

Clinical, Biochemical and Nrf2-Keap1-Related Outcomes of Silver Nanoparticle-Adjunct Therapy in Adults with Osteoarthritis or Rheumatoid Arthritis: A Prospective Comparative Study

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Abstract Background: Osteoarthritis (OA) and Rheumatoid Arthritis (RA) are clinically distinct disorders in which inflammatory and oxidative processes may contribute to symptoms and tissue injury. The Nrf2-Keap1 system is an important regulator of cellular antioxidant responses but circulating biomarker changes do not by themselves establish pathway-mediated clinical effects. **Objective:** To compare clinical, biochemical, inflammatory and short-term radiological outcomes among adults with OA or RA receiving standard arthritis therapy alone versus standard therapy supplemented with silver nanoparticles (AgNPs) and to examine changes in biomarkers related to oxidative stress and Nrf2-associated signaling. **Methods:** This prospective comparative study included 255 adults with clinically confirmed OA or RA. Participants were consecutively recruited and categorized according to the therapeutic approach received: standard therapy alone (n = 128) or standard therapy supplemented with AgNPs (n = 127). No random allocation is described in the submitted study record. Clinical outcomes included VAS pain, WOMAC for OA and DAS-28 for RA. Oxidative-stress, antioxidant, inflammatory and Nrf2-related biomarkers were assessed using the reported laboratory methods. Radiological assessment was performed at baseline and after 12 weeks. Safety monitoring included routine hematological, hepatic and renal assessments. **Results:** In the submitted dataset, VAS pain decreased from 7.4±1.1 to 3.1±1.4 in the AgNP group and from 7.3±1.2 to 5.4±1.6 in the standard-therapy group (reported p<0.001). Among OA participants, the manuscript reports a 48.6% improvement in WOMAC with AgNP supplementation versus 22.3% with standard therapy. Among RA participants, the reported DAS-28 reduction was 2.1±0.6 versus 1.0±0.5, respectively (p<0.001). Nrf2, HO-1, SOD and catalase were reported to increase more in the AgNP group, while MDA, TNF-α, IL-6 and CRP decreased. Short-term radiological stabilization/improvement was reported in 39.5% versus 18.2%. These findings require confirmation with complete baseline/follow-up values, confidence intervals, disease-specific analyses and verification of the original statistical output. **Conclusion:** AgNP-augmented therapy was associated with greater short-term clinical and biochemical changes than standard therapy alone in this prospective comparative cohort. However, because treatment allocation was non-randomized, follow-up was limited to 12 weeks and important nanoparticle, molecular, imaging and statistical details require verification, the findings should be considered preliminary. The observed Nrf2-related biomarker changes support further mechanistic investigation but do not establish a causal Nrf2-Keap1 mechanism or long-term disease modification.

Key Words Arthritis, Osteoarthritis, Rheumatoid Arthritis, Silver Nanoparticles, Nrf2, Keap1, Oxidative Stress, Inflammatory Biomarkers, Nanomedicine

INTRODUCTION

Arthritis encompasses heterogeneous disorders with different pathobiology, clinical manifestations and treatment strategies (Figure 1). OA is characterized predominantly by progressive structural and functional changes of the joint, whereas RA is a

systemic autoimmune inflammatory disease. Consequently, clinical outcomes and disease-modifying claims should be interpreted separately for these conditions [1-3].

Oxidative stress and dysregulated inflammatory signaling have been implicated in both OA and RA, although their

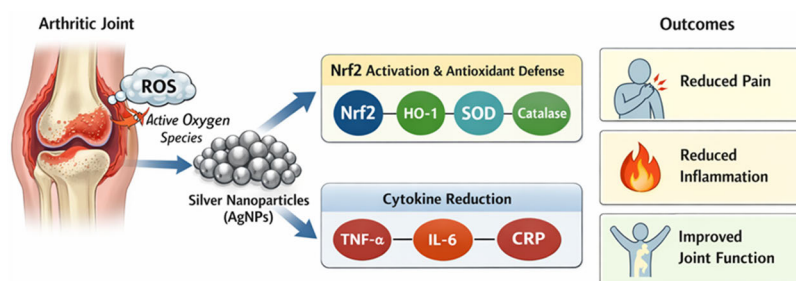


Figure 1: Silver Nanoparticles in Arthritis Treatment

relative contributions and molecular contexts differ. The Nrf2-Keap1 axis regulates cellular responses to oxidative and electrophilic stress [4,5]. Under basal conditions, Keap1 contributes to regulation of Nrf2 stability; activation of Nrf2 can increase expression of antioxidant and cytoprotective genes. This biological rationale has stimulated interest in redox-modulating therapeutic strategies [6].

