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ORIGINAL ARTICLE

Disease Activity and Severity in Postmenopausal Rheumatoid Arthritis Patients

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ABSTRACT

Introduction: The fact that the incidence of RA in women reaches its peak during menopause (45-55) years, highly recommends a strong estrogenic role in disease etiology. Although in some studies postmenopausal women who experienced RA had less joint scores than pre-menopausal patients, the post-menopausal period has been associated with increased disease activity and more severe functional disability.

Aim: The aim of our study was to evaluate the relation of serum estrogen (E2) and follicular stimulating hormone (FSH) in menopause and disease activity and severity in postmenopausal RA patients.

Methods: This is a cross-sectional study that was carried out in Rheumatology and Rehabilitation deparment, Faculty of Medicine, Zagazig University Hospitals on 84 postmenopausal RA patients. Disease activity was assessed using Disease Activity Score 28 (DAS 28). Severity of RA was assessed by the RA severity scale (RASS). Laboratory parameters were recorded including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP). Estrogen (E2) and follicular stimulating hormone (FSH) were measured for all patients.

Results: Our study showed a statistically significant difference between serum estrogen (E2) levels among different stratifications of DAS28 in postmenopausal RA patients. Moreover, there was a significant positive correlation between E2 levels and disease severity RASS score. FSH levels showed no significant correlations with disease parameters.

Conclusion: Although it is well known that menopausal women have very low levels of E2 compared to women of reproductive age, in postmenopausal RA patients, higher disease activity and severity was associated with higher levels of estrogen denoting its prominent pro-inflammatory effect even in the postmenopausal period.

Key words: rheumatoid arthritis, menopause, disease activity, sex hormones.

1. INTRODUCTION

Dyslipidemia is an increase in plasma cholesterol, Rheumatoid arthritis (RA) is a chronic, systemic autoimmune rheumatic disorder of unknown etiology affecting mainly the joints and spread to several other organs. RA affects 0.5–1 % of adult population (1). RA is characterized by extensive synovitis resulting in articular cartilage erosions and joint destruction and presents as symmetrical arthritis of small and large joints along with a wide spectrum of extra-articular manifestations (2).

The prevalence of RA was approximately 2 times higher in females than males (3). The mode of

action of Estradiol (E2) depends on its dose. Lower levels seem to increase production of pro-inflammatory cytokines such as tumor necrosis factor (TNF) or interleukin (IL-) 1 beta. Higher levels lead to anti-inflammatory effects by decreasing the signaling of pro-inflammatory cytokines, by stimulating release of anti-inflammatory cytokines (Th2 phenotype shift), and by triggering regulatory T cells (Tregs), respectively. Synovial fluid analysis presented elevated estrogen concentration in RA patients with synovitis for both sexes (4). The effect of female reproductive variations, such as pregnancy, menopause and hormonal replacement therapy, on the severity of disease is till now questionable (5).

Menopause means the discontinuation of menstruation resulting from the sudden withdrawal of ovarian follicular activity. Normal menopause is supposed to occur after 12 successive months of amenorrhea – the cessation of menstruation – for which there is no other clear pathological or physiological cause. The normal age for menopause ranges between 50 and 51 years, with consideration of variations among women living in different countries (6). Related with the aging procedure of the ovaries; the release of ovarian estrogen will diminish steadily. Menopausal women have extremely low degrees of estradiol contrasted with those of reproductive age (7).

The fact that the incidence of RA in women reaches its peak during menopause(45-55), highly recommends a strong estrogenic role in disease etiology (8). Although in some studies postmenopausal women who experienced RA had less joint scores than pre-menopausal patients, the post-menopausal period has been associated with increased disease activity and more severe functional disability (9).

The aim of our study was to evaluate the relation of serum estrogen (E2) and follicular stimulating hormone (FSH) in menopause and disease activity and severity in postmenopausal RA patients

2. MATERIALS AND METHODS

2.1. Study design and subjects:

This is an observational cross-sectional study that was carried out in Rheumatology and Rehabilitation department, Faculty of Medicine, Zagazig University Hospitals. Eighty-four postmenopausal RA patients who fulfilled the classification criteria of American college of rheumatology/ European league against rheumatism (ACR/EULAR2010) of RA were included in this study (10). Patients who underwent hysterectomy, those who reported early menopause before 40 years or those over the age of 55 years and did not report a cessation of menses were all excluded from the study. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

2.3. Clinical and Laboratory parameters of disease activity and severity:

Disease activity was assessed using Disease Activity Score 28 (DAS 28) (11). Grading of DAS 28 was mentioned as follow (Low disease activity is defined as DAS28 $\leq$ 3.2, Moderate as <3.2 but $\leq$ 5.1 and High as DAS28 > 5.1) (12). Severity of RA was assessed by the RA severity scale (RASS) (13). Laboratory parameters were recorded including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-cyclic-citrullinated peptide (anti-CCP) antibodies, and rheumatoid factor (RF). Estrogen (E2) (normal E2 level is 30 to 400 pg/mL for premenopausal women and 0 to 30 pg/mL for postmenopausal women) and follicular stimulating hormone (FSH) (Women who are still menstruating 4.7 to 21.5 IU/L and postmenopausal women 25.8 to 134.8 IU/L) were measured for all patients.

