International Journal of Medical Toxicology & Legal Medicine Volume 27, No. 3S, 2024
e-ISSN: 0974-4614
p-ISSN: 0972-0448

Investigating the Role of Oxidative Stress and Immune Response in Rheumatoid Arthritis

Sawsan Salman Hosi[1], Zainab Samir Yahya Hammo[2], Yaseen Khashman Hussein[3], Zaid Mohammed Mubarak Almahdawi[4]

[1]Department of Biochemistry, College of Medicine, University of Tikrit, Iraq, Email: sawsan.salman@tu.edu.iq
[2]Department of Physiology, College of Medicine, University of Tikrit, Iraq, Email: zainab.samir@tu.edu.iq
[3]Department of Physiology, College of Medicine, University of Tikrit, Iraq, Email: dr.yaseen_ykh@tu.edu.iq
[4]Alimam university college, Iraq, Email: dr_zaid@alimamunc.edu.iq

Received: 15.09.2024 Revised: 13.10.2024 Accepted: 10.11.2024

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune sickness characterized with the aid of persistent joint infection, leading to joint damage and useful impairment. The pathogenesis of RA is thought to be encouraged with the aid of each genetic and environmental elements, with immune device dysregulation playing a valuable role in ailment progression. Increasing proof shows that oxidative pressure, which results from an imbalance between reactive oxygen species (ROS) and antioxidant defenses, contributes to the inflammatory techniques and tissue harm seen in RA.

Objectives: This take a look at aimed to investigate the relationship among oxidative pressure and immune machine dysregulation inside the pathogenesis and progression of rheumatoid arthritis (RA).

Methodology: This look at turned into conducted from 1st April to 30 November 2024 and protected a total of 200 participants were covered inside the examiner, along with 150 RA patients (75 male and 75 female) and 50 wholesome controls (25 male and 25 lady). The individuals' ages ranged from 35 to 75 years. Blood samples were collected from the outpatient clinics at Tikrit Teaching Hospital among April and October 2024, and RA patients have been identified primarily based on medical criteria with the aid of the attending physicians. Oxidative strain markers, along with malondialdehyde (MDA) and glutathione (GSH), and pro-inflammatory cytokines, together with IL-1β, IL-17, and TNF-α, had been measured. Disease interest became assessed the usage of the Disease Activity Score 28 (DAS28).

Results: The effects revealed that each male and female RA patients had extensively higher levels of MDA and decrease GSH tiers compared to the healthy manage institution. Moreover, seasoned-inflammatory cytokines (IL-1β, IL-17, and TNF-α) had been appreciably improved in RA sufferers, indicating a country of chronic infection. The DAS28 ratings confirmed that a majority of the RA patients had moderate to excessive disorder hobby. No good sized gender-based variations have been discovered in oxidative strain markers, cytokine stages, or sickness interest rankings.

Conclusions: Our take a look at highlights the essential interaction among oxidative strain and immune dysregulation in RA. The determined correlations among oxidative markers, pro-inflammatory cytokines, and disease severity underscore the capability for focused on these pathways inside the management of RA. Future studies are warranted to in addition explore the healing ability of antioxidant-primarily based and anti-cytokine treatments in ameliorating RA-associated inflammation and joint damage. Further research is needed to explore the underlying mechanisms and capacity treatments focused on oxidative stress and immune modulation in RA.

Keywords: Rheumatoid Arthritis RA, Oxidative Stress, Cytokines, Disease Activity Score 28 (DAS28), Inflammation, Immune Dysregulation.

INTRODUCTION

Rheumatoid arthritis (RA) is a persistent autoimmune ailment that primarily influences the synovial joints, leading to infection, ache, and eventual joint destruction. Globally, RA influences approximately 1% of the populace and imposes a good sized burden on patients, caregivers, and healthcare systems (Smolen et al., 2016). The disease is characterized by way of chronic synovitis, systemic inflammation, and the presence of autoantibodies, together with rheumatoid issue (RF) and anti-citrullinated protein antibodies (ACPAs). Despite advancements in understanding its pathophysiology and the improvement of centered treatments, the precise mechanisms riding RA stay incompletely understood (Agorastos&Chrousos, 2022; Chmiel, 2024).

Recent evidence highlights the crucial role of oxidative pressure and immune system dysregulation in RA pathogenesis. Oxidative strain occurs whilst there is an imbalance between the manufacturing of reactive oxygen species (ROS) and the body's antioxidant defenses, leading to cellular and molecular harm. ROS are incredibly reactive molecules that could harm lipids, proteins, and DNA, contributing to irritation and autoimmunity. Markers of oxidative strain, which includes malondialdehyde (MDA), are accelerated in RA sufferers and correlate with ailment interest. Simultaneously, degrees of antioxidants, which include glutathione (GSH), are depleted, reflecting an impaired defense mechanism against oxidative harm (Ravi et al., 2021).