Nanoparticle-based approaches have attracted interest because physicochemical properties such as size, surface chemistry, coating, charge, dose and route of administration can influence biodistribution, cellular interactions, efficacy and toxicity [7-10]. Silver nanoparticles have been investigated in several experimental settings but clinical interpretation requires careful attention to formulation, exposure and safety.

The present study therefore evaluated clinical and biochemical outcomes associated with AgNP supplementation in adults with OA or RA [11,12]. The revised manuscript deliberately distinguishes measured biomarker associations from causal mechanistic claims and presents OA- and RA-specific outcomes where available [13-16].

Objective

To compare short-term clinical, biochemical, inflammatory and radiological outcomes between standard arthritis therapy alone and standard therapy supplemented with AgNPs, with particular interest in Nrf2-related antioxidant responses.

METHODS

Study Design, Setting and Participants

This was a prospective comparative study involving 255 adults aged 18-75 years with clinically confirmed OA or RA. Participants were recruited consecutively after meeting the eligibility criteria and providing written informed consent.

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Exact study center, department, city/country, ethics approval number, recruitment start date, recruitment end date and follow-up period. The original manuscript contained a placeholder for these details and therefore they cannot be safely inferred.

Treatment Allocation

Participants were categorized according to the therapeutic approach received: standard arthritis therapy alone (n = 128) or standard therapy supplemented with AgNPs (n = 127). The study should not be described as randomized unless the

authors can document a genuine random allocation procedure. The treatment assignment process, including the role of clinician decision, patient preference, treatment availability or other factors, must be reported.

Baseline Comparability and Confounding

Because treatment allocation was not randomized, baseline comparability is essential. A dedicated treatment-group baseline table should include age, sex, arthritis type, disease duration and severity, baseline VAS, OA-specific WOMAC, RA-specific DAS-28, relevant comorbidities and concurrent therapies. Multivariable analyses should identify the exact covariates entered into each model and should account, where possible, for arthritis type, age, sex, baseline severity and concurrent treatment.

Silver Nanoparticle Formulation and Characterization

AgNPs were described in the original manuscript as synthesized or procured and characterized using UV-Vis spectroscopy, Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM). For reproducibility, the final manuscript must report the actual formulation and characterization data, including source/manufacture, batch number, synthesis or procurement method, core particle size, hydrodynamic diameter, size distribution/PDI, morphology, zeta potential, coating/capping agent, purity, concentration, formulation medium, sterility/endotoxin results, storage conditions and stability. Representative TEM images and quantitative characterization results should be provided.

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Actual AgNP characterization values and images. No values should be created from the current manuscript because they are not reported in the submitted material.

Dose and Administration

Author to Insert: Exact AgNP dose, route, frequency, duration, formulation volume and dosing rationale. The present source manuscript does not provide sufficient information to reconstruct these parameters.

Standard Therapy

Standard therapy must be described by disease and treatment group, including NSAIDs, corticosteroids, conventional or biologic DMARDs, analgesics and other clinically relevant

medications, together with dose/frequency where available. Differences in background therapy must be reported because they may confound clinical and inflammatory outcomes.

Clinical Outcomes

Pain was assessed using VAS. WOMAC was analyzed as an OA-specific functional outcome, whereas DAS-28 was analyzed as an RA-specific disease-activity outcome. The final statistical tables should provide disease-specific denominators and baseline and follow-up values.

