incidence of RA occurs mainly during the fifth decade around the menopausal period in women ⁽³⁾. Physical function is an important RA outcome that reflects a patient's ability to achieve daily duties; it also decides their quality of life. Women with RA suffer from a severe decline in functional status and more disability compared to men. Women are supposed to have a more triggered immune system, showing stronger cellular and humoral immune responses. Women with RA report higher degrees of pain, more prominent disease-related fatigue and a less quality of life all of which intensifies the role of estrogen ⁽⁴⁾. Even in male RA patients, serum estradiol levels are higher compared to healthy men, and are correlated with disease activity. Despite this and other clinical data, estrogens do not always work pro-inflammatory in arthritis, as previously stated, but can be both pro-inflammatory and anti-inflammatory ⁽⁸⁾.

Menopause is the permanent cessation of menstruation which leads to a decrease in the development of ovarian follicle ⁽⁵⁾. The onset of menopause is associated with a hormonal deficiency ⁽⁶⁾. Many aspects of the disease are potentially associated with menopause. The first thing to consider is whether menopause increases the risk of RA, secondly, whether menopause affects the RA disease activity, severity and functional status.

For the last decades, it has been known that the decline in estrogen level during menopause is responsible for the disease deterioration during this period ⁽⁷⁾. Recently, estrogen decline during menopause is mostly responsible for the increased incidence of RA during menopausal period but not responsible for the increased disease activity, functional disability and deteriorated quality of life in postmenopausal patients. In addition, menopausal symptoms negatively affect the course of the disease and worsen outcomes of postmenopausal RA patients. In fact, the results of observational studies of menopause and estrogen hormones affecting RA patients are still variable and different ⁽⁸⁾.

This study is considered as a continuation of our accepted article in Zagazig University Medical Journal entitled 'Disease activity and severity in postmenopausal rheumatoid arthritis patients.' DOI: 10.21608/ZUMJ.2020.26616.1785, in which we studied the influence of sex hormones on disease activity and severity in postmenopausal RA patients ⁽⁹⁾. The

study in hand aimed to determine the effect of menopausal parameters including menopausal duration, E2 and FSH levels on functional disability and postmenopausal quality of life in an Egyptian group of postmenopausal RA patients.

2. Materials and Methods

2.1. Study design and subjects:

This cross-sectional study was carried out in Rheumatology and Rehabilitation inpatient and outpatient clinics at Zagazig University Hospitals. The sample was calculated to be 84 postmenopausal rheumatoid arthritis patients. Patients enrolled fulfilled the ACR/EULAR2010 classification criteria of RA ⁽¹⁰⁾. Exclusion criteria included patients who had hysterectomy, had menopause before the 40 years or over 55 years and those who did not report menstruation cessation.

2.2. Clinical and Laboratory measures:

Full history taking and thorough clinical examination was performed to all patients. Current disease activity was assessed using Disease Activity Score 28 (DAS 28) ⁽¹¹⁾. Disease severity was assessed by RA severity scale (RASS) ⁽¹²⁾. Laboratory investigations were recorded including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum albumin, hemoglobin, rheumatoid factor (RF), antibodies to cyclic citrullinated peptide (anti-CCP), serum estrogen (E2) and serum follicular stimulating hormone (FSH).

2.3. Functional Status & Disability assessment:

The Modified Health Assessment Questionnaire (MHAQ) is a questionnaire for assessing health status and disability in RA patients. It was designed to assess patient's perceived satisfaction and degree of difficulty performing daily activities. The MHAQ is a patient reported questionnaire that is a modification of the HAQ where the number of daily living activities was reduced from 20 to 8. Patients were asked to rate these daily activities on a scale of 1 to 4 ⁽¹³⁾.

2.4. Postmenopausal Quality of life assessment:

The Menopause Rating Scale (MRS) is a health-related quality of life scale (HRQoL) that was designed to measure the severity of the symptoms of aging in the early 1990s. In fact, the treating physician should have completed the first version of the MRS but the methodological criticisms lead to a new scale that women, rather than their doctor, can easily complete ^(14, 15).

2.5. Statistical Methods:

All data were collected and analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA 2011). Student's t-test and Mann Whitney U test were used to compare between groups. Spearman and Pearson correlation coefficients were used to correlate between various studied variables. P values < 0.05 were considered statistically significant.

3. Results

3.1. Demographic, clinical & laboratory characteristics of RA patients:

Table (1) shows the demographic, clinical and laboratory characteristics of RA patients. Mean age was 54.9 ± 6.1 .

