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Vitamin C Supplementation in Rheumatological Diseases: A Systematic Review

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Abstract Vitamin C (VC) is a potent antioxidant that was tested in a few rheumatic diseases. However, no updated systematic review is available in the literature. PubMed/MEDLINE, EMBASE, and Scielo were searched for articles on VC and rheumatologic diseases between 1966 and March 2023. Eight articles were found, including 227 patients. The investigated diseases were fibromyalgia (n=2), rheumatoid arthritis (n=2), systemic lupus erythematosus (n=1), antiphospholipid syndrome (n=1), Kawasaki disease (n=1) and vasculitis (Wegener's granulomatosis and microscopic polyangiitis) (n=1). Age varied from 7.1 to 53.5±2.7 years old, and female gender ranged from 50% to 100% in the included articles. Disease duration ranged from 10.2 to 14 ± 8 years. VC dosage ranged from 133 mg to 3,000 mg/day. Concerning outcomes, the fibromyalgia studies showed an improvement in clinical and laboratory parameters. Interestingly, one study in RA showed a significant decrease in disease activity after VC. The other studies showed an improvement in these oxidant levels. Specifically, the Kawasaki disease article showed an improvement in vasodilation after intravenous VC injection; while the lupus study did not observe this benefit. Vitamin C is a safe therapy for various rheumatologic diseases. The improved subjective complaints, objective signs and laboratory parameters are promising. However, reconfirmation in more well-controlled, double-blind, cross-over studies, is highly needed.

Keywords: *Vitamin C, anti-oxidants, anti-inflammatory, rheumatoid arthritis, fibromyalgia*

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1. Introduction

Pro-oxidant/antioxidant imbalance in patients with rheumatological diseases, including rheumatoid arthritis (RA) is extensively reported. The most accepted explanation is the acceleration of some cellular metabolic reactions or insufficiency of the antioxidant defense system [1]. Antioxidant supplementation might be an option to counterbalance, stabilize and restore balance in these inflammatory conditions. A series of antioxidant substances are described including vitamins (C and E), resveratrol, coenzyme Q10, lipoic acid and many others [2]. Vitamin C or ascorbic acid is a well-known free radical scavenger and is one of the hydrophilic antioxidants that accumulates in the aqueous phase of the cell. The hydroxyl groups at the double bond in the lactone ring are donors of protons and electrons, turning into the diketone moiety of DHA, which determines the strong reducing properties of VC and protects other cellular components from oxidation [3].

There are some studies investigating the use of VC in rheumatological conditions [4,5]. In fact, highly inflammatory diseases, e.g.: RA and gout, were treated with vitamin C, showing beneficial effects on the oxidative process [4].

In this line, the present study aimed to systematically review all studies that evaluated VC in rheumatic diseases, excluding gout in which systematic reviews are available [6].

2. Methods

2.1. Literature Review

A systematic search of articles published in PubMed/MEDLINE, EMBASE, and Scielo from 1966 to March 2023, using the following MeSH entry terms: "vitamin C" OR "ascorbic acid" AND "rheumatic" OR "rheumatologic" OR "systemic lupus erythematosus" OR "lupus" OR "fibromyalgia" OR " rheumatoid arthritis"

OR “spondyloarthritis” OR “ Sjögren’s syndrome” OR “ myositis” OR “ systemic sclerosis” OR “ vasculitis” OR “Takayasu disease” OR “Wegener’s disease” OR “granulomatosis with polyangiitis” OR “Kawasaki’s disease” OR “polyarteritis nodosa” OR “Livedoid vasculitis” OR Churg-Strauss” OR “eosinophilic granulomatosis with polyangiitis” OR "osteoarthritis" OR " gout" were used. The search had no language restriction. The reference lists of the selected articles were analyzed to identify additional publications.

Two authors (JFC and AL) initially performed the literature search and independently selected the study abstracts. Then, in the second stage, the same reviewers independently read the full-text articles selected by abstracts. The authors followed PRISMA guidelines [7]. Finally, a standardized form was designed to extract the information from relevant articles, including authors, year of publication, number of patients studied, demographic data, disease duration, study follow-up, vitamin C posology, outcomes, and side effects.