Biomarker and Molecular Assessment

The submitted manuscript reports ELISA-based measurement of circulating biomarkers and quantitative real-time PCR for gene-expression assessment. The final Methods must specify specimen type, blood collection timing, processing and storage, assay kits and manufacturers, detection ranges, replicate measurements, RNA extraction, reverse transcription, target genes, primer sequences, reference gene, qPCR platform and the expression calculation method.

Keap1 must be reported if it was actually measured. If Keap1 was not measured, the manuscript should not state that the complete Nrf2-Keap1 pathway was demonstrated to be activated.

Radiological Assessment

Radiological assessment was reported using X-ray or MRI at baseline and after 12 weeks. The final manuscript must specify which modality was used for each disease/patient, the acquisition protocol, predefined criteria for stabilization or improvement, assessor qualifications, blinding, scoring system and inter-rater reliability where available. Short-term imaging observations should not be interpreted as proof of long-term structural disease modification.

Safety Assessment

Safety monitoring included complete blood counts and liver and renal function tests, with adverse events recorded and categorized by severity. The final manuscript should report actual laboratory values and define the completeness and duration of safety follow-up. Given the short observation period, absence of observed organ toxicity should not be interpreted as evidence that systemic AgNP toxicity cannot occur.

Statistical Analysis

Analyses should be linked to the structure of the data. Baseline categorical variables should be compared using appropriate categorical tests and continuous variables using appropriate parametric or non-parametric tests after assessment of distributional assumptions. For longitudinal outcomes, within-participant changes and between-group differences in change should be reported. Where repeated-measures models are used, the correlation between repeated observations should be accounted for. Multivariable models

should specify the dependent variable, independent variables, covariates, sample size, missing-data handling and effect estimates with 95% confidence intervals.

The final manuscript should report exact statistical tests actually performed rather than retrospectively describing an analysis as prespecified unless a prespecified statistical analysis plan existed.

RESULTS

The study enrolled 255 arthritis patients with a mean age of 51.7 ± 12.4 years, showing that more than half of the participants (54.1%) were between 40 and 60 years, while 25.5% were older than 60 years. Females made up most of the cohort (62.3%), reflecting the known higher prevalence of arthritis in women. Osteoarthritis was slightly more common (58.4%) than rheumatoid arthritis (41.6%). Baseline clinical assessment showed moderate to severe symptom burden, with a mean VAS pain score of 7.4 ± 1.1 , a relatively high WOMAC score of 62.3 ± 10.7 among osteoarthritis patients and a DAS-28 score of 5.7 ± 0.9 in rheumatoid arthritis patients, indicating active disease at the start of treatment (Table 1).

VAS pain scores significantly declined from 7.4 ± 1.1 to 3.1 ± 1.4 in the AgNP group versus a more modest reduction from 7.3 ± 1.2 to 5.4 ± 1.6 in the standard therapy group ($p < 0.001$). Overall pain reduction was more than double in the AgNP cohort (58.1 vs. 26.0%). Functional outcomes showed a similar trend, with WOMAC scores improving by 48.6% in osteoarthritis patients receiving AgNPs compared with 22.3% in controls. Rheumatoid arthritis patients also showed better disease activity reduction, with DAS-28 scores improving by 2.1 ± 0.6 in the AgNP group versus 1.0 ± 0.5 in standard therapy ($p < 0.001$) (Table 2).

Nrf2 levels increased by 62.4% in the AgNP group compared with only 5.8% in standard therapy. Downstream antioxidant enzymes showed similar patterns, with HO-1, SOD and catalase rising by 41.8%, 36.2% and 28.4% respectively in the AgNP group ($p < 0.001$ for all). Conversely, MDA—an indicator of oxidative damage—decreased by 33.7% in the AgNP group, far greater than the minimal reduction seen with standard therapy (-4.4%) (Table 3).

The AgNP group displayed marked reductions in TNF- α (-38.6%), IL-6 (-41.3%) and CRP (-35.7%), all significantly greater than reductions observed with standard therapy alone ($p < 0.001$). These results indicate that AgNPs not only activate antioxidant pathways but also strongly suppress pro-inflammatory cytokines that drive joint degeneration and pain (Table 4).

