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# BIOCHEMICAL EVALUATION OF PROINFLAMMATORY MARKER UPREGULATION AND ITS ROLE IN THE PATHOGENESIS AND DIAGNOSTIC BIOMARKERS OF RHEUMATOID ARTHRITIS

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**Abstract**

Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily affecting joints, leading to significant inflammation, joint destruction, and functional impairment. The pathogenesis of RA is characterized by immune system dysregulation, causing an overproduction of proinflammatory cytokines, chemokines, and reactive oxygen species (ROS), which contribute to tissue damage. This study aims to evaluate the biochemical changes, specifically the upregulation of proinflammatory markers, and their role in the disease's pathogenesis and diagnostic biomarkers. The study included 50 patients with RA and 50 healthy controls, all recruited from the Department of Orthopedics at Allama Iqbal Medical College in Lahore, Pakistan. Biochemical analysis was conducted to evaluate various oxidative and inflammatory markers, including malondialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH), catalase, nitric oxide (NO), and antioxidant vitamins (C, E, and A). The results revealed significantly elevated levels of MDA (5.47±1.22 in RA patients vs. 0.86±0.0392 in controls, p=0.014), NO (32.16±6.58 in RA vs. 17.85±3.58 in controls, p=0.001), and a significant decrease in key antioxidants: SOD (0.112±0.0018 in RA vs. 1.034±0.056 in controls, p=0.025), GSH (4.43±1.28 in RA vs. 7.26±1.99 in controls, p=0.011), catalase (3.47±1.088 in RA vs. 5.23±1.45 in controls, p=0.004), and vitamins C (1.28±0.956 in RA vs. 3.48±0.956 in controls, p=0.018), E (6.35±1.44 in RA vs. 10.49±4.29 in controls, p=0.031), and A (254.98±21.58 in RA vs. 452.35±19.65 in controls, p=0.016). These findings underscore the critical role of oxidative stress and

proinflammatory cytokines in RA's progression. The results suggest that assessing these biomarkers could offer valuable insights for early detection, monitoring disease progression, and developing more effective treatments for RA.

**Keywords:** Rheumatoid Arthritis, Proinflammatory Markers, Oxidative Stress, Antioxidants, Diagnostic Biomarkers.

## Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease primarily affecting the joints, leading to inflammation, pain, and long-term joint damage. RA is characterized by the immune system's misguided attack on its own tissues, particularly the synovial membrane, which lines the joints (Jahid *et al*., 2023). This results in inflammation, synovial hyperplasia, cartilage damage, and ultimately bone erosion. Unlike other forms of arthritis, such as osteoarthritis, which is due to wear and tear on the joints, RA is an autoimmune disorder, meaning it is driven by the body's own immune cells (Butola *et al*., 2020). The pathogenesis of RA involves a complex interaction between genetic, environmental, and immunological factors, where an initial trigger leads to the production of autoantibodies and cytokines that perpetuate inflammation and tissue destruction (Alivernini *et al*., 2022).

The primary hallmark of RA is the overproduction of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukins (IL)-6 and IL-21, and the activation of immune cells such as T-cells and macrophages (Ding *et al*., 2023). These inflammatory mediators promote the recruitment of more immune cells to the joints, exacerbating the inflammatory process (Weyand & Goronzy, 2021). The continuous release of these proinflammatory factors leads to damage of the synovial lining, cartilage, and bone, resulting in the hallmark symptoms of RA—pain, swelling, stiffness, and ultimately joint deformities. These systemic effects may also extend beyond the joints, affecting other tissues such as the skin, eyes, lungs, and heart, further complicating the disease (Battancs, 2021).