2.4. Statistical Methods: All information was gathered, classified, and statistically analyzed utilizing SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA 2011). Quantitative information was demonstrated as the mean ± SD and median (range), and subjective information was demonstrated as absolute frequencies (number) and relative frequencies (percentages). Student\'s t-test was utilized to differentiate between two groups of parametric variables while Mann Whitney U test was utilized for non-parametric variables. Post hoc test was utilized to characterize significant difference between two groups when f test or Kruskall Wallis test is significant. Pearson correlation and Spearman correlation coefficient were determined to survey the connection between different examination factors. All tests were double sided. P-value < 0.05 was considered statistically significant (S), and p-value $\geq$ 0.05 was considered statistically insignificant (NS)

3. RESULTS

3.1. Demographic, clinical & laboratory characteristics

Table (1) shows the demographic, clinical measures and laboratory characteristics of our

patients. The mean age of our patients was 53.4 ± 5.3 years.

3.2. Disease activity markers and patients' characteristics

Figure (1) shows that majority (88.1%) of our studied group had moderate disease activity DAS28 score. Table (2) shows that there is a statistically significant difference between E2 levels among different grades of disease activity in menopausal RA patients. Post hoc test shows statistically significant difference of E2 value between low, moderate and high DAS28 (Low& high p= 0.008, moderate & high p= 0.001).

Table (3) shows a significant positive correlation of ESR with postmenopausal duration and E2 levels in postmenopausal RA patients. Table (4) shows significant positive correlation of disease severity RASS score with DAS28 and E2 levels among the studied patients.

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

Characters	RA patients
Demographic	
Age *(Mean ±SD)*	53.4±5.3
Age group	
≤50 years (n=27)	32.1%
>50 years (n=57	67.9%
Clinical features	
Disease duration (Mean ±SD)	6.0±4.0
TJC (Mean ±SD)	3.6±1.8
SJC (median(range))	1(0.00-5.00)
DAS 28 (Mean ±SD)	4.2±0.5
Laboratory findings *(Mean ±SD)*	
ESR (mm/1st hr)	33.2±16.2
CRP (mg/dl)	11.6±6.6
RF (IU/ml)	35.5±45.8
Anti-CCP (U/ml)	50.2±40.5
E2 (pg/mL)	5.5±5.1
FSH (IU/L)	72.1±23.2
Treatment	
NSAIDS	20 (23.5%)
Corticosteroids	51 (60.7%)
Hydroxychloroquine	54 (64.5%)
Methotrexate	34 (40.4%)
Sulfasalazine	7 (8.3%)
Arthfree	51 (60.7%)
Azathioprine	6 (7.1%)
Biological	0 (0%)

DAS28(Disease Activity Score) TJC(tender joint count) SJC(swollen joint count) SD(standard deviation) RF(rheumatoid factor)Anti-CCP(anti-Cyclic Citrullinated Peptide) ESR(erythrocyte sedimentation rate) CRP(c-reactive protein) E2 (estradiol), FSH (follicular stimulating hormone).

Table 2: Comparison of menopausal parameters among postmenopausal RA patients with different grades of disease activity.

Parameters	DAS28			F -test	P
	Low=5	Moderate=74	High=5		
Menopausal Duration Median(range)	3(3-6)	5(1-18)	8(2-10)	KW 3.343	0.188
E2 Median(range)	7.14(0-10.5)	5(0-14.7)	12.3(11-29.5)	KW 11.71	0.003
FSH Median(range)	77.85(72.1-113)	70.5(26-127.5)	59.57(47.4-122.6)	2.881	0.237

DAS28 (Disease Activity Score), SD (standard deviation), E2 (estradiol), FSH (follicular stimulating hormone)

Table 3: Correlation between activity markers and investigated parameters of menopausal RA patients.

