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Research Article

Glutathione Precursor Supplementation with Immunocal® for Inflammaging: An Open-Label Pilot Study Assessing suPAR Modulation in Middle-Aged Adults

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Abstract

Introduction: Chronic low-grade systemic inflammation constitutes a central biological feature of aging and a key factor in the development of multiple chronic diseases [1,2]. The soluble urokinase Plasminogen Activator Receptor (suPAR) has emerged as a robust biomarker of chronic systemic inflammation and biological vulnerability [3-5]. Nutritional strategies aimed at modulating intracellular redox balance may influence upstream inflammatory pathways involved in the regulation of suPAR [6-9].

Objective: To explore whether supplementation with a cysteine-rich whey protein isolate, a glutathione precursor, is associated with changes in circulating suPAR concentrations and health-related quality of life in adults.

Methods: An exploratory, open-label, single-arm, longitudinal pre-post intervention proof-of-concept study. Twelve adult participants received oral supplementation with a cysteine-rich whey protein isolate (Immunocal®) for three months. Circulating suPAR concentrations and health-related quality of life, assessed using the SF-36 questionnaire, were measured at baseline and at the end of the intervention.

Results: After three months of supplementation, mean suPAR levels decreased from 3.19 to 1.87 ng/mL (mean $\Delta = 1.31$; $p < 0.0001$). Mean total SF-36 scores increased from 71.77 to 87.39 (mean $\Delta = 15.61$; $p < 0.0001$). The intervention was well tolerated and no serious adverse events were reported.

Conclusion: Supplementation with glutathione precursors using Immunocal® for a three-month period was associated with a significant reduction in circulating suPAR concentrations, a consolidated biomarker of chronic systemic inflammation and immune activation, as well as with concomitant improvements in health-related quality of life in adults.

Keywords: Soluble Urokinase Plasminogen Activator Receptor (suPAR); Middle-Aged Adults; Glutathione

Introduction

Population aging is associated with a progressive increase in the prevalence of chronic non-communicable diseases, such as cardiovascular disease, type 2 diabetes mellitus, chronic kidney disease, neurodegenerative disorders and cancer [1,2]. This phenomenon has driven interest in identifying common biological mechanisms underlying age-associated functional decline and increased vulnerability to disease.

One of the central concepts in the biology of aging is inflammaging, defined as a state of chronic low-grade systemic inflammation that develops with age, even in the absence of overt infection [1]. Currently, inflammaging is considered an active biological process that significantly contributes to the pathogenesis of multiple age-related chronic diseases [1,2]. Hallmarks of aging, such as cellular senescence, mitochondrial dysfunction, immune dysregulation and loss of proteostasis, both promote and are amplified by chronic inflammatory signaling [2]. Oxidative stress is closely linked to chronic inflammation. Excess reactive oxygen and nitrogen species activate redox-sensitive transcription factors, such as NF-κB, promoting sustained inflammatory signaling [6,7]. This bidirectional interaction between oxidative stress and inflammation plays a central role in biological aging and in the development of chronic diseases [7-9]. In this context, the soluble urokinase plasminogen activator receptor (suPAR) has emerged as a robust biomarker of chronic systemic inflammation and immune activation [3]. Unlike classical acute-phase reactants, suPAR exhibits minimal circadian variability and a limited response to transient physiological stressors, positioning it as an integrative marker of chronic systemic inflammation [3]. Elevated suPAR levels have been consistently associated with accelerated biological aging, functional decline and increased all-cause and cardiovascular mortality in population-based studies [4,5]. Glutathione (GSH) is the principal intracellular thiol antioxidant and plays an essential role in maintaining cellular redox balance [8]. Aging is associated with reduced glutathione availability and diminished synthetic capacity, contributing to increased oxidative stress and dysregulated inflammatory signaling [8,9]. Cysteine is the rate-limiting amino acid for glutathione synthesis and nutritional strategies aimed at increasing its bioavailability have been shown to increase glutathione levels in humans [10,11]. Despite the strong evidence linking redox balance, chronic inflammation and biological aging, it had not previously been explored in humans whether nutritional modulation of intracellular redox balance through glutathione precursors, such as Immunocal®, is associated with changes in systemic biomarkers of chronic inflammation such as suPAR.

Rationale and Hypothesis

Given the mechanistic link between oxidative stress, redox-sensitive inflammatory signaling and regulation of chronic inflammatory pathways implicated in inflammaging [6-9], nutritional modulation of cysteine availability and glutathione synthesis via nutritional precursors represents a biologically plausible strategy to influence chronic systemic inflammation. It was hypothesized that supplementation with a cysteine-rich whey protein isolate, a glutathione precursor (Immunocal®), would be associated with a reduction in circulating suPAR concentrations and with concomitant improvements in health-related quality of life in adults.