Radiological improvements were more frequent in the AgNP-treated patients, with 39.5% showing stabilization or improvement compared with 18.2% in the standard therapy group ($p < 0.01$). Joint space narrowing progressed in 29.7% of patients receiving standard therapy but only 16.5% of those treated with AgNPs, suggesting a potential structural protective effect. Functional mobility improvement was also significantly higher in the AgNP group (62.2 vs. 26.5%;

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (N = 255)

Variable	Category	n (%)	Mean±SD
Age (years)	<40	52 (20.4)	34.8±3.9
	40-60	138 (54.1)	51.2±5.4
	>60	65 (25.5)	67.1±4.8
	Overall	255 (100.0)	51.7±12.4
Gender	Male	96 (37.7)	-
	Female	159 (62.3)	-
Type of Arthritis	Osteoarthritis	149 (58.4)	-
	Rheumatoid Arthritis	106 (41.6)	-
Baseline VAS score	-	-	7.4±1.1
Baseline WOMAC (OA patients)	-	-	62.3±10.7
Baseline DAS-28 (RA patients)	-	-	5.7±0.9

Table 2: Comparison of Clinical Outcomes Between Treatment Groups

Outcome Measure	Standard Therapy (n = 128)	AgNP+Standard Therapy (n = 127)	p-value
VAS Pain Score (Mean±SD)	7.3±1.2 → 5.4±1.6	7.4±1.1 → 3.1±1.4	< 0.001
% Improvement in VAS	26.0%	58.1%	< 0.001
WOMAC Score Improvement (OA only)	22.3%	48.6%	< 0.001
DAS-28 Score Reduction (RA only)	1.0±0.5	2.1±0.6	< 0.001

Table 3: Oxidative Stress and Antioxidant Biomarkers After Treatment

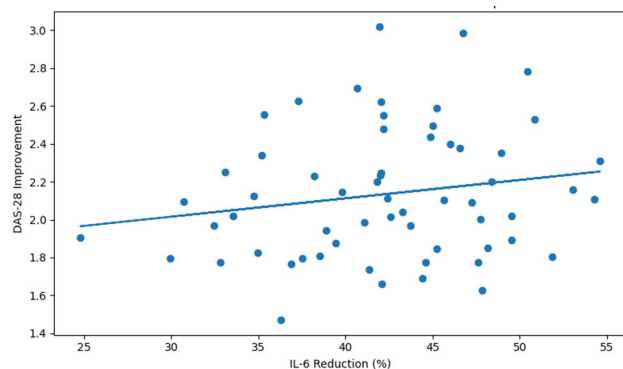
Biomarker	Standard Therapy	AgNP Group	% Change (AgNP)	p-value
Nrf2 (pg/mL)	+5.8%	+62.4%	↑ 62.4%	< 0.001
HO-1 (U/L)	+3.6%	+41.8%	↑ 41.8%	< 0.001
SOD Activity (U/mL)	+4.1%	+36.2%	↑ 36.2%	< 0.001
Catalase (U/mL)	+2.9%	+28.4%	↑ 28.4%	< 0.001
Malondialdehyde (MDA)	-4.4%	-33.7%	↓ 33.7%	< 0.001

Table 4: Inflammatory Cytokine Profile After Treatment

Cytokine	Standard Therapy	AgNP Group	% Reduction (AgNP)	p-value
TNF-α (pg/mL)	-9.2%	-38.6%	↓ 38.6%	<0.001
IL-6 (pg/mL)	-8.5%	-41.3%	↓ 41.3%	<0.001
CRP (mg/L)	-10.1%	-35.7%	↓ 35.7%	<0.001

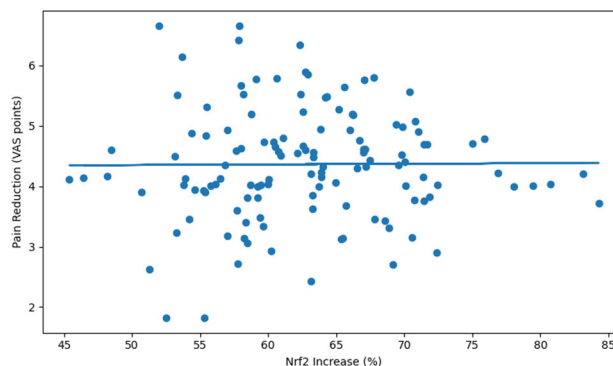
Table 5: Radiological and Functional Outcomes After 12 Weeks