Table 1. Studies of Vitamin C in Rheumatic Diseases

Study design	Country/ N	Age/ Gender	Disease/ Disease duration	Vitamin C dose (mg/day)	Follow-up	Outcome	Side effects	ref
Controlled clinical pilot study	Turkey 32	40.1±5.2 100% females	FM NA	500mg + 150m VE	12 weeks	Lipid peroxidation (LP) was higher in the patients at baseline than in controls, whereas LP levels were lower in the VC group. M symptoms did not change.	ND	[8]
Randomized, double-blind, placebo-controlled pilot trial	USA 34	51.7±12.1 93.8% females	FM NA	Myers cocktail* weekly or Ringer (placebo)	16 weeks	At 8 weeks: Myers group had significantly improved tender points, pain, depression, and quality of life directly following treatment, while the placebo had improved tender points only (p _ 0.05).	1 patient in Myers had dyspepsia, insomnia, depression, and a rise in blood pressure, gradually over the course of 3 weeks.	[9]
Randomized, placebo-controlled, double-blind, three-treatment cross-over design trial	Korea 20	52.1±10.3 95% females	RA 10.2 years	VC (133mg) + quercetin (166mg), or lipoic acid (300mg) or placebo	4 weeks	No differences were seen: ➢ Serum concentrations of pro-inflammatory cytokines and CRP. ➢ Scores of disease severity	ND	[10]
Randomized Placebo-Controlled	India 40	ND 74% females	RA ND	ND (VC, VA and VE)	12 weeks	The blood concentrations of total thiols, glutathione and VC were lower in RA as compared to controls, while the concentrations of MDA were much higher. A significant increase in these antioxidants, and a decrease in MDA concentrations after supplementation. RA disease activity index (RADAI) decreased after treatment (67±12.8 to 16.1±6.5).	ND	[11]
Double Blind, Placebo Controlled Pilot Study	Hong Kong 39	44 ± 6 100% females	SLE 14 ± 8 years	500 mg VC and 800 IU VE	12 weeks	After treatment: ➢ VC and VE increased ➢ Decrease MDA ➢ Other oxidative stress markers and antioxidant levels remained unchanged. Flow-mediated dilatation, vWF and PAI-1 levels remained unchanged.	ND	[12]
Cross-sectional	Italy 11	24-51 91% females	APS ND	2,000 mg VC and 900 IU VE	6 weeks	A significant decrease in isoprostanes and monocyte tissue factor antigen and activity.	ND	[13]

Study design	Country/ N	Age/ Gender	Disease/ Disease duration	Vitamin C dose (mg/day)	Follow-up	Outcome	Side effects	ref
Prospective open experimental trial	China 39	7.1 ± 2.7 72% males	KD ND	3,000mg intravenously for the brachial vasodilation test.	Minutes.	Intravenous VC significantly increased the percent change in diameter of the brachial artery induced by reactive hyperemia in KD (6.6±3.5% to 13.0±5.5%, p<0.0001).	ND	[14]
Prospective open trial	UK 12	53.5 50% females	WG (5), MPA (7) 40 weeks	1,000 mg VC and 800 IU VE	10 days	Reduction in superoxide production. Total antioxidant capacity increased.	None	[15]

*Myers cocktail: 5 mL of magnesium chloride hexahydrate (20%), 3 mL of calcium gluconate (10%), 1 mL of hydroxocobalamin (1,000 _g/mL), 1 mL of pyridoxine, hydrochloride (100 mg/mL), 1 mL of dexpanthenol (250 mg/mL), 1 mL of B-complex 100 containing: 100 mg of thiamine HCl, 2 mg of riboflavin, 2 mg of pyridoxine HCl, and 2 mg of panthenol, 100 mg of niacinamide, 2% benxyl alcohol,_ 5 mL of vitamin C (500 mg/mL), and_ 20 mL of sterile water.
APS: antiphospholipid syndrome; FM: fibromyalgia; KD: Kawasaki disease; MPA: microscopic polyangiitis; ND: not described; RA: rheumatoid arthritis; WG: Wegener's granulomatosis; VC: Vitamin C; VE: Vitamin E; VA: Vitamin A.

