J Health Sci Altern Med (2024)
DOI: 10.14456/jhsam.2024.21

Journal of
Health Science and Alternative Medicine

Original Article Open Access

Systematic Review of N-Acetylcysteine Supplementation in the Management of Rheumatic Diseases

Jozélio Freire de Carvalho[1] and Alisson Barbosa Silva[2]

[1] *College of Nursing and Health, Suansunandha Rajabhat University, Samut Songkhram 75000, Thailand*
[2] *Department of Emergency, Phramongkutklao Hospital, Bangkok 10400, Thailand*

Received June 30, 2024
Accepted September 2, 2024
Published December 31, 2024

***Corresponding author**:
Jozélio Freire de Carvalho
College of Nursing and Health,
Suansunandha Rajabhat University,
Samut Songkhram 75000, Thailand

E-mail:
jotafc@gmail.com

ABSTRACT

Introduction: N-acetyl cysteine (NAC) has been used to treat several rheumatological conditions. The study aimed to review the use of NAC in rheumatic diseases.

Methods: PubMed/MEDLINE, EMBASE, and Scielo databases were screened for articles on NAC and rheumatic diseases until September 2023.

Results: 23 articles were found with 13,603 patients. The investigated diseases were systemic sclerosis, systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjogren syndrome, bone metabolism, and a national cohort. Age varied from 17 to 64 ± 7 years old, and female gender ranged from 45.0% to 100.0% in the included articles. Disease duration ranged from 2 months to 12.1 ± 8.36 years. The NAC dosage ranged from 600 to 4,800mg/day. Concerning outcomes, the SSc articles showed improvement in digital ulcers, reduction in frequency and severity of Raynaud phenomenon, improvement in modified Rodnan skin score, reduction in pain visual analog scale, and one of them saw improvement in lung capacities. Regarding RA, all but one showed improvements in visual analog scale (VAS), health assessment questionnaire (HAQ), disease activity score- 28 joints (DAS28), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). In SLE, a reduction in SLE disease activity index (SLEDAI) and British Isles Lupus Assessment Group (BILAG) scores, glucose, CRP, and anti-dsDNA antibody levels were observed. An increase in CH50 was also seen. Unexpectedly increased risk of osteoarthritis in whom was under NAC. The side effects were mild in all studies.

Conclusion: NAC seems to be safe in treating some rheumatic conditions, especially lupus, rheumatoid arthritis, and Sjogren syndrome. Running title: NAC in rheumatic diseases.

Keywords: NAC; N-acetylcysteine; Rheumatic diseases; Systemic lupus erythematosus; Sjögren syndrome; Rheumatoid arthritis

Introduction

N-acetylcysteine (NAC) represents the acetylated variant of L-cysteine, an amino acid with potent anti-inflammatory and antioxidant characteristics. The liver metabolizes it to cysteine, a direct forerunner of intracellular glutathione synthesis, thereby replenishing the intracellular reduced GSH reservoir, frequently decreasing due to the elevated inflammation status and oxidative stress [1]. NAC is frequently used in patients with chronic obstructive pulmonary disease as a mucolytic. NAC has been shown to be beneficial for the clinical parameters in a wide range of immune-mediated and inflammatory conditions. These conditions include pulmonary fibrosis, systemic lupus erythematosus, ulcerative colitis, peripheral and coronary vascular diseases, Sjogren's syndrome, and sclerodermic Raynaud's phenomenon [2]. Autoimmune rheumatic disease is a rare disease with a prevalence that varies from 38.0/100,000 population in lupus, 23.5/100,000 population in Sjogren's syndrome, and 7.1/100,000 population in scleroderma [3].

According to experimental studies, NAC effectively removes free radicals, slows cartilage degradation, decreases synovial inflammation, and attenuates pain [4]. Regarding NAC's effects on rheumatic diseases, some studies evaluated the role of this antioxidant agent with the benefits observed. The

objective, therefore, was to summarize the data on NAC supplementation in rheumatological diseases.

