Postmenopausal Hormone, Hematology and Immune Modulation in Rheumatoid Arthritis Patients

Luma Qasim Ali [1], Firas Salih Abdulhadi [1], Ban Talib El-Haboby [1], Jamela Jouda [1*]

Abstract

Background: There is a significant hormonal shift in Postmenopausal women with low levels of estrogen and progesterone. These changes may cause the pathogenesis of autoimmune diseases, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), which exhibit a higher prevalence in women. It is crucial to determine the pathophysiology and treatment strategies and to understand the hematological, hormonal, and immunological differences in postmenopausal women with RA and SLE. This study determined the hematological, hormonal, and immunological parameters in postmenopausal RA and SLE patients. Methods: 75 postmenopausal women (aged 52-65 years) were recruited in this study, comprising 25 with RA, 25 with SLE, and 25 with healthy controls. Blood samples were collected for complete blood count (CBC), erythrocyte sedimentation rate (ESR), and serum hormone and immunoglobulin assays. Statistical analyses were conducted using Fisher's test, t-test, and ANOVA, with significance at $p < 0.05$. Results: In postmenopausal RA and SLE patients, significant blood parameter differences were observed versus controls. RA showed elevated WBC count (18.189±0.782) and PLT (373.778±14.644), lower RBC (4.009±0.149) and Hb (11.705±0.328). SLE had lower WBC (3.016±0.595), RBC (4.293±0.112), and Hb (12.270±0.312), and higher RDW (18.830±1.719) and lower MPV (8.327±0.314). Hormonal differences included higher FSH and lower LH, estrogen, and testosterone in both groups, while RA exhibited decreased cortisol and increased progesterone, and both diseases showed elevated rheumatoid factor (RF), ESR, and immunoglobulin E (IgE). Conclusion: Postmenopausal women with RA and SLE showed distinct hematological, hormonal, and immunological profiles compared to healthy controls. This study demonstrated the complex interplay between hormonal changes and autoimmune diseases, warranting further investigation into their underlying mechanisms and potential implications for treatment strategies.

Keywords: CBC, Cortisol, IgE, Postmenopausal, Rheumatoid arthritis (RA), Systemic Lupus Erythematosus (SLE), Hormonal changes, Hematological parameters

Significance | This research determined the significant hematological, hormonal, and immunological changes in postmenopausal women with RA or SLE in compared to controls. This investigation had a high potential for therapeutic intervention.

*Correspondence. Jamela Jouda, Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq, Email: jamela.jouda@uomustansiriyah.edu.iq

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Introduction

The postmenopausal transition requires significant hormonal and metabolic changes due to declining ovarian function, with average ages at natural menopause varying globally. Lower estrogen levels cause hormonal imbalances, particularly elevating luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels.

Author Affiliation.
[1] Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq

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"Postmenopausal" refers to women who haven't had menstrual flow for at least a year, assuming they still have a uterus and aren't pregnant (Kulkarni & Hiremath, 2019). In affluent countries, natural menopause occurs at around 51 years, while in developing countries, it's around 48 years. During this time, many hormonal and metabolic differences indicate declining ovarian function, with reproductive hormone levels continuing to fluctuate into postmenopause (Talsania & Scofield, 2017).

The transition from peri- to postmenopausal stage presents dramatic endocrine differences. The main cause of postmenopausal symptoms is the lower amount of circulating estrogen. In the ovary, particularly in the granulosa cells, the inability to react to pituitary hormones leads to a lack of feedback inhibition, resulting in increased levels of LH and FSH. Ovarian production of progesterone, estrogen, and inhibin stops (Park et al., 2023).

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease characterized by higher rates of incidence and prevalence in women compared to men. This sex difference has prompted studies investigating how female reproductive or hormonal factors influence RA onset or progression (Yousif & Ibraheem, 2020). Female hormones are considered crucial elements in the development of RA, although studying their effects is challenging due to fluctuating serum levels interacting with various environmental, genetic, immunological, and endocrine factors influencing autoimmunity (Zhang et al., 2022). Menopause-related sex hormones, particularly estrogen reduction, are believed to play a significant role in RA pathogenesis (Dos Santos et al., 2012).

