Open Access

Recent Progress in Nutrition

LIDSEN Publishing Inc.

Review

Selenium Supplementation in Rheumatoid Arthritis: Evidence from Controlled Clinical Trials and Mechanistic Insights

Jozélio Freire de Carvalho *, Rosangela Passos de Jesus

Núcleo de Pesquisa em Nutrição e Doenças Crônicas (NUPEN-DC), School of Nutrition from the Federal University of Bahia, Salvador, Bahia, Brazil; E-Mails: jotafc@gmail.com; rosangela.jpassos@gmail.com

* **Correspondence:** Jozélio Freire de Carvalho; E-Mail: jotafc@gmail.com

Academic Editor: Mauro Fisberg

Recent Progress in Nutrition
2026, volume 6, issue 1
doi:10.21926/rpn.2601002

Received: October 27, 2025
Accepted: February 09, 2026
Published: February 13, 2026

Abstract

Selenium (Se) is a key micronutrient integrated into selenoproteins such as glutathione peroxidases (GPx), which are responsible for crucial antioxidant and anti-inflammatory mechanisms. Oxidative stress contributes to the immunopathogenesis and chronic joint damage of rheumatoid arthritis (RA), supporting interest in selenium supplementation as an adjunct therapeutic strategy. This review was based on a structured literature search of major biomedical databases and evaluated six controlled clinical trials involving a total of 234 RA patients who received selenium supplementation at daily doses of 200-256 µg for 12-26 weeks. Given the substantial clinical and methodological heterogeneity among trials—including differences in disease stage, selenium formulation, outcome measures, and trial duration—a quantitative meta-analysis was not performed, and a qualitative synthesis was undertaken. Supplementation consistently increased circulating selenium levels and enhanced GPx activity, particularly in erythrocytes. Clinical outcomes were heterogeneous: one study in early RA demonstrated significant improvements in joint symptoms and functional parameters versus placebo, whereas trials in long-standing disease generally showed biochemical benefits without significant differences in pain, joint counts, or inflammatory markers compared with control groups. More recent studies reported favorable within-group reductions in ESR, CRP, and anti-CCP titers, but between-group differences

remained non-significant. This pattern highlights a dissociation between biochemical improvement and consistent clinical benefit, particularly in established RA. Selenium supplementation was well tolerated in all trials, with no major adverse events. These findings suggest that selenium may have therapeutic relevance in selected patient subgroups, including those with recent-onset disease or elevated oxidative burden. However, due to heterogeneity and limited sample sizes, conclusions should be interpreted with caution. Larger, rigorously designed clinical trials with standardized disease activity endpoints, stratification by disease stage and baseline selenium status, are needed to clarify selenium's role within contemporary RA management.

Keywords
Selenium supplementation; rheumatoid arthritis; controlled clinical trials; oxidative stress; disease stage

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovial inflammation, joint destruction, disability, and increased mortality. Oxidative stress is a well-described pathogenic mechanism in RA, driven by excessive generation of reactive oxygen species (ROS) by neutrophils and macrophages in inflamed joints, which promote lipid peroxidation, cellular dysfunction, and the perpetuation of inflammation [1, 2].

Selenium (Se) is an essential trace element required for the synthesis of several selenoproteins, including glutathione peroxidases (GPx), which are crucial for antioxidant defense and immune modulation. Patients with RA have shown significantly reduced selenium concentrations and decreased GPx activity compared with healthy individuals [1]. Further studies demonstrated that this impaired antioxidant response persists, particularly in polymorphonuclear cells, even after selenium repletion, suggesting increased susceptibility to oxidative damage [2].

Based on this biological rationale, selenium supplementation has been investigated as an adjuvant therapy in RA. The first controlled clinical trial in recent-onset RA demonstrated that selenium supplementation improved pain, morning stiffness, and joint counts, together with increased plasma selenium and GPx activity, highlighting a potential therapeutic role in early disease [3]. A later randomized study also reported clinical improvements with selenium supplementation alongside omega-3 fatty acids [4]. However, larger randomized controlled trials in patients with established RA found no significant superiority over placebo with respect to clinical activity, despite measurable biochemical responses [5]. A recent controlled trial has renewed interest by showing favorable trends in ESR, CRP, and anti-CCP levels during selenium treatment, although not statistically different from placebo [6].