Methods

A systematic search of publications is carried out in Scielo, LILACS, Web of Sciences, and PubMed/MEDLINE until September 2023. The search was based on specific MeSH entry terms, which included: "N-acetylcysteine" OR "acetylcysteine" OR "NAC" AND "rheumatologic" OR "rheumatic" OR “rheumatoid arthritis” OR “systemic lupus erythematosus” OR “Sjogren syndrome” OR “vasculitis” OR “systemic sclerosis” OR “myositis” OR "chondromalacia" OR “osteoarthritis" OR "gout" OR "fibromyalgia" were used. There were no language restrictions. The lists of references for the selected publications were analyzed to identify additional publications. Inclusion criteria were studies on NAC supplementation in rheumatic diseases. Exclusion criteria were in vivo and in vitro studies, as well as editorial and review articles.

The two authors (ABS and JFC) initially searched the literature and independently selected the included studies' abstracts. In the second step, the two authors independently read the full-text publications chosen on the basis of the abstracts. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5] were again followed. Finally, We designed a standardized form for extracting the following information from the relevant publications: authors, publication year, patient numbers, demographics, disease duration, follow-up, NAC dosage, results, and secondary effects.

Results

Twenty-three articles were found, including 13,603 patients. The countries that reported those selected articles were Italy (n=6), Iran (n=4), the United States (n=3), Netherlands (n=1), Australia (n=1), China (n=1), Brazil (n=1), Taiwan (n=1), India (n=1), Thailand (n=1) and the UK (n=1). Ten studies were double-blinded randomized and controlled trials; 7 were open prospective trials; 1 was a double-blinded crossover study; 1 was a retrospective trial; 1 was a national cohort; 1 was a case series; and 1 was a case report. The investigated diseases were systemic sclerosis (n=8), systemic lupus erythematosus (n=6), rheumatoid arthritis (n=5), Sjogren syndrome (n=2), bone metabolism (n=1), and a national cohort in Taiwan (n=1). Age varied from 17 to 64 ± 7 years old, and female gender ranged from 45% to 100% in the included articles. Disease duration ranged from 2 months to 12.1 ± 8.36 years. The NAC dosage ranged from 600 to 4,800mg/day, although 6/20 studies used a continuous infusion of 15mg/kg/h, and 1/20 article used eye drops NAC 5%. The follow-up of all studies ranged from 5 hours to 13 years [Table 1].

Table 1 Studies of N-Acetylcysteine supplementation in rheumatic diseases

Author, reference	Study design	CCountry	N	Age (years old)/gender	DDisease	Disease duration	NAC dose (mg/day)	Follow-up	Outcome	Side effects
Correa et al., 2014 [6]	Double-blinded randomized controlled trial	BBrazil	342	45.6 ± 9.5 100% females	SSSc	5.5 ± 1.9 years	600mg thrice a day vs. placebo	4 weeks	Reduced digital ulcer 0 vs. 2. Both groups improved the frequency and severity of Raynaud. Laser Doppler Imaging did not change after NAC.	2/25 had gastric pain and an increase in menstrual flow
Rosato et al., 2011 [7]	Retrospective study	IItaly	541	47.5 years (23-70) 90% females	SSSc	7.5 years (range 1-37)	15mg/kg/h over 5 hours every 14 days	2 years	NAC increases carbon monoxide diffusing capacity), vital capacity and total lung capacity	Two patients (5%) reported minor side effects (flushing and headache).
Rosato et al., 2009 [8]	Double-blind, placebo-controlled randomized clinical trial	IItaly	40	49 ± 15 97% females	SSSc	11.4±7.1 years	15mg/kg/h over 5 hours	ND	NAC reduced resistance index (RI) in renal artery in patients with early/active capillaroscopic pattern. Reduced modified Rodnan's Total Skin Score <14, and mild-moderate score to the vascular domain of Medsger Scleroderma Disease Severity Scale.	ND