Systemic Lupus Erythematosus (SLE) is an autoimmune disease affecting various tissues, organs, and systems, primarily targeting blood vessels, kidneys, lungs, heart, liver, nervous system, joints, and skin (Lee et al., 2006). Women are afflicted by SLE nearly ten times more frequently than men, typically starting in the third or fourth decade of life. Menopausal onset age influences the severity, course, and consequences of SLE and is considered a risk factor for the disease (Ganz, 2019).

Our study aimed to investigate differences in hematological, hormonal, and immunological parameters in postmenopausal women with RA or SLE.

Materials and methods

Study Setting and Participants

The investigation took place from September 2022 to February 2023 at Baghdad Medical City's Rheumatology and Rehabilitation Unit of the Baghdad Teaching Hospital. The study involved 75 postmenopausal women: 25 diagnosed with rheumatoid arthritis (RA), 25 diagnosed with systemic lupus erythematosus (SLE), and 25 healthy controls. The participants' ages ranged from 52 to 65 years.

Blood Collection and Processing

A total of 9ml of blood was collected from each participant using a disposable syringe. Of this, 2ml were placed in a tube with EDTA for immediate use in a complete blood count (CBC) test conducted with a fully automatic quantitative Samsung device. Another 2ml were used for the erythrocyte sedimentation rate (ESR) test, while the remaining 5ml were kept at room temperature in a gel clot activator tube until coagulation occurred. Subsequently, the samples were centrifuged for 15 minutes at 3000 rpm, and the serum was separated into Eppendorf tubes and stored at -20°C until further use.

Laboratory Analysis

The collected serum was utilized to determine hormone levels (FSH, LH, Prolactin, and Estradiol) and conduct immunological tests for rheumatoid factor (RF) and Immunoglobulin E (IgE) using enzyme-linked immunosorbent assay (ELISA) kits from Monobind/USA.

Measurement of ESR

The Westergren method, following standard protocol, was employed to measure the erythrocyte sedimentation rate (ESR). This involved mixing 0.2ml of 3.8% sodium citrate solution with 1.8ml of blood. The mixture was then submerged in a Westergren tube until the zero mark, placed upright in a holder with a spring clip on top and a rubber band on the bottom, and left for 60 minutes. The ESR level was measured in mm/hr.

Statistical Analysis

Results were expressed as mean ± SE or percentage (%) of case frequency. Data were analyzed for comparisons using one-way analysis of variance (ANOVA), Fisher's test, or t-test. Regression analysis utilizing analysis of combined variance (ANCOVA) was also performed. Statistical analysis was conducted using StatView 5.0, with differences considered significant at $p < 0.05$.

Results

Table 1 illustrated the variations in certain blood parameters (WBC, RBC, Hb, PLT, RDW, and MPV) among postmenopausal women with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) and the control group. The WBC count was notably higher in the RA group and lower in the SLE group compared to the control (18.189±0.782, 3.016±0.595, and 8.260±0.415 cells x 103/µl, respectively), deviating from the normal value. Conversely, the RBC count and Hb levels were lower in both patient groups, significantly in RA and non-significantly in SLE, in comparison to the control (4.009±0.149, 4.293±0.112, and 4.859±0.155 RBC cells x 106µl, respectively; and 11.705±0.328, 12.270±0.312, and 12.653±0.238 g Hb/dl, respectively). Notably, 60% of the RA group, 40% of the SLE group, and only 18% of the control group showed lower RBCs and Hb levels compared to normal values. Additionally, the PLT count was significantly higher in RA and lower in SLE compared to the control (373.778±14.644, 200.15±0.166, and 257.701±13.969 cells x

103/μl, respectively), while remaining within the normal range in RA patients and controls but lower in 40% of SLE patients. Moreover, RDW% was significantly higher in the patient groups (RA and SLE) compared to the control (18.830±1.719, 16.352±1.885, and 13.032±0.184%, respectively), exceeding the normal value, while MPV value was significantly lower in patients with RA and SLE compared to the control (7.698±0.319, 8.327±0.314, and 9.832±0.259 fl, respectively).

