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VITAMIN C FOR THE PREVENTION OF COMPLEX REGIONAL PAIN SYNDROME AFTER FOOT AND ANKLE FRACTURES OR SURGERY: A SYSTEMATIC REVIEW

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ABSTRACT – *Objective:* Complex regional pain syndrome type I (CRPS-I) is a debilitating pain disorder that can develop after trauma or surgery. This systematic review aims to evaluate the association between prophylactic oral vitamin C supplementation and the development of CRPS-I after foot and ankle fractures or surgery.

Materials and Methods: This systematic review was conducted according to the PRISMA guidelines. A comprehensive literature search of the PubMed, Embase and Cochrane databases was performed up to the 30th of April 2026. Four studies evaluating vitamin C for the prevention of CRPS-I following foot or ankle fractures or surgeries were therefore included. RoB 2 and NOS were used to evaluate the methodological quality of the studies.

Results: Interventions consisted of oral vitamin C supplementation, after elective surgery, operative and non-operative fracture management. Vitamin C supplementation was consistently associated with a lower incidence of CRPS-I, ranging from 1.28% to 4.9% compared with 9.6% to 21.7% for the control group. Multivariate analyses of two studies identified vitamin C intake as an independent protective factor against CRPS-I. One study evaluating adjunctive therapies including vitamin C reported lower postoperative complication rates. Reported independent risk factors for CRPS-I included previous history of CRPS-I, cast immobilization and alcohol abuse, whereas female sex, smoking, diabetes mellitus and psychological factors were not independently associated factors for CRPS-I.

Conclusions: Available evidence suggests the preventive role of vitamin C supplementation against CRPS-I following foot and ankle trauma or surgery, although further research based on foot or ankle orthopaedic patients is necessary.

KEYWORDS: Ascorbic acid, CRPS-I, Prophylaxis, Oral supplementation, Postoperative complication, Incidence, Risk factor.

INTRODUCTION

Complex regional pain syndrome (CRPS) is a debilitating pain syndrome that typically develops after trauma or surgery. It is characterized by persistent regional pain that is disproportionate in duration or intensity to the usual course of the inciting event. CRPS is often associated with distal predominance of signs and symptoms involving sensory, vasomotor, sudomotor, and/or motor or trophic alterations, including allodynia or hyperalgesia. This pathology shows a variable clinical

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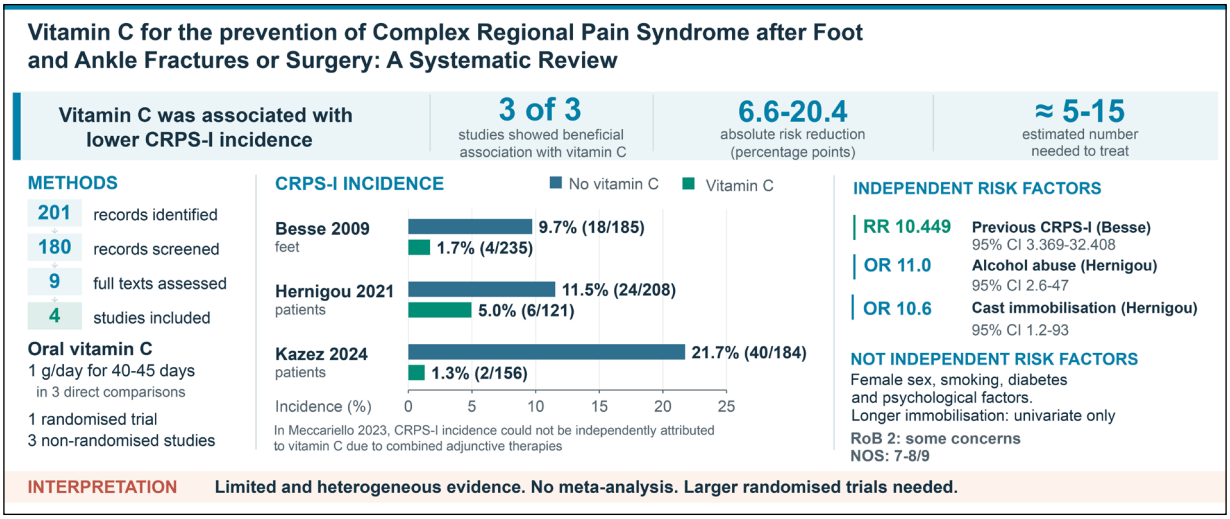

Graphical Abstract. This graphical abstract summarizes the findings of this systematic review evaluating vitamin C supplementation for the prevention of CRPS-I following foot and ankle fractures or surgery. The available evidence suggests a potential protective effect of vitamin C, with three direct comparisons favoring supplementation. However, methodological heterogeneity and limited evidence warrant cautious interpretation and further research.
CRPS-I: Complex regional pain syndrome type I; RR: Relative risk; OR: Odds ratio; CI: Confidence interval; RoB 2: Cochrane Risk of Bias 2 tool; NOS: Newcastle-Ottawa Scale. Absolute risk reductions and estimated numbers needed to treat are calculated from the three directly compared studies.

progression over time[1-3]. CRPS is classified into CRPS-I, occurring without a confirmed major peripheral nerve injury, and CRPS-II, associated with a distinct peripheral nerve lesion[1-3]. This review focuses on CRPS-I. Although uncommon, CRPS-I may result in important functional impairment and reduced quality of life[4,5]. Beyond trauma, stress fractures in athletes are another type of bone injury that may be considered in the broader context of CRPS-I[6].