3. Results

Table 1 summarizes the results of VC supplementation in rheumatic disease subjects. Eight articles were found, including 227 patients. The countries that reported those selected articles were China (n=1), Hong Kong (n=1), India (n=1), Italy (n=1), Korea (n=1), Turkey (n=1), United Kingdom (n=1), and the United States (n=1). Three studies were randomized and controlled; two were double-blinded non-randomized, two were open prospective, one was cross-sectional and one controlled non-randomized or double-blinded trial. The investigated diseases were fibromyalgia FM (n=2), RA (n=2), followed by systemic lupus erythematosus (n=1), antiphospholipid syndrome (n=1), Kawasaki disease (n=1) and vasculitis (Wegener's granulomatosis and microscopic polyangiitis) (n=1). Age varied from 7.1 ± 2.7 to 53.5 years old, and female gender ranged from 50% to 100% in the included articles. Disease duration ranged from 10.2 to 14 ± 8 years, although these data were available only in two studies. The VC dosage ranged from 133 mg to 3,000 mg/day, all but one study gave VC per oral, and 1 study gave it intravenously. The follow-up of all studies ranged from minutes to 16 weeks.

Concerning outcomes, the first FM study showed an improvement in laboratory parameters such as lipid peroxidation and reduction in malondialdehyde (MDA) levels [8]. The other article showed that patients improved at 8 weeks with the Myers cocktail that contains VC: tender points, pain, depression, and quality of life directly following treatment, while the placebo had improved tender points only [9]. Of the studies on RA, one of them did not observe any difference after VC supplementation [10]; and the other one observed decreased lipid peroxidation and MDA levels [11]. Interestingly, the study showed a significant decrease in disease activity after VS measured by the RA disease activity index (RADAI) [11]. The other studies showed an improvement in these oxidant levels [8,13,15] Specifically, the Kawasaki disease article showed an improvement in vasodilation after intravenous VC injection [14]; while the lupus study did not observe this benefit [12].

All the above-sited articles demonstrated improvements in diverse rheumatic diseases parameters, including pain intensity, function, disease activity (DAS 28), swelling joints, and reduced inflammatory biomarkers (interleukins 1 and 6, tumor necrosis factor, C-reactive protein, and erythrocyte sedimentation rate). Regarding side effects, they were not described in 6/8 studies, not present in 1/8 [15] and one patient had a moderate adverse effect in 1/8 study [9].

4. Discussion

This is the first study to systematically review the topic of vitamin C supplementation used in RDs.

Clinical evidence has suggested oxidative stress is elevated in RA and osteoarthritis patients implying reactive oxygen species are possible mediators of tissue damage [16]. Rheumatoid arthritis patients revealed higher levels of plasma malondialdehyde and lower plasma total antioxidant capacity, free thiols, and antioxidant enzyme activity compared to those of the healthy controls. The elevated level of reactive oxygen species (ROS) in synovial fluid of RA patients is thought to be generated by activated macrophages, monocytes, and granulocytes, as well as anoxic reperfusion reactions that may occur with the movement of affected joints [17]. ROS triggers a cascade of events through NFkB activation, which up-regulates gene expression of proinflammatory cytokines that mediates the immune responses causing inflammation. In-vitro studies have shown that dietary antioxidants effectively suppress the release of inflammatory cytokines by reducing available ROS [18].

Vitamin C has been successfully documented to restore exercise blood flow responses in older but not young individuals [19], which has been confirmed mechanistically to represent an improvement via endothelial NO availability [20]. Overall, these findings suggest that oxidative stress may contribute to exercise-blood flow impairments, which may be particularly beneficial in patient populations with increased ROS. In this manner, several authors documented the benefit of vitamin C-induced, flow-mediated dilation, in patients with Kawasaki disease [21,22].