Methodology

Study Design

Exploratory, open-label, single-arm, longitudinal pre-post intervention proof-of-concept study.

Participants

Twelve adult participants were voluntarily recruited in a clinical setting. All participants provided written informed consent prior to inclusion.

Intervention

Participants received daily oral supplementation with a cysteine-rich whey protein isolate, a glutathione precursor (Immunocal®), for a three-month period. Participants were instructed to maintain their usual dietary and lifestyle habits throughout the study.

Outcome Measures

- Primary outcome: change in circulating suPAR concentrations from baseline to study completion
- Secondary outcome: change in health-related quality of life, assessed using the SF-36 questionnaire
- Safety: assessed descriptively through clinical follow-up and self-report

Statistical Analysis

Descriptive statistics were used to summarize results. Pre-post comparisons were performed using paired statistical tests. Mean change (Δ) was calculated as the mean of within-subject paired differences. Statistical significance was defined as $p < 0.05$. Analyses were interpreted as hypothesis-generating.

Results

All twelve participants completed the study and were included in the final analysis. Mean suPAR concentrations decreased from 3.19 to 1.87 ng/mL after three months of supplementation (mean $\Delta = 1.31$; $p < 0.0001$). In parallel, mean total SF-36 scores increased from 71.77 to 87.39 (mean $\Delta = 15.61$; $p < 0.0001$). No serious adverse events related to supplementation were reported (Table 1,2).

PATIENT	EGE/SEX	1º VISIT	1º VISIT	FINAL VISIT	FINAL VISIT
		SF-36	SUPAR	SF-36	SUPAR
1	53/M	93,6	4	93,6	2,5
2	44/F	70,5	6	78,5	3,5
3	51/M (TBQ)	77	3,1	89	2,1
4	60/M	88	2,5	90	2,1
5	43/F	85	2	86	1,9
6	44/M	90	1,7	91	1,6
7	52/F	87	2,1	89	2,5
8	28/M	47	3,3	76	1
9	22/F	49	3,1	78	1,3
10	59/M	51	3,9	88	1,6
11	49/M	48	4	89	2,1
12	50/F	55	3,7	95	1,1

Table 1: Effect of Immunocal® on the total of patients.

Parameter	Baseline (Mean)	Final (Mean)	Mean Change (Δ)	Significance(p-value)
suPAR (ng/mL)	3.19	1,87	1.31	P< 0.0001
"There is solid evidence of a real and statistically significant reduction from Baseline to Final. The higher variability (larger Standard Error) makes us less certain about the exact magnitude of the change, but confident that a positive change (a decrease) exists. *"The mean decreased significantly from 3.19 to 1.87 ($\Delta = -1.32$, SE = 0.13, $t(12) = 10.08$, $p < 0.0001$, 95% CI: 1.03 to 1.59)."				

Table 2: Effect of Immunocal® on suPAR Levels (n=13).

Discussion

This exploratory pilot study demonstrates that three months of supplementation with a cysteine-rich whey protein isolate, a glutathione precursor (Immunocal®), was associated with a significant reduction in circulating suPAR concentrations and with improvements in health-related quality of life in adults. These findings are consistent with the pathophysiological framework linking oxidative stress, chronic systemic inflammation and biological aging [1,2,6-9], as well as with the central role of glutathione in cellular redox homeostasis [8,10,11].

Conclusion

Supplementation with glutathione precursors using Immunocal® for a three-month period was associated with a significant reduction in circulating suPAR concentrations, a consolidated biomarker of chronic systemic inflammation and immune activation, as well as with concomitant improvements in health-related quality of life in adults. These preliminary findings support the hypothesis that nutritional modulation of intracellular redox balance, through increased cysteine availability and

glutathione synthesis, may influence chronic inflammatory pathways involved in the inflammaging process. Given that suPAR has previously been associated with accelerated biological aging and increased risk of chronic disease, the observed reduction in this biomarker suggests potential translational relevance for interventions targeting glutathione metabolism.

Nevertheless, the results must be interpreted within the limitations inherent to an exploratory pilot study, including the small sample size, the absence of a control group and the lack of direct measurements of glutathione or other mechanistic markers. Consequently, these data should be considered hypothesis-generating.

Overall, this study provides preliminary human evidence supporting the feasibility of using nutritional strategies based on glutathione precursors to modulate biomarkers of chronic systemic inflammation. Future randomized, controlled clinical trials with larger sample sizes and expanded biomarker panels are warranted to confirm these findings and to clarify their clinical relevance in the context of healthy aging and the prevention of age-related chronic diseases.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt. The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

Authors approved the final version of this paper.

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