The pathogenesis of CRPS-I remains incompletely understood and is thought to involve neurogenic inflammation, autonomic dysfunction, and oxidative stress[7-11]. Based on these mechanisms, vitamin C has been proposed as a potential preventive strategy due to its antioxidant and anti-inflammatory properties[12,13].

Several studies have evaluated vitamin C intake for the prevention of CRPS-I, particularly following upper extremity fractures and surgery[14-19]. However, evidence regarding foot and ankle trauma or surgery remains limited and heterogeneous, with variations in study design, populations, supplementation protocols, follow-up duration, and diagnostic criteria[5,20-22]. Consequently, the clinical effectiveness of vitamin C in these populations remains uncertain.

The primary objective of this review is to compare the incidence of CRPS-I between patients receiving prophylactic vitamin C supplementation and control groups without vitamin C supplementation following foot or ankle fractures or surgery. The secondary aim is to analyze possible risk factors for CRPS-I development on these populations.

MATERIALS AND METHODS

Search strategy

A comprehensive literature search was performed in April 2026 using the PubMed, Embase, and Cochrane databases. All eligible studies published to date were considered for inclusion.

The search strategy used combinations of Medical Subject Headings (MeSH) and free-text keywords related to vitamin C, complex regional pain syndrome, and foot or ankle pathology. The following search string was used: ("vitamin C" OR "ascorbic acid" OR "ascorbate") AND ("foot" OR "feet" OR "ankle" OR "malleolar" OR "lower extremity" OR "leg" OR "tibia" OR "calcaneus") AND ("fracture" OR "fractures" OR "injury" OR "trauma" OR "surgery" OR "operation" OR "postoperative" OR "orthopaedic") AND ("complex regional pain syndrome" OR "CRPS"). Additionally, reference lists of eligible articles were manually screened to identify any potentially relevant study not captured by the initial database search.

Eligibility criteria

The inclusion criteria were established according to the PICO framework (Population, Intervention, Comparator, Outcome). Studies were included if they involved adults (≥18 years) with foot or ankle fractures treated either operatively or conservatively, or adults undergoing elective foot and ankle surgeries. The intervention evaluated was pro-

phylactic oral vitamin C supplementation. Studies were eligible regardless of vitamin C dosage or duration of treatment.

Exclusion criteria were: a) paediatric populations (<18 years); b) upper limb fractures or surgeries; c) populations not involving the foot or ankle region or not involving vitamin C supplementation; d) if vitamin C was administered only after CRPS diagnosis; e) if vitamin C was administered through a non-oral route; f) non-English language publications; g) case reports, small case series (n<10 patients), narrative or systematic reviews, editorials, conference abstracts, letters to the editor, expert opinions, and laboratory studies were excluded.

Study selection

The study selection process followed the PRISMA flow methodology[23]. This systematic review was prospectively registered in the PROSPERO (registration number: CRD420251271680). The initial search identified 201 records. After exclusion of 21 non-English publications, 180 studies remained for title and abstract screening. During the screening phase, studies were excluded for the following reasons: involvement of anatomical regions other than the foot or ankle (n = 95), absence of CRPS as an outcome (n = 15), absence of vitamin C supplementation (n = 59), and studies that were systematic reviews or meta-analyses including the foot or ankle region (n = 2). After this screening stage, nine studies were considered potentially eligible and retrieved for full-text assessment. Following full-text evaluation, five studies were excluded due to being letters to the editor (n = 2), case reports (n = 2), or non-human/ex-vivo studies (n = 1). Finally, four studies met all eligibility criteria and were included in the final systematic review (Figure 1).

Titles and abstracts were independently screened by two reviewers. Full-text articles were retrieved for all studies that appeared potentially eligible. Disagreements between reviewers regarding the study inclusion were resolved through discussion and consensus.