Author, reference	Study design	CCountry	N	Age (years old)/gender	DDisease	Disease duration	NAC dose (mg/day)	Follow-up	Outcome	Side effects
									A higher carbon monoxide diffusion was seen in patients with reduced RI.	
Rosato et al., 2009 [9]	Prospective observational study	IItaly	50	51±15.4 97% females	SSSc	9.5±8.8 years	15 mg/kg/h every 14 days.	3 years	NAC reduced digital ulcer (DU)/patient/year (4.5±3.1 vs. 0.81±0.79) and DU ulcer visual analog scale (VAS; 6.88±2.62 vs. 3.20±1.80), a decrease of the Raynaud's phenomenon (RP) number attacks (7.18±3.87 vs. 3±1.92), and RP VAS (6.24±1.92 vs 3.62±1.48). .	Minor side effects: flushing (2 patients) and headache (1 patient).
Rosato et al., 2009 [10]	Open-label study	Italy	40	49±15 97% females	SSc	11.4±7.1 years	15mg/kg/h over 5 hours	5 hours	In 22 selected patients with an active capillaroscopic pattern, modified Rodnan Total Skin Score (mRTSS) <18 and mild-moderate score to the vascular domain of disease severity scale (DSS), mean HFV increased significantly when compared with the mean	ND

Author, reference	Study design	CCountry	N	Age (years old)/gender	DDisease	Disease duration	NAC dose (mg/day)	Follow-up	Outcome	Side effects
									HFV of 18 SSc patients with late capillaroscopic pattern, mRTSS >18, and severe-end stage score to the vascular domain of DSS.	
Sambo et al., 2001 [11]	Multicenter, open clinical trial	Italy	22	49.63 ± 14.79 73% females	SSSc	12.18 ± 8.36 years	150 mg/kg as load and then 15 mg/kg/h IV for 5 days	11 weeks	Frequency and severity of Raynaud's attacks decreased. Reduced ulcers. Cold challenge test mean recovery time fell by 69.56%, 67.70%, 71.42%, and 71.05% on Days 12, 19, 33, and 61 from basal time.	Only mild effects. Most frequent: weight gain (31.81%), headache (22.72%), and epigastric pain (13.63%)
Salsano et al., 2005 [12]	Open prospective clinical trial	Italy	326	43.9 ± 12.8 85% females	SSSc	11.2±9.6 years	15mg/kg/h over 5 hours	2 years	NAC increased global hand perfusion and decreased adrenomedullin levels.	Mild effects: flushing, headache, nausea/vomiting, epigastric pain and arthralgia.
Furst et al., 1979 [13]	Prospective parallel, double-blind,	United States	22	45.8 ± 3.6 91% females	SSSc	9 ± 2.9 years	1-2g/day initially to a maximum 20g/day	1 year	No positive effect on skin, lung, muscle, and ANA/RF	ND

Author, reference	Study design	CCountry	N	Age (years old)/gender	DDisease	Disease duration	NAC dose (mg/day)	Follow-up	Outcome	Side effects
	placebo-controlled study									
Esalatmanesh et al., 2022 [14]	Randomized, double-blind, placebo-controlled study	Iran	74	48.21 ±} 12.80 82% females	RA	263.03 ± 42.55 months	600mg vs. Placebo	12 weeks	nt, NAC reduced morning stiffness, DAS-28, ESR, malondialdehyde, nitric oxide, hs-CRP, glucose, and L compared to basal pointDL-c. Increased glutathione peroxidase activity and HDL-c. Compared to placebo, NAC reduced glucose, NO and increased HDL-c.	38% vs. 25% of NAC and placebo group, p=NS
Jamali et al. 2021 [15]	Placebo-controlled randomized, double-blind clinical trial	Iran	1	54.14 ± 9.11 86% females	RA	10.5 ±.52 years	600mg twice a day vs. placebo	8 weeks	NAC improved DAS28, number of tender joints, swollen joints, ESR, and VAS.	Led to drug discontinuation in the study: nausea (n=3), heartburn (n=1), and hypertension (n=1). No serius side effect.