Table 2 depicted the differences in hormone levels (FSH, LH, cortisol, estrogen, progesterone, and testosterone) among postmenopausal women with RA or SLE and the control group. The FSH level was significantly higher in both patient groups, RA and SLE, compared to the control (123.310±2.352 IU/L, 123.648±3.609 IU/L, and 49.181±3.198 IU/L, respectively). Conversely, the LH, estrogen, and testosterone levels were significantly lower in the RA group (21.235±1.109 IU/L, 15.198±1.143 pg/ml, and 0.703±0.010 nmol/L, respectively) and the SLE group (20.904±1.515 IU/L, 15.698±0.998 pg/ml, and 0.741±0.007 nmol/L, respectively) compared to the control (36.092±2.333 IU/L, 23.381±0.717 pg/ml, and 811±0.013 nmol/L, respectively). Interestingly, the progesterone level decreased in RA but increased in SLE compared to the control (3.489±0.209, 6.894±0.222, and 4.379±0.097 ng/ml, respectively). Additionally, the cortisol level was significantly lower in both the RA and SLE groups compared to the control (24.74±2.02, 48.68±7.17, and 67.50±3.48 μg/ml, respectively).

Table 3 showed the differences in the levels of rheumatoid factor (RF), IgE, and ESR among postmenopausal women with RA or SLE and the control group. The levels of RF, ESR, and IgE were significantly higher in patients with RA (0.679±0.018 IU/ml and 37.852±4.012 mm/hr, 16.621±1.058UI/ml, respectively) and SLE (0.353±0.019 IU/ml and 33.348±2.757 mm/hr, 10.837±0.160 UI/ml, respectively) compared to the control (0.254±0.009 IU/ml and 14.701±0.924 mm/hr, 7.392±0.221 UI/ml, respectively).

Discussion

Understanding the complex relationship between hematological parameters, hormonal fluctuations, and autoimmune diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) in postmenopausal women poses significant challenges due to conflicting literature and unclear mechanisms. Specifically, the contradictory findings regarding the effects of estrogen, variations in leukocyte and platelet counts, anemia etiology, and hormonal imbalances necessitate further investigation to elucidate the underlying pathophysiological mechanisms and potential therapeutic targets.

Recent research suggests that hematological parameters—such as hemoglobin (Hb) and platelets (PLT)—as well as white blood cells (WBCs) are associated with chronic inflammation (Kounis et al., 2015; Stokes & Granger, 2012; Mirand & Gordon, 1966). However, literature presents conflicting views on the effect of estrogen, particularly in postmenopausal women. Some studies suggest estrogen decreases and suppresses erythropoiesis (Bodis et al., 2003; Milman et al., 1992), while others propose its potential to stimulate stem and progenitor cell growth, influencing hematopoiesis (EG, 1996, Ghufran et al., 2024). Consequently, some literatures indicate considerably higher mean total WBCs in postmenopausal women compared to other groups (Tekeoğlu et al., 2016). However, recent findings reveal that while postmenopausal women with rheumatoid arthritis (RA) tend to exhibit leukocytosis, those with systemic lupus erythematosus (SLE) often present with leukopenia (Chandrashekara et al., 2015; Starkebaum et al., 1978, Subasini 2023). The pathophysiological mechanisms underlying leukopenia in SLE remain unclear and may involve factors such as bone marrow decline, splenic modifications, or predisposition to autoimmunity (Mirzayan et al., 2000; Martinez-Banos et al., 2006). Notably, leukopenia serves as a classification criterion in both the Systemic Lupus International Collaborating Clinics and the American College of Rheumatology (Voulgarelis et al., 2000).

Anemia in chronic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) is attributed to increased hepcidin expression, which impedes iron incorporation into erythrocytes during maturation (Verga Falzacappa et al., 2007). Inflammatory cytokines, particularly Interleukin-6, regulate hepcidin by activating signal transducer and activator of transcription 3 (STAT3) (Baker & Ghio, 2009). Moreover, cytokines like tumor necrosis factor-alpha, interferon gamma, and IL-1 disrupt iron homeostasis by reducing transferrin receptor concentration and increasing ferritin production (Talukdar et al., 2017).

Although postmenopausal RA patients in our study exhibited only slight decreases in red blood cell (RBC) and hemoglobin (Hb) levels compared to SLE patients, anemia was prevalent in 60% of RA patients and 40% of SLE patients, contrasting with only 18% in the control group where RBC and Hb levels were below normal (Verga Falzacappa et al., 2007). Remarkably, the red cell distribution width percentage (RDW%) was elevated in both RA and SLE patients compared to the normal value, suggesting a potential contributor to the observed anemia.