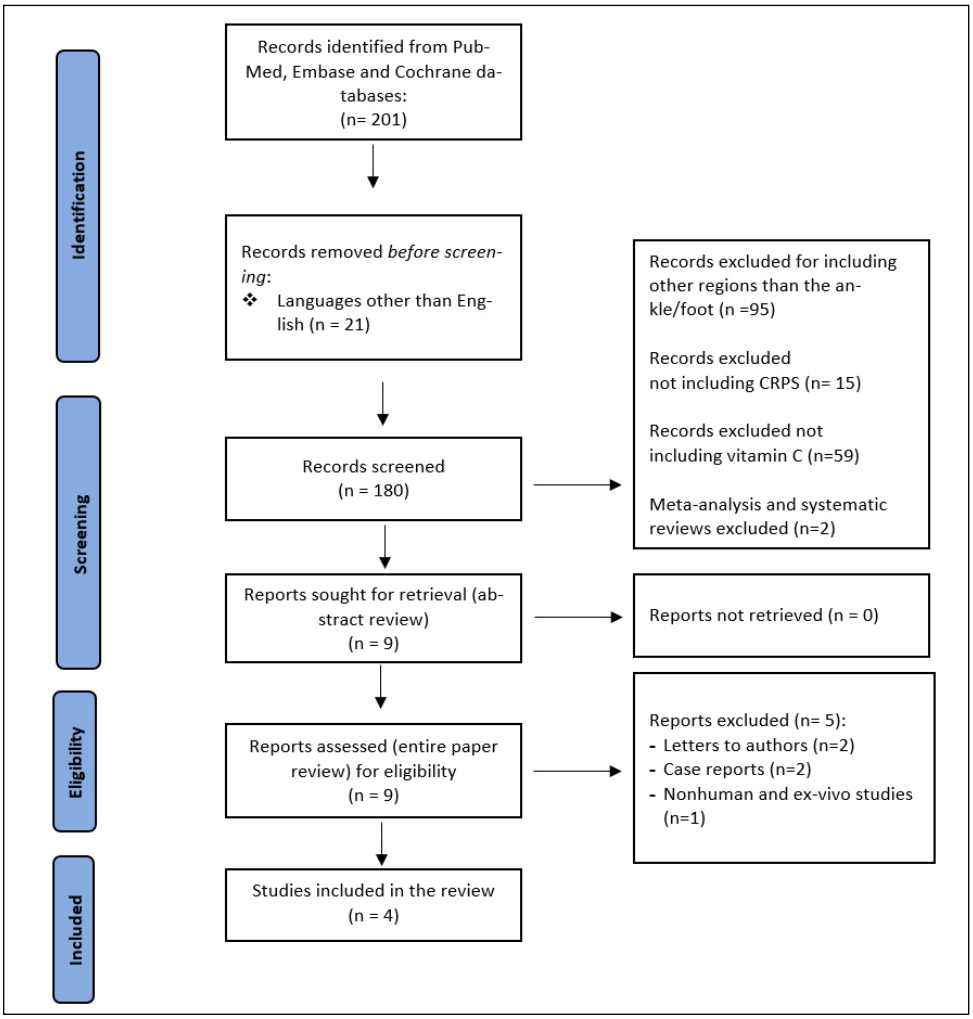

Figure 1. PRISMA flow diagram illustrating the selection process of studies included in the systematic review.

Risk of bias assessment

The methodological quality of the included studies was independently assessed according to the study design.

The randomized controlled trial (RCT) was appraised with the Cochrane Risk of Bias 2 (RoB 2)[24], analysing bias arising from the randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4), and selection of reported results (D5) with an overall judgement of low risk, some concerns, or high risk.

Non-randomized studies were assessed using the Newcastle-Ottawa Scale (NOS) tool[25], which evaluates the bias from three categories: selection (4 stars), comparability (2 stars), and outcome assessment (3 stars), for a maximum score of 9 stars. As the NOS does not provide validated cut-offs for risk of bias categories, the results are presented as star ratings and interpreted qualitatively.

Any discrepancies were resolved through discussion and consensus by the authors. The results of the risk of bias assessment were considered during the interpretation of the results and discussion of the findings.

RESULTS

Study design characteristics

A total of 4 studies were included in the present systematic review, which included different types of studies (one randomized controlled trial, one prospective quasi-experimental before-after study, one prospective non-randomized comparative cohort study, and one retrospective cohort study), with heterogeneous populations undergoing foot and ankle surgery or fracture management. The studies investigated the efficacy of vitamin C in the prevention of CRPS-I in conservatively treated fractures, trauma surgery, and elective foot and ankle surgery.

The size of the populations varied between the studies (n=61-392 patients). All studies were conducted in Europe.

Across the included studies, the diagnostic criteria varied: Hernigou et al[5] and Kazez et al[22] applied the Budapest criteria[26], Besse et al[20] used 1994 IASP criteria[1,2] and Meccariello et al[21] did not report the used criteria.

In three studies, vitamin C supplementation was administered at a dose of 1 g/day for approximately 40-50 days following trauma or surgery. However, Meccariello et al[21] did not specify the dosage of vitamin C. Follow-up duration varied across studies, from early postoperative assessments at 10-15 days to final follow-ups at 12 months.

The four included studies involved different populations, fracture types, fracture management, surgical procedures (trauma or elective), diagnostic criteria, duration of the vitamin C intake and follow up periods. Therefore, the studies show clinical heterogeneity.

A synopsis of the studies is shown in Table I.