Author, reference	Study design	CCountry	N	Age (years old)/gender	DDisease	Disease duration	NAC dose (mg/day)	Follow-up	Outcome	Side effects
Batooei et al., 2018 [16]	Randomized, Double Blind Clinical Trial	Iran	51	53.2 ± 12.5 82% females	RA	710 ± 7.0 years	600mg twice a day	12 weeks	NAC improved global health, pain Visual Analog Scale, and Health Assessment Questionnaire (HAQ). DAS and ESR did not differ.	2 out of each group withdrew from the study
Vreugdenhil and Swaak,1990 [17]	Open-label pilot study	Netherlands	13	64±7 years 85% females	RA treated with gold	38±5 years	3g/day for 7 days	1 week	NAC increased plasma and urinary gold concentrations.	None
Jonsson et al., 1986 [18]	Open-label trial	ND	7	ND	RA	ND	600-1200mg/day	1 year	No benefit.	ND
Abbasifard et al. 2023 [19]	Randomized double-blind clinical trial study	Iran	40	36.1• ± 0.1 63% females	SLE	1.0 ± 4.9 years	600mg thrice a day vs. Conventional treatment	12 weeks	NAC reduced BILAG and SLEDAI and increased complement levels (CH50).	None
Garcia et al., 2022 [20]	Randomized, blinded, controlled trial	United States	49	45.9 ± 1.8 94% females	SSLE	ND	2.4 or 4.8g/day	12 weeks	Attention Deficit and Hyperactivity Disorder Scores were higher in SLE than controls and improved after NAC.	ND
Li et al., 2015 [21]	Case series	China	2	17 and 26 yo 100% females	SLE	2 and 6 months	600mg twice a day	12 weeks	NAC improved blood counts, 24-hour urine protein, erythrocyte sedimentation rate, and the SLEDAI. NAC increased	None

Author, reference	Study design	CCountry	N	Age (years old)/gender	DDisease	Disease duration	NAC dose (mg/day)	Follow-up	Outcome	Side effects
									glutathione level and 8-iso-prostaglandin F2α declined in both cases.	
Lai et al., 2012 [22]	Randomized double-blind placebo-controlled study	United States	36	44.6 ± 1.8 94% females	SLE	ND	1.2 04 2,4 or 4.8g or placebo	12 weeks	2.4 g and 4.8 g NAC reduced: SLEDAI and glucose. NAC increased mitochondrial transmembrane potential in all T cells, reduced mTOR activity, enhanced apoptosis and reversed expansion of CD4−/CD8− T cells, stimulated Foxp3 expression in CD4+/CD25+ T cells, and reduced anti-DNA production.	Reversible nausea with 4.8g
Kudaravalli et al. 2011 [23]	Prospective open controlled	India	32	29 ± 8 90% females	SLE	229 ± 10 months	600mg thrice a day or atorvastatin 10mg/day for 2 weeks	2 weeks	NAC and atorvastatin reduced the reflection index and Stiffness index. NAC reduced CRP and malondihaldeyde.	None
Tewthanom et al., 2010 [24]	Case report	Thailand	1	46 Female	SLE	10 years	600mg thrice a day	12 weeks	Prednisolone was tapered, fatigue disappeared, and urine protein decreased to 1 +. GSH level	None

