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Comparative Study on The Impact of Pre-and Postmenopausal Status in Women With Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is among the most common rheumatic diseases and an important women's health problem, particularly in Middle Eastern women, where rheumatism and metabolic disorders are prevalent. The current study aimed at evaluating clinical, inflammatory and hormonal changes in Iraqi women during the pre- to postmenopausal transition stage with and without RA. In this cross-sectional study conducted from March to September 2025, a total of 64 women with rheumatic arthritis (RA) specifically recruited by patients' age (32 premenopausal and 32 postmenopausal subjects) and 60 matched controls were enrolled from Nasiriyah city, Iraq. ANOVA and correlation were used to test disease response and laboratory biomarkers ($p < 0.05$). Background Postmenopausal RA patients had elevated DAS28, ESR, CRP, RF, anti-CCP and IL-6 and TNF-α levels compared with premenopausal RA patients, consistent with the disease, while oestradiol was lower, but FSH and LH were higher. Oestradiol levels harboured inverse correlations, while gonadotropins had positive associations with inflammatory markers concerning disease activity. Hormonal changes in menopause play a key role in the increased inflammatory response and disease severity of RA after menopause, underscoring the importance of appropriate menopause-directed management.

Keywords: Autoimmune inflammation, Menopausal transition, Rheumatoid Arthritis

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Introduction:

RA is a chronic and systemic autoimmune disease [1-2]. It is characterised by persistent synovial inflammation. The disease is characterised by progressive joint destruction and substantial morbidity [1-3]. The disease can begin at any point in time. However, most cases occur within the ages of 40 to 60 [4]. It affects approximately two women for every man diagnosed [5]. The estimated percentage of the population diagnosed with RA is between 1 and 3 at this time [6]. This number is hypothesised to be rather large due to the longer life expectancy of patients with this illness. The majority of patients diagnosed are over 60 years of age [4], [7]. Sex hormones, particularly estrogen, are known to influence autoimmunity, which is very important for the body's autoimmunity and defence against disease manifestation [8-9]. During midlife, an important change in the endocrine system is the decrease in progesterone and estrogen levels. This, in turn, increases gonadotropin levels. This set of changes has the potential to alter the levels of regulatory substances, cytokines, and synthesised substances involved in the restoration of injured tissue [10-12].

Most researchers agree that estrogen is an important immunomodulatory factor. During the menstrual phase, women tend to have less severe disease markers and reduced radiographic progression than postmenopausal women [13]. This is the stage where estrogen is most influential, lowering the levels of, e.g., IL-6, TNF-α, and IFN-γ signalling, as well as regulatory T-cells (Treg) and osteoclasts, and suppressing the formation of T-lymphocytes. However, it is generally recognised that the menopause marks the point at which a woman ceases ovarian oestrogen production and is associated with an overproduction of pro-inflammatory Th1/Th17 cytokines, increased macrophage activity, and elevations of RF and anti-CCP [14-15]. The dysregulation of hormonal-immune equilibrium certainly explains, for example, the heightened disease activity in postmenopausal women, where the disease is most active, and the spread is

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extensive.

Recent evidence indicates an independent association between menopausal status and RA disease activity, independent of age. A meta-analysis by [16-17] showed that an increased Disease Activity Score in 28 joints (DAS28) score and lower levels of physical functioning were associated with premature menopause and natural menopause. Likewise, a study by [18] observed that postmenopausal women with RA experience increased rates of functional decline and faster progression to disability. While estrogen deficiency alongside inflammatory processes contributes to disease progression and treatment response, the novelty of this study lies in its first characterisation of these relationships—specifically, the inverse correlation between oestradiol and DAS28—in Iraqi women from Nasiriyah, a Middle Eastern population underrepresented in prior research.

Furthermore, recent research has shown that the gonadotropic hormones FSH and/or luteinizing hormone function as pro-inflammatory cytokines and may promote osteoclast activity and increase bone resorption, as described in [19]. These may also result in increased systemic inflammation, as characterised by [20-21]. Several studies have reported on sex differences in RA prevalence; however, this relationship has not been elucidated in the Middle East and the Iraqi population. In such populations, genetics, lifestyle, and environment may alter the hormonal-immune system interaction. This is particularly evident in Iraq, where RA prevalence is rising among middle-aged women, yet clinical and biochemical characterisation of menopause-related changes remains limited.

Consequently, the authors of this research investigate and contrast the demography, clinical, biochemical, hormonal, and psychosocial factors of pre- and postmenopausal patients with RA

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alongside their respective controls. The purpose of this study was to evaluate the influence of the menopausal status and immune dysregulation, as well as the disease activity during RA, against the background of inflammatory and hormonal factors. This study has several implications, including the improvement of treatment access for female RA patients and the incorporation of hormonal therapies, as well as the development of menopause management policies for outpatient rheumatology clinics. This study characterises menopause-related factors in women with RA. Our findings reveal stronger inflammatory and hormonal dysregulation in postmenopausal RA patients, highlighting the need for tailored regional management strategies

Method

Study Design and Setting

This cross-sectional study specifically examines menstrual function and the clinical, biochemical, and hormonal changes induced by menopause in women with RA. This study was conducted at three tertiary care hospitals in Nasiriyah, Iraq (Al Nasiriyah Teaching Hospital, Bint Al Huda Hospital for Women and Children, and Al Haboubi General Hospital) from March to September 2025. The study's hospitals are characterised by the specialisation in rheumatology, the diversity of patients, and the availability of essential resources needed for multiple immunological and hormonal tests. The study used an observational approach to ascertain the numerous changes sustained by women with RA before and after menopause, and in contrast with healthy women. The study used an observational approach to ascertain the numerous changes sustained by women with RA before and after menopause, and in contrast with healthy women. This design enables concurrent assessment of disease state and hormonal levels across groups. The study was performed in compliance with the principles of the revised Declaration of Helsinki (2013).