Parallel to oxidative strain, immune system dysregulation performs a pivotal role in RA improvement and progression (Smallwood et al., 2018). The immune response in RA is characterised by means of the activation of T cells, B cells, and macrophages, which release seasoned-inflammatory cytokines. Key cytokines, inclusive of interleukin-1β (IL-1β), interleukin-17 (IL-17), and tumor necrosis element-alpha (TNF-α), contribute to the inflammatory milieu, main to synovial hyperplasia, cartilage degradation, and bone erosion. IL-17, in general produced by Th17 cells, has been implicated in amplifying inflammatory cascades and recruiting neutrophils to the synovium, exacerbating tissue harm. Similarly, TNF-α is a grasp regulator of infection in RA and a healing goal for lots biologic remedies (Ilich et al., 2020; Huang et al., 2022).

The interplay between oxidative stress and immune gadget dysregulation is more and more identified as a vital aspect in RA pathogenesis. ROS no longer simplest at once harm tissues but also activate immune cells and sell the manufacturing of pro-inflammatory cytokines, developing a vicious cycle of inflammation and oxidative harm. This dynamic contributes to the chronicity and severity of RA, in addition to systemic manifestations, along with cardiovascular disease, which can be frequently observed in RA patients (Kumar et al., 2016).

Clinically, assessing the connection among oxidative stress, cytokine profiles, and disease activity presents treasured insights into RA pathophysiology (Schwetlik et al., 2022). The Disease Activity Score 28 (DAS28), a typically used clinical device, quantifies sickness severity via incorporating swollen and smooth joint counts, inflammatory markers, and patient-stated consequences. Elevated DAS28 rankings are regularly related to expanded oxidative pressure and cytokine ranges, further underscoring their importance as biomarkers of sickness hobby and potential therapeutic goals (Yin et al., 1999; Komatsu et al., 2022).

Despite the provision of sickness-editing antirheumatic pills (DMARDs) and biologic healing procedures, a full-size proportion of RA sufferers enjoy incomplete remission or treatment resistance. Understanding the jobs of oxidative stress and immune dysregulation may also pave the manner for novel therapeutic procedures that address these underlying mechanisms. Antioxidants, cytokine inhibitors, and aggregate cures concentrated on both oxidative and inflammatory pathways keep promise for improving outcomes in RA (Kuchroo et al., 2012).

In this look at, we aim to discover the connection between oxidative strain and immune system dysregulation in RA patients. By comparing oxidative pressure markers and pro-inflammatory cytokines in RA patients and healthy controls, and correlating those findings with DAS28 ratings, we are seeking to clarify their contributions to RA pathogenesis and progression.

METHODOLOGY

This observe was conducted from 1st April to 30th November 2024 and included a total of 2 hundred participants, with a long time starting from 35 to 75 years. The pattern consisted of 75 male and seventy five girl patients recognized with rheumatoid arthritis (RA), in conjunction with 50 healthful controls (25 male and 25 woman), matched by using age and gender. The members were recruited from outpatient clinics at Tikrit Teaching Hospital, and the analysis of RA turned into confirmed by means of qualified physicians primarily based at the American College of Rheumatology (ACR) standards. The control group consisted of folks who were free from autoimmune or persistent inflammatory illnesses, with out a known records of RA or associated situations.

Blood samples have been accumulated from all contributors after obtaining knowledgeable consent. The individuals were instructed to fast in a single day previous to blood collection. Venous blood samples (about 5 mL) had been drawn and right now processed for in addition evaluation. Oxidative stress markers, including malondialdehyde (MDA) and glutathione (GSH), were measured using spectrophotometric techniques. Serum concentrations of pro-inflammatory cytokines, specially interleukin-1β (IL-1β), interleukin-17 (IL-17), and tumor necrosis component-alpha (TNF-α), were quantified using enzyme-related immunosorbent assays (ELISA). Disease interest in RA sufferers became assessed using the Disease Activity Score 28 (DAS28), which includes tender and swollen joint counts, erythrocyte sedimentation charge (ESR), and affected person-suggested consequences.

Statistical Analysis

The statistics were analyzed the usage of SPSS model 22 (Statistical Package for the Social Sciences). Descriptive information, such as mean, widespread deviation (SD), and frequency distributions, were used to summarize the demographic and medical traits of the members.

To compare oxidative stress markers (MDA and GSH) and cytokine tiers (IL-1β, IL-17, TNF-α) between rheumatoid arthritis (RA) patients and healthful controls, impartial t-exams have been performed. The significance level was set at $p < 0.05$ for all statistical checks.

Pearson's correlation coefficient became used to evaluate the connection between oxidative stress markers, cytokine levels, and the Disease Activity Score 28 (DAS28) in RA patients. Correlation values of $p < 0.01$ were considered statistically good sized. Additionally, the Shapiro-Wilk test became completed to assess the normality of the statistics distribution. The degree of statistical significance for all analyses changed into set at $p < 0.05$.