In addition to inflammatory cytokines, oxidative stress plays a critical role in RA. The balance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses is disrupted in RA, leading to increased oxidative damage in the joints (Zamudio-Cuevas *et al*., 2022). Oxidative stress is not only involved in joint destruction but also contributes to the systemic manifestations of the disease, influencing the pathophysiology of RA. Increased levels of markers such as malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH) have been reported in RA patients, indicating a heightened state of oxidative stress (Ponist *et al*., 2019). Understanding the biochemical alterations, especially the role of proinflammatory cytokines and antioxidants, is crucial for developing effective early diagnostic biomarkers and therapeutic strategies for RA (Islam *et al*., 2023).

Despite advancements in treatment, RA remains a major cause of disability worldwide, with no definitive cure. The ongoing challenge lies in the early detection of the disease and preventing joint damage. Identifying proinflammatory markers and understanding their role in RA's progression will contribute significantly to the development of more precise diagnostic tools and targeted therapies (Riaz *et al*., 2025). This study aims to assess the biochemical changes in RA, focusing on proinflammatory markers, and their potential as diagnostic biomarkers for early detection of the disease.

## Methodology

The study involved 50 patients with RA, aged 35 to 45 years, diagnosed based on the American College of Rheumatology's criteria, along with 50 healthy controls matched for age and gender, all recruited from the Department of Orthopedics at Allama Iqbal Medical College in Lahore, Pakistan. All control subjects were free from autoimmune diseases, metabolic disorders, and chronic medication. Blood samples were collected from both groups through antecubital venipuncture. A total of 5 milliliters of venous blood was drawn from each participant, allowed to coagulate, and the serum

was separated by centrifugation at 3,000 rpm for 10 minutes. The serum samples were then stored at -70°C until further analysis. Biochemical analyses were conducted to assess various proinflammatory and antioxidative markers. MDA, a marker of oxidative stress, was quantified using the thiobarbituric acid reactive substances (TBARS) assay, where MDA reacts with thiobarbituric acid to form a colored product measured at 532 nm. SOD activity, which indicates antioxidant defense, was measured by its ability to inhibit the reduction of nitroblue tetrazolium (NBT) in the presence of xanthine oxidase, with absorbance recorded at 550 nm. GSH, an important antioxidant, was assessed using the 5,5'-Dithiobis(2-nitrobenzoic acid) (DTNB) reagent, measuring absorbance at 412 nm. Catalase activity, another key antioxidant enzyme, was determined by measuring the decomposition of hydrogen peroxide at 240 nm. Nitric oxide (NO) levels, indicative of inflammation, were measured using the Griess reagent, and absorbance was recorded at 540 nm. Additionally, antioxidant vitamins C, E, and A were quantified using spectrophotometric methods, with vitamin C measured using the 2,4-dinitrophenylhydrazine (DNPH) method and vitamins E and A assessed by solvent extraction and UV-Vis spectrophotometry. The data were analyzed using SPSS version 5.0. Descriptive statistics were calculated, and comparisons between RA patients and controls were made using the Student's t-test. Correlation analysis was performed to examine the relationships between oxidative stress markers and antioxidants. A *p-value* of less than 0.05 was considered statistically significant.

## Results

The study included 50 patients with RA and 50 healthy controls. The demographic characteristics of both groups were similar in terms of age and gender (Table 1). The mean age of RA patients was 40.2 ± 4.5 years, and the mean age of the healthy controls was 39.6 ± 5.2 years. Both groups consisted of 50% males and 50% females, ensuring a balanced representation of gender. None of the control subjects had autoimmune diseases, metabolic disorders, or were on chronic medication.