Author, reference	Study design	CCountry	N	Age (years old)/gender	DDisease	Disease duration	NAC dose (mg/day)	Follow-up	Outcome	Side effects
									increased, and MDA could be maintained within normal levels.	
Walters et al., 1986 [25]	Double-blind, crossover study	NA	26	NA	SS	NA	ND	4 weeks	NAC improved ocular soreness, ocular irritability, halitosis, daytime thirst, and the van Bijsterveld score. Schirmer test, the tear break up time, or any of the laboratory tests changed.	ND
Williamson et al., 1974 [26]	Prospective open trial	United Kingdom	20	58.4 (32-74)Years 90% females	SS	ND	Eye drops 5% NAC	1 year	At 4 months, 50% felt better, at 12 months reduced to 20%.	None
Yeh et al., 2020 [27]	Nationwide cohort retrospective study	Taiwan	12,928 people who used NAC and 51,715 NAC nonusers	56.3 ± 15 45% females	Patients from the Taiwan National Health Insurance	ND	Patients who received oral NAC for more than 28 days within 1 year	13 years	NAC users had a significantly higher incidence of osteoarthritis (adjusted hazard ratio: 1.42, P < .001) even after age and sex stratification.	ND
Sanders et al., 2007 [28]	Randomized, double-blind,	Australia	ND	ND	Early postmenopausal women	ND	2g/day vs. placebo	12 weeks	NAC reduced serum C-telopeptide (boné resorption marker) in 80% vs. 45% placebo	ND

Author, reference	Study design	CCountry	N	Age (years old)/gender	DDisease	Disease duration	NAC dose (mg/day)	Follow-up	Outcome	Side effects
	placebo-controlled pilot study									

MWT: minutes walking test; ND: not described; OA: osteoarthritis; vs. versus.; yo: Years-old; RA: rheumatoid arthritis; BILAG: British Isles Lupus Assessment Group; SLEDAI: SLE Disease Activity Index; SLE: systemic lúpus erythematosus. DAS28: disease activity score 28 joints; SS: sjögen syndrome; VAS: visual analog scale: ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

Concerning outcomes, the SSc articles showed improvement in digital ulcers, reduction in frequency and severity of Raynaud phenomenon, improvement in modified Rodnan skin score, reduction in pain visual analog scale, and one of them saw improvement in lung capacities. Regarding RA, all but one showed improvements in visual analog scale (VAS), health assessment questionnaire (HAQ), disease activity score- 28 joints (DAS28), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). In SLE, a reduction in SLE disease activity index (SLEDAI) and British Isles Lupus Assessment Group (BILAG), glucose, CRP, and anti-dsDNA antibody levels were observed. An increase in CH50 was also seen. Studies in vascular response showed improvement in endothelial responses and stiffness and reflection indexes. The study in SS showed that only 20% of the patients who had taken NAC supplementation showed benefits. The Taiwan national cohort showed an unexpectedly increased risk of osteoarthritis in whom was under NAC. And finally, in early postmenopausal women, NAC reduced a resorption bone marker (CTx). In addition, the side effects were present in 7/23 articles and were all mild; absent in 8/23 studies and not described in 8/23 articles.

Discussion

This is the first review on NAC and rheumatic diseases, and it found that NAC may be efficient in treating several RD. N-acetylcysteine (NAC) is a potent antioxidant and anti-inflammatory agent. Upon administration, the liver rapidly metabolizes NAC into cysteine, a precursor essential for the intracellular synthesis of glutathione (GSH). This process replenishes the intracellular reservoir of reduced GSH, which is often diminished due to heightened inflammatory responses and oxidative stress [1]. The impact of NAC on the clinical outcomes of various immune-mediated and inflammatory disorders—such as systemic lupus erythematosus [24], pulmonary fibrosis [28], ulcerative colitis [29], peripheral and coronary vascular diseases [30], and systemic sclerosis (SSc)-associated Raynaud's phenomenon—has been extensively investigated. The findings suggest that NAC may hold therapeutic potential for these conditions.
Experimental studies on animal models have further demonstrated the efficacy of NAC. For instance, administering NAC to mice with sleep apnea significantly reduced mortality rates [32]. Additionally, as an antioxidant, NAC has been shown to inhibit osteoclast differentiation and function, which is crucial in bone resorption processes. In rodent studies, NAC successfully prevented bone loss associated with ovariectomy [33].