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Ethics clearance was obtained from the University of Thi-Qa'r, College of Science, Department of Biology, and all participating hospitals' administrators provided permission before the start of the study. Every participant was informed of the study's core aim, method, associated risks, and benefits, and was asked to provide written informed consent before the study.

Participants

Eligible subjects are female patients with a diagnosis of RA according to the 2010 ACR/EULAR criteria and age-matched female controls. A total of 124 individuals participated in this study. These comprised 64 patients with RA (32 premenopausal and 32 postmenopausal) as well as 60 age-matched healthy controls without a history of autoimmune or endocrine disorders. The RA patients were recruited from outpatient rheumatology clinics at the participating hospitals, while the control group consisted of healthy female volunteers recruited from hospital staff and the local community, with no history of autoimmune or endocrine disorders.

The participants were women aged 30 to 60, who had a history of RA for a year and had been on a stable dose (standard management) of DMARD therapy for more than 3 months. Self-reported menopausal status or clinical assessment of menopause (12 months of amenorrhea and confirmed with serum tests (FSH and oestradiol)) was defined in this study.

Exclusion criteria included, but were not limited to, pregnancy and lactation, active HRT therapy, and the presence of comorbid conditions, such as established hypertension, chronic renal or hepatic insufficiency, DM, cardiovascular disease, and malignancies. All participants underwent a complete clinical assessment, including anthropometric and laboratory evaluations. We tried to avoid the selection bias by using systematic random sampling. All the clinical and laboratory aspects across the 3 study sites were identical, and they were therefore treated as a

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single entity.

Data Collection and Measurements

The anthropometric indices, along with the laboratory indices and other clinical evaluations, were integrated and executed in line with established protocols. Rheumatologists and laboratory personnel documented and oversaw data to mitigate variability and reinforce the importance of trustworthy, reproducible results. The reviews analysed both the clinical and medical records, taking into account the patient's medical history of the disease, the associated disabilities, and the joints involved. The patient was rated for stiffness and pain using Visual Analogue Scale (VAS). Relative to disease and activity (Disease Activity Score 28 joints; DAS28; total joint counts (TJC), swollen joint number (SJ), erythema sedimentation rate (ESR) and the patient's global health assessment.

Venous blood samples were collected in the morning (8:00 to 10:00 a.m.) following overnight fasting by standard venipuncture techniques. Samples were processed, and haematological, biochemical and hormonal analyses were carried out. The serum was separated through centrifugation and stored at −20°C until it was analysed in the laboratory.

Monobind Inc. (USA) enzyme-linked immunosorbent assay (ELISA) kits were used to measure all serum levels of oestradiol, LH, FSH, progesterone and cortisol. ESR was determined by the Westergren method, whereas CRP was assessed at high sensitivity by turbidimetric assay. Quotations from medical professionals who sell practice questioning common perceptions.

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Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 26.0. The Shapiro–Wilk test was used to examine the normality of distribution. Continuous variables were described as mean ± standard deviation (or median (interquartile range)), and categorical variables were summarised with counts and proportions. For group comparisons, one-way ANOVA or the Kruskal–Wallis test and applicable post hoc tests were used. Associations between hormonal parameters and inflammatory markers were measured using Pearson or Spearman correlation analyses. Univariate statistical tests for categorical variables and multivariable linear regression analysis to determine the independent predictors of disease activity. A p-value < 0.05 was considered statistically significant.

Results

The study included 124 women: 32 premenopausal and 32 postmenopausal rheumatoid arthritis (RA) patients and 60 healthy controls matched by age. Hormonal and inflammatory activity parameters of RA patients were analysed with a control group included for baseline reference values and comparative analysis. All subjects underwent clinical and laboratory evaluation. National cohort analyses excluded cases with missing or incomplete testing results.

Demographic and Clinical Characteristics

Postmenopausal RA patients were significantly older: 55.8 ± 5.3 years compared with 36.1 ± 4.4 years, $p < 0.001$. The mean BMI among postmenopausal patients was higher than that of premenopausal (25.1 ± 2.8 kg/m²) and control subjects (24.8 ± 2.4 kg/m²; $p = 0.048$), with postmenopausal participants (27.0 ± 3.2 kg/m²) having a significantly higher BMI. Although

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residence, education, and occupation were equally divided, a positive family history of RA was higher in postmenopausal patients (28.1%) than in controls (8.3%, p = 0.041). A lower proportion of physically active individuals was seen in both RA groups, especially postmenopausal women (p = 0.029).

The indicators of clinical interest shown in Table 2 indicated an increase in disease activity with advancing menopause stages. Postmenopausal RA subjects had longer morning stiffness, more tender and swollen joints, and higher DAS28 scores (4.48 ± 0.61 vs 3.65 ± 0.55 in premenopausal RA; p < 0.001). There was also a higher prevalence of functional class III-IV disability (21.9%) observed in the postmenopausal group, indicating more severe disease activity.