Regarding mean platelet volume (MPV), previous studies have yielded conflicting results (Işık et al., 2014; Tekeoğlu et al., 2016; Voulgarelis et al., 2006). Talukdar et al. reported a notable elevation in MPV among RA patients with high disease activity, whereas Tekeoğlu et al. and Işık et al. found higher MPV in patients in remission. However, our study found no difference in MPV levels between RA and control groups. Disparities in sample sizes and disease activity stages may explain the varied results. Future research should classify patients according to disease progression for clearer insights.

Table 1. Hematological parameters of patients and control groups

Parameter	Group	Mean±S.E	P.value
WBCx10^3/uL	Control	8.260±0.415	RA vs. SLE<0.0001
	RA patients	18.189±0.782	RA vs. Control<0.0001
	SLE patients	3.16±0.595	SLE vs. Control<0.0001
RBC x10^6/uL	Control	4.859±0.155	RA vs. SLE=0.1640
	RA patients	4.009±0.149	RA vs. Control= <0.0001
	SLE patients	4.293±0.112	SLE vs. Control=0.0074
Hb (g/dL)	Control	12.653±0.238	RA vs. SLE=0.1843
	RA patients	11.705±0.328	RA vs. Control=0.0243
	SLE patients	12.270±0.312	SLE vs. Control= 0.3746
RDW%	Control	13.032±0.184	RA vs. SLE=0.2389
	RA patients	18.830±0.171	RA vs. Control=0.0058
	SLE patients	16.352±0.188	SLE vs. Control= 0.1225
Plt ×10^3/µL	Control	257.701±13.969	RA vs. SLE=<0.0001
	RA patients	373.778±14.644	RA vs. Control=<0.0001
	SLE patients	200.15±0.166	SLE vs. Control=0.031
MPV (fL)	Control	9.832±0.259	RA vs. SLE=0.1436
	RA patients	7.698±0.319	RA vs. Control=<0.0001
	SLE patients	8.327±0.314	SLE vs. Control= 0.0009

Table 2. Hormonal level of patients and control groups

Parameter	Group	Mean±SE	P.value
FSH (IU/L)	Control	49.181± 3.198	RA vs. SLE=0.9378
	RA patients	123.310± 2.352	RA vs. Control<0.0001
	SLE patients	123.648± 3.609	SLE vs. Control<0.0001
LH (IU/L)	Control	36.092± 2.333	RA vs. SLE=0.8921
	RA patients	21.235± 1.109	RA vs. Control<0.0001
	SLE patients	20.904± 1.515	SLE vs. Control= 0.001
Cortisol (µg/ml)	Control	67.50±3.48	RA vs. SLE<0.0001
	RA patients	24.74±2.02	RA vs. Control<0.0001
	SLE patients	48.68±7.17	SLE vs. Control= 0.001
Estrogen (pg/ml)	Control	23.381±0.717	RA vs. SLE=0.7204
	RA patients	15.198±1.143	RA vs. Control<0.0001
	SLE patients	15.698±0.998	SLE vs. Control= 0.001
Progesterone (ng/ml)	Control	4.379±0.097	RA vs. SLE<0.0001
	RA patients	3.489±0.209	RA vs. Control=0.001
	SLE patients	6.894±0.222	SLE vs. Control<0.0001
Testosterone nmol/L	Control	0.811±0.013	RA vs. SLE<0.0001
	RA patients	0.703±0.010	RA vs. Control<0.0001
	SLE patients	0.741±0.007	SLE vs. Control= 0.0490
Normal reference of LH 14.2- 52.3 IU/L; FSH25.5-134.8 IU/L; cortisol 5-25 ng/ml; Estrogen 0-30 pg/ml; Progesterone <40 ng/ml; testosterone 2.5 nmol/L			

Table 3. The level of RF, IgE and ESR in patients and control groups

Parameter	Group	Mean±S.E	P.value
RF(IU/ml)	**Control**	0.254±0.009	RA vs. SLE=<0.0001
	RA patients	0.679±0.018	RA vs. Control=<0.0001
	SLE patients	0.353±0.019	SLE vs. Control= 0.001
IgE(UI/ml)	**Control**	7.392±0.221	RA vs. SLE=<0.0001
	RA patients	16.621±1.058	RA vs. Control=<0.0001
	SLE patients	10.837±0.160	SLE vs. Control= 0.008
Esr (mm/hr)	**Control**	14.701±.924	RA vs. SLE=0.2854
	RA patients	37.852±4.012	RA vs. Control=<0.0001
	SLE patients	33.348±2.757	SLE vs. Control=<0.0001
Normal reference of RF<15 IU/mL; IgE=150-300IU/mL and ESR Women over 50 years old: less than 30 mm/hr			