3.2. Menopausal parameters among our RA patients

Table (2) shows menopausal parameters among our postmenopausal patients. The mean E2 level of our patients was 5.59 ± 6.2 .

3.3. Functional status and postmenopausal quality of life among postmenopausal RA patients and its correlations:

Figure (1) shows that majority (63.1%) of our studied patients had moderate functional disability. Table (3) shows significant positive correlation between functional status MHAQ score and menopausal duration. Also shows significant positive correlation with all disease activity parameters (TJC, SJC, ESR, CRP and DAS28) and E2 levels. Also a significant positive correlation was found between quality of life MRS total score and most of disease activity markers (SJC, ESR and DAS28) and also MHAQ score. Figure 2 shows the correlation of MRS with MHAQ and DAS28.

3.4. Immunological parameters:

This table (6) shows significant difference regarding menopausal parameters (MRS total score, somatic and urogenital scores) among RF positive and RF negative postmenopausal RA patients. Table (7) shows significant difference regarding menopausal parameters (menopausal duration and E2 level) among Anti-CCP positive and Anti-CCP negative patients in postmenopausal RA patients.

4. Discussion:

Functional disability in RA patients is a major concern for physicians. Although treating RA with anti-inflammatory drugs improves daily duties, it is not easy to manage the condition. Declined physical function and quality of life is common in RA due to the presence of joint swelling, stiffness and deformities. RA affects daily activities such as dressing, eating, holding, and walking. ⁽¹⁶⁾

The majority of our postmenopausal patients (63.1%) were suffering from moderate functional disability with a mean value 1.57 ± 0.33 . In our study, disease activity parameters showed positive correlation with MHAQ scores. In agreement with Omata et al., ⁽¹⁷⁾ we found a significant positive correlation between disease activity DAS28 score and functional disability MHAQ score in postmenopausal RA patients. In agreement with Benitha and Tinkly ⁽¹⁸⁾ we also found significant positive correlations between the laboratory markers of disease activity (ESR and CRP), with the MHAQ. Also similar to the results of Hammad et al., ⁽¹⁹⁾ who found significant correlations of MHAQ and activity parameters in a group of Egyptian RA patients. This reflects the great impact of disease activity on physical disability of postmenopausal RA patients.

In 2018 Mollard et al., ⁽⁴⁾ reported worsening of functional disability in postmenopausal women in a recent longitudinal study also. In addition, Kuiper et al., ⁽²⁰⁾ indicated that both old age and postmenopausal state increase physical disability. This explains the significant correlations we found between menopausal parameters and MHAQ. We found a significant positive correlation between functional status MHAQ and menopausal parameters (menopausal duration and E2 level). These findings explain that postmenopausal status affect functional disability not only disease activity and joint destruction.

Various tools have been developed to quantify and evaluate symptoms during menopause; among them is MRS that ranks a profile of symptoms ^(14, 15). Overall, hormonal fluctuations or variations in estrogen metabolism during menopause may be linked to musculoskeletal symptoms being documented as one of the most common menopausal symptoms. Although estrogen acts directly on central nervous system, psychosocial factors are important triggers for severity of menopausal symptoms and should be considered in the clinical evaluation. A recent study on postmenopausal women Thapa and yang ⁽²¹⁾ found that the mean Total MRS in 25 postmenopausal participants with RA was 15.36 ± 6.26 ; stratified as somatic (6.68 ± 2.79), psychological (6.72 ± 2.97) and urogenital symptoms (1.96 ± 1.99). RA was associated with higher somatic, psychological and total MRS scores. This study found lower frequency of urogenital symptoms than somatic and psychological ones in studied postmenopausal group. In agreement with previous studies we found a higher somatic (9.11 ± 1.62), psychological (7.7 ± 1.94) and total MRS (21.85 ± 4.204) scores while less affected urogenital score (5.06 ± 1.63) in our studied postmenopausal RA patients. We also found significant positive correlation of total MRS with disease activity markers (ESR, SJC and DAS28) and functional status (MHAQ) of postmenopausal RA patients. These results show the effect of RA disease parameters on postmenopausal quality of life in RA patients especially those with high disease activity and great functional disability.