Table (1). Sociodemographic Characteristics of Participants

Variable	Premenopausal RA (n=32)	Postmenopausal RA (n=32)	Control (n=60)	p-value
Age (years, mean ± SD)	36.1 ± 4.4	55.8 ± 5.3	36.0 ± 3.9	<0.001
BMI (kg/m², mean ± SD)	25.1 ± 2.8	27.0 ± 3.2	24.8 ± 2.4	0.048
Residence: Urban (%)	62.5	59.4	70.0	0.48
Educational level: ≥ Secondary (%)	56.3	43.8	61.7	0.22
Occupation: Housewife (%)	68.8	75.0	60.0	0.36
Marital status: Married (%)	90.6	96.9	88.3	0.39
Family history of RA (%)	21.9	28.1	8.3	0.041
Smoking (%)	15.6	18.8	6.7	0.19

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Table (2). Clinical Characteristics and Disease Activity Parameters (RA Patients Only)

Variable	Premenopausal RA (n=32)	Postmenopausal RA (n=32)	p-value
Disease duration (years)	5.8 ± 2.3	7.6 ± 3.1	0.032
Morning stiffness (min)	19.4 ± 7.8	34.2 ± 10.0	<0.001
Tender joint count (28)	8.6 ± 2.9	11.4 ± 3.7	0.002
Swollen joint count (28)	6.3 ± 2.7	9.5 ± 3.4	<0.001
Pain VAS (0–100 mm)	45.2 ± 11.1	63.9 ± 13.7	<0.001
DAS28 score	3.65 ± 0.55	4.48 ± 0.61	<0.001
Functional class III–IV (%)	9.4	21.9	0.044

Hematological and Inflammatory Profiles

As shown in Table 3, there were also some differences in the haemoglobin parameter values between groups. *Postmenopausal RA patients had significantly lower haemoglobin levels (11.3 ± 1.2 g/dL) than premenopausal (12.0 ± 1.1 g/dL) and control patients (13.1 ± 1.0 g/dL; p = 0.013). There was an increase in WBC and platelet counts in postmenopausal RA, suggesting inflammation.* Figure 1 shows the distribution of ESR (mm/hr) values among the study groups, illustrating differences between premenopausal RA patients, postmenopausal RA patients, and healthy controls.

Table (3). Hematological and Inflammatory Biomarkers

Parameter	Control (n=60)	Premenopausal RA (n=32)	Postmenopausal RA (n=32)	p-value
Hemoglobin (g/dL)	13.1 ± 1.0	12.0 ± 1.1	11.3 ± 1.2	0.013
WBC count (×10⁹/L)	6.8 ± 1.3	8.1 ± 1.5	9.0 ± 1.8	0.028

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Platelets (×10⁹/L)	260 ± 41	301 ± 46	336 ± 52	0.019
ESR (mm/hr)	12.0 ± 4.2	31.0 ± 9.8	46.7 ± 12.2	<0.001
CRP (mg/L)	3.1 ± 1.0	8.1 ± 3.4	15.2 ± 4.6	<0.001

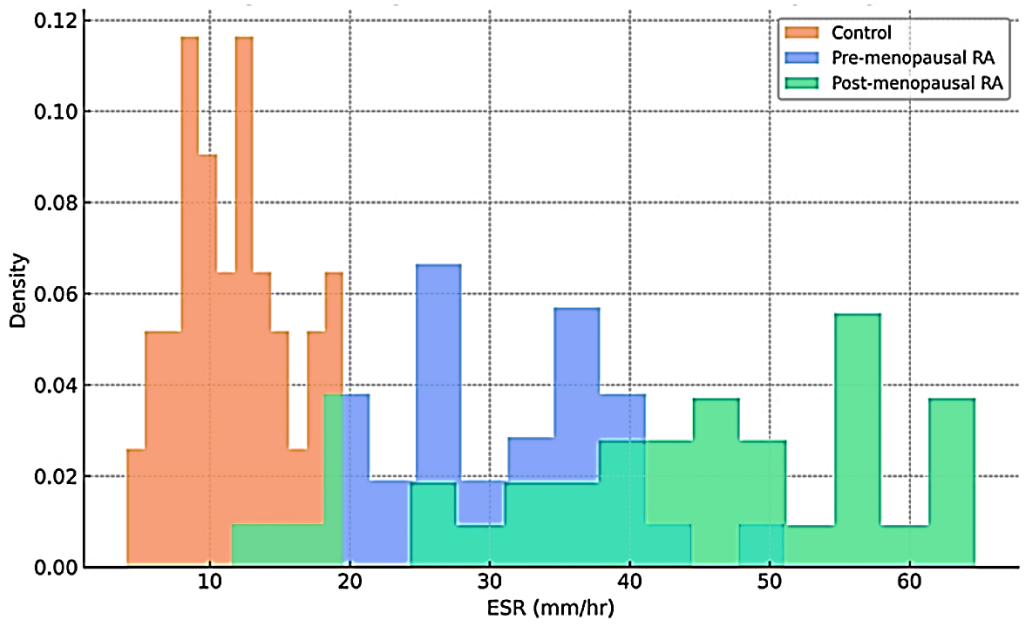

Figure (1). Histogram of ESR (mm/hr) Distribution by Group

Autoimmune and Cytokine Markers

Table 4 presents the immune biomarker profiles of RF and anti-CCP antibodies, as well as those of all other RA participants who, compared with their control counterparts, had a biomarker profile of greater magnitude. The postmenopausal female profile RF 66.5 13.8 (+16.5 13.8) to 4.8; Anti-CCP 54.8 10.3 U/mL (p 0.001) in the RF and Anti-CCP group is the most significant profile. The cytokine profile in postmenopausal females showed elevated IL-6, TNF (16.5 ± 5.2), and IL-1β (14.9 ± 4.9), with the suppressive IL-10 (3.4 ± 1.3; p = 0.009). Alongside a drop in the cytokine IL-10, chronic and severe inflammatory activities of the postmenopausal women were revealed. Levels of hypothesised cytokines of the Th1/Th17 subclass are suggested in

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chronically and severely inflamed postmenopausal females. Increased immune system activity and oestrogen deficiency may contribute to disease progression. These data indicate that the postmenopausal cohort shows a broader, taller distribution along the y-axis, suggesting a more profound immune dysfunction.

