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Physiological and hormonal changes between postmenopausal rheumatoid arthritis and systemic lupus erythematosus in women

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Abstract

It is thought that sex hormones are playing an actual role in the pathogenesis of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The purpose of this study was to determine the differences of some hematological, hormonal and immunological parameters between the postmenopausal women with rheumatoid arthritis and systemic lupus erythematosus. This study contained 75 postmenopausal women (52-65 years old). They included 25 women diagnosed with rheumatoid arthritis, 25 diagnosed with systemic lupus erythematosus and 25 normal controls. Blood was collected and used to determine complete blood count (CBC) and erythrocyte sedimentation rate (ESR) tests. Serum was separated and used to determine Follicle-stimulating hormone (FSH), Luteinizing Hormone (LH), Prolactin, cortisol, Estrogen, progesterone, testosterone, rheumatoid factor (RF) and Immunoglobulin E (IgE). The results indicated that both patients' groups had anemia. However, the RA group had leukocytosis, but the SLE group had leukopenia. Moreover, thrombopenia occurred only in SLE patients. Although the levels of FSH and cortisol were significantly higher, the levels of LH, Estrogen and testosterone had significantly dropped in both patient groups. Interestingly, the level of progesterone was higher in the SLE and lower in the RA group. Moreover, the levels of RF, ESR and IgE were significantly increased in both patients' groups. In conclusion, there were many differences in hematological and hormonal levels between postmenopausal women with rheumatoid arthritis and systemic lupus erythematosus. Such findings need future work to find out the reasons for these differences and how they could be used in future treatment strategies.

Keywords: Compete Blood Count, Cortisol, Immunoglobulin E, Postmenopausal, Sex hormones

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Introduction

The term "postmenopausal" pertains to women who have experienced the absence of menstrual flow for at least one year, provided they still possess a uterus and are not pregnant.[1] In wealthier nations, the typical age for natural menopause is around 51 years, whereas in less developed countries, it tends to occur around age 48. Throughout this period, various hormonal and metabolic changes

suggest a decrease in ovarian function. Even after menopause, a woman's reproductive hormone levels continue to decline and undergo fluctuations.[2]

The shifting to postmenopausal from the peri phase brings about significant endocrine changes. The primary factor behind postmenopausal symptoms is the reduced levels of circulating estrogen. Consequently, the ovary, particularly in its granulosa cells, becomes unresponsive to pituitary hormones. This lack of feedback inhibition leads to an increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, while the production of progesterone, estrogen, and inhibin by the ovaries ceases.[3]

Rheumatoid arthritis (RA) is a systemic inflammatory and chronic disease. Women exhibit twice the incidence and prevalence rates of RA compared to men. The sex disparity in RA prevalence has prompted investigations into how female reproductive or hormonal factors impact the progression and onset of RA in women.[4] Hormones in females constitute a significant component in the development of RA. However, studying the hormonal aspects in females is challenging due to the fluctuations in serum levels across a woman's lifespan and their interaction with various environmental, genetic, immunological, and endocrine factors influencing autoimmunity.[5] Menopause-related sex hormones are believed to play a pivotal role in RA pathogenesis. The decline in estrogen levels, notably prominent during menopause, has been increasingly implicated as a direct contributor to menopausal difficulties in recent years as explained by Zhanget al., 2023.[6]

Systemic Lupus Erythematosus (SLE) is an autoimmune disorder that affects various systems, organs and tissues within the human body. Although it can impact multiple areas, the primary targets include blood vessels, kidneys, lungs, heart, liver, and the nervous system, as well as joints and skin. In SLE, the immune system erroneously attacks these targets, resulting in inflammation and damage.[7] Women are disproportionately affected by the condition, experiencing it nearly ten times more often than men. Typically, SLE onset occurs during the third or fourth decade of life. The age at which menopause begins influences the severity, progression, and outcomes of SLE, serving as a risk factor for the disease.[8]

Therefore, according to the above, both diseases affect women, but is there a difference between the effects of two diseases on women after menopause? So, the current study aimed to find the variances between the impacts of RA and SLE on some hormonal, hematological, and immunological parameters in postmenopausal females.

Subjects and Methods

The current investigation was conducted from September 2022 to February 2023 at Baghdad Medical City's Rheumatology and Rehabilitation Unit of the Baghdad Teaching Hospital. A total of 75 postmenopausal women participated in this study. They included 25 females diagnosed with RA, 25 diagnosed with SLE and 25 served as normal controls. Their ages ranged between 52-65 years.