Altogether, the available evidence suggests a biologically plausible but clinically variable effect of selenium in RA, warranting a comprehensive synthesis to identify contexts in which supplementation may offer benefit.

2. Materials and Methods

This systematic narrative review included only controlled clinical trials that evaluated oral selenium supplementation in adult patients with rheumatoid arthritis. A structured literature search was conducted in PubMed/MEDLINE, Scopus, and Web of Science from database inception to July 2025, using combinations of the following keywords: “selenium”, “selenium supplementation”, “rheumatoid arthritis”, “oxidative stress”, and “clinical trial”. The literature sources were the original studies provided by the author in full text, comprising randomized double-blind placebo-controlled trials and prospective controlled studies conducted in Europe and the Middle East [4-8]. Animal studies, in vitro assays, pediatric populations, case reports, and review articles were excluded.

To ensure accurate extraction of clinical and biochemical outcomes, each study had to meet the following inclusion criteria:

1. diagnosis of RA according to internationally accepted clinical criteria;
2. intervention consisting of daily selenium supplementation at a specified dose;
3. presence of a control group (placebo or standard therapy alone);
4. assessment of outcomes directly relevant to RA disease activity, inflammatory markers, or oxidative stress parameters; and
5. minimum follow-up duration of 12 weeks to allow biologically relevant changes in selenoprotein expression.

Data extracted from each study included: sample size, sex distribution, disease duration, dose and formulation of selenium (selenium-enriched yeast, sodium selenite, or selenomethionine), concomitant pharmacologic therapy, and reported effects on clinical variables (e.g., joint pain and swelling counts, morning stiffness), laboratory inflammatory markers (ESR, CRP), immunological biomarkers, and oxidant/antioxidant indices (serum selenium and GPx activity) [4-8].

Due to variability among included studies in sample size, disease severity, baseline selenium status, clinical endpoints, and biochemical methodologies, a quantitative meta-analysis was not feasible. Results were therefore synthesized narratively and presented by study design, major outcomes, and mechanistic interpretation. Safety findings, when reported, were systematically documented across all studies [4-8]. The study selection process adhered to PRISMA guidelines and is summarized in a flow diagram (Figure 1).