Pancytopenia, characterized by decreased red blood cells (RBCs), white blood cells (WBCs), and platelets, is less common than isolated cytopenias but can occur in systemic lupus erythematosus (SLE) (Wanitpongpun et al., 2012; González Naranjo, 2008). In our study, WBC levels were lower in all SLE patients, with RBCs lower in 60% and platelets lower in about 40%, despite mean values within normal ranges. Hypocellularity and bone marrow necrosis, linked to autoimmune mechanisms, are common findings in bone marrow aspirates. Factors such as macrophage activation syndrome may contribute, characterized by large-scale macrophage activation in the bone marrow and other tissues (Yousif & Ibraheem, 2020). Mild thrombocytopenia (platelet count 100,000 to 150,000 cells/μL) was observed in 25% to 50% of SLE patients, consistent with our findings of about 40% (Wanitpongpun et al., 2012; González Naranjo, 2008).

Regarding platelet counts in rheumatoid arthritis (RA) patients, findings vary. Isık et al. reported greater platelet counts in RA patients with high disease activity, while Voulgarelis et al. found no difference in platelet levels in RA patients, consistent with our results (Isık et al., 2014; Voulgarelis et al., 2006).

As women age, hormonal levels change due to alterations in functional ovaries, with postmenopausal women exhibiting high follicle-stimulating hormone (FSH) and low luteinizing hormone (LH) levels due to decreased estrogen and progesterone synthesis (Cross et al., 2014). Autoimmune diseases, including RA and SLE, show a female predominance, with a female-to-male ratio of approximately 3:1, suggesting a role for sex hormones in their pathophysiology (Goemaere et al., 1991). The peak prevalence of RA at menopause underscores the potential protective effect of elevated female sex hormones during pregnancy, while decreased hormone levels post-menopause increase RA risk (Raine & Giles, 2022). However, the precise connection between sex hormones and RA pathophysiology remains unclear (Mok & Lau, 2000). Our study found increased FSH levels and decreased LH, estrogen, and progesterone levels in postmenopausal women with SLE.

However, several investigations have demonstrated increased serum estradiol levels in female SLE patients compared to healthy age-matched controls (Goemaere et al., 1991; Raine & Giles, 2022; Mok & Lau, 2000), while some other studies have not observed any variations (Verthelyi et al., 2001). Conversely, serum progesterone levels in adult SLE patients have not been extensively studied; however, progesterone levels in postmenopausal SLE patients were found to be considerably higher than in matched controls (Durán-Barragán, 2021). Certain research suggests a minimal role of progesterone in the pathophysiology of SLE, but further studies with larger samples are needed to confirm this (Tengstrand et al., 2009). Our results showed increased levels of follicle-stimulating hormone (FSH) and progesterone, while luteinizing hormone (LH) and estrogen levels decreased in postmenopausal women with SLE.

Women with SLE typically exhibit lower serum testosterone levels, suggesting a potential protective effect against the onset of SLE (Imrich et al., 2009). Conversely, postmenopausal females with RA had decreased mean serum levels of testosterone compared to the control group (Gilliver, 2010). These findings are consistent with our results, which showed decreased testosterone levels in postmenopausal women with RA or SLE. Testosterone has anti-inflammatory properties that can suppress both humoral and cellular immune systems (Hall et al., 1996), and its replacement has been considered as a potential treatment for RA (Silverman & Sternberg, 2012).

The hypothalamus-pituitary-adrenal (HPA) axis plays a crucial role in the stress response and immune regulation. Impaired HPA axis function may increase the risk of autoimmune diseases, as it is a target of cytokine activation (Chover-Gonzalez et al., 2000). However, studies have shown conflicting results regarding the association between HPA axis reactivity and inflammatory diseases (Harbuz et al., 2003). Preliminary evidence suggests that a defective HPA axis is present in SLE, with active, untreated female SLE patients exhibiting lower cortisol levels than healthy controls (Straub et al., 2002; Gutierrez *et al.*,1998). Research on HPA axis function in SLE patients is limited and often complicated by concomitant glucocorticoid treatment. Variations in HPA axis reaction to stress may help differentiate patients with similar illnesses but different treatment responses (Lechner et al., 2000).