Table (4). Autoimmune and Cytokine Markers

Parameter	Control	Pre-menopausal RA	Postmenopausal RA	p-value
Rheumatoid factor (IU/mL)	10.5 ± 2.9	43.2 ± 10.9	66.5 ± 13.8	<0.001
Anti-CCP antibody (U/mL)	8.2 ± 2.3	33.5 ± 8.5	54.8 ± 10.3	<0.001
IL-6 (pg/mL)	3.4 ± 1.3	8.7 ± 3.5	14.9 ± 4.9	<0.001
TNF-α (pg/mL)	4.8 ± 1.4	9.9 ± 3.7	16.5 ± 5.2	<0.001
IL-10 (pg/mL)	5.5 ± 1.8	4.2 ± 1.6	3.4 ± 1.3	0.009

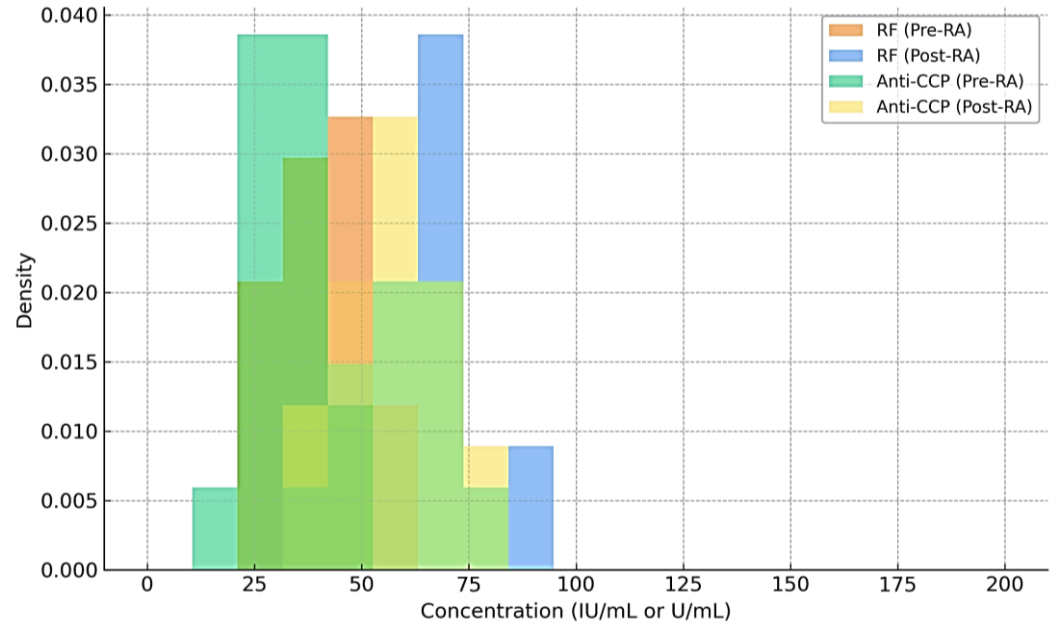

Figure (2). Dual Histogram of RF and Anti-CCP

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Hormonal and Endocrine Profiles

Table 5 depicts the changes within the endocrine system post-menopause. Regarding the control group, oestradiol was 125.9 ± 30.1 pg/mL, which decreased to 111.3 ± 28.4 pg/mL and then to 21.5 ± 6.3 pg/mL in premenopausal RA and postmenopausal patients, respectively. This was all statistically significant ($p<0.001$). Still, some changes were substantial and did not change over time, e.g., LH and FSH levels started and continued to increase proportionally (FSH: 63.2 ± 15.5 mIU/mL; LH: 46.4 ± 12.3 mIU/mL). There was a hormonal change with a significant decrease in progesterone 0.3 ± 0.1 ng/mL). The greater the decrease in estradiol, the higher the DAS28 score. This confirms a reverse connection between estradiol and DAS28 scores ($r = -0.52$, $p < 0.001$) (Figure 3), indicating a positive modulatory influence of oestrogen on RA activity.

Table (5). Hormonal and Endocrine Profile

Hormone	Control	Pre-menopausal RA	Postmenopausal RA	p-value
Estradiol (pg/mL)	125.9 ± 30.1	111.3 ± 28.4	21.5 ± 6.3	<0.001
FSH (mIU/mL)	6.9 ± 2.9	8.2 ± 3.0	63.2 ± 15.5	<0.001
LH (mIU/mL)	7.8 ± 3.0	8.9 ± 2.9	46.4 ± 12.3	<0.001
Progesterone (ng/mL)	1.5 ± 0.4	1.2 ± 0.3	0.3 ± 0.1	<0.001
Prolactin (ng/mL)	12.6 ± 2.8	13.4 ± 3.2	15.8 ± 3.7	0.017
Cortisol (µg/dL)	13.7 ± 3.0	15.4 ± 3.5	18.8 ± 4.4	0.031