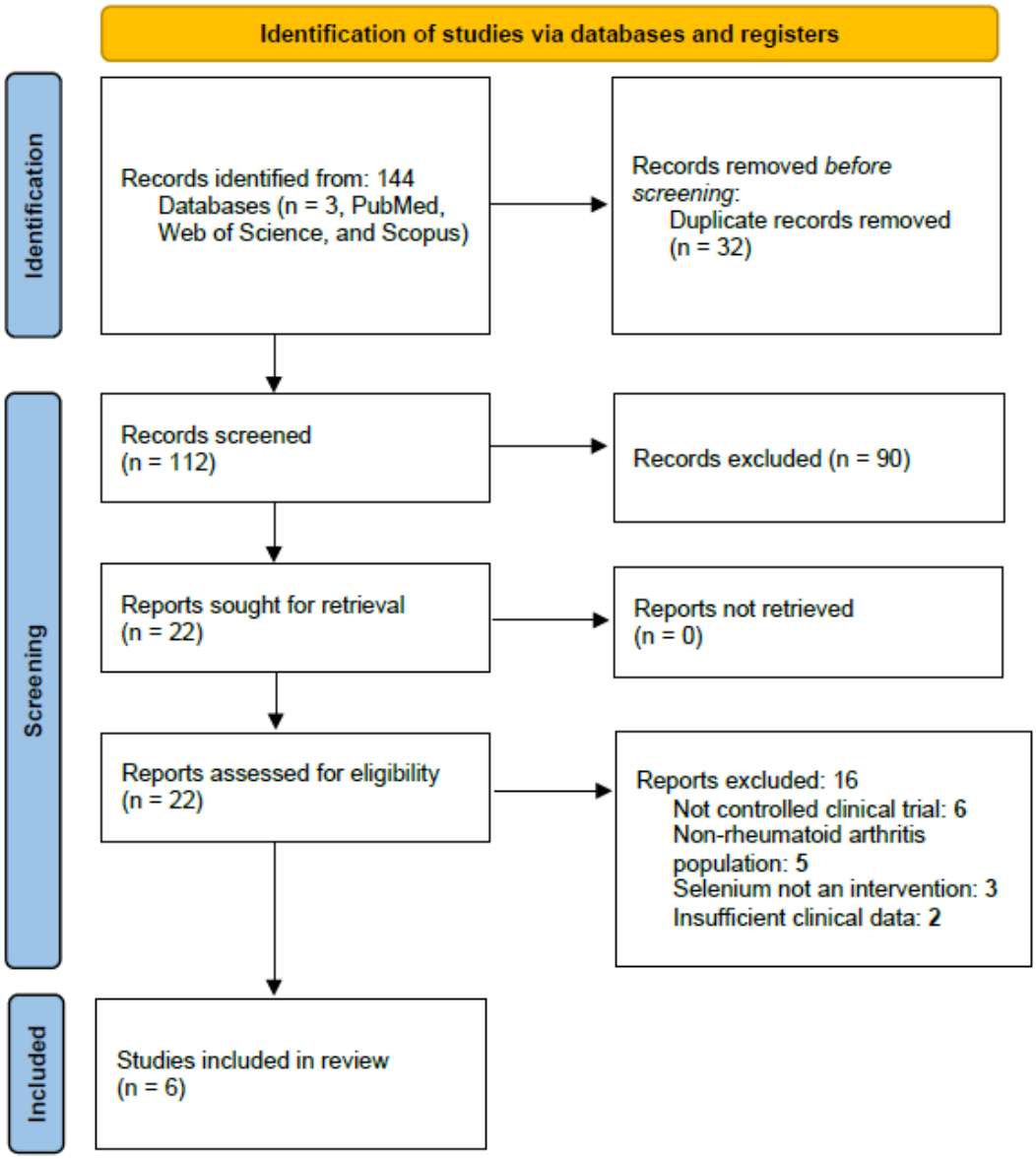

Figure 1 Flowchart of the included studies.

3. Results

3.1 Study Selection and General Characteristics

Six controlled clinical trials evaluating selenium supplementation in patients with rheumatoid arthritis were included in this review, comprising a total of 234 participants [1-6]. The main characteristics of the included studies—study design, geographic origin, patient demographics, disease duration, selenium formulation and dosage, intervention length, clinical and biochemical outcomes, and safety data—are summarized in Table 1. The study selection process followed PRISMA recommendations and is presented in Figure 1.

Table 1 Controlled clinical trials evaluating selenium supplementation in rheumatoid arthritis.