The role of oxidative stress, driven by increased free radical activity, has been implicated in the pathogenesis and progression of SSc. Repeated ischemia-reperfusion episodes in these patients lead to endothelial cell activation, disrupting the balance between vasoconstrictors and vasodilators and increasing the production of reactive oxygen species (ROS) and other toxic byproducts. This cascade of events significantly contributes to the vascular damage characteristic of SSc and can activate fibroblasts and immune cells [34]. As a thiol-containing compound, NAC exhibits robust antioxidant properties. It directly neutralizes free radicals by interacting with hydroxyl radicals and hydrogen peroxide. It indirectly enhances antioxidant defenses by stimulating GSH synthesis, which plays a critical role in scavenging free radicals and protecting against oxidative stress [35]. These attributes have made NAC a widely studied treatment option for respiratory diseases and conditions related to oxidative stress or glutathione deficiency.

In patients with SSc, open-label studies employing high doses of intravenous (IV) NAC have demonstrated notable improvements in blood perfusion, reduced frequency and severity of Raynaud's phenomenon, and decreased active digital ulcers. Despite these promising outcomes, the continuous infusion requirement and high treatment costs limit its widespread application. However, oral administration of NAC has shown promising results in recent studies.

The use of NAC in RA demonstrated improvement in several parameters, including VAS pain and HAQ, and disease activity variables such as DAS 28, ESR, and CRP, showing potential benefits in using NAC in this rheumatic condition. Furthermore, NAC also showed advantages in lupus patients. In fact, the studies showed improvement in complement levels, reduction in anti-dsDNA antibodies and CRP, and improvements in disease activity indexes (BILAG and SLEDAI). In regard to bone metabolism, it was demonstrated that NAC was able to reduce resorption bone markers for the first time.

Regarding side effects, 9/23 studies reported their presence. Although all of them were mild, they consisted of epigastric pain, nausea, flushing, and headache. The present study's strengths are 1. the inclusion of all studies on NAC in RD; 2. the use of international criteria for rheumatic diseases; 3. an extensive literature search was performed. The limitations include only one study, which does not fulfill systematic analysis criteria. Future studies using NAC in rheumatic conditions are desired.

Conclusion

NAC seems to improve rheumatic diseases in the studies herein analyzed, especially lupus, rheumatoid arthritis, and Sjogren syndrome. Moreover, it also seems to be safe, with only minor side effects. More studies, including those on other rheumatic disorders, are indeed necessary to be performed.

Author's contributions

JFC, AL: screened the literature, designed and wrote the manuscript; MFLdSR: screened the literature and edited the manuscript. The three authors agreed to the published version of the manuscript.

Disclosure of interest

The author has no conflicts of interest to declare.

References

[1] Tenório MCDS, Graciliano NG, Moura FA, Oliveira ACM, Goulart MOF. N-Acetylcysteine (NAC): impacts on human health. Antioxidants (Basel). 2021; 10(6): 967.
[2] Wyman B, Perl A. Metabolic pathways mediate pathogenesis and offer targets for treatment in rheumatic diseases. Curr Opin Rheumatol. 2020; 32(2): 184-91.
[3] Kim H, Cho SK, Kim JW, Jung SY, Jang EJ, Bae SC, et al. An increased disease burden of autoimmune inflammatory rheumatic diseases in Korea. Semin Arthritis Rheum. 2020; 50(3): 526-33.

