

A Cross-Sectional Study of Serum Leptin, Estrogen, Insulin, Cortisol, GH and TSH in Women with Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is increasingly being recognized as a systemic disease with important metabolic and endocrine features. However, the combined pattern of serum metabolic hormone levels in women with RA remains insufficiently characterized. **Objective:** This study aimed to compare serum levels of leptin, estradiol, insulin, cortisol, growth hormone (GH), and thyroid-stimulating hormone (TSH) in women with RA with healthy controls and to examine their associations with selected clinical and metabolic characteristics. **Methods:** This cross-sectional study was conducted in the Basrah Governorate, Iraq, between October and December 2022. The final analysis included 43 women, including 23 patients with RA and 20 healthy controls. Demographic and clinical data included age, body mass index (BMI), rheumatoid factor (RF) status, disease activity, disease duration, medication use, glucocorticoid use, menopausal status, and family history. Serum hormone levels were measured using an enzyme-linked immunosorbent assay. Data were analyzed according to the distribution. Between-group comparisons were performed using the independent-samples t-test or Mann-Whitney U test. Exploratory correlation and adjusted regression analyses were performed in the RA

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group. Results: RA patients had significantly higher serum cortisol [84.76 (66.10–98.29) vs. 22.80 (16.98–31.79) ng/mL, $p < 0.001$], insulin [15.54 (10.68–18.54) vs. 3.54 (2.09–4.65) mU/L, $p < 0.001$], and leptin (724.45 ± 149.79 vs. 243.98 ± 113.60 pg/mL, $p < 0.001$) levels compared with controls. Estradiol and TSH levels did not differ significantly between the groups. Within the RA group, exploratory adjusted analysis showed an association between RF status and log₁₀ insulin levels after adjusting for age, glucocorticoid use, and BMI ($\beta = -0.045$, 95% CI -0.081 to -0.008 , $p = 0.022$). Conclusion: Women with RA in this cohort showed differences in selected serum hormones compared to controls, mainly characterized by higher leptin, insulin, and cortisol levels and lower GH levels. Larger RA-specific endocrine-metabolic phenotype studies are required to confirm these findings. The adjusted regression model for insulin was exploratory.

Keywords: rheumatoid arthritis, leptin, insulin, estradiol, growth hormone, thyroid-stimulating hormone

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affecting 0.5% to 1% of the global population [1,2]. Although early diagnosis and treatment have improved outcomes, many patients still experience persistent synovial inflammation, joint pain, fatigue, progressive joint damage, and extra-articular manifestations, all of which contribute to a reduced quality of life and long-term disability [3,4].

RA is widely acknowledged to be a systemic condition characterized by immune, endocrine, and metabolic pathways [5,6]. Patients with RA have a greater metabolic burden owing to abnormal adipokine activity, insulin resistance, altered body composition, and increased cardiovascular risk [6]. These alterations may not only co-occur with inflammation, but can also be coupled with immune activation, leading to effects on disease activity, treatment response, and long-term complications [6,7]. Therefore, metabolomic-related hormones may be clinically relevant in RA [8]. Leptin is a predominantly adipose tissue-derived adipokine that demonstrates immunomodulatory and pro-inflammatory roles in RA and may impact synovial inflammation and the risk of cardiometabolic injury [9]. Estrogen may modulate immune responses and partly account for sex differences in RA vulnerability and disease expression [10]. Insulin is critically involved in glucose metabolism, and an association between insulin resistance and inflammatory pathophysiology has already been demonstrated in RA [11]. Growth hormone (GH), cortisol, and thyroid-stimulating hormone (TSH)

are also involved in immune modulation, energy metabolism, and inflammation regulation [12–14].

However, hormonal patterns in women with RA are yet to be fully explored. Although individual hormones have been studied in RA, the integrated serum profiles of leptin, estrogen, insulin, cortisol, GH, and TSH remain poorly characterized. Most previous studies have examined single hormones, used synovial rather than serum measurements, or lacked adjustments for important confounders that can impact the results, leaving a research gap in understanding the endocrine phenotype of RA [15].

Therefore, the current study aimed to compare serum levels of leptin, estrogen, insulin, cortisol, GH, and TSH in women with RA with healthy controls and to examine their associations with selected clinical and metabolic characteristics.