Study quality

The results of the assessment by the RoB 2 tool[24] for the RCT is detailed in Figure 2. For non-randomized trials, the assessment made by the NOS tool[25] is shown in Table II. The results from the RoB 2 were presented as "traffic-light" visualizations, and the ones from the NOS as "stars" in Figure 2 and Table II, respectively.

The included studies demonstrated moderate to high methodological quality. Hernigou et al[5] presented some concerns according to the RoB 2 mainly in randomization process and the selection of the reported result. The three non-randomized studies[20-22] scored between 7 and 8 stars on the NOS tool, mainly due to an incomplete adjustment for confounding variables and an insufficient reporting of follow-up procedures.

Baseline characteristics and risk factors for CRPS-I

The different variables were heterogeneous and not consistently reported across studies.

The mean age ranged from 43.7 years (Meccariello et al[21]) to 53.8 years (Hernigou et al[5]) in the vitamin C group and from 42.3 years (Meccariello et al[21]) to 55.7 years (Hernigou et al[5]) in the control groups. Kazez et al[22] did not specify the age distribution for the vitamin C and control groups, providing only the mean age of the overall study cohort (45.5 years). None of the included studies found a significant association between age and CRPS-I occurrence.

Sex distribution varied between cohorts, with Kazez et al[22] reporting a larger male cohort (n=258/340; 75.9%), and Besse et al[20] and Hernigou et al[5] showing a predominantly female cohort (n=303/392; 77.29% and n=231/329; 70.21%, respectively). Meccariello et al[21] reported a slight male predominance in the three groups of the study. In Kazez et al[22], women were significantly more likely to develop CRPS-I than men (47.6% *vs.* 20.8%, $p<0.001$), which could not be confirmed by the other three studies included in the review.

Table I. Synopsis of all the articles included in the present systematic review.

Study	Study design	Setting	Treatment groups N total	Gender (M:F)	Mean age (Range)	Vitamin C protocol	Fracture/ surgery types	Diagnostic criteria	CRPS Vit C, n/N (%)	CRPS Control, n/N (%)	*p*-value	Effect size *p*-value	Follow-up	Primary outcome
Besse et al[20] (2009)	Prospective quasi-experimental before-after study (non-randomised controlled study)	Elective foot and ankle surgery	No vitamin C: 185 feet, 177 patients Vitamin C: 235 feet, 215 patients N=420 feet, 392 patients	44:133 feet 48:137 patients 49:166 feet 55:180 patients	47.1 (16-78) 51 (15-87)	Vitamin C prophylaxis 1 g/day for 45 days	Forefoot surgery (Hallux valgus correction, metatarsal osteotomies, toe corrections) Midfoot and Hindfoot surgeries (Arthrodesis, ankle ligament reconstruction) Hardware removal	1994 IASP criteria	4/235 (1.7%)‡	18/185 (9.6%)‡	$p < 0.0001$*	RR 0.197 95% CI (0.063- 0.611)¶ $p<0.005$*	10th, 21st and 45th day post-operatively, and then every 3 months	Incidence of CRPS-I
Hernigou et al[5] (2021)	Prospective randomised controlled clinical trial	Foot and ankle surgery (both trauma and elective cases)	No vitamin C: 208 patients Vitamin C: 121 patients N=329 patients	62:146 36:85	55.7 (NR) 53.8 (NR)	Vitamin C prophylaxis 1 g/day for 40 days	Trauma surgery ORIF malleolar fractures and Achilles suture ORIF of the talus or the calcaneus ORIF of the tarse or the metatarses Elective foot and ankle surgery Forefoot procedures (Hallux valgus osteotomies, toe corrections, metatarsal corrections) Midfoot arthrodesis Hindfoot /ankle arthrodesis and ligament reconstruction Hardware removal	Budapest criteria + scintigraphy	6/121 (4.9%)	24/208 (11.5%)	p=0.039*	OR 0.19 95% CI (0.05-0.8)¶ p=0.021*	12th day, at 6 weeks, 3 and 6 months, and then every year	Incidence of CRPS-I

Continued

Table I *(continued)*. Synopsis of all the articles included in the present systematic review.

