

Chronic regional pain syndrome following calcaneal fractures: what causes it and how may Vitamin C aid?

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The purpose of the current study is to determine which variables influence the onset of chronic regional pain syndrome (CRPS) following Sanders type 1 calcaneal fractures, which are treated conservatively, and to discover how Vitamin C (VC) supplementation, which is often mentioned in the literature, affects the outcomes of these fractures.

The study incorporated individuals who had a Sanders type 1 fracture that was both closed and non-displaced and were treated with conventional plaster. The current study retrospectively reviewed medical records to gather demographic data, duration of immobilization, smoking habits, administration of VC supplementation, and presence of diabetes mellitus (DM). The Budapest criteria were employed to make the clinical diagnosis of CRPS.

The study cohort comprised 258 (75.9%) males and 82 (24.1%) females aged between 18 and 90 years who had sustained Sanders type 1 calcaneal fractures and were managed non-operatively. CRPS was detected in 42 (12.4%) of the 340 subjects. CRPS patients had a statistically higher immobilization duration than those without CRPS ($p < 0.05$). Smoking and DM were more common among patients with CRPS ($p < 0.05$) and CRPS patients had a much lower rate of VC consumption (4.8%) ($p < 0.05$).

The current study is the first to examine risk variables for CRPS after calcaneal fractures. Long periods of immobility, female gender, and lack of VC supplementation increase the risk of CRPS. CRPS also increases with diabetes and smoking.

Keywords: Calcaneus fracture, chronic regional pain syndrome, vitamine C

INTRODUCTION

Hyperalgesia and allodynia are hallmarks of complex regional pain syndrome (CRPS), a chronic pain disorder that typically manifests itself in the limbs and often follows a traumatic event or surgical procedure on an extremity¹⁻³. There is still much to learn about the pathophysiology of CRPS, and it is thought that dysfunction in both the central and peripheral nervous systems contributes to the development of the illness⁴. Over time, both our understanding of and ability to diagnose CRPS have evolved. Reflex sympathetic dystrophy, causalgia, algoneurodystrophy, and Sudeck's atrophy are some of the terms that have been used to identify this ailment in the past⁵⁻⁶. There are two forms of CRPS, with CRPS-I affecting those who haven't had any verified nerve injuries and CRPS-II affecting those who have⁵. Nevertheless, due to a lack of diagnostic testing, clinicians often depend on clinical data to make a diagnosis⁷. Edema, erythema, and pain due to circulatory disruption describe the

'hot phase', whereas bone demineralization, restricted motion in the afflicted joint, stiffness, and retracted tendons characterize the 'cold phase' of clinical progression. Though rare in the general population, 4%-7% of individuals who suffer an extremity fracture or have extremity surgery develop CRPS⁸. According to population-based research conducted in the Netherlands, fractures are the leading cause of CRPS, accounting for 44% of all occurrences⁹. To date, most studies the incidence of CRPS have focused on wrist fractures^{2,10,11,12}. There are few studies of the occurrence of this condition after surgeries performed on the foot and ankle¹³⁻¹⁵ and none that address its prevalence following calcaneal fractures. The initial stage of CRPS-I can be identified by the presence of inflammation and microangiopathy, which results in deterioration of the endothelial barrier. This can lead to elevated pain sensation and swelling. Various studies have reported the efficacy of vitamin C (VC) administration in the prevention of CRPS-I, although some have yielded inconsistent clinical outcomes.

Preventing CRPS-I with VC is controversial since the way it works, and its effectiveness are unclear. But VC is relatively affordable, easily obtainable, and free of serious negative consequences. Hence, our hypothesis claims that the administration of VC supplements may have an inhibitory effect on the progression of CRPS in patients undergoing conservative treatment for Sanders type 1 calcaneal fractures. The purpose of the current study is to determine which variables influence the onset of CRPS following calcaneal fractures, which are treated conservatively, and to discover how VC treatment, which is often mentioned in the literature, affects the outcomes of calcaneal fractures.

MATERIALS AND METHODS

A retrospective review of patients who were treated for calcaneal fractures between January 1, 2019, and January 1, 2022, was conducted. All procedures were performed in accordance with the ethical standards (institutional and national) of the committee responsible for human experiments and the 1975 Declaration of Helsinki as amended in 2008. Considering the retrospective aspect of the study, informed consent was waived.

Patients who were admitted to the emergency room with a traumatic calcaneal fracture underwent standard diagnostic examination, and those with isolated non-displaced, and closed Sanders type 1 fractures treated with conventional plaster were included in the study. Patients were not included if they had an open fracture or additional fracture, a fracture type apart from a Sanders type 1 fracture, were followed for less than a year, had missing data in the hospital's electronic medical record system, or had refused participation in the study. Participants who were instructed to take VC for 40 days on a regular basis but who reported not doing so were also excluded. The data on demographic information, duration of immobilization, smoking status, and having diabetes mellitus were retrospectively harvested from medical records. One of the authors of the current study (MK) strongly recommended that patients with calcaneal fractures take 1 g of VC daily for around 40 days, and he reminded patients of this treatment at each follow-up to ensure continuity of treatment. The cohort of patients who adhered to the prescribed daily VC treatment for a continuous period of 40 days constituted the specific group of patients who underwent VC supplementation therapy. In the current study, the group of patients who were not administered VC consisted of those who were observed by the clinician (MY), who is also another author of the current study. Patients who