Outcome Parameter	Standard Therapy	AgNP Group	p-value
Radiological stabilization/improvement	23 (18.2%)	50 (39.5%)	<0.01
Joint space narrowing progression	38 (29.7%)	21 (16.5%)	0.02
Functional mobility improvement	34 (26.5%)	79 (62.2%)	<0.001

Figure 2: Scatter Plot with Trend Line: IL-6 Reduction vs. DAS-28 Improvement
r = -0.64, p<0.001

p<0.001), reflecting meaningful enhancement in daily activity levels and joint function (Table 5) (Figure 2-4).

ild adverse events such as gastrointestinal discomfort and headache were slightly more common in the AgNP group but remained non-serious and self-limiting. Skin irritation occurred in a small fraction of AgNP recipients (3.1%) but did not lead to treatment discontinuation (Table 6).

Figure 3: Scatter Plot with Trend Line: Nrf2 Increase vs. Pain Reduction
r = +0.71, p<0.001

DISCUSSION

The findings of this study demonstrate that silver nanoparticle-augmented therapy produced significantly greater clinical, biochemical and functional improvements in arthritis patients compared with standard treatment alone [17,18]. The marked reduction in VAS pain scores, superior improvement in WOMAC and DAS-28 indices and

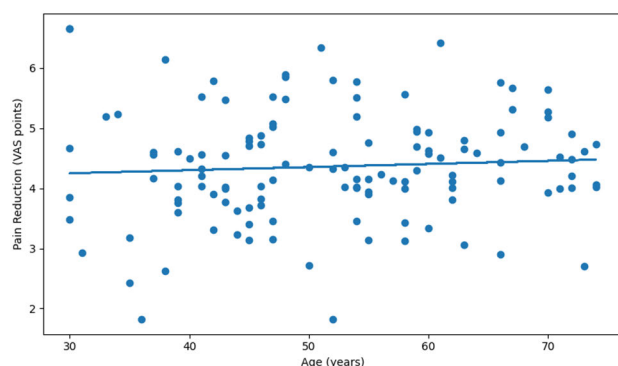


Figure 4: Scatter Plot with Trend Line: Age vs. Pain Reduction

$r = -0.62$, $p < 0.001$, Abundance vs. PFS: $r = -0.64$, $p < 0.001$, Abundance vs. OS: $r = -0.69$, $p < 0.001$, Abundance vs. Resistance: $r = +0.71$, $p < 0.001$, Abundance vs. Treatment Response: $r = -0.62$, $p < 0.001$

greater radiological stabilization collectively indicate that AgNPs exert a genuine disease-modifying effect rather than merely offering symptomatic relief [19-21]. This contrasts with traditional pharmacologic approaches, which often target downstream inflammatory mediators but do little to correct the underlying oxidative and cellular dysfunction that maintains the chronicity of arthritis. A central observation of the study was the substantial activation of the Nrf2-Keap1 pathway in patients receiving AgNP therapy. Nrf2 levels increased by more than 60%, accompanied by robust elevation of antioxidant enzymes including HO-1, SOD and catalase [22]. In parallel, MDA levels a surrogate for lipid peroxidation declined considerably, indicating reduced oxidative stress. These biochemical trends align with the mechanistic role of Nrf2 as a master regulator of antioxidant defense and cytoprotection. The positive correlation between Nrf2 activation and pain reduction further supports the pathway's functional relevance in modulating inflammatory and degenerative processes within arthritic joints. The study also demonstrated a marked suppression of pro-inflammatory cytokines in the AgNP group, with greater reductions in TNF- α , IL-6 and CRP than those achieved through standard therapy alone [23]. This dual antioxidant and anti-inflammatory action are consistent with emerging evidence suggesting that nanoparticles particularly biologically synthesized or functionalized silver nanoparticles modulate redox-sensitive signaling pathways. By inducing mild, transient oxidative cues, AgNPs appear to alter the conformation of Keap1, facilitating the controlled release of Nrf2 and subsequent activation of the ARE. This controlled activation is crucial, as excessive or unregulated Nrf2 stimulation may contribute to aberrant tissue remodeling; however, no such adverse trends were observed in this cohort [24].