RESULTS

The total number of participants in the study was 200, with 150 patients diagnosed with rheumatoid arthritis (RA) and 50 healthy controls. The gender distribution was balanced, with 50% male and 50% female participants in both the RA and control groups. The age distribution was similar between the RA and control groups, with no significant difference in mean age ($p = 0.712$) (Table1). The following tables summarize the demographic characteristics, Disease Activity Score 28 (DAS28) scores, and other key parameters by gender and group.

Table 1: Demographic Characteristics

Parameter	RA Group (n=150)	Control Group (n=50)	p-value
Total Participants	150 (75%)	50 (25%)	1.000
Male (%)	75 (50%)	25 (50%)	1.000
Female (%)	75 (50%)	25 (50%)	1.000
Mean Age (years)	55.4 ± 9.8	54.8 ± 10.1	0.712

The DAS28 scores for RA patients were used to classify the disease activity into four categories. Among male RA patients, 10% were in remission (DAS28 < 2.6), 16% had low disease activity (DAS28 2.6–3.2), 40% had moderate disease activity (DAS28 3.3–5.1), and 33% had high disease activity (DAS28 > 5.1). Among female RA patients, 9% were in remission, 17% had low disease activity, 43% had moderate disease activity, and 31% had high disease activity. There was no significant difference in DAS28 scores between male and female RA patients ($p = 0.423$) (Table2).

Table 2: Disease Activity Score 28 (DAS28) in RA Patients

DAS28 Category	Male RA Patients (n=75)	Female RA Patients (n=75)	Total RA Patients (n=150)	p-value
Remission (DAS28 < 2.6)	8 (10%)	7 (9%)	15 (10%)	0.423
Low Disease Activity (DAS28 2.6–3.2)	12 (16%)	13 (17%)	25 (17%)	
Moderate Disease Activity (DAS28 3.3–5.1)	30 (40%)	32 (43%)	62 (41%)	
High Disease Activity (DAS28 > 5.1)	25 (33%)	23 (31%)	48 (32%)	
Mean DAS28	5.1 ± 1.2	5.3 ± 1.4	5.2 ± 1.3	

Both male and female RA patients exhibited significantly higher levels of malondialdehyde (MDA), a marker of oxidative stress, compared to the control group. The MDA level in male RA patients was 8.4 ± 1.6 µmol/L and in female RA patients was 7.2 ± 1.4 µmol/L, both significantly higher than the control group's 3.1 ± 0.7, 3.3 ± 0.4 µmol/L respectively ($p< 0.001$). Similarly, both male and female RA patients had significantly lower glutathione (GSH) levels (1.3 ± 0.5 µmol/L for males and 1.1 ± 0.4 µmol/L for females) compared to the controls male and female respectively (3.9 ± 0.6 and 3.3 ± 0.4 µmol/L) ($p< 0.001$) (Table3, Figure 1).

Table 3: Oxidative Stress Markers

Parameter	Male RA (75)	Control Male (25)	Female RA (75)	Control Female (25)	p-value
MDA (µmol/L)	8.4 ± 1.6	3.5 ± 0.9	7.2 ± 1.4	3.1 ± 0.7	< 0.001
GSH (µmol/L)	1.3 ± 0.5	3.9 ± 0.6	1.1 ± 0.4	3.3 ± 0.4	< 0.001