2. Materials and Methods

Study design and participants

This cross-sectional study was conducted in the Basrah Governorate, Iraq, between October and December 2022. The study protocol was reviewed and approved by the College of Health and Medical Technology, Southern Technical University (approval number [no. 103 on 30/08/2022]). This study was performed in accordance with the principles of the Declaration of Helsinki. All participants were informed of the purpose of the study before enrollment. Written informed consent was obtained prior to blood sample collection and data recording.

Eligible women aged 20–60 years with established RA and apparently healthy women who were available during the study period were included. RA patients were recruited through a private clinical laboratory after a previous clinical diagnosis by a qualified physician. Specifically, RA diagnosis was based on the clinical assessment of the treating physician and medical records. Patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA [16]. Controls were selected from the same general population and had no known autoimmune, endocrine, metabolic, or chronic inflammatory disease.

Exclusion criteria included the presence of diseases that might alter hormonal and metabolic measures, including diabetes mellitus, thyroid disorders, disorders of the pituitary or adrenal glands, ovarian or other

gynecological disorders, chronic kidney or liver disease, neoplasm, acute infection, pregnancy, lactation, or any autoimmune diseases other than RA in the patient group. Women using hormonal treatments, such as oral contraceptives, estradiol, or hormone replacement therapies, were also excluded. Participants with incomplete clinical data or inadequate serum samples were excluded from analysis.

Data collection

Data were collected using structured datasheets. The following variables were recorded for all subjects: age, height, weight, body mass index (BMI), menstrual status, family history of autoimmune disease, and current medications. The formula used for calculating BMI was calculated as weight in kilograms divided by height in metres squared.

For patients with RA, additional clinical data were recorded: duration of disease, seropositive status for RF, level of disease activity, and usage of glucocorticoids. Disease duration was recorded in years (less than 5 or greater than 5 years). RF was recorded as seropositive or seronegative based on the laboratory findings. Disease activity was categorized based on clinical assessment recorded by treating rheumatologists that was routinely documented in the medical records by using DAS28 [17] as either low (≥ 2.6 to ≤ 3.2), moderate (> 3.2 and ≤ 5.1), or high (> 5.1). The use of glucocorticoids as positive or negative; however, information about dose and duration was unavailable, which is described in limitations and as one of the major recommendations in future studies.

Primary laboratory measurements were performed for serum leptin, estradiol, insulin, cortisol, GH, and TSH levels. The levels of these hormones were measured because of their involvement in metabolism, endocrine regulation, immunity, and inflammation.

Blood sample collection and hormone measurements

Blood samples were collected aseptically from all subjects and were fasting samples that were collected on morning day time from 8 O'clock to 10 O'clock. Venous blood samples (approximately 5 ml each) were allowed to clot at room temperature, and serum was separated by centrifuging the blood at 3000 rpm for 10-15 minutes. Serum samples were aliquoted and frozen at 20 °C until the assay.

Serum leptin, estradiol, insulin, cortisol, GH, and TSH levels were measured using commercial enzyme-linked immunosorbent assay kits (ELISA) from SunLong Biotech Co., Ltd. (China). The assays were performed according to

the manufacturer's instructions and included antibody-coated microplates, standards, enzyme conjugates, substrate solutions, stop solutions, and washing buffers required for the measurements.

Leptin, insulin, GH, and TSH levels were measured using a sandwich ELISA assay in which the samples were incubated in the wells of the antibody-coated plates, and then enzyme-linked detection antibodies and substrate solution were added to the wells. A color reaction was formed and read using an ELISA microplate reader, and the concentration was calculated from the standard curves.

For estradiol and cortisol measurements, a competitive ELISA was used, in which the hormones in the sample competed with enzyme-linked hormones for binding sites on antibodies in the wells, and the concentration was calculated from the corresponding standard curve.

The absorbance was measured using an ELISA microplate reader (Infitek Co., Ltd., Shenzhen, Hong Kong).

Statistical analysis

Statistical analysis was performed using MedCalc version 23.5.1 (MedCalc Software Ltd, Ostend, Belgium). The distribution of continuous variables was assessed using the Shapiro–Wilk test.

Continuous data are presented as mean and standard deviation ($M \pm SD$) or median with interquartile range [Me (Q25–Q75)] according to the data distribution. Categorical data are presented as numbers and percentages.