Author, Year (Ref.)	Study Design	Country	N/Sex/Age	Disease Duration	Disease Stage	Selenium Dose & Duration	Outcomes	Adverse Events	Overall Interpretation of Findings
Peretz et al., 1992 [1]	Randomized double-blind placebo-controlled	Belgium	15/100% F/61 ± 11 yrs	<5 yrs	Early RA	200 µg/day × 3 months	↓ pain, ↓ tender/swollen joints, ↓ morning stiffness; ↑ plasma selenium and GPx	None	Early RA: clinical and biochemical benefit
Tarp et al., 1987 [2]	Prospective controlled	Denmark	6 RA + 6 controls/83% F/53.5 yrs (42.3-68.6)	14.1 yrs (4-29)	Established RA	256 µg/day × 26 weeks	↑ plasma selenium and GPx; incomplete granulocyte GPx response	None	Established RA: biochemical improvement without clinical response
Tarp et al., 1992 [3]	Prospective controlled	Denmark	9 RA + 8 controls/89% F/54.1 yrs	NR	Established RA	250 µg/day × 6 months	↑ serum selenium and GPx; persistent PMN antioxidant deficiency	None	Persistent cellular redox dysfunction despite supplementation
Heinle et al., 1997 [4]	Randomized double-masked placebo-controlled	Germany	70/92% F/58.2 ± 12.8 yrs	12.7 ± 8.3 yrs	Long-standing RA	200 µg/day × 12 weeks	↓ tender/swollen joints, ↓ morning stiffness; ↓ CRP, α2-globulin, PGE_2	NR	Clinical and inflammatory improvement with adjunctive supplementation
Peretz et al., 2001 [5]	Randomized double-masked controlled	Belgium	55/72% F/61 ± 13 yrs	NR	Established RA	200 µg/day × 3 months	↓ pain and joint counts in both groups; no superiority vs placebo; ↑ QoL	Comparable to a placebo	No superiority over placebo under optimized therapy
Zamani et al., 2024 [6]	Randomized placebo-controlled	Iran	59/NR/NR	NR	Established RA	200 µg/day × 12 weeks	↓ DAS-CRP, DAS-ESR, CRP, ESR, anti-CCP (within-group only)	NR	Within-group improvement only; no between-group superiority

Abbreviations: RA, rheumatoid arthritis; GPx, glutathione peroxidase; PMN, polymorphonuclear leukocytes; CRP, C-reactive protein; DAS, Disease Activity Score; QoL, quality of life; NR, not reported.

The trials were conducted between 1987 and 2023 and displayed substantial heterogeneity in patient populations, disease stage, selenium formulations, background pharmacologic therapy, outcome measures, and duration of follow-up. This heterogeneity precluded quantitative pooling of data and justified a qualitative comparative synthesis.

3.2 Biochemical Effects of Selenium Supplementation

Across all included trials, selenium supplementation consistently increased systemic selenium exposure, as evidenced by elevations in circulating selenium concentrations and/or glutathione peroxidase (GPx) activity [4-9]. These biochemical effects were observed regardless of disease duration, selenium formulation, or geographic setting.

Several studies demonstrated robust increases in GPx activity in plasma or erythrocytes following supplementation [4, 5, 7, 8]. However, in trials that specifically assessed cellular compartments, particularly polymorphonuclear leukocytes, selenium repletion resulted in incomplete restoration of GPx activity [5, 6]. This persistent cellular antioxidant deficiency was most evident in patients with long-standing or severe disease and was not corrected despite normalization of serum selenium levels [5, 6].

Overall, the biochemical data indicate that selenium supplementation reliably enhances systemic antioxidant markers but may have limited capacity to fully restore intracellular antioxidant defenses in chronic rheumatoid arthritis [5, 6].

3.3 Clinical Outcomes and Inflammatory Markers

Clinical outcomes varied substantially across studies. In a randomized, placebo-controlled trial of patients with recent-onset rheumatoid arthritis, selenium supplementation was associated with significant improvements in pain intensity, tender and swollen joint counts, and duration of morning stiffness compared with placebo [4]. This trial also reported concomitant improvements in immune responsiveness, suggesting a clinically meaningful effect in early disease [4].

In contrast, trials enrolling patients with long-standing or established rheumatoid arthritis generally failed to demonstrate significant superiority of selenium supplementation over placebo for core clinical endpoints, including pain scores, joint counts, and functional measures [5, 6, 8]. In these studies, both selenium and control groups often showed parallel improvements over time, likely reflecting background pharmacologic therapy and regression toward the mean [8].

Regarding inflammatory biomarkers, results were heterogeneous. Some trials reported reductions in C-reactive protein and other inflammatory markers during selenium supplementation [7]. At the same time, more recent data showed within-group decreases in ESR, CRP, and anti-CCP titers in the selenium arm, with between-group comparisons remaining non-significant [9]. Taken together, these findings indicate that selenium supplementation does not consistently translate biochemical improvements into measurable clinical benefit, particularly in patients with established disease receiving contemporary antirheumatic therapy [5, 6, 8, 9].