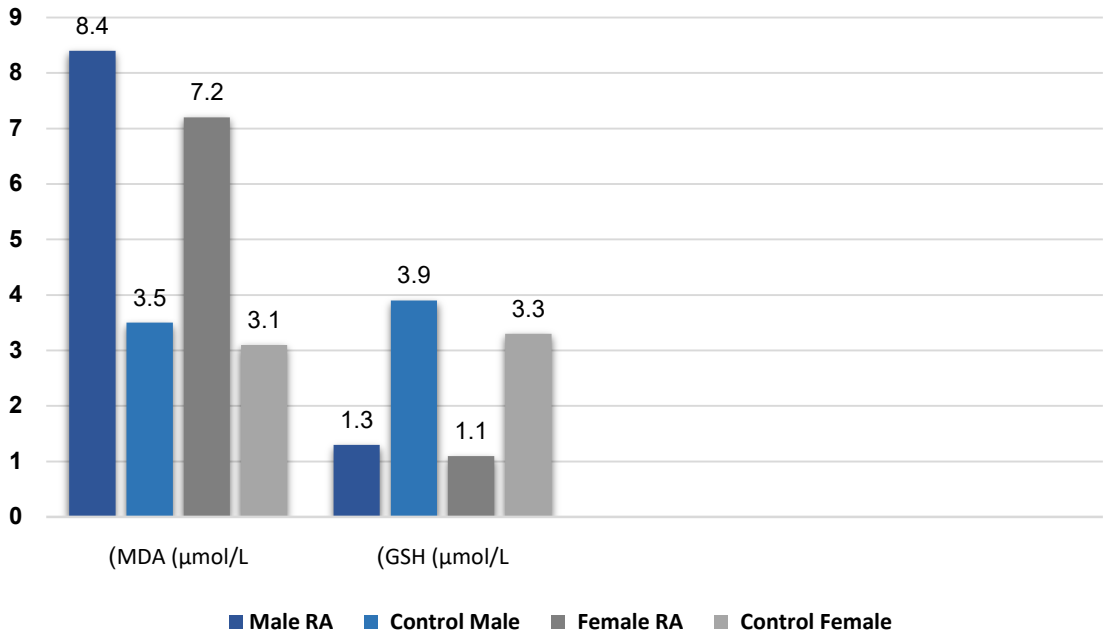

Figure 1: Levels of Oxidative Stress Markers

Pro-inflammatory cytokine levels were significantly higher in both male and female RA patients compared to controls. The serum levels of IL-1β, IL-17, and TNF-α were markedly elevated in the RA group, with IL-1β levels of 43.5 ± 5.6 pg/mL in male RA patients and 40.9 ± 5.0 pg/mL in female RA patients. The control group had much lower IL-1β levels (14.5±4.3 and 12.3 ± 4.1 pg/mL) (p< 0.001). Similarly, IL-17 and TNF-α levels were also higher in both male and female RA patients than in controls, with IL-17 levels of 36.0 ± 5.1 pg/mL for males and 34.9 ± 4.3 pg/mL for females, and TNF-α levels of 70.5 ± 7.3 pg/mL for males and 65.8 ± 6.0 pg/mL for females. These results indicate a significant association between elevated cytokine levels and rheumatoid arthritis activity (Table4, Figure 2).

Table 4: Cytokine Levels

Parameter	Male RA (75)	Control Male (25)	Female RA (75)	Control Female (25)	p-value
IL-1β (pg/mL)	43.5 ± 5.6	14.5±4.3	40.9 ± 5.0	12.3 ± 4.1	< 0.001
IL-17 (pg/mL)	36.0 ± 5.1	11.4±3.6	34.9 ± 4.3	10.2 ± 3.4	< 0.001
TNF-α (pg/mL)	70.5 ± 7.3	16.2±5.8	65.8 ± 6.0	15.5 ± 5.3	< 0.001

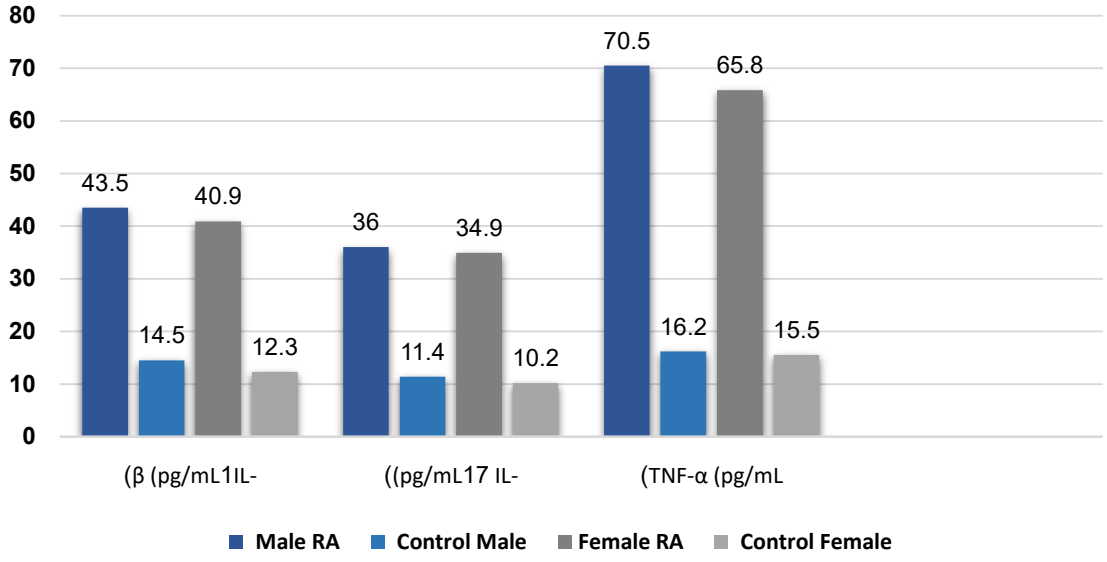

Figure 2: Levels of Cytokine

The correlation analysis revealed several significant associations between oxidative stress markers, pro-inflammatory cytokines, and DAS28 scores in RA patients:

MDA and Oxidative Stress: A strong positive correlation was found between MDA and DAS28 ($r = 0.56$, $p < 0.01$), suggesting that higher oxidative stress, indicated by increased MDA levels, is associated with greater disease activity in RA patients. Additionally, MDA showed significant positive correlations with pro-inflammatory cytokines such as IL-1β ($r = 0.47$, $p < 0.05$), IL-17 ($r = 0.39$, $p < 0.05$), and TNF-α ($r = 0.52$, $p < 0.01$).