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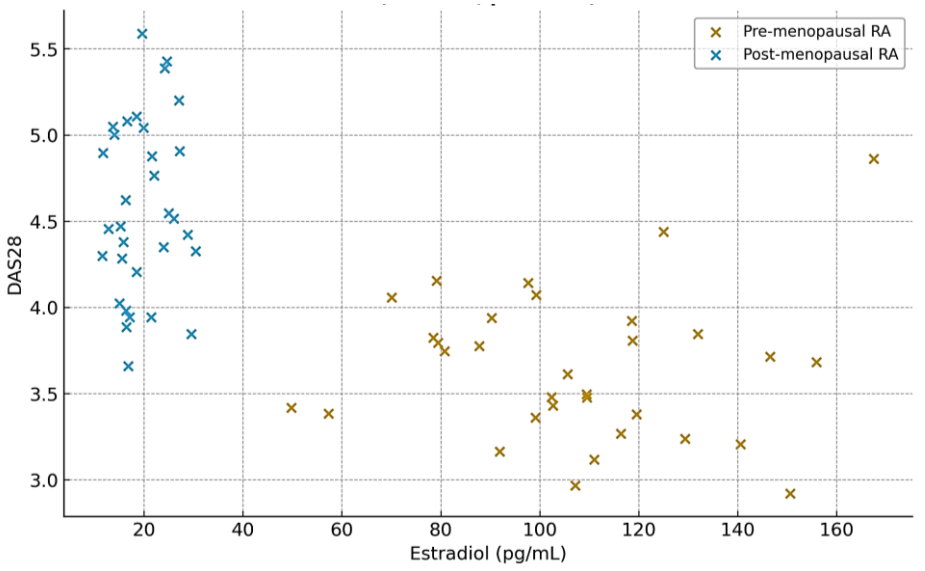

Figure (3). Scatter Plot of Estradiol vs DAS28 (r = 0.63, p < 0.001)

Metabolic and Treatment-Related Parameters

Further clinical context is presented in Tables 6 and 7 for the study findings. Table 6 shows the liver and metabolic function parameters for the control, premenopausal RA and postmenopausal RA groups. Postmenopausal RA patients demonstrated significantly elevated liver enzymes (ALT, AST), uric acid, creatinine, total cholesterol and triglycerides with decreased HDL-C levels compared to the other groups in the study. These metabolic changes may mirror the joint effects of systemic inflammation, hormonal changes brought by menopause and disease activity in rheumatoid arthritis.

RA patients belonging to 1 or more MTX strata per category (with/without DMARDs, with/without biologics, with/without corticosteroids, and with/without NSAIDs) were identified

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from the main dataset (Table 7). The treatments were also comparable between the premenopausal and postmenopausal patients, suggesting that the differences in inflammatory and hormonal parameters are predominantly related to menopausal status rather than large differences in treatment.

Table (6). Liver and Metabolic Function

Parameter	Control	Pre-menopausal RA	Postmenopausal RA	p-value
ALT (U/L)	23.5 ± 4.1	25.7 ± 4.9	29.5 ± 6.3	0.011
AST (U/L)	21.8 ± 3.4	24.8 ± 4.3	28.1 ± 5.4	0.008
Uric acid (mg/dL)	4.4 ± 0.8	5.3 ± 0.9	6.0 ± 1.0	0.019
Creatinine (mg/dL)	0.8 ± 0.1	0.9 ± 0.1	1.0 ± 0.2	0.046
Total cholesterol (mg/dL)	182 ± 24	196 ± 30	214 ± 33	0.025
HDL-C (mg/dL)	55 ± 9	48 ± 8	43 ± 7	0.027
Triglycerides (mg/dL)	136 ± 22	153 ± 28	171 ± 33	0.019

Table (7). Medication and Treatment Profile (RA Groups Only)

Treatment category	Premenopausal RA (n=32)	Postmenopausal RA (n=32)	p-value
Methotrexate monotherapy (%)	40.6	31.3	0.41
Combination DMARDs (%)	43.8	50.0	0.58
Biologic agent use (%)	6.3	12.5	0.41
Corticosteroid use (%)	68.8	84.4	0.09
NSAID regular use (%)	78.1	90.6	0.14
Vitamin D supplementation (%)	50.0	46.9	0.79
Adverse drug reactions reported (%)	18.8	28.1	0.36

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Discussion

The objective of this study was to evaluate and compare the effect of menopause status on clinical manifestations and inflammatory and autoimmune biomarkers, as well as the hormonal profile, in Iraqi women with rheumatoid arthritis (RA). Overall, postmenopausal RA patients, when compared with premenopausal RA and healthy control subjects, had higher levels of disease activity and elevated levels of autoimmune antibodies, as well as significant hormonal variations. Notably, DAS28 scores were significantly elevated in postmenopausal patients, and ESR, CRP, RF, and anti-CCP antibodies were greater as well; furthermore, these patients exhibited significantly higher levels of pro-inflammatory cytokines like IL-6 or TNF-α. In turn, oestradiol levels were significantly decreased, and gonadotropins (FSH and LH) as well became significantly increased. Importantly, a significant inverse relationship between oestradiol levels and disease activity was observed, suggesting a potential immunomodulatory role of oestrogen in RA. These findings provide unique evidence supportive of the notion that endocrine changes during menopause worsen disease severity in RA.

These results suggest that menopause can play a role in exacerbating RA clinical signs. Many other studies done in other countries found similar results as well. For example, Park et al. found that postmenopausal women with RA had significantly higher disease activity scores and functional outcomes compared to premenopausal patients. Likewise, [22] found that early menopause was linked with higher RA disease activity independently of inflammatory markers. These findings suggest that the endocrine decline of menopause might increase the severity of RA.

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The inflammatory profile seen in the current study adds to several studies, such as [23-25], suggesting that menopause is associated with increased systemic inflammation. The concentrations of ESR and CRP in postmenopausal RA patients were significantly higher than in premenopausal patients as well as controls (Table 3; Figure 1). Both markers are well-established indicators of inflammatory activity and are closely associated with disease progression in RA. The higher inflammatory markers might indicate the loss of immunomodulatory effects by oestrogen in postmenopausal women. Oestrogen has been shown in previous studies [26-27] to have an anti-inflammatory role by inhibiting the production of pro-inflammatory cytokines and modulating immune cell activity. Thus, declining oestrogen levels after menopause might promote the increase of inflammatory responses and disease exacerbations.