Study	Study design	Setting	Treatment groups N total	Gender (M:F)	Mean age (Range)	Vitamin C protocol	Fracture/ surgery types	Diagnostic criteria	CRPS Vit C, n/N (%)	CRPS Control, n/N (%)	*p*-value	Effect size *p*-value	Follow-up	Primary outcome
Meccariello et al[21] (2023)	Prospective non-randomized comparative cohort study	Bimalleolar fracture (surgical treatment)	OS: 22 patients I+B+C : 18 patients B+C: 21 patients N= 61 patients	12:10 10:8 11:10	42.3 (18-64) 43.7 (18-64) 42.6 (18-64)	Vitamin C combined with bromelain (dose not specified) ± ion resonance for 50 days	ORIF of fractures type Weber A, Weber B1, Weber B2, Weber B3	NR	I+B+C: 0/18[§] B+C: 1/21 (4.54%)[§]	OS: 1/22 (4.54%)[§]	*p*=0.001*	—	1 month 3 months (final outcome)	Incidence of postoperative complications (including CRPS, stiffness, soft tissue complications)
Kazez et al[22] (2024)	Retrospective cohort study	Calcaneal fractures treated conservatively	Vitamin C: 156 patients No vitamin C: 184 patients N=340 patients[†]	NR NR 258: 82[†]	NR NR 45.5 (18-90)[†]	Vitamin C prophylaxis 1 g/day for 40 days	Calcaneal fractures: Sanders type I (treated conservatively by cast for 4-6 weeks without bearing weight)	Budapest criteria	2/156 (1.28%)	40/184 (21.7%)	*p*<0.001*	—	15, 30, and 45 days post-trauma and then every 2 months for 12 months	Incidence of CRPS-I

[†]Kazez et al22 reported age and sex distribution for the entire study cohort but did not provide these variables separately for the vitamin C and control groups;
[‡]In these results following the original study, the percentages are calculated based on N as feet (N =235 in vitamin C group or N= 185 in control group) and not as N patients (N=215 in vitamin C group or N=177 in control group);
[§]CRPS-I incidence could not be independently attributed to vitamin C due to combined adjunctive therapies. The vitamin C group includes patients receiving bromelain and/or ion resonance in addition to vitamin C. The reported p-value refers to the comparison across three groups in the original study;
[¶]The reported RR and p-value correspond to the multivariate logistic regression analysis;
*A *p*-value < 0.05 was considered statistically significant;
NR: Not reported; CI: Confidence interval; OS: only surgery; I+B+C: ion resonance+bromelain+vitamin C; B+C: bromelain+vitamin C, ORIF: Open Reduction and Internal Fixation, IASP: International Association for the Study of Pain, RR: Relative Risk.

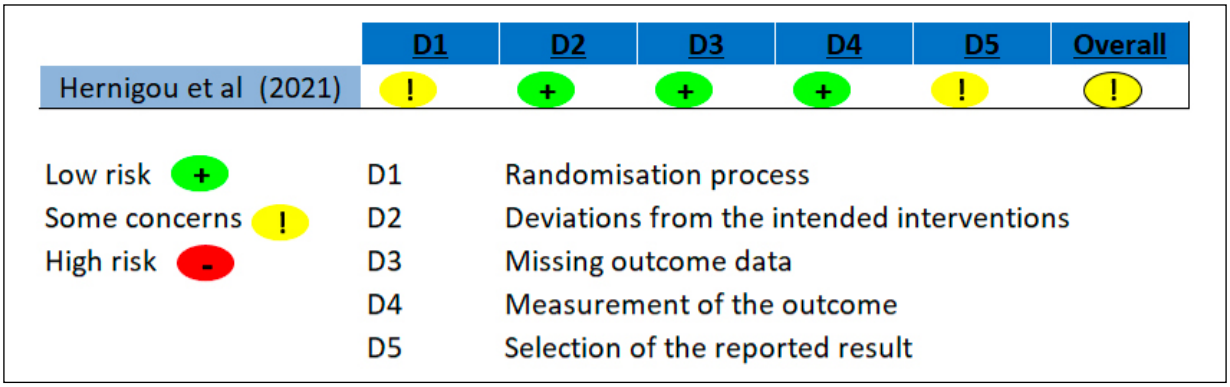

Figure 2. Risk of bias assessment for randomized trials using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2)[24].

Table II. Risk of bias assessment for non-randomized studies using the Newcastle-Ottawa Scale (NOS)[25].

	Besse et al[20] (2009)	Meccariello et al[21] (2023)	Kazez et al[22] (2024)
Selection			
Representativeness	★	★	★
Selection of non-exposed cohort	★	★	★
Ascertainment of exposure	★	★	★
Outcome not present at start of study	★	★	★
Comparability			
Comparability of cohorts	★★	★	★
Outcome			
Assessment of outcome	★	★	★
Follow-up duration	★	—	★
Adequacy of follow-up	—	★	★
Total score	**8/9**	**7/9**	**8/9**

— = No star; ★ = One star; ★★= Two stars. A maximum of two stars can be given for the comparability section.

Univariate analyses performed by Kazez et al[22] demonstrated significant associations between CRPS-I occurrence and smoking, diabetes mellitus, and prolonged immobilization. Smoking (33.3% *vs.* 13.1%, p=0.002) and diabetes mellitus (21.4% *vs.* 9.7%, p=0.030) were more frequent among CRPS-I patients. Patients who developed CRPS-I had longer immobilization periods than those that did not develop CRPS-I (43.24 ± 5.47 days *vs.* 36.21 ± 7.52 days, p<0.001).