GSH and Disease Activity: A significant negative correlation was observed between GSH levels and DAS28 ($r = -0.45$, $p < 0.05$), indicating that lower antioxidant levels are associated with higher disease activity. Furthermore, GSH was inversely correlated with cytokines like IL-1β ($r = -0.41$, $p < 0.05$), IL-17 ($r = -0.28^{ns}$, $p < 0.05$), and TNF-α ($r = -0.34$, $p < 0.05$), suggesting that reduced antioxidant capacity is linked to higher inflammation.

Cytokines and Disease Activity: Pro-inflammatory cytokines, along with IL-1β, IL-17, and TNF-α, showed sturdy wonderful correlations with each different, with the highest correlation among IL-17 and TNF-α ($r = 0.75$, $p < 0.01$), indicating that these cytokines are closely associated inside the inflammatory approaches in RA. Additionally, all cytokines were significantly correlated with DAS28, with TNF-α showing the very best correlation ($r = 0.74$, $p < 0.01$), suggesting a sturdy association between irritation and disease severity. These effects help the speculation that oxidative strain and immune machine dysregulation are key contributors to the pathogenesis and development of rheumatoid arthritis. The nice correlations between oxidative markers and inflammatory cytokines with DAS28 ratings emphasize the capacity role of those biomarkers in assessing disease hobby in RA patients (Table5).

Table 5: The Correlation Analysis

Parameter	MDA	GSH	IL-1β	IL-17	TNF-α	DAS28
MDA (µmol/L)		-0.35*	0.47*	0.39*	0.52**	0.56**
GSH (µmol/L)	-0.35*		-0.41**	-0.28^{ns}	-0.34*	-0.45*
IL-1β (pg/mL)	0.47*	-0.41*		0.72**	0.68**	0.65**
IL-17 (pg/mL)	0.39*	-0.28^{ns}	0.72**		0.75**	0.68**
TNF-α (pg/mL)	0.52**	-0.34*	0.68**	0.75**		0.74**
DAS28 (score)	0.56**	-0.45*	0.65**	0.68**	0.74**	

Note: **Significant correlation at $p < 0.01$ (denoted by **);*Significant correlation at $p < 0.05$ (denoted by *)

This take a look at aimed to explore the connection among oxidative pressure, immune machine dysregulation, and sickness pastime in rheumatoid arthritis (RA). The effects imply a substantial association between increased oxidative stress and pro-inflammatory cytokines in RA patients, further highlighting the significance of those elements in the pathogenesis and development of the disease. Our findings align with numerous previous studies that emphasize the pivotal role of oxidative strain and immune response inside the exacerbation of RA.

DISCUSSION

The findings of our examine assist the hypothesis that oxidative strain plays a pivotal role within the pathogenesis and progression of rheumatoid arthritis (RA). The large boom in oxidative pressure markers which includes malondialdehyde (MDA) and the depletion of antioxidants like glutathione in RA sufferers correlate with expanded ailment severity, as contemplated by better Disease Activity Score 28 (DAS28) rankings. These outcomes are consistent with research indicating that oxidative strain contributes to inflammatory tactics, which might be central to RA development (Acabchuk et al., 2017; Chaudhary et al., 2023; Chan et al., 2023).

The role of oxidative stress in RA has been well-documented. For example, malondialdehyde (MDA) stages, a marker of lipid peroxidation, have been considerably better in RA patients than in controls, suggesting that oxidative damage is commonplace in RA pathophysiology (Gavrilă et al., 2016). Similarly, the findings of Merino de Paz et al. (2024) further corroborate this result by using reporting multiplied MDA ranges in a massive cohort of RA sufferers. Moreover, antioxidant depletion, in particular of glutathione, in RA sufferers as observed in our take a look at, has been connected to a faded capability to neutralize reactive oxygen species (ROS), in addition exacerbating joint infection (Wang et al., 2023; Haykin& Rolls 2021).

The relationship between cytokines and oxidative stress also emerges as a important pathway in RA. The expanded stages of seasoned-inflammatory cytokines including TNF-α, IL-17, and IL-1β in RA sufferers help the findings of preceding studies which have diagnosed these cytokines as key players in each the initiation and progression of RA (Chakraborty et al., 2023; Hu et al., 2024). The cytokine cascade no longer best drives irritation however additionally amplifies oxidative pressure, thereby growing a vicious cycle that promotes tissue damage and joint degradation (Meng et al., 2024; Yan et al., 2017). In unique, TNF-α has been proven to stimulate the manufacturing of ROS in synovial cells, which further contributes to oxidative harm (Zimmerman et al., 2017; Seiler 2019).