**Table 1: Demographic variables of participants**

| Variable | RA Patients (n=50) | Healthy Controls (n=50) |
|---|---|---|
| **Mean Age (Years)** | 40.2 ± 4.5 | 39.6 ± 5.2 |
| **Gender Distribution** | 50% Male, 50% Female | 50% Male, 50% Female |
| **Autoimmune Diseases** | Present in RA patients only | None |
| **Metabolic Disorders** | Present in RA patients only | None |
| **Chronic Medication** | Some RA patients on medication | None |

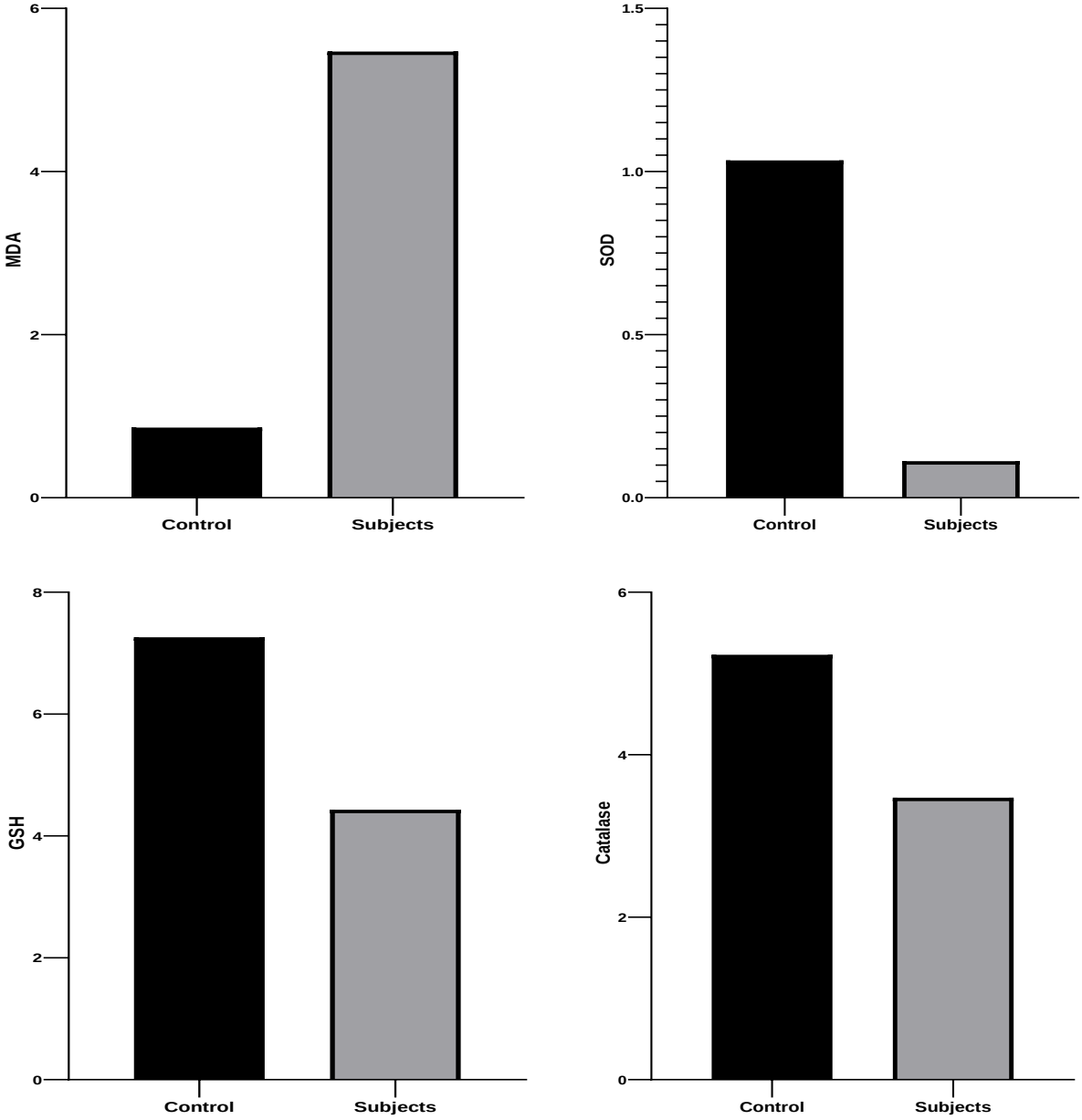
The biochemical analysis revealed significant differences in the levels of oxidative stress markers and antioxidants between RA patients and healthy controls, highlighting the presence of oxidative stress and inflammation in RA. In table 2, MDA a marker of lipid peroxidation and oxidative stress, was significantly elevated in RA patients, with a mean level of 5.47 ± 1.22 compared to 0.86 ± 0.0392 in the control group, showing a *p-value* of 0.014, reflecting heightened oxidative stress that contributes to joint and tissue damage in RA. SOD, a key antioxidant enzyme, was significantly reduced in RA patients, with the control group exhibiting a mean level of 1.034 ± 0.056, while RA patients had only 0.112 ± 0.0018 (*p-value* of 0.025), indicating impaired antioxidant defense. Similarly, GSH another important antioxidant, was significantly lower in RA patients (4.43 ± 1.28) compared to the control group (7.26 ± 1.99) with a *p-value* of 0.011, suggesting an impaired antioxidant response in RA. Catalase, an enzyme responsible for breaking down hydrogen peroxide, was also significantly reduced in RA patients, with a mean level of 3.47 ± 1.088 compared to 5.23 ± 1.45 in the control group (*p-value* 0.004), further emphasizing a compromised ability to neutralize oxidative stress. NO a known proinflammatory mediator, was significantly elevated in RA patients, with a mean of 32.16 ± 6.58 compared to 17.85 ± 3.58 in controls (*p-value* 0.001), reflecting enhanced inflammation in RA. Vitamin E, a potent antioxidant, was significantly lower in RA patients (6.35 ± 1.44) compared to controls (10.49 ± 4.29) with a *p-value* of 0.031, suggesting compromised protection against oxidative damage. Vitamin C was also significantly decreased in RA patients (1.28 ± 0.956) compared