[4] Ozcamdalli M, Misir A, Kizkapan TB, Uzun E, Duygulu F, Yazici C, et al. Comparison of intra-articular injection of hyaluronic acid and N-Acetyl Cysteine in the treatment of knee osteoarthritis: a pilot study. Cartilage. 201; 8(4): 384-90.
[5] Age MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
[6] Correa MJ, Mariz HA, Andrade LE, Kayser C. N-acetilcisteína oral no tratamento do fenômeno de Raynaud secundário à esclerose sistêmica: ensaio clínico randomizado, placebo-controlado e duplo-cego [Oral N-acetylcysteine in the treatment of Raynaud's phenomenon secondary to systemic sclerosis: a randomized, double-blind, placebo-controlled clinical trial]. Rev Bras Reumatol. 2014; 54(6): 452-8.
[7] Rosato E, Rossi C, Molinaro I, Giovannetti A, Pisarri S, Salsano F. Long-term N-acetylcysteine therapy in systemic sclerosis interstitial lung disease: a retrospective study. Int J Immunopathol Pharmacol. 2011; 24(3): 727-33.
[8] Rosato E, Cianci R, Barbano B, Menghi G, Gigante A, Rossi C, et al. N-acetylcysteine infusion reduces the resistance index of renal artery in the early stage of systemic sclerosis. Acta Pharmacol Sin. 2009; 30(9): 1283-8.
[9] Rosato E, Zardi EM, Barbano B, Menghi G, Cianci R, Amoroso A, et al. N-acetylcysteine infusion improves hepatic perfusion in the early stages of systemic sclerosis. Int J Immunopathol Pharmacol. 2009;22(3):763-72.
[10] Rosato E, Borghese F, Pisarri S, Salsano F. The treatment with N-acetylcysteine of Raynaud's phenomenon and ischemic ulcers therapy in sclerodermic patients: a prospective observational study of 50 patients. Clin Rheumatol. 2009; 28(12): 1379-84.
[11] Sambo P, Amico D, Giacomelli R, Matucci-Cerinic M, Salsano F, Valentini G, et al.. Intravenous N-acetylcysteine for treatment of Raynaud's phenomenon secondary to systemic sclerosis: a pilot study. J Rheumatol. 2001; 28(10): 2257-62.
[12] Salsano F, Letizia C, Proietti M, Rossi C, Proietti AR, Rosato E, et al. Significant changes of peripheral perfusion and plasma adrenomedullin levels in N-acetylcysteine long term treatment of patients with sclerodermic Raynauds phenomenon. Int J Immunopathol Pharmacol. 2005; 18(4): 761-70.
[13] Furst DE, Clements PJ, Harris R, Ross M, Levy J, Paulus HE. Measurement of clinical change in progressive systemic sclerosis: a 1 year double-blind placebo-controlled trial of N-acetylcysteine. Ann Rheum Dis. 1979; 38(4): 356-61.
[14] Esalatmanesh K, Jamali A, Esalatmanesh R, Soleimani Z, Khabbazi A, Malek Mahdavi A. Effects of N-acetylcysteine supplementation on disease activity, oxidative stress, and inflammatory and metabolic parameters in rheumatoid arthritis patients: a randomized double-blind placebo-controlled trial. Amino Acids. 2022; 54(3): 433-40.
[15] Jamali F, Ahmadzadeh A, Sahraei Z, Salamzadeh J. Study of the effects of N-acetylcysteine on inflammatory biomarkers and disease activity score in patients with rheumatoid arthritis. Iran J Allergy Asthma Immunol. 2021; 20(5): 574-83.
[16] Batooei M, Tahamoli-Roudsari A, Basiri Z, Yasrebifar F, Shahdoust M, Eshraghi A, et al. Evaluating the effect of oral N-acetylcysteine as an adjuvant treatment on clinical outcomes of patients with rheumatoid arthritis: a randomized, double-blind clinical trial. Rev Recent Clin Trials. 2018; 13(2): 132-8.
[17] Vreugdenhil G, Swaak AJ. Effects of oral N-acetylcysteine on gold levels in rheumatoid arthritis. Br J Rheumatol. 1990; 29(5): 404-5.
[18] Jonsson H, Wollheim FA, Svensson B. No effect of acetylcysteine on refractory rheumatoid arthritis. Clin Exp Rheumatol. 1986; 4(4): 363-4.
[19] Abbasifard M, Khorramdelazad H, Rostamian A, Rezaian M, Askari PS, Sharifi GTK, et al. Effects of N-acetylcysteine on systemic lupus erythematosus disease activity and associated complications: a randomized double-blind clinical trial study. Trials. 2023; 24(1):129.
[20] Garcia RJ, Francis L, Dawood M, Lai ZW, Faraone SV, Perl A. Attention deficit and hyperactivity disorder scores are elevated and respond to N-acetylcysteine treatment in patients with systemic lupus erythematosus. Arthritis Rheum. 2013; 65(5):1313-8.
[21] Li M, Gao W, Ma J, Zhu Y, Li X. Early-stage lupus nephritis treated with N-acetylcysteine: A report of two cases. Exp Ther Med. 2015;10(2): 689-92.
[22] Lai ZW, Hanczko R, Bonilla E, Caza TN, Clair B, Bartos A, et al. N-acetylcysteine reduces disease activity by blocking mammalian target of rapamycin in T cells from systemic lupus erythematosus patients: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2012; 64(9): 2937-46.
[23] Kudaravalli J. Improvement in endothelial dysfunction in patients with systemic lupus erythematosus with N-acetylcysteine and atorvastatin. Indian J Pharmacol. 2011; 43(3): 311-5.
[24] Tewthanom K, Janwitayanujit S, Totemchockcyakarn K, Panomvana Na Ayudhya D. The effect of high dose of N-acetylcysteine in lupus nephritis: a case report and literature review. J Clin Pharm Ther. 2010; 35(4): 483-5.
[25] Walters MT, Rubin CE, Keightley SJ, Ward CD, Cawley MI. A double-blind, crossover study of oral N-acetylcysteine in Sjögren's syndrome. Scand J Rheumatol Suppl. 1986; 61: 253-8.