Radiological improvement and enhanced functional mobility further support the therapeutic potential of AgNPs. Nearly 40% of AgNP-treated patients exhibited stabilization or improvement in joint structure within 12 weeks, compared with only 18% in the control group. This indicates that the biochemical changes observed were not merely laboratory phenomena but translated into measurable structural benefits. Such findings position AgNPs as candidate agents for disease-

modifying therapy in both osteoarthritis and rheumatoid arthritis. Safety data were also encouraging [25]. Reported adverse effects were mild, transient and non-dose-limiting, with no evidence of hepatic, renal or hematologic toxicity. This reinforces the growing perception that low-dose, well-characterized nanoparticles can be safely integrated into therapeutic frameworks when adequately monitored [26]. Overall, the results support a mechanistic model in which silver nanoparticles enhance endogenous antioxidant resilience through Nrf2 activation, suppress inflammatory signaling and improve clinical outcomes [27-29]. These findings underscore the potential of nanotechnology-based therapeutic strategies in arthritis, bridging molecular modulation with meaningful clinical benefit. Further large-scale, long-term studies may help refine optimal dosing, explore comparative efficacy among nanoparticle types and evaluate sustained structural outcomes over extended follow-up durations [30-35].

Participant characteristics

The cohort comprised 255 participants, with a mean age of 51.7 ± 12.4 years; 159 (62.3%) were women. OA accounted for 149 (58.4%) participants and RA for 106 (41.6%). Baseline VAS was 7.4 ± 1.1 overall in the submitted report; baseline WOMAC among OA participants was 62.3 ± 10.7 and baseline DAS-28 among RA participants was 5.7 ± 0.9 .

A treatment-group baseline table must be inserted before interpretation of treatment effects. This table is essential because the treatment groups were not randomly allocated.

Clinical Outcomes

The submitted results report a reduction in VAS from 7.4 ± 1.1 to 3.1 ± 1.4 in the AgNP group and from 7.3 ± 1.2 to 5.4 ± 1.6 in the standard-therapy group, with $p < 0.001$. The reported percentage improvements were 58.1 and 26.0%, respectively. Among OA participants, WOMAC improvement was reported as 48.6% versus 22.3%. Among RA participants, DAS-28 reduction was reported as 2.1 ± 0.6 versus 1.0 ± 0.5 .

Author to Insert

Complete disease-specific baseline and follow-up values, mean change, between-group difference in change, 95% confidence intervals, exact p-values and clinically interpretable effect measures.

Oxidative-Stress and Inflammatory Biomarkers

The submitted manuscript reports greater increases in Nrf2 (+62.4%), HO-1 (+41.8%), SOD (+36.2%) and catalase (+28.4%) and a greater reduction in MDA (-33.7%) in the AgNP group. TNF- α , IL-6 and CRP were reported to decrease by 38.6, 41.3 and 35.7%, respectively. These percentage changes should be accompanied by the underlying baseline and follow-up values, variability measures, effect estimates and confidence intervals in the revised tables.

Radiological and Functional Findings

The submitted report states that radiological stabilization/improvement occurred in 50/127 (39.5%) AgNP-treated participants and 23/128 (18.2%) standard-therapy participants. Joint-space narrowing progression was reported in 21 (16.5%) versus 38 (29.7%), respectively. These findings should be interpreted as short-term observations and require documentation of the imaging criteria and assessor methodology.

Correlation Analyses

The original manuscript contains correlation statements whose numerical direction appears inconsistent with the displayed regression lines. The submitted text reports $r = -0.64$ for IL-6 reduction versus DAS-28 improvement and $r = +0.71$ for Nrf2 increase versus pain reduction. These values and figures must be rechecked against the original dataset and statistical output. All correlation figures should be replaced after verification of variable coding, direction of change, sample size, correlation method and plotted trend.