to the control group (3.48 ± 0.956) with a *p-value* of 0.018, contributing to the imbalance between oxidants and antioxidants in RA. Lastly, Vitamin A levels were significantly lower in RA patients (254.98 ± 21.58) compared to the control group (452.35 ± 19.65) with a *p-value* of 0.016, further indicating oxidative stress and compromised cellular protection in RA.

**Table 2: Inflammatory and antioxidative profile of different variables in patients suffering from Rheumatoid arthritis.**

| Variables | Control (n=50) | Subjects (n=50) | *p-value* |
|---|---|---|---|
| **MDA** | 0.86±0.0392 | 5.47±1.22 | 0.014** |
| **SOD** | 1.034±0.056 | 0.112±0.0018 | 0.025* |
| **GSH** | 7.26±1.99 | 4.43±1.28 | 0.011*** |
| **Catalase** | 5.23±1.45 | 3.47±1.088 | 0.004* |
| **NO** | 17.85±3.58 | 32.16±6.58 | 0.001** |
| **Vit-E** | 10.49±4.29 | 6.35±1.44 | 0.031** |
| **Vit-C** | 3.48±0.956 | 1.28±0.956 | 0.018** |
| **Vit-A** | 452.35±19.65 | 254.98±21.58 | 0.016* |

***Shows *p-values* that are less than 0.05 i-e significant**



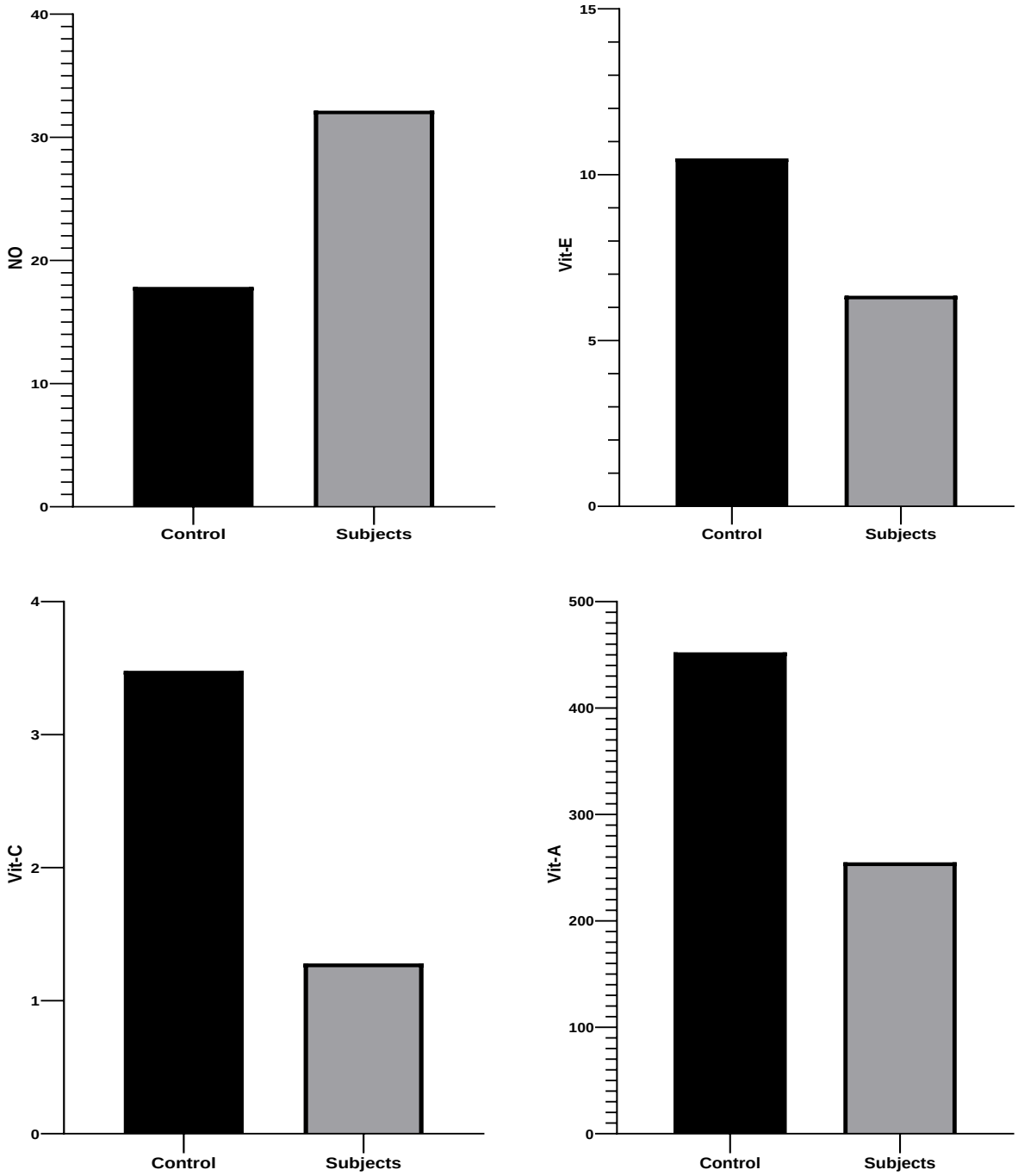



**Figure 1: Comparison of biochemical markers between control and RA patients.**

The figure displays the levels of MDA, SOD, GSH, catalase activity, NO, and antioxidant vitamins (E, C, and A) in both control and RA groups. Red bars represent RA patients, while blue bars represent the control group. Significant differences in the levels of these markers indicate increased oxidative stress and decreased antioxidant defenses in RA patients.