Our take a look at additionally determined widespread correlations between DAS28 scores and the stages of each oxidative stress markers and cytokines. This finding aligns with research indicating that multiplied oxidative stress and cytokine production are associated with higher ailment pastime and worse clinical effects in RA (Xiang et al., 2023). The strong correlation between DAS28 and inflammatory cytokines, which include IL-17 and TNF-α, underscores the inflammatory nature of the disease and the role of immune dysregulation in RA pathogenesis (Yan et al., 2022).

Additionally, our results display gender-unique differences in oxidative strain and inflammatory markers. Similar findings have been pronounced in the literature, in which gender differences in oxidative balance and the hazard of RA were found (Meng et al., 2024). The mechanisms behind those differences can also contain hormonal impacts, as estrogen is understood to have antioxidant houses, which can shield ladies from higher oxidative pressure tiers as compared to guys (Sayyaf et al., 2024).

These findings suggest that focused on both oxidative strain and inflammatory cytokines could offer therapeutic advantages in RA remedy. Studies have confirmed the ability of antioxidant cures, consisting of methotrexate, which not handiest suppresses irritation however also well-knownshows direct antioxidant consequences by means of scavenging ROS (Peilin et al., 2024). Additionally, the modulation of cytokine pathways via biologics targeting TNF-α and IL-17 has proven promise in decreasing disorder interest and enhancing affected person effects (Zhang et al., 2024; Yang et al., 2024).

In end, our examine highlights the crucial interplay among oxidative pressure and immune dysregulation in RA. The located correlations among oxidative markers, pro-inflammatory cytokines, and ailment severity underscore the capability for focused on these pathways inside the control of RA. Future research are warranted to further explore the healing capacity of antioxidant-based and anti-cytokine treatments in ameliorating RA-related infection and joint harm (Liao et al., 2024). Further studies is wanted to explore the underlying mechanisms and ability treatments concentrated on oxidative strain and immune modulation in RA.

Ethical Considerations

This look at became authorised by means of the Ethics Committee of Tikrit University College of Medicine and Tikrit Teaching Hospital. Informed consent became received from all members, who have been fully knowledgeable about the study's cause, tactics, and their proper to withdraw at any time. Participants' privateness changed into maintained with the aid of anonymizing records, and all techniques adhered to moral recommendations. Any clinical issues diagnosed throughout the take a look at were directly addressed by using the observe crew, making sure participant nicely-being and confidentiality throughout.

Acknowledgments

We would love to thank the participants of this examine for their cooperation, as well as the team of workers at Tikrit Teaching Hospital and Tikrit University College of Medicine for his or her support and assistance at some point of the research manner.

REFERENCES

1. Acabchuk, R. L., Kamath, J., Salamone, J. D., & Johnson, B. T. (2017). Stress and chronic illness: The inflammatory pathway. Social Science & Medicine, 185, 166–170. https://doi.org/10.1016/j.socscimed.2017.04.039
2. Agorastos, A., &Chrousos, G. P. (2022). The neuroendocrinology of stress: The stress-related continuum of chronic disease development. Molecular Psychiatry, 27(1), 502–513. https://doi.org/10.1038/s41380-021-01224-9
3. Chakraborty, S., Gupta, R., Kubatzky, K. F., Kar, S., Kraus, F. V., Souto-Carneiro, M. M., Lorenz, H. M., Kumar, P., Kumar, V., & Mitra, D. K. (2023). Negative impact of interleukin-9 on synovial regulatory T cells in rheumatoid arthritis. Clinical Immunology, 257, 109814. https://doi.org/10.1016/j.clim.2023.109814
4. Chan, K. L., Poller, W. C., Swirski, F. K., & Russo, S. J. (2023). Central regulation of stress-evoked peripheral immune responses. Nature Reviews Neuroscience, 24(10), 591–604. https://doi.org/10.1038/s41583-023-00729-2
5. Chaudhary, R., Azam, M. A., Dowand, B., Singh, A., Rehman, M., Agarwal, V., Kumar, A., Kaushik, A. S., Srivastava, S., Srivastava, S., & Mishra, V. (2024). Chronic stress-mediated dysregulations in inflammatory, immune, and oxidative circuitry impairs the therapeutic response of methotrexate in experimental autoimmune disease models. Naunyn-Schmiedeberg's Archives of Pharmacology. Advance online publication. https://doi.org/10.1007/s00210-024-03529-2
6. Chaudhary, R., Prasad, A., Agarwal, V., Rehman, M., Kumar, A., Kaushik, A. S., Srivastava, S., Srivastava, S., & Mishra, V. (2023). Chronic stress predisposes to the aggravation of inflammation in autoimmune diseases with focus on rheumatoid arthritis and psoriasis. International Immunopharmacology, 125(Pt A), 111046. https://doi.org/10.1016/j.intimp.2023.111046