Parameters	ESR		CRP	
	(r)	P	(r)	P
Menopausal duration	0.261	0.016*	0.191	0.082
E2	0.244	0.026*	0.176	0.11
FSH	0.101	0.362	0.114	0.3

E2 (estradiol) FSH (follicular stimulating hormone), ESR(erythrocyte sedimentation rate)CRP(c-reactive protein)

Table (4): Correlations with disease severity (RASS) in postmenopausal RA patients:

Parameters	RASS	
	(r)	P
Age	0.2	0.069
Disease duration	0.076	0.493
DAS28	0.576	0.0001**
Menopausal duration	0.212	0.053
E2	0.309	0.004**
FSH	0.081	0.462

E2 (estradiol), FSH (follicular stimulating hormone), DAS28 (Disease Activity Score), RASS(Rheumatoid arthritis severity scale), * p-value < 0.05 statistically significant **p-value < 0. 01 statistically significant

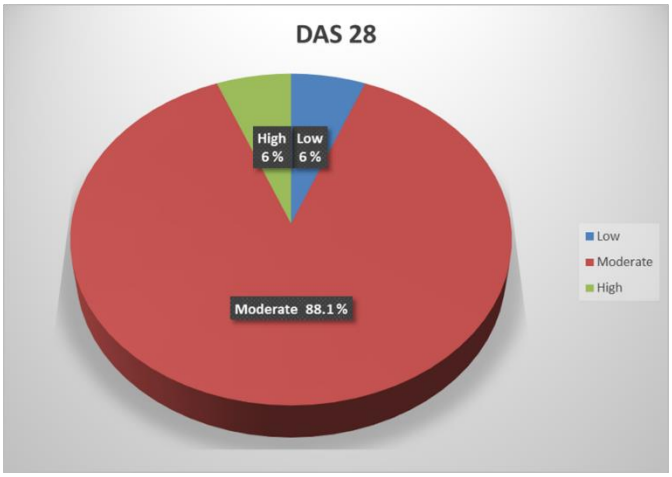

Figure (1): DAS28 grading among postmenopausal RA patients

DISCUSSION

The Disease Activity Score 28 has been well developed to quantify disease activity in RA both in daily clinical practice and in clinical trials. The DAS28 is a continuous evaluation of RA disease activity that merges data[from swollen joints, tender joints, acute phase reactant and general health (14). The conflict about the role of estrogen (having both anti-inflammatory and pro-inflammatory roles) depends on some influencing factors (the immune cells involved), the target organ, the reproductive status in a woman, the concentration of estrogens, and the expression of ERα and ERβ (15).

This observational cross-sectional study was carried out in Zagazig University Hospitals on 84 postmenopausal RA patients who fulfilled the classification criteria of ACR/ EULAR. The goal of our study was to evaluate serum estrogen and FSH levels in postmenopausal RA patients and its relation to disease activity and severity in postmenopausal RA patients.

Regarding menopausal factors, menopausal duration ranged between 1-18 years with a mean of 6.63±4.13years. In our study, the mean values of E2 and FSH hormones in postmenopausal RA patients were 5.5±5.1 and 72.1±23.2 respectively. In this study, as regards to disease activity, 5 RA cases (6%) had mild disease activity, 74 RA cases (88.1%) had moderate disease activity, 5 RA cases (6%) had severe disease activity. This means that majority of our studied patients had moderate disease activity despite regular follow up and receiving suitable medications. This indicates the

impact of postmenopausal status on disease activity in agreement with Kuiper et al., (16) who stated that disease activity in postmenopausal patients was significantly increased compared to patients in other reproductive groups indicating the effect of postmenopausal state on the course of RA.

The importance of female sex hormones in progression of RA is still far from clear. Estrogens have both stimulatory and inhibitory effects on the immune system (17). In agreement with Zautra et al., (18) who reported significant positive correlation between E2 hormone levels and disease activity of RA patients, our study found that there is significant positive correlation between E2 level and disease activity markers (DAS28 and ESR). We also found no significant correlation between FSH hormone levels and any of disease activity markers. These results agree with the findings of Kåss et al., (19) who stated that there is no significant correlation between FSH level and disease activity among RA patients.

Regarding the menopausal duration, our study found significant correlation between menopausal duration and ESR level. Regarding steroid use, 60.7% of our patients were treated by corticosteroids. Our study found no significance relation between corticosteroid use and any of menopausal studied parameters.

The appraisal of RA severity is critical for evaluating the clinical course of the disease. Rheumatoid Arthritis Severity Scale (RASS) assesses disease activity, functional impairment and physical damage. The mean value of RASS score of our studied patients was 68.3±24.87. In this study a significant positive correlation of disease severity RASS score with DAS28 and E2 levels among the studied patients was noted. To our knowledge no previous studies discussed the relation between disease severity represented as RASS and menopausal factors in postmenopausal RA patients.

There were few restrictions in the present work; first, the relatively small sample size; secondly, it was a single-center study.

In conclusion, although it is well known that postmenopausal women have very low levels of E2 compared to women of reproductive age, in postmenopausal RA patients, higher disease activity and severity was associated with higher levels of estrogen denoting its prominent pro-inflammatory effect even in the postmenopausal period.

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