A blood sample (9 ml) was collected from every participated woman by a disposable syringe. Of these, 2 ml were placed in a tube with Ethylene diamine tetra acetic acid (EDTA) and used immediately in complete blood count (CBC) test using a fully automated quantitative device (Samsung company, Korea), according to the manufacturer’s instructions. Another 2 ml were used for the erythrocyte sedimentation rate (ESR) test by the Westergren method. The final 5 ml were used to separate serum samples, stored at - 20°C until used.

The collected serum was used to determine some hormones (FSH, LH, prolactin, progesterone, testosterone, estrogen and cortisol) and some immunological tests as rheumatoid factor (RF) and Immunoglobulin E (IgE) by the enzyme-linked immunosorbent assay (ELISA) using different kits from clinical diagnostic company (Monobind, USA), according to the manufacturer’s instructions.

Statistical Analysis

Results are expressed in terms of mean ± SE or percentage (%) of case frequency. The data were examined for multi-comparisons by one-way analysis of variance (ANOVA) following by

Fisher's test using a statistical application (Stat view version 5.0.). A *p* value of <0.05 was considered significant.

Results

Table 1 shows the differences in some blood parameters, white blood cells (WBCs), red blood cells (RBCs), hemoglobin (Hb), platelet (PLT) count, red cell distribution (RDW) and the mean platelet volume (MPV), among postmenopausal women with RA or SLE patients and the control group. The number of WBCs was significantly higher in the RA and lower in the SLE groups, compared to the control group (p<0.05). However, the number of RBCs and the value of Hb were significantly lower in the RA patient group (p<0.05), but were not different in the SLE group, compared to the control group. In comparing with normal values, RBCs and Hb were significantly lower in 60% of RA group, 40% of SLE group and only 18% of control group (p<0.05).

Moreover, the PLT count was significantly higher in the RA group and lower in the SLE group compared to the control group (p<0.05). They were still within the normal value in RA patients and control while significantly lower in 40% of SLE patients (p<0.05). In addition, compared to the control group. The RDW% was significantly higher in the patient groups (RA and SLE) compared to the control group (<0.05). Furthermore, they were higher than the normal value. While the MPV value was significantly lower in patients' groups than in the control group (p<0.05).

Table 1. Hematological parameters levels in the patients and control groups.

Parameter	Group	Mean ± S.E.	*p*-value
RBC x10^6/µL	Control	4.860±0.154	RA vs. SLE=0.1640 (NS)
	RA patients	4.010±0.148	RA vs. Control; p<0.0001
	SLE patients	4.294±0.111	SLE vs. Control, p=0.0074
WBCx10^3/µL	Control	8.202±0.413	RA vs. SLE p<0.0001
	RA patients	18.188±0.783	RA vs. Control p<0.0001
	SLE patients	3.015±0.596	SLE vs. Control p<0.0001
Hb (g/dL)	Control	12.655±0.240	RA vs. SLE, p=0.1843 (NS)
	RA patients	11.708±0.330	RA vs. Control, p=0.0243 (NS)
	SLE patients	12.272±0.311	SLE vs. Control, p=0.3746 (NS)
PLT ×10^3/µL	Control	258.703±13.970	RA vs. SLE, p<0.0001
	RA patients	374.780±14.645	RA vs. Control, p<0.0001
	SLE patients	201.16±0.167	SLE vs. Control, p=0.0310 (NS)
MPV (femtoliters, fL)	Control	9.829±0.261	RA vs. SLE, p=0.14370 (NS)
	RA patients	7.691±0.321	RA vs. Control, p<0.0001
	SLE patients	8.331±0.316	SLE vs. Control, p=0.0009
RDW%	Control	13.029±0.183	RA vs. SLE, p=0.23890 (NS)
	RA patients	18.832±1.691	RA vs. Control, p=0.00581 (NS)
	SLE patients	16.349±0.1885	SLE vs. Control, p= 0.12252 (NS)

RBC: Red Blood Cell, WBC: White Blood Cell, Hb: Hemoglobin, PLT: Platelets, MPV: Mean Blood Volume, RDW: Red Cell Distribution Width, RA: Rheumatoid Arthritis, and SLE: Systemic Lupus Erythematosus. p > 0.05 is not significant (NS).

Table 2 shows the differences in some hormone levels (LH, FSH, Estrogen, Cortisol, Testosterone and Progesterone) among postmenopausal women with RA or SLE and the control group. The level of FSH value was significantly higher in both patient groups, RA and SLE, compared to the control group (p<0.05). However, the levels of LH, Estrogen and testosterone were significantly lower in RA group and SLE group compared with the control group (p<0.05). The level of cortisol was significantly lower in the RA and SLE groups compared to the control group (p<0.05), while the level of progesterone was significantly decreased in RA but increased in SLE compared to the control group (p<0.05).