These patterns are visually summarized in Table 1.

3.4 Comparative Synthesis of Evidence Strength and Heterogeneity

When analyzed comparatively rather than chronologically, a consistent pattern emerges across the six trials. Selenium supplementation produced consistent biochemical effects, as evidenced by increased selenium levels and GPx activity across all studies [4-9]. In contrast, clinical efficacy was context-dependent and heterogeneous.

Trials involving patients with early or less-advanced rheumatoid arthritis demonstrated a clearer clinical benefit [4]. In contrast, studies of long-standing or treatment-refractory disease have predominantly shown biochemical improvement without parallel clinical response [5, 6, 8, 9]. Disease stage, therefore, appears to be a key determinant of treatment responsiveness.

Additional sources of heterogeneity included selenium formulation, dosing regimen, duration of supplementation, background pharmacologic therapy, and outcome selection [4-9]. In studies where selenium was administered alongside optimized antirheumatic treatment or additional nutritional interventions, any incremental clinical benefit attributable to selenium was modest and difficult to distinguish from control responses [7, 8].

Importantly, heterogeneity was also evident at the cellular level. Studies documenting incomplete recovery of granulocyte antioxidant activity despite normalized systemic selenium status suggest that compartmentalized redox dysfunction may limit clinical translation in chronic disease [5, 6].

3.5 Safety and Tolerability

Selenium supplementation was well tolerated across all trials. No serious adverse events attributable to selenium were reported, and adverse effects were comparable between the selenium and placebo groups when reported [4-9]. Doses ranging from 200 to 256 μg/day administered for up to 26 weeks did not result in clinically significant toxicity [4-9].

3.6 Summary of Results

In summary, controlled clinical trials consistently demonstrate that selenium supplementation enhances systemic antioxidant markers in patients with rheumatoid arthritis [4-9]. However, evidence for clinically meaningful improvement is inconsistent and appears to depend on disease stage, baseline oxidative burden, cellular antioxidant responsiveness, and concomitant therapy [4-9]. These findings underscore substantial heterogeneity across studies and support the use of qualitative synthesis rather than meta-analysis.

4. Discussion

As demonstrated in the comparative analysis of the Results, clinical benefits of selenium supplementation were predominantly observed in early disease. In contrast, biochemical improvements without clinical translation were observed in established RA. Selenium supplementation in rheumatoid arthritis produces consistent biochemical engagement, with increases in circulating Se and GPx activity across trials, supporting the biological plausibility of attenuating ROS-driven synovitis and cartilage damage. As highlighted by the comparative synthesis of the Results, this biochemical consistency contrasts with substantial heterogeneity in clinical outcomes, underscoring that clinical efficacy remains context-dependent. The most favorable signal

appears in recent-onset RA, where inflammatory circuits may be more labile and less confounded by cumulative structural damage or entrenched immune dysregulation [4]. In contrast, trials with severe or longstanding disease often show restored serum or erythrocyte antioxidant indices without parallel clinical gains, a pattern plausibly explained by incomplete correction of granulocyte (neutrophil) redox defenses, a key source of ROS within inflamed joints [5-7]. This dissociation between systemic antioxidant normalization and limited clinical response mirrors the biochemical–clinical gap identified across trials in the Results section. This compartmental limitation aligns with broader mechanistic work highlighting neutrophil-centric oxidative pathways and implicating extracellular GPx3 and selenoprotein transport in synovial biology [10].

