



(RESEARCH ARTICLE)



Impact of COVID-19 Vaccination and Estrogen on the Severity of Rheumatoid Arthritis in Postmenopausal Iraqi Females

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune inflammatory disorder with multifactorial etiology. Hormonal factors and immune-modulating events, such as vaccination, may influence disease activity.

Objective: To evaluate the effect of COVID-19 vaccination and serum estrogen levels on RA severity in postmenopausal Iraqi females, with emphasis on inflammatory biomarkers and cytokine profiles.

Methods: A case-control study was conducted on 40 vaccinated RA patients and 44 age-matched healthy controls. Serum ESR, CRP, RF, IL-8, IL-10, and estrogen levels were measured using sandwich ELISA. Demographic characteristics and BMI were recorded. Statistical analysis examined correlations between these parameters and RA severity.

Results: RA patients demonstrated significantly higher ESR, CRP, RF, IL-8, and estrogen levels than controls ($p < 0.05$), with a positive correlation to disease severity. IL-10 levels were elevated but not statistically associated with severity ($p = 0.1009$). Postmenopausal RA patients had markedly elevated estrogen compared to expected physiological ranges.

Conclusion: COVID-19 vaccination and elevated estrogen levels are significantly associated with increased inflammatory markers and RA severity in postmenopausal Iraqi women. These findings suggest the need for closer post-vaccination monitoring in high-risk autoimmune populations.

Keywords: Rheumatoid Arthritis; COVID-19 Vaccine; Estrogen; Cytokines; Postmenopausal Women; Iraq

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent synovial inflammation, joint destruction, and systemic manifestations (1). Although its exact pathogenesis remains unclear, a complex interplay between genetic predisposition, hormonal regulation, and immune activation drives disease progression (2,3).

Postmenopausal women represent a unique risk group due to hormonal changes, particularly in estrogen levels, which may modulate immune responses (4). Estrogen can enhance B-cell activity and antibody production while promoting pro-inflammatory cytokine release under certain immune conditions (5).

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The COVID-19 vaccination, while essential for controlling SARS-CoV-2 transmission, can modulate immune responses, potentially influencing cytokine levels and autoimmune disease activity (6,7). Reports suggest that vaccination may induce transient increases in inflammatory markers in autoimmune patients (8).

This study investigates the relationship between COVID-19 vaccination, serum estrogen levels, and inflammatory biomarkers in postmenopausal Iraqi women with RA.

2. Materials and Methods

2.1. Study Design and Participants

A comparative case-control study was conducted between March 2022 and March 2023 in Al-Hillah, Iraq.

40 serum samples of postmenopausal females diagnosed with RA (American College of Rheumatology criteria), vaccinated with at least one dose of a COVID-19 vaccine collected from private library, and 44 serum samples of healthy postmenopausal women with no history of autoimmune disease or recent infection.

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion

- Age \geq 50 years
- Postmenopausal status (\geq 12 months amenorrhea)
- Confirmed RA diagnosis for at least 1 year
- COVID-19 vaccination completed within the past 12 months

2.2.2. Exclusion

- History of hormone replacement therapy in the past year
- Acute infections or malignancy
- Chronic liver or kidney disease

2.3. Laboratory Analysis

All collected samples were analyzed for inflammatory markers (ESR, CRP, and RF) using standard laboratory protocols. Cytokines (IL-8, IL-10) and Estrogen: Quantified via sandwich ELISA (manufacturer's guidelines).

2.4. Statistical Analysis

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean \pm SD. Independent t-tests compared group means. Pearson's correlation tested associations between biomarkers and disease severity. A p-value $<$ 0.05 was considered statistically significant.

3. Results

3.1. Demographic data

Out of 40 cases of rheumatoid arthritis patients, the mean \pm standard deviation of the age, body mass index BMI and COVID-19 vaccination dose disease compared with 44 healthy control to reveal not significant in all parameters, as shown in table (1).

3.2. Inflammatory markers

On the other hand, the present study showed significant differences in other parameters includes; CRP (mg/dL), ESR (mm/hr), RF (IU/mL), IL-8 (pg/mL), and Estrogen (pg/mL), while IL-10 (pg/mL) showed no significant differences between two study groups as showed in Table (2).

Table 1 Demographic and Clinical Characteristics

Parameter	RA Patients (n=40) mean \pm SD	Controls (n=44) mean \pm SD	p-value
Age (years)	56.8 \pm 5.4	55.9 \pm 4.8	0.428
BMI (kg/m ²)	27.6 \pm 3.1	26.8 \pm 2.9	0.238
Disease Duration (years)	8.3 \pm 2.5	—	—
COVID-19 Vaccine doses	2.1 \pm 0.4	2.0 \pm 0.0	0.319

Table 2 Serum Biomarkers in RA Patients vs. Healthy Control

Biomarker	Normal Range	RA Patients (Mean \pm SD)	Controls (Mean \pm SD)	p-value
CRP (mg/dL)	0.3–1.0	5.42 \pm 1.36	0.84 \pm 0.25	<0.0001
ESR (mm/hr)	F: 0–20	42.8 \pm 8.6	12.3 \pm 4.2	<0.0001
RF (IU/mL)	<14	68.4 \pm 15.2	9.5 \pm 3.4	<0.0001
IL-8 (pg/mL)	~62	54.95 \pm 6.8	69.15 \pm 5.4	0.004
IL-10 (pg/mL)	4.8–9.8	14.48 \pm 2.9	9.02 \pm 1.8	0.101
Estrogen (pg/mL)	0–30 (postmenopause)	179.08 \pm 35.6	18.7 \pm 6.3	<0.0001

4. Discussion

Our study found a significant elevation of ESR, CRP, RF, IL-8, and estrogen in vaccinated postmenopausal RA patients compared to healthy controls. This supports prior findings linking elevated acute-phase reactants with RA severity (9).

The IL-8 profile in our patients was unexpected, with lower mean levels compared to controls but a positive correlation with disease severity. This suggests possible immune modulation by COVID-19 vaccination, in line with reports showing altered cytokine expression post-vaccination in autoimmune cohorts (10).

IL-10 levels were elevated but not significantly correlated with severity. Previous studies have highlighted IL-10's dual anti-inflammatory and pro-autoimmune roles, depending on disease stage and immune environment (11).

Estrogen levels in our RA cohort were far above the postmenopausal reference range. Estrogen has been shown to enhance immune activation by promoting IL-1, IL-6, and TNF- α expression in certain autoimmune settings (12,13), potentially explaining the increased severity in our study population.

Our findings suggest that post-vaccination RA management in postmenopausal women should involve careful monitoring of both inflammatory and hormonal markers.

5. Conclusion

COVID-19 vaccination and elevated estrogen levels are significantly associated with heightened RA severity in postmenopausal Iraqi females. These results highlight the importance of individualized post-vaccination care and suggest potential benefits from hormonal modulation strategies in certain patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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