Table 2. Hormonal level in patients and control groups.

Parameter	Group	Mean±SE	*p* value
LH (IU/L)	Control	36.089± 2.329	RA vs. SLE, *p*=0.89211 (NS)
	RA patients	21.238± 1.110	RA vs. Control, *p*<0.0001
	SLE patients	20.906± 1.517	SLE vs. Control, *p*= 0.001
FSH (IU/L)	Control	49.179± 3.197	RA vs. SLE, *p*=0.93780 (NS)
	RA patients	123.311± 2.349	RA vs. Control, *p*<0.0001
	SLE patients	123.651± 3.611	SLE vs. Control, *p*<0.0001
Estrogen (pg/ml)	Control	23.379±0.719	RA vs. SLE, *p*=0.72040 (NS)
	RA patients	15.201±1.144	RA vs. Control, *p*<0.0001
	SLE patients	20.906± 1.517	SLE vs. Control, *p*= 0.001
Cortisol (µg/ml)	Control	67.49±3.46	RA vs. SLE, *p*<0.0001
	RA patients	24.76±2.03	RA vs. Control, *p*<0.0001
	SLE patients	48.70±7.15	SLE vs. Control, *p*= 0.001
Testosterone nmol/L	Control	0.810±0.010	RA vs. SLE, *p*<0.0001
	RA patients	0.704±0.011	RA vs. Control, *p*<0.0001
	SLE patients	0.742±0.006	SLE vs. Control, *p*= 0.0490
Progesterone (ng/ml)	Control	4.381±0.101	RA vs. SLE, *p*<0.0001
	RA patients	3.491±0.210	RA vs. Control, *p*=0.001
	SLE patients	6.889±0.224	SLE vs. Control, *p*<0.0001

Normal reference of Luteinizing Hormone (LH)=14.2- 52.3IU/L, Follicle-stimulating hormone (FSH)= 25.5-134.8 IU/L, cortisol= 5-25 ng/ml, Estrogen= 0-30 pg/ml, progesterone<40 ng/ml, testosterone= 2.5 nmol/L.
p > 0.05 is not significant (NS).

Table 3 shows the differences in the level of RF, IgE and ESR among postmenopausal women with RA or SLE disease compared with the control group. The levels of RF, ESR and IgE were significantly increased in patients with RA and SLE diseases compared with the control group (*p*<0.05).

Table 3. The level of rheumatoid factor (RF), Immunoglobulin E (IgE) and erythrocyte sedimentation rate (ESR) in the patients and control groups.

Parameter	Group	Mean ± S. E	*p* value
RF (IU/ml)	Control	0.254±0.008	RA vs. SLE, *p*<0.0001
	RA patients	0.680±0.020	RA vs. Control, *p*<0.0001
	SLE patients	0.355±0.021	SLE vs. Control, *p*= 0.001
IgE (UI/ml)	Control	7.389±0.223	RA vs. SLE, *p*<0.0001
	RA patients	16.624±1.060	RA vs. Control, *p*<0.0001
	SLE patients	10.835±0.159	SLE vs. Control, *p*= 0.008
ESR (mm/hr)	Control	14.698±.925	RA vs. SLE, *p*=0.2854 (NS)
	RA patients	37.855±4.014	RA vs. Control, *p*<0.0001
	SLE patients	33.351±2.754	SLE vs. Control, *p*<0.0001

The normal references: rheumatoid factor (RF) = <15 IU/mL; Immunoglobulin E (IgE) =150-300IU/mL and Erythrocyte Sedimentation Rate (ESR) of Women over 50 years old is less than 30 mm/hr. *p* > 0.05 is not significant (NS).

Discussion

It is thought that menopause-related sex hormones could play a pivotal role in RA and SLE pathogenesis.[6, 8] So, the current study aimed to find out the variances between the impacts of RA and SLE on some hormonal, hematological, and immunological parameters in postmenopausal females.

Researchers have proposed a connection between hematological parameters such as Hb, PLT, and WBCs and chronic inflammation.[9, 10, 11]

However, in the literature there are conflicting views on the impact of estrogen, which decreases post menopause. Some studies suggested that estrogen is associated with reduced levels of this hormone and the suppression of erythropoiesis,[12, 13] while others proposed that estrogen might stimulate the growth of stem and progenitor cells, influencing hematopoiesis.[14] Consequently, Bovill et al., 1996, indicated significantly higher mean total WBC counts in postmenopausal women compared to other groups.[15] Considering these findings collectively, postmenopausal women might exhibit leukocytosis.