Between-group comparisons were performed using the independent-samples t-test or Mann–Whitney U test, depending on the data distribution. For non-normally distributed variables, between-group differences were presented as Hodges–Lehmann median differences with 95% confidence intervals (CI). For leptin, the difference represents the mean difference with a 95% CI. Because BMI differed significantly between patients with RA and controls, age- and BMI-adjusted regression models were performed for the main hormones that differed between groups in the unadjusted analysis. Hormone variables with skewed distributions were log₁₀-transformed before regression analysis. In these models, RA status was entered as the main predictor, whereas age and BMI were entered as covariates. The results were reported as adjusted regression coefficients, 95% CIs, p-values, and model fit statistics. Within the RA group, exploratory associations between hormone levels and clinical variables were assessed using the Spearman's rank correlation coefficient. An exploratory adjusted

regression analysis was also performed within the RA group, when clinically relevant. Statistical significance was set at $P < 0.05$.

3. Results

Cohort characteristics

A total of 43 women were included in this study. Of these, 23 patients had RA, and 20 were apparently healthy controls. Demographic and clinical characteristics of the participants are shown in Table 1.

Table 1. Clinical and demographic characteristics of the study cohort.

Variable	Controls (n = 20)	RA patients (n = 23)	P-value
Age, years	41.6 ± 11.5	38.6 ± 12.2	0.406
BMI, kg/m ²	20.3 ± 3.6	28.5 ± 5.8	<0.001
RF-positive, n (%)	—	15 (65.2 %)	—
RF-negative, n (%)	—	8 (32.8 %)	—
Low disease activity, n (%)	—	7 (30.4 %)	—
Moderate disease activity, n (%)	—	8 (34.8 %)	—
High disease activity, n (%)	—	8 (34.8 %)	—
Disease duration <5 years, n (%)	—	10 (43.5 %)	—
Disease duration ≥5 years, n (%)	—	13 (56.5 %)	—
Glucocorticoid use, n (%)	—	17 (73.9 %)	—
Premenopausal status, n (%)	11 (55.0 %)	16 (69.6 %)	0.328
Postmenopausal status, n (%)	9 (45.0 %)	7 (30.4 %)	
Family history of autoimmune disease, n (%)	5 (25.0 %)	11 (47.8 %)	0.127

Data are presented as $M \pm SD$. Between-group comparisons were performed using an independent-samples t-test for continuous variables and the chi-squared test for categorical variables, as appropriate. RF, rheumatoid factor; BMI, body mass index.

As presented in Table 1, the RA and control groups were comparable in terms of age, menopausal status, and family history of autoimmune disease. The BMI was significantly higher in patients with RA than in controls. In the RA group, most patients were RF positive, had a disease duration of at least 5 years, and reported glucocorticoid use. Disease activity was distributed across low, moderate, and high categories.

Serum hormone levels in RA patients and controls

Serum hormone levels in RA patients and healthy controls are shown in Table 2.

Table 2. Serum hormone levels in RA patients and healthy controls.

Variable	Controls (n = 20)	RA patients (n = 23)	Difference (95% CI)	P-value
Cortisol, µg/dL	22.8 (16.9–31.8)	84.8 (66.1–98.3)	55.4 (45.2 to 67.2)	<0.001
Estradiol, pg/mL	161.4 (130.5–193.3)	145.6 (126.1–196.7)	–4.42 (–38.9 to 20.9)	0.644
GH, pg/mL	775.6 (577.9–948.5)	230.9 (123.2–339.9)	–525.1 (–650.4 to –399.6)	<0.001
Insulin, mU/L	3.5 (2.1–4.6)	15.5 (10.7–18.5)	11.3 (8.1 to 14.5)	<0.001
Leptin, pg/mL	243.9 ± 113.6	724.4 ± 149.8	480.5 (399.1 to 561.8)	<0.001
TSH, µIU/L	175.8 (121.3–200.4)	169.8 (112.5–194.2)	–10.1 (–51.5 to 30.9)	0.592

Data are presented as Me (Q25–Q75) for non-normally distributed variables and as $M \pm SD$ for normally distributed variables. Between-group differences are shown as RA minus the control. For non-normally distributed variables, the difference represents the Hodges–Lehmann median difference with a 95% CI. For leptin, the difference represents the mean difference with a 95% CI. GH, growth hormone; TSH, thyroid-stimulating hormone.