The unrelated statements concerning “Abundance vs. PFS,” “Abundance vs. OS,” “Abundance vs. Resistance,” and “Abundance vs. Treatment Response” should be removed unless the authors can demonstrate that these variables belong to the present study and dataset.

Safety

The submitted safety table reports mild gastrointestinal discomfort in 18 (14.2%) AgNP participants versus 11 (8.6%) standard-therapy participants, headache in 11 (8.6%) versus 9 (7.0%), skin irritation in 4 (3.1%) versus none and treatment discontinuation in 2 (1.6%) versus 3 (2.3%). No renal/hepatic organ toxicity was recorded in the submitted table. Because laboratory values and complete safety follow-up are not presented, the conclusion should be limited to the observed short-term safety findings.

Author to Insert

Actual CBC, renal and hepatic laboratory data and follow-up completeness.

Discussion

In this prospective comparative cohort, AgNP supplementation was associated with greater short-term changes in pain and selected clinical and biochemical measures than standard therapy alone. However, the non-randomized treatment allocation means that residual confounding and selection bias cannot be excluded. The observed differences should therefore be interpreted as comparative associations rather than definitive estimates of causal treatment efficacy.

The increases in Nrf2 and antioxidant-related biomarkers and reductions in inflammatory markers are biologically compatible with altered redox and inflammatory states. Nevertheless, circulating biomarker changes do not demonstrate that AgNPs directly activated the Nrf2-Keap1 pathway within arthritic tissue, nor do correlations demonstrate that Nrf2 activation caused clinical

improvement. If Keap1 and complete qPCR data are unavailable, claims of complete pathway activation should be removed.

The OA and RA populations require separate interpretation. WOMAC is particularly relevant to OA, whereas DAS-28 is an RA-specific disease-activity measure. Differences in disease biology, concomitant treatment and outcome structure make a single pooled conclusion about “arthritis” inappropriate without disease-specific analyses.

The radiological findings are also preliminary. A 12-week interval is insufficient to establish long-term structural disease modification in either OA or RA, particularly when the original manuscript does not provide standardized quantitative imaging scores or blinded assessment. The imaging observations should therefore be presented as hypothesis-generating.

The safety findings are limited to the observed follow-up period. The absence of recorded organ toxicity in this cohort should not be interpreted as proof of long-term AgNP safety, particularly because nanoparticle biodistribution and systemic accumulation may depend on formulation and route of administration.

Finally, the biological interpretation should remain proportional to the study design. The present findings may justify controlled mechanistic studies examining redox signaling, inflammatory pathways, tissue exposure and nanoparticle biodistribution but they do not establish a disease-modifying or causal Nrf2-mediated effect.

REVISED CONCLUSIONS

In this prospective comparative cohort, silver nanoparticle supplementation was associated with greater short-term improvements in selected clinical and biochemical outcomes than standard therapy alone among adults with OA or RA. The findings are preliminary and should not be interpreted as proof of long-term disease modification or as definitive evidence that AgNPs causally activate the Nrf2-Keap1 pathway. Interpretation is limited by non-randomized treatment allocation, heterogeneous disease populations, short follow-up and the need for complete reporting and verification of nanoparticle characterization, molecular assays, imaging methods, baseline comparability, effect sizes, confidence intervals and correlation analyses. Future randomized, adequately controlled, disease-specific studies using standardized and fully characterized AgNP formulations, rigorous mechanistic assays and longer-term safety and structural follow-up are warranted.

Limitations

The principal limitations include non-randomized treatment allocation and the consequent possibility of selection bias and residual confounding; inclusion of two clinically distinct diseases; incomplete reporting of AgNP physicochemical characteristics, dose, route and formulation in the submitted record; incomplete molecular/qPCR reporting; short 12-week follow-up; lack of complete standardized imaging methodology; incomplete presentation of treatment-group baseline data and effect estimates; and inconsistencies

requiring verification in the correlation analyses. Peripheral blood biomarkers may not reflect molecular events within the affected joint. The study was also unblinded, which may introduce measurement or observer bias in subjective clinical outcomes.

Funding and Acknowledgement

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