The autoimmune biomarkers measured in this study also demonstrated significant differences between groups. Postmenopausal RA patients exhibited substantially higher levels of rheumatoid factor and anti-CCP antibodies compared with premenopausal patients (Table 4; Figure 2). These autoantibodies are well-established markers of RA severity and are strongly associated with disease progression and joint destruction. The increased antibody levels observed in postmenopausal patients suggest heightened autoimmune activation after menopause. Similar findings were reported by [28], who observed elevated RF and anti-CCP titres in female RA patients with more severe disease manifestations. Furthermore, previous studies [29-30] have indicated that anti-CCP positivity is associated with increased inflammatory activity and radiographic joint damage, highlighting its importance as a prognostic indicator.

Immune signalling pathways were altered, as shown by analysis of several cytokines. Levels of IL-6, TNF-α and IL-1β were significantly higher in postmenopausal RA individuals compared to premenopausal individuals, whereas concentrations of the anti-inflammatory cytokine, IL-10,

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were significantly lower. These cytokines have central roles in RA pathogenesis by promoting synovial inflammation. Elevated concentrations of IL-6 and TNF-α, in particular, have been closely associated with disease progression and are regarded as critical therapeutic targets in modern RA treatment strategies. Therefore, postmenopausal women having more of these cytokines is already indicative of enhanced inflammatory signalling associated with a loss of hormonal availability. According to experimental and clinical studies [31-33], oestrogen deficiency exacerbates pro-inflammatory immune responses caused by activated Th1 and Th17 pathways, leading to elevated cytokine production.

Significantly lower levels of oestrogen and significantly higher FSH and LH levels (Table 5) for RA patients than with healthy control subjects or premenopausal RA patients. Notably, the inverse relationship of oestradiol with DAS28 scores indicates that declining oestrogen levels may directly contribute to increased disease activity (Figure 3). Oestrogen is protective, as it modulates cytokine production, regulates T-cell responses, and inhibits osteoclast activity. Consequently, the decline of oestrogen during the menopause can disturb immune homeostasis and promote chronic inflammatory processes. “The findings are consistent with other studies suggesting that oestrogen deficiency results in increased RA activity and escalation of joint damage [34-35].

Other recent studies suggested that gonadotropins such as FSH participated in the inflammation processes associated with autoimmunity [36-37]. FSH as a promoter of osteoclast differentiation and bone resorption indicates that elevated FSH may contribute to RA. Zhang et al. correlated with increased RA disease activity and inflammatory markers among patients with high circulating FSH concentrations. The elevated gonadotropin levels described could therefore represent an additional mechanism linking menopause with RA progression.

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In the present study, liver enzymes, uric acid and total cholesterol and triglyceride levels of postmenopausal patients were significantly higher than those of premenopausal subjects, while their HDL cholesterol level was significantly lower (Table 6). These metabolic changes might illustrate the cumulative effects of persistent systemic inflammation, hormonal dysregulation and prolonged RA treatment. Patients with RA are more prone to cardiovascular diseases, most of which are believed to be due to dyslipidaemia, promoting atherosclerosis secondary to chronic inflammation. As a result, postmenopausal women with RA may be uniquely susceptible to metabolic disorders and cardiovascular disease.

Importantly, treatment patterns in premenopausal versus postmenopausal RA patients were largely comparable (Table 7), suggesting that differences in therapy do not drive differences in inflammatory and hormonal parameters. By contrast, the endocrine changes taking place at menopause appear to be more significant for disease severity. This also explains the importance of taking menopausal status into account as an independent factor for disease progression in RA.

While the association of menopause and RA has been explored in some international cohorts, data from the Iraqi population are sparse. Different populations may therefore have varying interaction patterns between their hormonal and immune systems based on genetic background and lifestyle factors. This study highlights the relevance and implications of hormonal-immune interfacing in Iraqi women with RA, thereby providing important context-specific evidence that can be translated into a clinical management strategy in this regional cluster.

There are strengths and limitations in this study that warrant discussion. There are several plausible explanations for our findings: the studies were cross-sectional; therefore, we are not

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able to make a causative inference regarding the association between menopausal status and disease progression. It also included a relatively small number of subjects and was done in one geographic area. More multicentre long-term studies in larger cohorts are needed to clarify the mechanisms linking menopause, hormonal alteration and RA progression.

Conclusion

The data collected show that menopausal status correlates with the level of disease activity, inflammatory markers, and hormonal levels in RA patients, which supports the hypothesis of the effect of menopausal status on disease condition. Among postmenopausal patients, there was an increased prevalence of moderate abnormalities in ESR, CRP, RF, AntiCCP, IL-6, and TNF-α, accompanied by a dip in estradiol and a rise in FSH and LH, indicating heightened autoimmune and inflammatory responses. In this population, the inverse relationship between estradiol and disease activity (DAS28) suggests that oestrogen levels may be associated with disease activity and systemic inflammation. As the menopause transition may be conceived of as one particular point along the immunoendocrine continuum, which could exacerbate the severity of RA, thus making the disease even more difficult to manage, it speaks to the potential scope of the management model. These results indicate that the implementation of menopause-aware management—the combination of DMARDs and some form of hormone therapy and/or lifestyle intervention and/or management—may ease the burdens of RA and maintain an acceptable level of quality of life (QoL) over the long term. Future research should focus on the pathways of hormonal (estrogen) deficiency and immune dysregulation as they pertain to the HA management of postmenopausal

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RA with hormonal therapies (or other combinations) and on the many available multi-centre longitudinal studies on the safety and efficacy of those therapies.