RA patients had significantly higher serum cortisol, insulin, and leptin levels than controls. GH levels were significantly lower in RA patients. No significant differences in estradiol and TSH levels were observed between the two groups.

Because BMI differed significantly between patients with RA and controls, adjusted analyses were performed to assess whether the main between-group hormone differences remained after accounting for age and BMI. Table 3 presents the results.

Table 3. Age- and BMI-adjusted group differences in serum hormones.

Hormone outcome (n = 43)	Group effect (95% CI)	P-value	Adjusted R ²	Model F	Model P
log10 insulin	0.65 (0.55; 0.75)	<0.001	0.96	F(3,10) = 104.2	<0.001
Leptin	462.2 (342.4; 581.9)	<0.001	0.75	F(3,39) = 44.2	<0.001
log10 GH	–0.59 (–0.79; –0.39)	<0.001	0.62	F(3,39) = 23.9	<0.001
log10 cortisol	0.49 (0.35; 0.63)	<0.001	0.71	F(3,37) = 33.4	<0.001

Linear regression models were used for adjusted between-group comparisons. Group status was entered as the main predictor and age and BMI were included as covariates. The group effect represents patients with RA compared to controls. Insulin, GH, and cortisol levels were log10-transformed before analysis. Leptin was analyzed without transformation because it was normally distributed. GH, growth hormone.

As shown in Table 3, after adjusting for age and BMI, RA status was still significantly associated with higher leptin, insulin, and cortisol levels, and lower levels of growth hormone. The adjusted regression model for insulin was exploratory.

Within the RA group, the Spearman analysis showed that disease activity was positively correlated with BMI ($\rho = 0.603$, $p = 0.002$). A weaker positive correlation was also observed between disease activity and TSH level ($\rho = 0.429$, $p = 0.041$). Leptin levels showed a weak positive correlation with age (Figure 1).

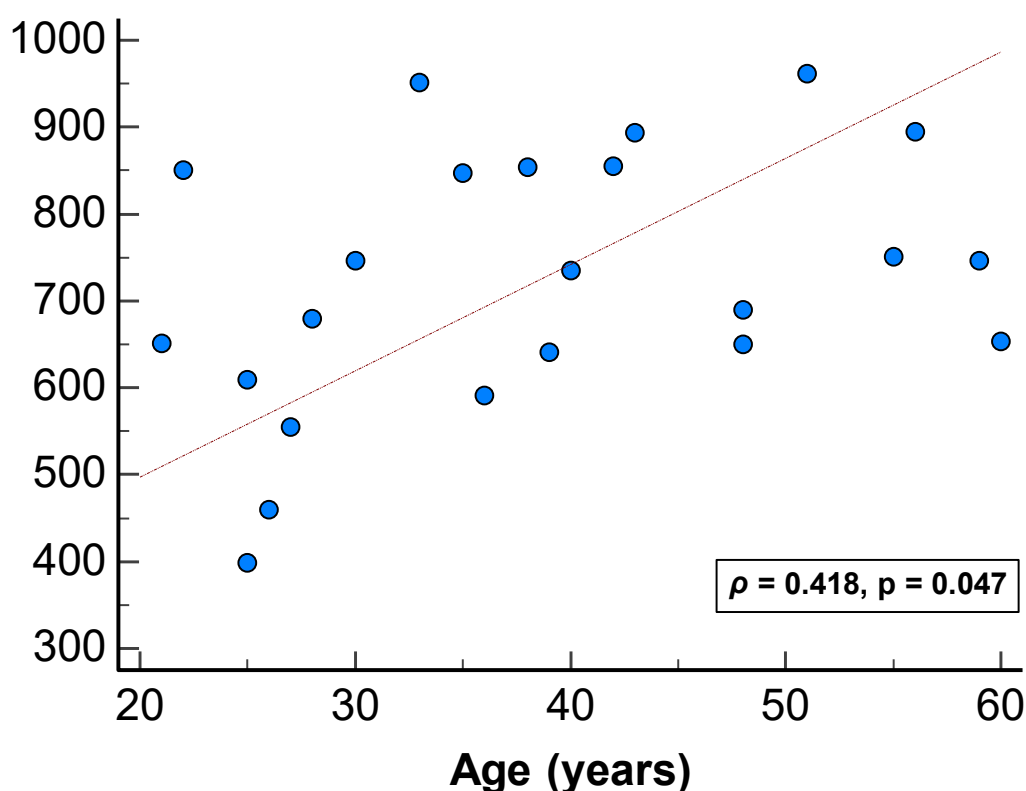


Figure 1. Association between age and serum leptin levels in RA patients.