In this study, only postmenopausal women with RA exhibited leukocytosis, whereas those with SLE showed leukopenia, consistent with findings from another researcher who observed leukocytosis in RA patients.[16] This may indicate more active arthritis, and leukopenia in SLE patients, typically associated with disease severity. The underlying causes of leukopenia in SLE are not fully understood but are believed to involve decreased bone marrow production, alterations in splenic and marginal pools, and increased peripheral granulocyte destruction,[17] potentially predisposing individuals to autoimmunity, particularly when accompanied by thrombocytopenia. It is important to note that leukopenia serves as a classification criterion for both the Systemic Lupus International Collaborating Clinics and the American College of Rheumatology.[18]

Anemia can arise from chronic conditions like RA and SLE.[19] This occurs due to heightened expression of hepcidin, which impedes the incorporation of iron into erythrocytes during their maturation. Inflammatory cytokines, particularly interleukin 6, appear to regulate hepcidin by activating signal transducer and activator of transcription 3, thereby promoting hepcidin production.[20]

In this study, although the mean levels of RBCs and Hb were only slightly decreased in postmenopausal RA patients compared to those with SLE, approximately 60% of RA patients and 40% of SLE patients exhibited anemia, whereas only 18% of the control group showed RBC and Hb levels below the normal range. Interestingly, the percentage of RDW% was higher in both RA and SLE patients compared to the normal value. This finding may shed light on the underlying cause of anemia observed in RA and SLE patients, as discussed previously.

Talukdar et al., 2017,[21] reported a noteworthy increase in the MPV level among RA patients with high disease activity, whereas Tekeoglu et al., 2016,[22] found that patients in remission had significantly higher MPV levels. However, our study showed no difference in MPV levels between RA patients and controls. Discrepancies in sample sizes and the stages of disease activity across the studied populations may explain the divergent findings among these research studies. Talukdar et al., 2017,[21] included only patients within specific disease activity levels (ranging from low to high phases).

In this study, the WBC levels were lower in all SLE patients, while RBCs and PLTs levels were lower in 60% and 40% of SLE patients, respectively, despite that their mean values falling within the normal range. Hypocellularity and bone marrow necrosis, which are associated with the autoimmune mechanisms of the disease, are common findings in bone marrow aspirates. There are numerous contributing factors, some of which are more severe, such as macrophage activation syndrome, triggered by immune dysregulation leading to widespread activation of macrophages in the bone marrow and other tissues. Although hemophagocytosis often occurs in the bone marrow, it neither confirms the diagnosis nor is a pathognomonic on its own.[23]

In the present study, 25% to 50% of patients, mild thrombocytopenia (platelet count of 100,000 to 150,000 cells/µl) was observed, consistent with our findings of approximately 40%, as mentioned earlier. Additionally, research on platelet counts in RA patients presented conflicting results. The study by Işık et al., 2014,[24] reported that RA patients with high disease activity exhibited higher platelet counts than those in remission, whereas the study by Tekeoglu et al., 2016,[22] found no difference in PLT levels among RA patients, aligning with our findings.

It is widely recognized that women experience changes in their sex hormone levels

with aging, coinciding with variations in ovarian function. Feedback mechanisms regulate certain hormones, contributing to hormonal differences between pre- and post-menopausal periods. For example, reduced synthesis of progesterone and estrogen results in elevated FSH and decreased LH levels post-menopause.[25] Many autoimmune diseases exhibit a female predominance, with a female-to-male ratio of about 3:1.[26] Although this gender gap is less pronounced compared to rheumatic diseases like SLE. Additional observations supporting the role of sex hormones in RA pathophysiology including its peak prevalence at menopause.[27] These trends suggest that elevated levels of female sex hormones during pregnancy offer protection, while declining levels of estrogen and progesterone post-menopause increase RA risk. Our findings revealed increasing FSH levels and decreasing LH, estrogen, and progesterone levels in postmenopausal women with SLE. A research study suggested a minimal role of progesterone in SLE pathophysiology, necessitating further investigation with larger sample sizes.[28] In our study, we observed increased FSH and progesterone levels alongside decreased LH and estrogen levels in postmenopausal women with SLE.