The majority of our studied postmenopausal RA patients were seropositive for anti-CCP (61.9%) with a mean of 46.17 ± 39.6 and RF positive (67.9%) with a mean of 34.2 ± 45.8 . A significant relation was found in our study between RF positivity and MRS total score. After comparing Anti-CCP level with menopausal parameters of postmenopausal RA patients, we found significant difference between Anti-CCP positive and Anti-CCP negative regarding E2 level; E2 level was higher in Anti-CCP positive patients than those negative. These findings disagree with Al-Salman, ⁽²²⁾ who found no significance between Anti-CCP and E2 level. This may be because this study was done on women with different reproductive stages while our study was done on postmenopausal women only. We also found significant difference between menopausal duration and anti-CCP level; in which longer menopausal duration was associated with increased seropositivity for anti-CCP while shorter menopausal duration was associated with seronegativity for anti-CCP.

There were few limitations in our work; the sample size is relatively small; secondly, it was a single-center study.

In conclusion, our findings suggest an increased functional disability in RA patients throughout menopause which in turn causes deterioration of their quality of life. Post-menopausal RA patients require a closer medical follow-up because of their potentially less favorable functional evolution. Early and optimal management of disease activity is necessary to manage functional impairment and improve their postmenopausal quality of life.

Conflict of interest: None to declare.

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Table (1): Demographic, clinical and laboratory characteristics of RA patients

RA patients (Mean ± SD)	
Demographic characteristics	
<i>Age</i>	54.9±6.1
Clinical characteristics	
<i>Disease duration</i>	6.25±1.44
<i>TJC</i>	3.55±1.1
<i>SJC Median(range)</i>	1(0 -5.00)
<i>DAS28</i>	4.34±0.53
<i>RASS</i>	68.3±24.87
<i>MHAQ</i>	1.57±0.33
Laboratory findings	
<i>ESR Median(range)</i>	30 (5-85)
<i>CRP Median(range)</i>	11(0.73-33.85)
<i>RF</i>	34.2 ± 45.8
<i>Anti-CCP</i>	46.17 ± 39.6

SD(standard deviation) TJC(tender joint count) SJC(swollen joint count) DAS28(Disease Activity Score) RASS(Rheumatoid arthritis severity scale) MHAQ(modified health assessment questionnaire) ESR(erythrocyte sedimentation rate)CRP(c-reactive protein) RF(rheumatoid factor)Anti-CCP(anti-Cyclic Citrullinated Peptide)

Table (2): Menopausal parameters among RA patients

<i>Characters</i>	Mean ± SD
Menopause duration	6.63±4.13
MRS parameters:	
Psychological •	7.7±1.94
Somatic •	9.11±1.62
Urogenital •	5.06±1.63
E2	5.59±6.2

FSH 72.97±22.7

MRS (menopause rating scale), E2(estradiol), FSH(follicular stimulating hormone)

Table (3): Correlations with MHAQ and MRS in postmenopausal RA patients:

<i>Parameters</i>	MHAQ		MRS	
	(r)	P	(r)	P
Age	0.149	0.177	0.162	0.142
Disease duration	0.194	0.077	0.174	0.114
TJC	0.578	0.0001**	0.184	0.094
SJC	0.347	0.001**	0.288	0.008**
DAS28	0.778	0.0001**	0.476	0.0001**
RASS	0.454	0.000**	0.175	0.112
WBCs	0.134	0.224	0.120	0.278
Platelets	0.025	0.821	0.060	0.588
HB	0.181	0.099	0.013	0.907
ESR	0.360	0.001**	0.368	0.001**
CRP	0.318	0.003**	0.186	0.09
Menopausal duration	0.246	0.024*	0.048	0.663
E2	0.228	0.037*	0.031	0.783
FSH	0.079	0.474	0.055	0.619

SD (standard deviation) MRS (menopause rating scale) TJC(tender joint count) SJC(swollen joint count) E2 (estradiol) FSH (follicular stimulating hormone) DAS28(Disease Activity Score),RASS(Rheumatoid arthritis severity scale),MHAQ(modified health assessment questionnaire) ESR(erythrocyte sedimentation rate)CRP(c-reactive protein)WBCs(white blood cells)HB(hemoglobin) RF(rheumatoid factor)Anti-CCP(anti-Cyclic Citrullinated Peptide). * p value < 0.05 statistically significant. ** p value < 0.01 statistically significant

Table (4): Comparison of menopausal parameters regarding RF positivity among postmenopausal RA patients

Parameters	RF		T	p-value
	Seropositive (n=57)	Seronegative (n=27)		
MENOPAUSAL DURATION Median(range)	7(1-15)	4(2-18)	MW 1.685	0.092
MRS Mean ± SD	22.6±4.17	20.18±3.8	2.57	0.012
1. Psychological Mean ± SD	8.0±2.06	7.11±1.52	1.99	0.05
2. Somatic Mean ± SD	9.35±1.56	8.59±1.64	2.04	0.045
3. Urogenital Mean ± SD	5.3±1.64	4.52±1.5	2.1	0.036
E2 Median(range)	6(0-29.5)	0(0-12.2)	MW 0.890	0.374
FSH Mean ± SD	74±23	70.79±22.35	0.603	0.54