The other associations between serum hormone levels and RA-related clinical variables were not statistically significant.

Adjusted regression analysis was performed within the RA group to explore whether the selected clinical variables were independently associated with serum hormone levels. Most adjusted models did not show statistically significant associations. The only significant association was observed for log10-transformed insulin levels. After adjusting for age, glucocorticoid use, and BMI, RF status was associated with log10 insulin levels ($\beta = -0.045$, 95% CI -0.081 to -0.008 , $p = 0.022$). Age was also positively associated with log10 insulin ($\beta = 0.002$, 95% CI 0.000 – 0.003 , $p = 0.033$), while BMI was not significant. The overall model showed borderline significance ($R^2 = 0.603$, adjusted $R^2 = 0.454$, $p = 0.050$). This result was considered exploratory owing to the small sample size.

4. Discussion

The main finding of our study was that women with RA had higher serum leptin, insulin, and cortisol levels and lower GH levels than the healthy controls. Estradiol and TSH levels did not differ significantly between the groups. Our findings suggest that RA is associated with a distinct endocrine-metabolic pattern, rather than isolated changes in a single hormone. Few studies have evaluated several metabolism-related hormones simultaneously in early RA, including cortisol, estradiol, GH, TSH, glucose, insulin, triglycerides, and free fatty acids, showing that RA is associated with endocrine metabolic changes [18-20].

Patients with RA had significantly higher leptin levels. Leptin is mainly released by adipose tissue but carries immune and inflammatory effects due to adipose tissue activity and immune activation [18,19,21]. This can affect T cell responses, cytokine production, and synovial inflammation [19]. In addition, they hypothesized that leptin could be a part of inflammation and cardiometabolic risk in RA [22,23]. In our study, the RA group showed a weak positive correlation between leptin level and age. However, leptin levels were not clearly associated with disease activity, RF status, disease duration, or glucocorticoid use. This suggests that leptin may be more closely related to the general metabolic state than to short-term clinical activity.

Serum insulin levels were also higher in RA patients, indicating altered glucose-related metabolic regulation due to chronic inflammation mediators, such as tumor necrosis factor- α and interleukin-6 [11]. Previous studies have linked RA with insulin resistance and metabolic dysfunction [24,25]. However, the present study only measured insulin levels. No fasting glucose levels were observed. Therefore, insulin resistance could not be directly assessed and HOMA-IR could not be calculated. For this reason, the insulin result should be interpreted as higher serum insulin level, not as confirmed by insulin resistance. In addition, in the exploratory adjusted analysis within the RA group, log₁₀-transformed insulin levels were associated with RF status after adjustment for age, glucocorticoid use, and BMI. However, this result should be interpreted cautiously because of the small sample size and exploratory nature of the model, which is primarily used to investigate potential associations rather than test a prespecified hypothesis.

Cortisol is an important stress-related hormone with anti-inflammatory properties. Increased cortisol levels in RA may reflect the activation of the hypothalamic-pituitary-adrenal axis in response to chronic inflammation

[14]. Previous studies have reported altered cortisol secretion in RA, particularly in relation to inflammatory activity and circadian symptoms [19,26]. The higher cortisol levels in this study may represent a compensatory response to systemic inflammation, which is more cautious, given the high proportion of glucocorticoid users in the RA group. However, cortisol interpretation is limited because a detailed glucocorticoid dose is unavailable.

The GH levels were significantly lower in patients with RA. This is one of the strongest differences observed in the present study. GH plays an important role in metabolic and immune functions. It modifies protein, carbohydrate, and lipid metabolism and can also influence immune cell activity [12]. Lower GH levels may result from endocrine adaptations to chronic inflammatory diseases, alterations in pituitary gland control, or medication-induced effects. Previous studies have suggested that the GH and glucocorticoid pathways may be involved in the inflammatory balance in RA [12,27]. The inverse direction of GH compared to leptin, insulin, and cortisol supports the idea of a broader endocrine-metabolic shift in RA.