Considering that women with SLE typically exhibit lower serum testosterone levels, it has been suggested that testosterone might confer a protective effect against the onset of SLE.[29] Conversely, postmenopausal females with RA were observed to have decreased mean serum testosterone levels compared to the control group.[30] This suggests a potential relationship between serum testosterone levels and the onset of SLE and RA. These findings align with our results, which revealed decreased testosterone levels in postmenopausal women with RA or SLE. Moreover, testosterone possesses anti-inflammatory properties capable of suppressing both humoral and cellular immune systems.[31] The main component of the stress system is the hypothalamus-pituitary-adrenal (HPA) axis. This axis plays a crucial role in preventing auto-reactive or excessive amplification of the immune response through the stress-induced elevation of glucocorticoid blood concentrations, thereby curbing self-injury and autoimmunity.

An impaired HPA axis function may heighten the risk of developing autoimmune diseases, as cytokines primarily activate the HPA axis. Reduced HPA axis responsiveness to corticotropin-releasing hormone or hypoglycemia stimulation has been observed in various autoimmune conditions such as Sjogren's syndrome, fibromyalgia, RA, and SLE.[32] However, the connection between HPA axis reactivity and inflammatory diseases has been questioned by studies showing that in high-stress situations, rats with a robust corticosterone response to stress experienced more severe inflammation than those with a less pronounced corticosterone response.[33, 34]

All the aforementioned evidence indicates that the HPA axis is affected, leading to decreased cortisol levels in patients with RA or SLE. However, the exact location of this defect within the axis whether it occurs in the hypothalamus, pituitary, or adrenal stage has not yet been determined. Our findings revealed decreased cortisol levels in both untreated postmenopausal women with either RA or SLE. Notably, these levels were below the normal levels without any external stimulus, suggesting a possible suppression of the HPA axis. The suppression of the HPA axis could potentially result from defects in the nerves of the sympathetic nervous system during the immune response in RA and SLE patients. However, further research is needed to explore this observation in depth.

RA is an inflammatory condition affecting multiple body parts, characterized by symmetrical polyarthritis and the presence of autoantibodies such as RF and anti-citrullinated protein antibodies.[35] While increased RF levels are indicative of RA, they are also commonly found in patients with SLE and are associated with a milder disease course.[36] Conversely, elevated ESR is observed in both SLE and RF patients due to faster sedimentation of RBCs. Normally, RBCs settle slowly, but inflammation causes them to aggregate, forming heavier clumps that settle more rapidly.[37] In our study, ESR and RF levels were higher in

postmenopausal women with RA and SLE compared to the control group.

Serum from RA patients was previously tested for high total IgE titers, yet research studies have not consistently shown a higher or lower incidence of atopy in RA patients.[38, 39] The only known reported specificity for IgE in RA was directed against the Fc fragment (IgE-RF) and is associated with extra-articular rheumatoid vasculitis and cartilage collagen.[33] While IgE may potentially play a role in RA, this remains unconfirmed. In our comparison of sera from RA patients and controls, we observed elevated levels of IgE in the sera of RA patients compared to controls. Similar findings were noted by another research study regarding other immunoglobulins, suggesting a generalized immune hyperactivity.[40]

Elevated polyclonal IgE levels in serum have also been noted in SLE patients compared to healthy individuals. Although there were suggestions of a correlation with disease activity, these findings were drawn from previous research involving a small number of patients and did not differentiate between auto-reactive and polyclonal IgE components.[41] Furthermore, in our study, we observed higher total IgE levels in SLE patients compared to controls. Generally, SLE patient cohorts exhibit increased total IgE levels.[42]

In conclusion, our results showed that there were many differences in the hematological, hormonal and immunological changes between postmenopausal women with RA and SLE. While both RA and SLE patients' groups had anemia, leukocytosis occurred in the RA group, but in the SLE group leukopenia occurred. Moreover, thrombopenia occurred only in SLE. Although the levels of FSH and cortisol were significantly higher, there was a significant decrease in the levels of LH, estrogen and testosterone in both patient groups. Interestingly, the level of progesterone was higher in the SLE and lower in the RA. The levels of RF, ESR and IgE were significantly increased in both patients' groups compared to the control group. These differences need future work to find out their reasons and how they could be used in future treatment strategies.

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Author Contributions

LQA and FSA; collected study data and shared in preparation of the manuscript. While BE and JJ shared conceptualization, supervision, and review of the manuscript. All LQA, FSA, BE and JJ reviewed the final manuscript and approved its final version.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of the College of Science Mustansiriyah University, (Reference Number: BCSMU/0530/0046Z, Dated June 5, 2023).

Informed consent

A signed consent form was obtained from each study participant.

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