Conflicts of Interest

No conflicts of interest

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References

[1] A. A. Starshinova, I. V. Kudryavtsev, A. A. Rubinstein, A. Malkova, H. Ling, M. Zhuang, ..., and D. A. Kudlay, "Autoimmune disorders in patients with granulomatosis diseases after COVID-19: T and B-cells subsets function," Infektsiya i Immunitet, vol. 14, no. 2, pp. 251–266, 2024

[2] S. R. Harrison, D. Li, L. E. Jeffery, K. Raza, and M. Hewison, "Vitamin D, autoimmune disease and rheumatoid arthritis," Calcified Tissue International, vol. 106, no. 1, pp. 58–75, 2020

[3] M. Jahid, K. U. Khan, and R. S. Ahmed, "Overview of rheumatoid arthritis and scientific understanding of the disease," Mediterranean Journal of Rheumatology, vol. 34, no. 3, pp. 284–291, 2023

[4] L. Serhal, M. N. Lwin, C. Holroyd, and C. J. Edwards, "Rheumatoid arthritis in the elderly: characteristics and treatment considerations," Autoimmunity Reviews, vol. 19, no. 6, p. 102528, 2020

[5] E. G. Favalli, M. Biggioggero, C. Crotti, A. Becciolini, M. G. Raimondo, and P. L. Meroni, "Sex and management of rheumatoid arthritis," Clinical Reviews in Allergy & Immunology, vol. 56, no. 3, pp. 333–345, 2019

[6] K. B. Almutairi, J. C. Nossent, D. B. Preen, H. I. Keen, and C. A. Inderjeeth, "The prevalence of rheumatoid arthritis: a systematic review of population-based studies," The Journal of Rheumatology, vol. 48, no. 5, pp. 669–676, 2021

ISSN (print): 2706- 6908, ISSN (online): 2706-6894

Vol.21 No.1 Mar

[7] E. G. Favalli, G. Maioli, M. Biggioggero, and R. Caporali, "Clinical management of patients with rheumatoid arthritis during the COVID-19 pandemic," Expert Review of Clinical Immunology, vol. 17, no. 6, pp. 561–571, 2021

[8] E. G. Favalli, M. Biggioggero, C. Crotti, A. Becciolini, M. G. Raimondo, and P. L. Meroni, "Sex and management of rheumatoid arthritis," Clinical Reviews in Allergy & Immunology, vol. 56, no. 3, pp. 333–345, 2019

[9] L. R. Sammaritano, B. L. Bermas, E. E. Chakravarty, C. Chambers, M. E. Clowse, M. D. Lockshin, ..., and K. E. D'Anci, "2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases," Arthritis & Rheumatology, vol. 72, no. 4, pp. 529–556, 2020

[10] D. Alpízar-Rodríguez and A. Finckh, "Environmental factors and hormones in the development of rheumatoid arthritis," in Seminars in Immunopathology, vol. 39, no. 4, pp. 461–468, Berlin, Heidelberg: Springer, 2017

[11] D. Alpízar-Rodríguez, N. Pluchino, G. Canny, C. Gabay, and A. Finckh, "The role of female hormonal factors in the development of rheumatoid arthritis," Rheumatology, vol. 56, no. 8, pp. 1254–1263, 2017

[12] M. W. Tang, S. Garcia, D. M. Gerlag, P. P. Tak, and K. A. Reedquist, "Insight into the endocrine system and the immune system: a review of the inflammatory role of prolactin in rheumatoid arthritis and psoriatic arthritis," Frontiers in Immunology, vol. 8, p. 720, 2017

University of Thi-Qar Journal

ISSN (print): 2706- 6908, ISSN (online): 2706-6894

Vol.21 No.1 Mar

[13] Y. G. Kim, S. M. Lee, S. Bae, T. Park, H. Kim, Y. Jang, ..., and D. Y. Kim, "Effect of aging on homeostasis in the soft tissue of the periodontium: a narrative review," Journal of Personalized Medicine, vol. 11, no. 1, p. 58, 2021

[14] E. G. Favalli, "Understanding the role of interleukin-6 (IL-6) in the joint and beyond: a comprehensive review of IL-6 inhibition for the management of rheumatoid arthritis," Rheumatology and Therapy, vol. 7, no. 3, pp. 473–516, 2020

[15] F. Pandolfi, L. Franza, V. Carusi, S. Altamura, G. Andriollo, and E. Nucera, "Interleukin-6 in rheumatoid arthritis," International Journal of Molecular Sciences, vol. 21, no. 15, p. 5238, 2020

[16] E. Mollard, S. Pedro, E. Chakravarty, M. Clowse, R. Schumacher, and K. Michaud, "The impact of menopause on functional status in women with rheumatoid arthritis," Menopause, vol. 25, no. 11, pp. 1275–1281, 201

[17] E. H. Park, E. H. Kang, Y. J. Lee, and Y. J. Ha, "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," RMD Open, vol. 9, no. 1, p. e002722, 2023

[18] Y. Yang, P. W. Jia, H. W. Zheng, J. Pan, Z. M. Ouyang, Y. W. Zou, ..., and L. Dai, "Early menopause is associated with worse patient-reported outcomes in postmenopausal-onset patients with rheumatoid arthritis: a cross-sectional study," Annals of the Rheumatic Diseases, vol. 83, pp. 1579–1580, 2024

[19] Q. Niu, J. Hao, Z. Li, and H. Zhang, "Helper T cells: a potential target for sex hormones to ameliorate rheumatoid arthritis?," Molecular Medicine Reports, vol. 30, no. 6, pp. 1–16, 2024

[20] G. M. B. Elalfy, I. A. Elboghdady, Z. M. Tawhid, N. A. Salem, and O. M. M. Gharbia, "Bone mineral density in female patients with rheumatoid arthritis in relation to anti-cyclic citrullinated peptide antibody and rheumatoid factor," Egyptian Journal of Hospital Medicine, vol. 92, no. 1, 2023.