Estradiol and TSH levels did not differ significantly between patients with RA and the controls. Therefore, these findings should be interpreted with caution. Estradiol levels vary with age, menstrual phase, menopausal status, and ovarian function [10,26]. In this study, menopausal status was recorded; however, the menstrual cycle phase was not standardized. This may have reduced their ability to detect group differences. Although estradiol is associated with sex differences in RA susceptibility and immune regulation, a single serum measurement may not fully capture its role in RA pathophysiology [28]. The lack of significant differences in TSH levels between patients with RA and controls is consistent with previous studies [29]. However, thyroid dysfunction has been linked to RA in large observational studies and meta-analyses [13,30]. A recent systematic review found that patients with RA had a higher risk of thyroid dysfunction, particularly hypothyroidism [13]. Therefore, normal or nonsignificantly different TSH levels in our cohort did not exclude thyroid involvement in RA.

In general, our data also confirm that RA is not only a joint disorder, but also a systemic inflammatory disorder with metabolic and endocrine characteristics [3,4,7]. The relationship between increased leptin, insulin, and cortisol concentrations and decreased GH levels could be due to the interdisciplinary interaction of inflammation, adipose tissue, glucose regulation, stress-axis activation, and pituitary functions [5,7]. This profile

may also be an important factor in explaining cardiometabolic risk in patients with RA [6].

Nevertheless, this study had several limitations. First, the sample size was small, which substantially limited the statistical power and raised the risk of overinterpretation, particularly for RA-only correlation and regression analyses. Therefore, these analyses are considered exploratory and should be confirmed in larger cohorts in the future. Second, fasting glucose was not quantified, and insulin resistance could not be assessed because HOMA-IR is a widely used surrogate marker of insulin resistance, and the lack of these data limits the ability to directly assess insulin resistance and weaken related interpretations. Third, glucocorticoid exposure was recorded as use or non-use without a detailed dose or duration. Fourth, information about the dose and duration of glucocorticoids was unavailable as glucocorticoids may substantially influence cortisol, insulin, leptin, and metabolic parameters, which is one of the major recommendations to be estimated in future studies. Fifth, the adjusted R^2 value (0.96) for the insulin model was unexpectedly high for the biological dataset of this size. A careful recheck of the regression analysis of the underlying data was performed to confirm the accuracy of these findings. The high explanatory power may reflect strong correlations between the selected predictors and outcome variable within this dataset. Nevertheless, the fact that such values are unusually high may raise concerns about potential overfitting. A recommendation elaborated on additional model diagnostics (assessment of residuals, multicollinearity, and model assumptions) and validation procedures are required and explicitly note this limitation in this study, which should be interpreted cautiously and would benefit from validation in larger, independent cohorts. Sixth, the present study lacked the potential confounding effects of adiposity. BMI differed between patients with RA and controls, and leptin, in particular, was strongly determined by fat mass. Therefore, part of the observed increase in leptin and potentially other metabolic hormones may reflect differences in body composition rather than RA-specific endocrine alterations. Although BMI was included in the exploratory adjusted analyses, a comprehensive multivariable adjustment for adiposity was not performed for all hormones. Nevertheless, leptin has recognized immunomodulatory functions, and previous studies have reported elevated leptin levels in RA independently, suggesting that both metabolic and inflammatory pathways may contribute. Future studies using more precise measures of body composition (e.g., fat mass or adiposity) and multivariable adjustment are required to disentangle the independent effects of RA-related inflammation and adiposity on endocrine-metabolic

profiles. Finally, the cross-sectional design does not allow conclusions to be drawn about cause and effect.

5. Conclusions

In conclusion, women with RA in this cohort showed differences in selected serum hormones compared to controls, characterized by higher leptin, insulin, and cortisol levels and lower GH levels. Estradiol and TSH levels were not significantly different between patients with RA and the controls. These findings suggest that endocrine metabolic changes may accompany systemic inflammation in patients with RA. Future studies should include RA-specific endocrine-metabolic phenotypes, larger cohorts, fasting glucose, HOMA-IR, standardized disease activity scores, and detailed glucocorticoid exposure to clarify the clinical significance of these hormonal changes.

Declarations

Author Contributions

Conceptualization: D.F.A.; Methodology: D.F.A.; Formal analysis: D.F.A.; Investigation: D.F.A.; Writing – original draft: D.F.A.; Writing – review & editing: D.F.A.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the College of Health and Medical Technology, Southern Technical University (no. 103 in 30/08/2022).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available upon reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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