In Hernigou et al[5] both alcohol abuse and cast immobilization were identified as significant risk factors for CRPS-I. Alcohol abuse was associated with a markedly increased risk of postoperative CRPS-I (OR 11; 95% CI 2.6-47; p=0.001) and cast immobilization was also significantly associated with CRPS-I occurrence (OR 10.6; 95% CI 1.2-93; p=0.034). However, these findings are not directly comparable with those of Kazez et al[22], who evaluated immobilization duration rather than cast immobilization as a binary variable. The findings of Kazez et al[22] could not be confirmed by Hernigou et al[5]. In their study population, immobilization was not significantly associated with CRPS-I. Smoking was also evaluated but was not identified as an independent risk factor in the multivariate analysis. Diabetes mellitus was reported among baseline characteristics but was not included in the multivariate risk factor analysis.

Besse et al[20], showed that an anxio-depressive context was associated with CRPS-I occurrence in univariate analyses. However, after multivariate analyses, only previous history of CRPS-I remained a significant independent risk factor, increasing the risk approximately tenfold (RR 10.449; 95% CI 3.369-32.408; p<0.001). This last variable was excluded in Hernigou et al[5] and not reported in the remaining studies.

Meccariello et al[21] did not formally evaluate independent risk factors for CRPS-I, as the study primarily focused on postoperative complications (including CRPS-I) and functional outcomes. However, he did not show a significant association between CRPS-I and female sex or age.

A summary of this qualitative analysis is shown in Table III.

Table III. Qualitative reported risk factors for CRPS-I.

Study	Female	Smoking	Diabetes	Immobilization†	Previous history of CRPS-I	Psychological context of anxio-depression	Alcohol abuse
Besse et al[20] (2009)	✗	NR	Excluded	✗	✔	Associated in univariate analysis only	NR
Hernigou et al[5] (2021)	✗	✗	✗	✔	Excluded psychiatric disorders	Excluded all	✔
Meccariello et al[21] (2023)	NR	NR	NR	NR	NR	NR	NR
Kazez et al[22] (2024)	Associated in univariate analysis only	Associated in univariate analysis only	Associated in univariate analysis only	Associated in univariate analysis only	NR	NR	NR

Values are reported qualitatively according to each study;
†The immobilization variable was assessed differently across studies: Hernigou et al[5] evaluated the cast immobilization, whereas Kazez et al[22] evaluated duration of immobilization;
✔ Independent risk factor for CRPS-I;
✗: No significant association reported;
NR: Not reported; Excluded: Variable excluded by study design or exclusion criteria.

Clinical outcomes

The main outcome reported across studies was the incidence of CRPS-I or, also, in Meccariello et al[21], postoperative complications (including CRPS-I). These studies showed that vitamin C supplementation was associated with a reduced incidence of CRPS-I.

In Besse et al[20], the incidence of CRPS-I was observed in 1.7% of patients receiving vitamin C compared to 9.6% in the control group (p<0.0001). Multivariate analysis showed a protective effect of vitamin C supplementation against CRPS-I (RR 0.197; 95% CI 0.063- 0.611; p=0.005).

Hernigou et al[5] reported a significantly lower incidence of CRPS-I in patients receiving vitamin C supplementation compared with the control group (4.9% *vs.* 11.5%, respectively; p=0.039). Furthermore, multivariate analysis demonstrated a significant protective effect of vitamin C intake (OR 0.19; 95% CI 0.05-0.8; p=0.021).

Meccariello et al[21] reported a statistically significant difference in overall postoperative complication rates (including skin or wound problems, CRPS-I, and ankle stiffness) among treatment groups (p=0.022), with complication rates of 40.9% in the only surgery group, 16.7% in the ion resonance + bromelain + vitamin C group, and 33.3% in the bromelain + vitamin C group. CRPS-I occurrence also differed significantly among treatment groups (p=0.001), with one case observed in the surgery-only group, no cases in the ion resonance + bromelain + vitamin C group, and one case in the bromelain + vitamin C group. However, the interpretation of CRPS-I outcomes is limited by the very small number of events, the use of combined treatment protocols, and the absence of specific diagnostic criteria.

In Kazez et al[22], the CRPS-I incidence in each group was not directly reported as percentages. Therefore, these rates were calculated from the number of CRPS-I cases divided by the total number of patients in each group: 2/156 patients in the vitamin C group and 40/184 patients in the control group. This corresponded to a CRPS-I incidence of 1.28% and 21.7%, respectively (p<0.001).

These findings are summarized in Table I.

DISCUSSION

Magnitude of vitamin C benefit and sources of heterogeneity

This systematic review indicates that vitamin C supplementation is associated with both a clinically relevant absolute as well as relative reduction in CRPS-I incidence. In Besse et al[20], CRPS-I incidences decreased from 9.6% in the control group to 1.7% in the vitamin C group, corresponding to an absolute risk reduction of 7.9 percentage points and a relative reduction of 82.3%. In Hernigou et al[5], CRPS-I incidence decreased from 11.5% to 4.9%, corresponding to an absolute risk reduction

of 6.6 percentage points and a relative reduction of 57.4%. In Kazez et al[22], CRPS-I incidences decreased from 21.7% to 1.28%, corresponding to an absolute risk reduction of 20.4 percentage points and a relative reduction of 94.1%. Based on these absolute risk reductions, the estimated number needed to treat (NNT) ranged from 5 to 15 patients in the included directly comparable studies. Meccariello et al[21] could not be included in this calculation, because vitamin C was administered as part of a combined treatment and the study included three treatment groups.