7. Chmiel, J., Stasiak, M., Skrzypkowska, M., Samson, L., Łuczkiewicz, P., &Trzonkowski, P. (2024). Regulatory T lymphocytes as a treatment method for rheumatoid arthritis - Superiority of allogeneic to autologous cells. Heliyon, 10(17), e36512. https://doi.org/10.1016/j.heliyon.2024.e36512
8. Gavrilă, B. I., Ciofu, C., & Stoica, V. (2016). Biomarkers in rheumatoid arthritis, what is new? Journal of Medicine and Life, 9(2), 144–148. PMID: 27453744
9. Haykin, H., & Rolls, A. (2021). The neuroimmune response during stress: A physiological perspective. Immunity, 54(9), 1933–1947. https://doi.org/10.1016/j.immuni.2021.08.023
10. Hu, F., Shi, L., Liu, X., Chen, Y., Zhang, X., Jia, Y., Liu, X., Guo, J., Zhu, H., Liu, H., Xu, L., Li, Y., Wang, P., Fang, X., Xue, J., Xie, Y., Wei, C., Song, J., Zheng, X., Liu, Y. Y., Li, Y., Ren, L., Xu, D., Lu, L., Qiu, X., Mu, R., He, J., Wang, M., Zhang, X., Liu, W., & Li, Z. (2024). Proinflammatory phenotype of B10 and B10pro cells elicited by TNF-α in rheumatoid arthritis. Annals of the Rheumatic Diseases, 83(5), 576–588. https://doi.org/10.1136/ard-2023-224878
11. Huang, C., Zhang, F., Li, P., & Song, C. (2022). Low-dose IL-2 attenuated depression-like behaviors and pathological changes through restoring the balances between IL-6 and TGF-β and between Th17 and Treg in a chronic stress-induced mouse model of depression. International Journal of Molecular Sciences, 23(22), 13856. https://doi.org/10.3390/ijms232213856
12. Ilich, J. Z., Gilman, J. C., Cvijetić, S., &Boschiero, D. (2020). Chronic stress contributes to osteosarcopenic adiposity via inflammation and immune modulation: The case for more precise nutritional investigation. Nutrients, 12(4), 989. https://doi.org/10.3390/nu12040989
13. Komatsu, N., & Takayanagi, H. (2022). Mechanisms of joint destruction in rheumatoid arthritis — immune cell–fibroblast–bone interactions. Nature Reviews Rheumatology, 18(7), 415–429. https://doi.org/10.1038/s41584-022-00793-5
14. Kuchroo, V. K., Ohashi, P. S., Sartor, R. B., &Vinuesa, C. G. (2012). Dysregulation of immune homeostasis in autoimmune diseases. Nature Medicine, 18(1), 42–47. https://doi.org/10.1038/nm.2621
15. Kumar, L. D., Karthik, R., Gayathri, N., & Sivasudha, T. (2016). Advancement in contemporary diagnostic and therapeutic approaches for rheumatoid arthritis. Biomedicine & Pharmacotherapy, 79, 52–61. https://doi.org/10.1016/j.biopha.2016.02.001
16. Liao, H., Zheng, J., Lu, J., & Shen, H. L. (2024). NF-κB signaling pathway in rheumatoid arthritis: Mechanisms and therapeutic potential. Molecular Neurobiology. Advance online publication. https://doi.org/10.1007/s12035-024-04634-2
17. Meng, F., Lu, S., Li, L., Qian, T., Zhang, C., Liu, X., & Hou, X. (2024). Different gender of oxidative balance score on the risk of rheumatoid arthritis in the US population from NHANES. International Journal of Rheumatic Diseases, 27(7), e15237. https://doi.org/10.1111/1756-185X.15237
18. Merino de Paz, N., Quevedo-Abeledo, J. C., Gómez-Bernal, F., de Vera-González, A., Abreu-González, P., Martín-González, C., González-Gay, M. Á., & Ferraz-Amaro, I. (2024). Malondialdehyde serum levels in a fully characterized series of 430 rheumatoid arthritis patients. Journal of Clinical Medicine, 13(3), 901. https://doi.org/10.3390/jcm13030901
19. Peilin, Z., Wenqiang, W., Yongzhen, L., Xiang, C., Yongjun, M., Hongjie, S., Xinyu, N., &Qikai, H. (2024). Inflammatory cytokines, metabolites, and rheumatoid arthritis. Postgraduate Medical Journal. Advance online publication. https://doi.org/10.1093/postmj/qgae146
20. Ravi, M., Miller, A. H., & Michopoulos, V. (2021). The immunology of stress and the impact of inflammation on the brain and behaviour. BJPsych Advances, 27(3), 158–165. https://doi.org/10.1192/bja.2020.82
21. Sayyaf, A., Ghaedi, E., Haidari, F., Rajaei, E., Ahmadi-Engali, K., & Helli, B. (2024). Effects of soy bread on cardiovascular risk factors, inflammation, and oxidative stress in women with active rheumatoid arthritis: A randomized double-blind controlled trial. Clinical Nutrition Research, 13(1), 22–32. https://doi.org/10.7762/cnr.2024.13.1.22
22. Schwetlik, S. N., Baldock, K. L., Hill, C. L., & Ferrar, K. (2022). Chronic stress and arthritis: A scoping review. Arthritis Care & Research, 74(6), 982–996. https://doi.org/10.1002/acr.24528
23. Seiler, A., Fagundes, C. P., & Christian, L. M. (2019). The impact of everyday stressors on the immune system and health. In A. Choukèr (Ed.), Stress challenges and immunity in space: From mechanisms to monitoring and preventive strategies (pp. 71–92). Springer International Publishing. https://doi.org/10.1007/978-3-030-16996-1_6
24. Smallwood, M. J., Nissim, A., Knight, A. R., Whiteman, M., Haigh, R., &Winyard, P. G. (2018). Oxidative stress in autoimmune rheumatic diseases. Free Radical Biology and Medicine, 125, 3–14. https://doi.org/10.1016/j.freeradbiomed.2018.05.086
25. Smolen, J. S., Aletaha, D., & McInnes, I. B. (2016). Rheumatoid arthritis. The Lancet, 388(10055), 2023–2038. https://doi.org/10.1016/S0140-6736(16)30173-8
26. Wang, Q., Liu, Y., Wu, J., Chen, S., Hu, T., Liu, Y., Li, X., Li, X., Wu, Y., Yu, J., Zeng, T., Luo, Y., Hu, X., & Tan, L. M. (2023). Potential significance of changes in serum levels of IL-17, TNF-α, and DKK-1 in