SD (standard deviation) MRS (menopause rating scale) E2 (estradiol) FSH (follicular stimulating hormone) MW (Mann whitney test of significant) RF(rheumatoid factor). P<0.05 =significant., p≥ 0.05 non-significant

Table (5): Comparison of menopausal parameters regard Anti-CCP grading among postmenopausal RA patients

Parameters	Anti-CCP		t-test	p-value
	Seropositive (n=52)	Seronegative (n=32)		
Menopause Duration Median(range)	7(2-18)	4(1-11)	MW=3.454	0.001
MRS Mean ± SD	21.25±4.5	22.8±3.5	1.77	0.08
1. Psychological Mean ± SD	7.53±2.05	8±1.7	1.06	0.29
2. Somatic Mean ± SD	8.94±1.66	9.37±1.53	1.19	0.24
3. Urogenital Mean ± SD	4.78±1.71	5.5±1.41	1.96	0.053

E2				
Median(range)	7.1(0-29.5)	0(0-12.2)	MW=3.15	0.002
FSH				
Mean ± SD	73.79±24	71.62±20.76	0.42	0.67

SD (standard deviation) MRS (menopause rating scale) E2 (estradiol) FSH (follicular stimulating hormone) MW (Mann whitney test of significant) Anti-CCP(anti-Cyclic Citrullinated Peptide. $P < 0.05$ =significant. $p \geq$ non-significant rating scale), E2(estradiol), FSH(follicular stimulating hormone)

Figure (1): MHAQ grading of studied postmenopausal RA patients.

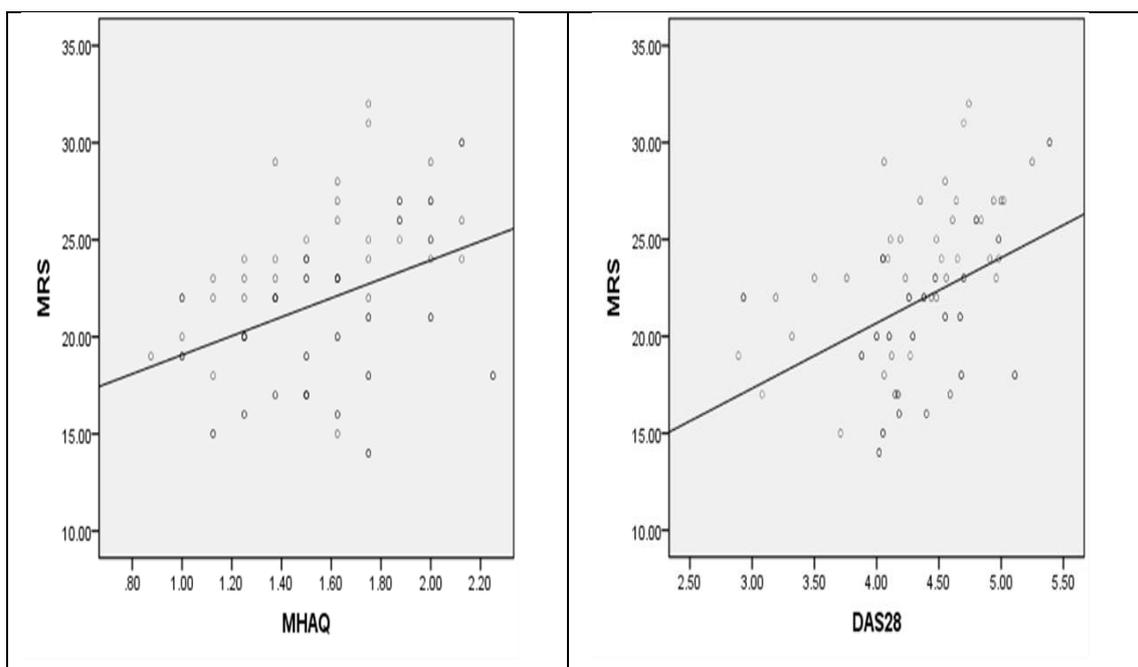


Figure (2) A: Scatter graph showing the correlation between MHAQ score and MRS of menopausal RA patients ($r: 0.405, P=0.0001$). B: Scatter graph showing the correlation between DAS28 score and MRS of menopausal RA patients ($r: 0.476, P=0.0001$).