Although the available evidence suggests a favorable effect of vitamin C supplementation in reducing the occurrence of CRPS-I, several methodological and clinical sources of uncertainty should be considered when interpreting these findings.

First, the diagnostic criteria used for CRPS-I were not uniform. Besse et al[20] used the 1994 IASP criteria[1,2], whereas Hernigou et al[5] and Kazez et al[22] applied the Budapest criteria[26].

This distinction is clinically relevant, as the Budapest criteria have demonstrated higher diagnostic specificity than the IASP criteria while maintaining high sensitivity[26]. Harden et al[26] showed that the IASP criteria had excellent sensitivity but poor specificity, potentially leading to over diagnosis, whereas the Budapest criteria retained an almost identical sensitivity but substantially improved specificity. This may be explained by the fact that the Budapest criteria require both patient symptoms and objective signs across different categories, thereby reducing the risk of false positives compared with the IASP criteria.

Second, the absolute clinical benefit of vitamin C supplementation depends strongly on the baseline incidence of CRPS-I. In the three studies allowing a direct comparison between the groups (Besse et al[20], Hernigou et al[5], and Kazez et al[22]), the estimated NNT ranged from approximately 5 to 15 patients. In contrast, Bullen et al[27] reported a CRPS-I rate of 0.3% after operated and not operated foot and ankle fractures without vitamin C prophylaxis, using the Budapest criteria[26]. This estimate was based on 1 of 306 patients and should therefore be interpreted with caution. If such a low incidence was confirmed in larger cohorts, the NNT for the vitamin C prophylaxis would be substantially higher than suggested by the studies included in this review. Therefore, although the relative reduction observed in the available studies appears favourable, the magnitude of the benefit remains uncertain and should be confirmed in studies with a large cohort using the Budapest criteria.

Third, the populations were clinically heterogeneous. Besse et al[20] included patients undergoing elective foot and ankle surgery, Meccariello et al[21] patients with trauma ankle surgery, Hernigou et al[5] patients treated surgically for either trauma or elective foot or ankle pathologies, and Kazez et al[22] calcaneal fractures treated conservatively. Thus, the incidence of CRPS-I could differ between these populations.

This limitation is relevant because the reported incidence of CRPS-I in foot and ankle populations varies widely across the literature. Among patients with foot and ankle fractures, Riou et al[28] reported an incidence of 13.6% using IASP criteria in a cohort with both surgically and conservatively treated fractures, whereas Bullen et al[27] reported an incidence of 0.3%. In elective foot and ankle surgery, Rewhorn et al[29] reported a CRPS-I incidence rate of 4.36% in a retrospective cohort of 390 patients diagnosed according to IASP criteria. These differences may reflect variations in population characteristics, trauma severity, treatment groups, or diagnostic criteria.

Different studies evaluating distal radio fractures suggest that trauma severity, fracture pattern, and surgical fixation may influence the risk of CRPS-I[29-33], although other studies have found no clear association between fracture severity and CRPS-I occurrence[31,34]. Therefore, patients undergoing trauma surgery may have a different baseline risk of CRPS-I than those undergoing elective procedures. Because trauma and elective surgery patients were mixed together into the groups, the studies could not clearly compare CRPS-I rates between the two groups.

Another source of heterogeneity is the timing of the vitamin C administration. In elective surgery, supplementation can be planned and started immediately after the procedure. In trauma cases vitamin C cannot be planned in advance, and surgery may take place several days after the initial injury. This delay may influence the effectiveness of supplementation, since tissue damage has already occurred before treatment is started. Therefore, future studies should standardize and evaluate a protocol for vitamin C administration.

Vitamin C: Properties, safety and adherence considerations

The findings of the present review are consistent with the proposed pathogenesis of CRPS-I, as it is thought to be developed by neurogenic inflammation, sympathetic nervous system dysfunction, and oxidative stress[7-11]. Vitamin C has antioxidant and anti-inflammatories properties[12,13] and represents a low-cost therapy with a safety profile[35-37]. Furthermore, vitamin C is available in multiple commercially oral formulations (tablets, capsules powders, and liquid preparations), to facilitate treatment adherence during postoperative period[38]. Few adverse effects have been associated to vitamin C,

being nausea, heartburn, abdominal cramps and diarrhea when high doses of vitamin C (>3 g/day) are taken[35]. However, the included studies used 1 g/day for approximately 45-50 days showing already a beneficial effect. This is in line with current evidence for extremity trauma and surgery[36,37].