Table 3 presents the correlation coefficients between various oxidants and antioxidants in patients with RA. The significant positive relationship between MDA, a marker of oxidative stress, and several antioxidants, such as SOD, GSH, catalase, and vitamins E, C, and A. Specifically, MDA shows the strongest correlation with NO (0.547), indicating that as oxidative stress increases, so does NO production, a proinflammatory marker. Additionally, SOD exhibits moderate correlations with GSH, CAT, and the antioxidant vitamins, suggesting a cooperative antioxidant response in RA. Notably, NO is strongly associated with vitamins E (0.255) and C (0.457), indicating their protective roles against oxidative damage. These correlations reflect the intricate balance between oxidative stress

and antioxidant defenses in RA patients, where increased oxidative stress is often accompanied by enhanced antioxidant responses, though an imbalance may contribute to the disease's progression.

**Table 3: Correlation coefficients matrix of oxidants and antioxidants in patients suffering from Rheumatoid arthritis.**

| VAR. | MDA | SOD | GSH | CAT | NO | V-E | V-C | V-A |
|---|---|---|---|---|---|---|---|---|
| **MDA** | - | 0.533 | 0.424 | 0.354 | 0.547 | 0.467 | 0.355 | 0.013 |
| **SOD** | | - | 0.158 | 0.341 | 0.257 | 0.321 | 0.257 | 0.325 |
| **GSH** | | | - | 0.284 | 0.341 | 0.156 | 0.341 | 0.124 |
| **CAT** | | | | - | 0.359 | 0.011 | 0.260 | 0.145 |
| **NO** | | | | | - | 0.255 | 0.457 | 0.263 |
| **Vit-E** | | | | | | - | 0.244 | 0.153 |
| **Vit-C** | | | | | | | - | 0.264 |
| **Vit-A** | | | | | | | | - |

## Discussion

RA is a chronic, systemic autoimmune disease primarily affecting the joints, resulting in inflammation, pain, stiffness, and, if untreated, joint destruction. Unlike osteoarthritis, which arises from mechanical wear and tear, RA occurs when the body's immune system mistakenly attacks its own tissues, particularly the synovium—the lining of the joints. The exact cause of RA remains uncertain, but it is believed to be due to a combination of genetic, environmental, and immunological factors. RA is more prevalent in women, particularly between the ages of 30 and 50, and its clinical presentation can vary, but it typically involves joint pain, stiffness (often worse in the mornings), edema, and redness. Early diagnosis and treatment are critical to managing the disease, preventing irreversible joint damage, and improving patients' quality of life. Treatments generally include disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and sometimes biologic therapies. However, despite these therapeutic advancements, there is no definitive cure, and ongoing research aims to improve early diagnosis, disease monitoring, and therapeutic options.

Past studies have investigated the role of rheumatoid factor (RF) and other inflammatory markers in RA. The Mini-Finland Health Survey, for instance, highlighted the correlation between elevated RF levels and the onset of seropositive RA, confirming RF as an important marker for diagnosis and prognosis in RA (Ingegnoli *et al*., 2022). The present study sought to investigate the relationship between oxidative stress markers and antioxidants in RA patients, given that oxidative stress plays a crucial role in the pathogenesis of the disease. The study found significant alterations in both proinflammatory and antioxidative markers in RA patients, confirming previous research that oxidative stress is a critical component in RA pathology.

The current study's findings regarding MDA levels align with previous studies linking increased oxidative stress to RA. The observed MDA levels in RA patients (5.47 ± 1.22) were significantly higher than in controls (0.86 ± 0.0392), with a *p-value* of 0.014. This finding corroborates studies such as those by Pourhabibi-Zarandi *et al*. (2024), who reported higher MDA levels in RA patients, suggesting that lipid peroxidation plays a crucial role in the inflammatory process of RA (Pourhabibi-Zarandi *et al*., 2024). Elevated MDA reflects increased oxidative stress, which exacerbates joint inflammation and cartilage damage, further supporting the idea that oxidative damage contributes significantly to RA pathology.