The present systematic review shows that almost all studies, herein included, VC supplementation reduced oxidative levels of substances such as MDA and lipid peroxidation, and also of inflammatory cytokines. Furthermore, a benefit on disease activity was reported in RA. In fact, patients reduced significantly the RA disease activity index (RADAI) after antioxidant intake, including VC [11,23]. Intriguingly and logically, intravenous VC was recently suggested to be beneficial in the oxidative stress and hyper-Inflammation in severe covid-19 and long covid syndrome [24] and to modulate the overwhelming oxidative stress in critically ill patients with organ failure, severe sepsis, trauma, and reperfusion after ischemia [25,26,27]. Recently, VC was suggested to be an effective alternative therapy in boosting myelin repair in demyelinating conditions [28] in various respiratory, allergic and immunological diseases [29] and even in gliadin-induced mucosal immune inflammatory response in celiac disease patients [30]. It can be summarized that VC is a universal antioxidant, immunomodulatory and anti-inflammatory molecule. Figure 1 summarizes the various diseases that VC might be beneficial to and the main mechanisms allocated to VC's beneficial profile.

The present study's strengths are 1. Only patients fulfilling international criteria for RDs were included; and 2. the inclusion of all kinds of study designs applying VC in RDs, excluding human and animal studies and in vitro studies. In this way, the authors believe all published cases of VC supplementation in rheumatic patients were collected.

Some limitations are observed in the present study. No comparison was available between classical pharmaceutical treatments and VC supplementation for RDs. In addition, the number of participants was relatively low, and follow-up time was short for such chronic conditions. Finally, only a few rheumatic diseases were included (RA, SLE, Kawasaki disease and vasculitis). It is desired to evaluate the effect of VC in other rheumatological and autoimmune conditions. Future studies should include larger patient samples with more long-term observation and better academically designed protocols to decipher the therapeutic mechanism and the role of VC supplementation in rheumatic conditions.

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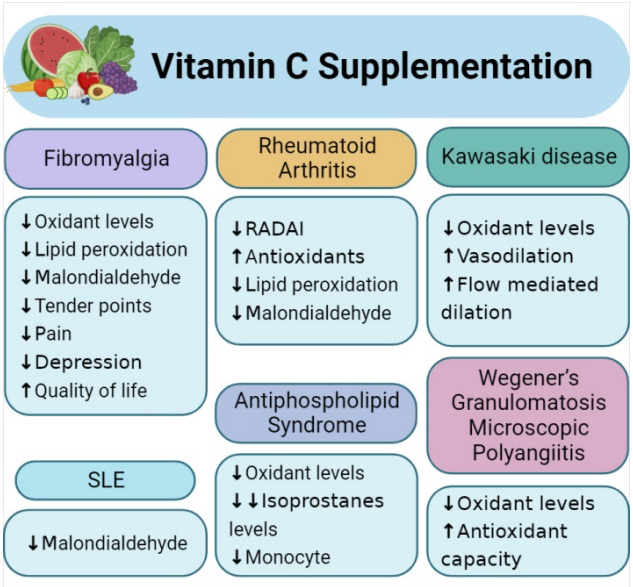

Figure 1. A summary of the various diseases that VC might be beneficial to and the main mechanisms allocated to VC's beneficial profile. Created with BioRender.com. SLE: systemic lupus erythematosus, RADAI: RA disease activity index.

5. Conclusion

Only a few articles in the literature evaluate the effects of vitamin C in rheumatological diseases, and only five disorders were assessed: fibromyalgia, RA, lupus, and vasculitis (Kawasaki diseases, Wegener's granulomatosis and microscopic polyangiitis). Only in RA, did one study show a decrease in disease activity. Nevertheless, almost all included studies demonstrated that this nutritional supplement is efficacious in reducing oxidative parameters such as MDA and superoxide, without side effects. Based on the above, it is concluded that VC emerges as an exciting option to be thoroughly explored in the rheumatological field.

Abbreviations

APS: antiphospholipid syndrome; FM: fibromyalgia; KD: Kawasaki diseases; MPA: microscopic polyangiitis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; VC: vitamin C: WG: Wegener's granulomatosis; ROS: reactive oxygen species.

Conflicts of Interest

Author AL, Author JFdC, Author MH and Author CB declare that they have no conflict of interest.

Author Contributions:

Aaron Lerner: writing review and editing, supervision, Jozélio Freire de Carvalho: conceptualization, data

curation, formal analysis, methodology, validation, writing the original draft. Motti Haimi: writing and editing, Carina Benzvi: writing, visualization, software.

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