Vitamin C prophylaxis in upper limb trauma

Previous evidence, derived mainly from studies assessing distal radius fractures, suggest that vitamin C supplementation may be associated with a reduced incidence rate of CRPS-I[14-17,19]. This effect has not been consistently demonstrated across all studies[18,39]. Therefore, extrapolating these findings from upper limb trauma to foot and ankle pathology should be done with caution, as these anatomical regions differ in terms of weight-bearing, immobilization, and postoperative rehabilitation[40].

Associated factors and independent risk factors for CRPS-I

As reported in the results, Besse et al[20] found that patients with a previous history of CRPS-I had an approximately tenfold higher risk of developing CRPS-I after surgery, which has already been described in literature[41]. Recently, this finding was supported by evidence from total knee arthroplasty, where patients with a previous history of CRPS had a markedly higher postoperative CRPS rate than patients without previous CRPS[42].

Concerning alcohol abuse, Hernigou et al[5] identified alcoholism as an independent risk factor for CRPS-I. This is biologically plausible as chronic alcohol consumption is linked to undernutrition, vitamin deficiencies and a pro-oxidative environment[43,44]. This result should be interpreted prudently, since a recent meta-analysis on radius fractures did not identify alcohol abuse as a significant risk factor for CRPS[45].

Immobilization may be an important factor associated with CRPS-I. As proposed by Hernigou et al[5], postoperative cast immobilization was independently associated with a higher probability of CRPS-I after foot and ankle surgery, although the duration of cast immobilization was not significantly different between patients with and without CRPS-I. Kaya et al[46] found that prolonged immobilization after distal radius fracture was independently associated with CRPS-I. In a retrospective cohort, Allen et al[4] found that 47% of patients with CRPS had immobilization.

Non-independent factors found in the studies were female sex, smoking, diabetes or psychological factors. Recent studies have associated female sex[30,33,45,47], anxiety, depression or psychological stress[45] as risk factors in extremity surgeries[30,33]. Likewise, smoking[48] and diabetes[49] could enhance the probability of developing CRPS, based on retrospective studies. However, in some recent meta-analyses[45] of radius fractures, smoking or diabetes were not identified as risk factors.

These results further highlight the importance of proper patient risk assessment. Therefore, despite the limitations of current evidence, prophylactic supplementation should be considered in patients with foot and ankle surgery or fractures, particularly in those at increased risk of developing CRPS-I.

Despite the apparent protective effect observed with vitamin C prophylaxis, the evidence should be interpreted with caution. Although methodological quality was generally moderate to high, the reliability of the available evidence remains limited. Three of the four included studies were non-randomized, and the only randomized trial presented some concerns regarding the randomization process and selection of reported results (Figure 2 and Table II). Also, there were multiple possible additional factors, which could have influenced the probability of developing CRPS-I with or without vitamin C supplementation. Therefore, the magnitude of the protective effect of vitamin C must be interpreted in the context of the heterogeneity of the included studies.

Limitations

This review has several limitations. First of all, the small number of articles included in this paper, as well as the differences in the methodology, population, diagnostic criteria, fracture treatment and surgeries performed, follow-up, and outcomes, restricted the ability to compare the results directly and prevented a meta-analysis. Furthermore, the variables reported were not consistently analyzed among studies. Some included studies were non-randomized, introducing potential sources of bias. This heterogeneity makes a direct comparison between the studies difficult and limits the generalization of the results.

This is the first systematic review specifically evaluating vitamin C prophylaxis for CRPS-I after foot and ankle trauma or surgery while considering different diagnostic criteria, populations, and associated risk factors.

CONCLUSIONS

Evidence shows that vitamin C supplementation reduces the incidence rate of CRPS-I after foot and ankle trauma or surgery. The included studies reported favorable protective association, with clinically relevant absolute and relative reductions in

CRPS-I incidence, primarily by the intake of 1 g/day of vitamin C for 40-50 days after foot or ankle trauma or surgery. Given its cost-effective and safe profile, vitamin C may represent a practical preventive strategy. However, the magnitude of the benefit remains uncertain due to the clinical and methodological heterogeneity. Larger double-blind randomized controlled studies using Budapest criteria are needed to confirm the preventive effect of vitamin C and to properly assess potential risk factors on foot or ankle trauma and surgery.

Authors' Contributions

M.T.C.Z.: conceptualization, methodology, investigation, data curation, formal analysis, writing - original draft, writing - review and editing. R.G.: conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, writing – review and editing. P.I.F.: conceptualization, methodology, data curation, formal analysis, validation, writing – review and editing. S.S.: methodology, validation, supervision, writing – review and editing. A.S.: methodology, validation, supervision, writing – review and editing. All authors have read and approved the final version of the article.

Data Availability

Data supporting this review are available in the studies included and cited in this article. No new datasets were generated.

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Not applicable due to the design of the article.

Conflicts of Interest

The authors declare that they have no conflict of interest to disclose.

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