[26] Williamson J, Doig WM, Forrester JV, Tham MH, Wilson T, Whaley K, et al. Management of the dry eye in Sjogren's syndrome. Br J Ophthalmol. 1974; 58(9): 798-805.
[27] Yeh YT, Liang CC, Chang CL, Hsu CY, Li PC. Increased risk of knee osteoarthritis in patients using oral N-acetylcysteine: a nationwide cohort study. BMC Musculoskelet Disord. 2020; 21(1): 531.
[28] Sanders KM, Kotowicz MA, Nicholson GC. Potential role of the antioxidant N-acetylcysteine in slowing bone resorption in early postmenopausal women: a pilot study. Transl Res. 2007;150(4): 215.
[29] Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. New Eng J Med. 2005; 353(21): 2229-42.
[30] Guijarro LG, Mate J, Gisbert JP, et al. N-acetyl-L-cysteine combined with mesalamine in treating ulcerative colitis: randomized, placebo-controlled pilot study. World J Gastroenterol. 2008; 14(18): 2851-7.
[31] Andrews NP, Prasad A, Quyyumi AA. N-acetylcysteine improves coronary and peripheral vascular function. J Am Coll Cardiol. 2001; 37(1): 117-23.
[32] Suwannaroj S, Lagoo A, Keisler D, McMurray RW: Antioxidants suppress mortality in the female NZB x NZW F1 mouse model of systemic lupus erythematosus (SLE). Lupus. 2001;10: 258-65
[33] Lean J, Davies J, Fuller K, Jagger CJ, Kirstein B, Partington GA, et al. A crucial role for thiol antioxidants in estrogen-deficiency bone loss. J Clin Invest. 2003; 112: 915–23.
[34] Servettaz A, Guilpain P, Goulvestre C, Chéreau C, Hercend C,Nicco C, et al. Radical oxygen species production induced by advanced oxidation protein products predicts clinical evolution and response to treatment in systemic sclerosis.Ann Rheum Dis. 2007; 66: 1202-9.
[35] Kelly GS. Clinical applications of N-acetylcysteine. Altern MedRev. 1998; 3: 114–27.