the progression of rheumatoid arthritis. Autoimmunity, 56(1), 2276068. https://doi.org/10.1080/08916934.2023.2276068
27. Xiang, Y., Zhang, M., Jiang, D., Su, Q., & Shi, J. (2023). The role of inflammation in autoimmune disease: A therapeutic target. Frontiers in Immunology.https://doi.org/10.3389/fimmu.2023.1267091
28. Yan, F., Mo, X., Liu, J., Ye, S., Zeng, X., & Chen, D. (2017). Thymic function in the regulation of T cells, and molecular mechanisms underlying the modulation of cytokines and stress signaling (Review). Molecular Medicine Reports, 16(5), 7175–7184. https://doi.org/10.3892/mmr.2017.7525
29. Yan, S., Kotschenreuther, K., Deng, S., & Kofler, D. M. (2022). Regulatory T cells in rheumatoid arthritis: Functions, development, regulation, and therapeutic potential. Cellular and Molecular Life Sciences, 79(10), 533. https://doi.org/10.1007/s00018-022-04563-0
30. Yang, H., Liu, C., Lin, X., Li, X., Zeng, S., Gong, Z., Xu, Q., Li, D., & Li, N. (2024). Wogonin inhibits the migration and invasion of fibroblast-like synoviocytes by targeting the PI3K/AKT/NF-κB pathway in rheumatoid arthritis. Archives of Biochemistry and Biophysics, 755, 109965. https://doi.org/10.1016/j.abb.2024.109965
31. Yin, Z., Siegert, S., Neure, L., Grolms, M., Liu, L., Eggens, U., Radbruch, A., Braun, J., &Sieper, J. (1999). The elevated ratio of interferon gamma-/interleukin-4-positive T cells found in synovial fluid and synovial membrane of rheumatoid arthritis patients can be changed by interleukin-4 but not by interleukin-10 or transforming growth factor beta. Rheumatology (Oxford, England), 38(11), 1058–1067. https://doi.org/10.1093/rheumatology/38.11.1058
32. Zhang, J., Liu, H., Chen, Y., Liu, H., Zhang, S., Yin, G., & Xie, Q. (2024). Augmenting regulatory T cells: New therapeutic strategy for rheumatoid arthritis. Frontiers in Immunology, 15, 1312919. https://doi.org/10.3389/fimmu.2024.1312919
33. Zimmerman, M. C., Clemens, D. L., Duryee, M. J., Sarmiento, C., Chiou, A., Hunter, C. D., Tian, J., Klassen, L. W., O'Dell, J. R., Thiele, G. M., Mikuls, T. R., & Anderson, D. R. (2017). Direct antioxidant properties of methotrexate: Inhibition of malondialdehyde-acetaldehyde-protein adduct formation and superoxide scavenging. Redox Biology, 13, 588–593. https://doi.org/10.1016/j.redox.2017.07.018