[21] L. Wang, L. Hua, X. Hong, F. Chen, and H. Du, "Association of serum anti-carbamylated protein antibodies with disease activity and bone loss in rheumatoid arthritis," Clinica Chimica Acta, vol. 546, p. 117371, 2023

[22] Z.-M. Ouyang, Y.-W. Zou, Y. Lu, J. Pan, T. Wu, P.-W. Jia, H.-W. Zheng, Y. Su, L.-F. Chen, J.-Z. Lin, K.-M. Yang, P.-Y. Lin, J.-Y. Han, J.-D. Ma, and L. Dai, "Early menopause is associated with higher disease activity independent of inflammation in postmenopausal-onset rheumatoid arthritis," BMC Women's Health, vol. 25, p. 138, 2025,

[23] F. Motta, N. Di Simone, and C. Selmi, "The impact of menopause on autoimmune and rheumatic diseases," Clinical Reviews in Allergy & Immunology, vol. 68, p. 32, 2025,

[24] N. Namavari, M. Jokar, A. Ghodsian, H. K. Jahromi, and V. Rahmanian, "Menopausal state and rheumatoid arthritis: a systematic review and meta-analysis," BMC Rheumatology, vol. 8, p. 48, 2024,

[25] A. Stojanovic, M. Veselinovic, N. Draginic, M. Rankovic, M. Andjic, J. Bradic, and V. Jakovljevic, "The influence of menopause and inflammation on redox status and bone mineral density in patients with rheumatoid arthritis," Oxidative Medicine and Cellular Longevity, vol. 2021, p. 9458587, 2021,

[26] J. L. Wautier and M. P. Wautier, "Pro- and anti-inflammatory prostaglandins and cytokines in humans: a mini review," International Journal of Molecular

Sciences, vol. 24, p. 9647, 2023,

[27] A. A. Al-Qahtani, F. S. Alhamlan, and A. A. Al-Qahtani, "Pro-inflammatory and anti-inflammatory interleukins in infectious diseases: a comprehensive review," Tropical Medicine and Infectious Disease, vol. 9, p. 13, 2024,

[28] M. Hossain, D. M. A. Habib, and D. M. M. Asraf, "Comparative socio-demographic and disease related characteristics between anti-CCP positive and negative rheumatoid arthritis patients," Scholars Journal of Applied Medical Sciences, vol. 4, pp. 612–620, 2021,

[29] M. Manzoor, R. Nadeem, S. A. Khan, S. Aggarwal, and N. Ayubi, "Rheumatoid factor and anti-CCP antibodies as diagnostic and prognostic biomarkers in rheumatoid arthritis: a comprehensive review," Vascular and Endovascular Review, vol. 8, pp. 182–186, 2025

[30] N. Ullah, A. Waris, A. Zeb, M. Rehman, S. Ali, and M. Imran, "The association of anti-CCP positivity with extra-articular manifestations in patients with rheumatoid arthritis: anti-cyclic citrullinated peptide positivity and extra-articular rheumatoid arthritis," Pakistan BioMedical Journal, pp. 29–33, 2024.

[31] G. AbdulHussain, F. Azizieh, M. A. Makhseed, and R. Raghupathy, "Effects of progesterone, dydrogesterone and estrogen on the production of Th1/Th2/Th17 cytokines by lymphocytes from women with recurrent spontaneous miscarriage," Journal of Reproductive Immunology, vol. 140, p. 103132, 2020,

[32] M. P. Piccinni, R. Raghupathy, S. Saito, and J. Szekeres-Bartho, "Cytokines, hormones and cellular regulatory mechanisms favoring successful reproduction," Frontiers in Immunology, vol. 12, p. 717808, 2021,

[33] A. T. Harding and N. S. Heaton, "The impact of estrogens and their receptors on immunity and inflammation during infection," Cancers, vol. 14, p. 909, 2022,

[34] U. S. D. Nguyen, F. R. Saunders, and K. R. Martin, "Sex difference in OA: should we blame estrogen?," European Journal of Rheumatology, vol. 11, pp. S7–S14, 2024,

[35] D. Chakraborty, A. Sarkar, S. Mann, P. Agnihotri, M. Saquib, S. Malik, and S. Biswas, "Estrogen-mediated differential protein regulation and signal transduction in rheumatoid arthritis," Journal of Molecular Endocrinology, vol. 69, pp. R25–R43, 2022,

[36] K. Barabás, E. Szabó-Meleg, and I. M. Ábrahám, "Effect of inflammation on female gonadotropin-releasing hormone (GnRH) neurons: mechanisms and consequences," International Journal of Molecular Sciences, vol. 21, p. 529, 2020,

[37] A. Milosevic, M. M. Janjic, I. Lavrnja, D. Savic, I. D. Bozic, K. Tesovic, and I. Bjelobaba, "The sex-specific patterns of changes in hypothalamic-pituitary-gonadal axis during experimental autoimmune encephalomyelitis," Brain, Behavior, and Immunity, vol. 89, pp. 233–244, 2020,