In RA patients, norepinephrine and cortisol have recently been shown to exhibit anti-inflammatory cooperativity. RA patients with synovial sympathetic nerve fibers and prednisolone therapy demonstrated fewer histological indicators of synovial inflammation compared to patients without prednisolone therapy or sympathetic innervation (Rey et al., 2003). However, studies have shown that sympathetic innervation is decreased in inflammatory processes such as in lupus lpr/lpr mice (Miller et al., 2000), RA patients (Mei et al., 2002), and diabetic rats (Schedlowski et al., 1996). Reduced levels of androgens and cortisol combined with loss of sympathetic nerve fibers would create a proinflammatory microenvironment in inflamed tissue (Shrivastava et al., 2015).

All the above evidence suggests that the HPA axis is affected, leading to decreased cortisol levels in patients with RA or SLE. However, the exact location of this defect in the axis, whether it is in the hypothalamus, pituitary, or adrenal stage, has not been determined. Our results indicate decreased cortisol levels in both untreated postmenopausal women with RA or SLE. Interestingly, these levels were below the normal value without any stimulation, suggesting HPA axis suppression. The reason for this suppression of the HPA axis could be the defect in the nerves of the sympathetic nervous system during the immune response in RA and SLE patients; however, this observation requires further research.

RA is an inflammatory disease that affects multiple parts of the body, leading to symmetrical polyarthritis and characterized by the formation of autoantibodies such as rheumatoid factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA) (Mok & Lau, 2000). RF and erythrocyte sedimentation rate (ESR) are rudimentary indicators of inflammation (Katsuyama et al., 2014). While increased RF levels are characteristic of RA, they are also commonly found in patients with SLE and have been associated with a more benign disease course in SLE (Pizzorno & Murray, 2020). Elevation in ESR has been noted in both SLE and RA patients due to faster sedimentation of red blood cells, which clump together as a result of inflammation, leading to quicker sinking (Grennan & Palmer, 1979). In this study, ESR and RF levels were higher in postmenopausal women with RA and SLE compared to the entire control group.

Serum from RA patients has been found to have high total IgE titers or a lower incidence of atopy compared to controls (Hunder & Gleich, 1974; O'DRISCOLL et al., 1985; Hassan et al., 1994). The only known specificity for IgE in RA is against Fc (IgE-RF), which is associated with extra-articular rheumatoid vasculitis and against cartilage collagen (Allanore et al., 1998; Bartholomew et al., 1991). Although IgE may play a potential role in RA, it is not entirely confirmed. Our comparison of sera from RA patients and controls revealed elevated levels of IgE in the sera of RA patients. Similar findings were reported by other researchers with other immunoglobulins, suggesting generalized immune hyperactivity (Mizushima et al., 1984).

Polyclonal IgE levels in the serum have also been observed to be higher in SLE patients compared to healthy individuals. Although there is a suggestion of correlation with disease activity, previous research with a small number of patients did not distinguish between auto-reactive and polyclonal IgE components (Camussi et al., 1982). In our research, we found that SLE patients had higher total IgE levels than controls. Overall, SLE patient cohorts tend to exhibit increased total IgE levels (Parks et al., 2010).

Conclusion

The study revealed notable disparities between postmenopausal women with RA and SLE compared to age-matched controls: both groups experienced anemia, yet RA patients exhibited leukocytosis while SLE patients had leukopenia, and thrombocytopenia was exclusive to SLE. Despite higher FSH and cortisol levels, LH, estrogen, and testosterone were significantly reduced in both groups, with higher progesterone in SLE and lower in RA. Additionally, RF, ESR, and IgE levels were elevated in both patient groups. These findings underscore the need for further research into the hematological and hormonal variations between RA and SLE postmenopausal women to inform future treatment strategies.

Author contribution

L.Q.A., F.A.A., B.T.E., J.J. conceptualized and developed the study's methodology, carried out all data collection and analysis, wrote the original draft, and reviewed, edited, and finalized the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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