Differences in baseline selenium status, disease stage, and concomitant therapy likely modulate response. In the German double-blind trial using sodium selenite in addition to omega-3 and standard care, selenium was associated with reductions in joint counts, morning stiffness, and inflammatory proteins, consistent with additive anti-inflammatory effects rather than monotherapy efficacy [7]. Conversely, in the Belgian multicenter RCT under optimized NSAID/DMARD therapy, selenium did not outperform placebo over 90 days, illustrating how background treatment intensity can attenuate the detectable incremental benefit of nutritional interventions, and suggesting that any incremental benefit may be small and easily masked by modern treatment regimens [8]. The recent RCT reported within-group declines in CRP/ESR and anti-CCP on selenium. Still, between-group differences remained non-significant, reinforcing the notion of modest effect sizes and the need for adequate power and enrichment strategies [9].

Evidence external to these six trials helps contextualize expectations. A classic general review underscored selenium's narrow therapeutic window and its centrality to selenoproteins (including GPx isoenzymes) that shape immune and inflammatory responses [8]. A focused RA-oriented narrative review synthesized observational data indicating lower Se/SELENOP/GPx3 levels in RA versus controls. It is proposed that deficient Se-dependent pathways may aggravate disease activity, particularly under high inflammatory burden [11]. An earlier systematic appraisal of antioxidant trials in arthritis identified methodological limitations and heterogeneous outcomes, paralleling the variability observed in the controlled selenium trials summarized here, and cautioned against overinterpretation of small studies and emphasized the need for rigorous designs and validated endpoints [9].

Beyond RA-specific RCTs, meta-analytic data across inflammatory/metabolic conditions suggest selenium can lower hs-CRP in selected contexts and formats, with the strongest anti-inflammatory signal for parenteral formulations and less consistent effects with oral dosing. This observation aligns with the mixed clinical outcomes observed in RA and suggests that formulation and bioavailability are testable contributors to heterogeneity [11]. Moreover, new cross-sectional data in RA link trace-element patterns, including selenium, with surrogate cardiovascular risk markers (e.g., carotid IMT, augmentation index), broadening the potential clinical relevance of optimizing selenium status beyond joint outcomes alone, toward comorbidity risk modification [12]. Consistent reductions in SELENOP and GPx3 in inflammatory RMDs relative to healthy or OA comparators further support an inflammation-associated selenium transport/antioxidant deficit that could be therapeutically targetable in selected patients [13].

Taken together, selenium is biologically active and generally safe at the doses tested in RA trials, but clinical benefits are modest and not universal. In line with the comparative evidence synthesis, the most rational path forward emphasizes patient stratification rather than universal

supplementation, including selection based on disease stage (early RA), biochemical evidence of low Se/SELENOP/GPx3, and markers of heightened oxidative stress. Methodological modernization (DAS28, ultrasound/MRI synovitis, validated PROs), longer follow-up, and formulation/dose optimization (including exploration of strategies improving neutrophil compartment delivery) are needed [14]. Within contemporary RA management, selenium should be considered an adjunct for carefully profiled subgroups, pending confirmatory, adequately powered randomized studies.

5. Conclusions

Selenium supplementation consistently improves systemic antioxidant status in patients with rheumatoid arthritis by increasing circulating selenium concentration and enhancing glutathione peroxidase activity. These biochemical benefits align with the mechanistic rationale that oxidative stress plays a relevant role in sustaining synovial inflammation and joint tissue damage in rheumatoid arthritis. However, evidence supporting a clinically meaningful improvement in disease activity remains inconsistent across controlled trials. The strongest therapeutic signal has been observed in recent-onset disease, whereas studies enrolling patients with long-standing rheumatoid arthritis have generally not demonstrated significant superiority over placebo. Differences in disease stage, baseline selenium nutritional status, concomitant pharmacological therapy, and the limited recovery of granulocyte antioxidant capacity appear to modulate treatment response. Based on the currently available data, selenium should not yet be recommended as a routine adjunct therapy for all patients with rheumatoid arthritis. Nonetheless, it remains a safe, inexpensive, and biologically plausible intervention that may offer benefit to carefully selected subgroups characterized by high oxidative stress or an early disease course. Well-designed, adequately powered clinical trials using modern validated outcome measures are required to define the precise role of selenium within current rheumatoid arthritis management strategies.