SOD, a critical antioxidant enzyme, was found to be significantly reduced in RA patients (0.112 ± 0.0018 vs. 1.034 ± 0.056 in controls, p = 0.025), consistent with findings from Zhao *et al*. (2018), who reported decreased SOD activity in RA patients, suggesting that the body's capacity to combat ROS is compromised. This reduction in SOD activity indicates an impaired antioxidant defense, which leaves the joints and tissues more vulnerable to oxidative damage. The present study also found a significant decrease in GSH levels (4.43 ± 1.28 in RA vs. 7.26 ± 1.99 in controls, p = 0.011),

reinforcing the results of Ling *et al*. (2022), who found that GSH levels were significantly lower in RA patients (Ling *et al*., 2022). As an essential antioxidant involved in detoxifying free radicals and ROS, reduced GSH levels further support the oxidative stress observed in RA.

The catalase enzyme, which neutralizes hydrogen peroxide (H2O2), was significantly lower in RA patients (3.47 ± 1.088 in RA vs. 5.23 ± 1.45 in controls, p = 0.004). This finding is consistent with previous studies such as Kumar *et al*. (2016), which demonstrated decreased catalase activity in RA patients, implicating catalase's role in reducing oxidative stress (Kumar *et al*., 2016). The significant decrease in CAT activity suggests that RA patients have a reduced ability to neutralize ROS, further contributing to inflammation and tissue damage.

The present study also found elevated NO levels in RA patients (32.16 ± 6.58 in RA vs. 17.85 ± 3.58 in controls, p = 0.001), corroborating findings from Maiuolo *et al*. (2021), who showed that NO is elevated in RA and plays a central role in the inflammatory process (Maiuolo *et al*., 2021). As a signaling molecule, NO is involved in vasodilation and immune modulation, and its upregulation in RA contributes to the systemic inflammation and joint destruction characteristic of the disease.

The decreased levels of vitamins E, C, and A in RA patients observed in this study (*p-value*s of 0.031, 0.018, and 0.016, respectively) align with previous research, including Bilski and Nuszkiewicz (2019), who found that RA patients have significantly lower antioxidant vitamin levels, further exacerbating oxidative stress (Bilski & Nuszkiewicz, 2025). The reduction in these antioxidants weakens the body's ability to mitigate oxidative damage, thereby accelerating the progression of RA. The present findings are in line with Kondo *et al*. (2023), who noted that antioxidant vitamins, such as E and C, are significantly depleted in RA patients, suggesting a disrupted antioxidant defense system (Bilski & Nuszkiewicz, 2025; Kondo *et al*., 2023).

The correlation analysis in this study also revealed significant positive associations between MDA and several antioxidant variables, including SOD, GSH, CAT, NO, and vitamins E, C, and A. These correlations are consistent with those found by Turrubiates-Hernandez *et al*. (2020), who demonstrated a complex interplay between oxidative stress markers and antioxidants in RA patients (Turrubiates-Hernández *et al*., 2020). The positive correlation between MDA and NO (0.547) highlights the interdependence between oxidative stress and inflammation, while the correlations with antioxidants such as SOD and GSH underscore the compensatory response to oxidative damage.

## Conclusion

Increased oxidative stress plays a pivotal role in the pathophysiology of RA, contributing to the development of joint pain, chronic inflammation, and joint degeneration. The heightened production of reactive oxygen species, coupled with a disruption in the body’s antioxidant defenses, leads to persistent pain and tissue damage. This study highlights the significant role of oxidative stress in RA, with elevated levels of MDA and NO, alongside reduced antioxidant defenses (SOD, GSH, catalase, and vitamins C, E, and A). The findings show a strong correlation between oxidative stress markers and inflammatory responses, underlining their critical involvement in RA's development. The results suggest that oxidative stress markers could serve as valuable diagnostic tools for early RA detection and disease monitoring. Future research should focus on exploring antioxidant therapies as adjunctive treatments to restore the balance between oxidants and antioxidants, aiming to improve patient outcomes and quality of life.

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