Author Contributions

J.F. Carvalho has done all parts of this manuscript (conceptualization, literature search, formal analysis, writing, edition, submission). R.P Jesus has done literature search, formal analysis, writing, and revision.

Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

No additional data was generated to this study. All data is already included in the present format.

AI-Assisted Technologies Statement

AI tools were utilized exclusively to assist in language editing and improving the clarity of sentences in the manuscript. All ideas, data synthesis, and conclusions presented in this study are entirely the responsibility of the authors.

References

1. Peretz A, Neve J, Duchateau J, Famaey JP. Adjuvant treatment of recent onset rheumatoid arthritis by selenium supplementation: Preliminary observations. Rheumatology. 1992; 31: 281-282.
2. Tarp U, Hansen JC, Overvad K, Thorling EB, Tarp BD, Graudal H. Glutathione peroxidase activity in patients with rheumatoid arthritis and in normal subjects: Effects of long-term selenium supplementation. Arthritis Rheum. 1987; 30: 1162-1166.
3. Tarp U, Stengaard-Pedersen K, Hansen JC, Thorling EB. Glutathione redox cycle enzymes and selenium in severe rheumatoid arthritis: Lack of antioxidative response to selenium supplementation in polymorphonuclear leucocytes. Ann Rheum Dis. 1992; 51: 1044-1049.
4. Heinle K, Adam A, Gradl M, Wiseman M, Adam O. Selenkonzentration in den Erythrozyten bei Patienten mit rheumatoider Arthritis (in German). Med Klin. 1997; 92: 29-31.
5. Peretz A, Siderova V, Nève J. Selenium supplementation in rheumatoid arthritis investigated in a double blind, placebo-controlled trial. Scand J Rheumatol. 2001; 30: 208-212.
6. Zamani B, Taghvaee F, Akbari H, Mohtashamian A, Sharifi N. Effects of selenium supplementation on the indices of disease activity, inflammation and oxidative stress in patients with rheumatoid arthritis: A randomized clinical trial. Biol Trace Elem Res. 2024; 202: 1457-1467.
7. Tarp U. Selenium and the selenium-dependent glutathione peroxidase in rheumatoid arthritis. Dan Med Bull. 1994; 41: 264-274.
8. Rayman MP. Selenium and human health. Lancet. 2012; 379: 1256-1268.
9. Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: A systematic review of randomized clinical trials. Rheumatology. 2007; 46: 1223-1233.
10. Avery JC, Hoffmann PR. Selenium, Selenoproteins, and Immunity. Nutrients. 2018; 10: 1203.
11. Gholizadeh M, Khalili A, Roodi PB, Saeedy SA, Najafi S, Mohammadian MK, et al. Selenium supplementation decreases CRP and IL-6 and increases TNF-alpha: A systematic review and meta-analysis of randomized controlled trials. J Trace Elem Med Biol. 2023; 79: 127199.
12. Vera E, Vallvé JC, Linares V, Paredes S, Ibarretxe D, Bellés M. Serum levels of trace elements (magnesium, iron, zinc, selenium, and strontium) are differentially associated with surrogate markers of cardiovascular disease risk in patients with rheumatoid arthritis. Biol Trace Elem Res. 2025; 203: 3570-3584.
13. Wahl L, Chillon TS, Seemann P, Ohrndorf S, Ochwadt R, Becker W, et al. Serum selenium, selenoprotein P and glutathione peroxidase 3 in rheumatoid, psoriatic, juvenile idiopathic arthritis, and osteoarthritis. J Nutr Biochem. 2025; 135: 109776.
14. Hariri M, Amirkalali B, Baradaran HR, Gholami A. The Effect of Parenteral Selenium Therapy on Serum Concentration of Inflammatory Mediators: A Systematic Review and Dose-Response Meta-Analysis of Randomized Clinical Trials. Biol Trace Elem Res. 2024; 202: 1910-1925.