opted for the conservative treatment were plastered and immobilized for 4-6 weeks without bearing weight. Soft tissue edema and skin blisters, if present, were allowed to subside using a splint and elevation before cast immobilization was performed. Following the removal of the cast, ankle exercises were initiated in all patients, and weight bearing was permitted only upon radiographic confirmation of complete union¹⁶. Weight-bearing restrictions, and immobilization intervals were all left up to the treating orthopaedic surgeon and were not influenced by the research. They were documented as part of the investigation since they have been shown to contribute to the onset of CRPS¹⁴. Radio-clinical follow-up was performed on patients on days 15, 30, and 45 post-traumatically and then every two months afterwards. The same two surgeons checked up on all of the patients (MK and MY).

The Budapest Criteria

The Budapest criteria were employed to make the clinical diagnosis of CRPS I (Table I). The Budapest criteria are now the most widely recognized diagnostic criteria, and they have recently been verified as having increased specificity compared to previously suggested criteria¹⁷. The Budapest criteria show that a decision rule for the clinical diagnosis of CRPS is confirmed with a sensitivity of 0.85 and a specificity of 0.69¹⁸.

Statistics

While evaluating the findings obtained in the study, the IBM SPSS Statistics 22 (IBM SPSS, Turkey) programme was used for statistical analysis. While evaluating the study data, the conformity of the parameters to the normal distribution was evaluated with the Shapiro-Wilks test. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, and frequency), the Student's t test was used for the comparison of normally distributed parameters between two groups, and the Mann-Whitney U test was used for comparisons between two groups of parameters that did not show a normal distribution. The chi-square test, Fisher's exact test, Fisher Freeman Halton test, and continuity (Yates) correction were used to compare qualitative data. Significance was evaluated at the $p < 0.05$ level.

RESULTS

The medical records of 396 patients who were treated for calcaneal fractures were reviewed. The flowchart of

Table I. — In order to determine the clinical diagnosis of CRPS, the following four criteria (the Budapest Criteria) must be met

Symptom No	Criteria	Categories			
		Sensory	Vasomotor	Sudomotor/Edema	Motor/Trophic
1	Continuing pain, disproportionate to any inciting event	--	--	--	--
2	Symptoms: Must report at least one symptom in three of the four categories shown to the right	Hyperesthesia; Allodynia	Temperature asymmetry; Changes in skin color; Skin color asymmetry	Edema; Sweating changes; Sweating asymmetry	Decreased range of motion; Motor dysfunction; Trophic changes (hair, nails, skin)
3	Signs: At the time of evaluation, must have at least one sign in two or more of the categories shown to the right	Hyperalgesia (pinprick); Allodynia (light touch or temperature); Deep somatic pressure; Joint movement	Skin temperature asymmetry (>1°C); Changes in skin color; Skin color asymmetry	Edema; Sweating changes; Sweating asymmetry	Decreased range of motion; Motor dysfunction (weakness, tremor, dystonia); Trophic changes (Hair, nails, sin)
4	No other diagnosis can better explain the patient's signs and symptoms	--	--	--	--

Table II. — Evaluation of age and gender according to the presence of CRPS

		CRPS		Total <i>(Min-Max)-(Mean±SD)</i>	P
		Absent <i>(Min-Max)-(Mean±SD)</i>	Present <i>(Min-Max)-(Mean±SD)</i>		
Age		(18-90)-(45,91±14,17)	(21-66)-(42,67±15,42)	<i>(18-90)-(45,51±14,35)</i>	¹ 0,204
		n (%)	n (%)	n (%)	
Gender	Male	236 (%79,2)	22 (%52,4)	258 (%75,9)	² 0,000*
	Female	62 (%20,8)	20 (%47,6)	82 (%24,1)	

¹Student t Test; ²Chi-Square Test; *p<0.05

the current study is shown in Figure 1. Overall, 340 patients with calcaneal fractures, of whom all were treated conservatively, aged 18 to 90, participated in the final study cohort, including 258 (75.9%) males and 82 (24.1%) females. Cases averaged 45.51±14.35 years of age (Table II). There were 298 participants (87.6%) who did not have CRPS and 42 participants (12.4%) who did have CRPS (Table III).

There was no statistically significant difference between the patients with and without CRPS in terms of mean age (p>0.05). Women were more likely to be affected than men (p:0.000; p<0.05). Immobilization time values in patients with CRPS were found to be statistically significantly higher than those without CRPS (p:0.000; p<0.05) (Table III).

Smoking was more common among patients with CRPS (33.3%) than among those without CRPS (13.1%) (p:0.002; p<0.05). Patients with CRPS had a considerably greater incidence of diabetes (21.4% vs. 9.7%) than those without CRPS (p:0.030; p<0.05). The rate of VC consumption among CRPS patients (4.8%) was statistically substantially lower than among individuals without CRPS (51.7%) (p:0.000; p<0.05) (Table III).

DISCUSSION

The most noteworthy aspect of the current study is that it is the first of its kind to evaluate the risk factors linked to the onset of CRPS after calcaneal fractures. Besides,

Table III. — Evaluation of operating parameters according to the presence of CRPS

		CRPS		Total	p
		Absent	Present		
		(Min-Max)- (Mean±SD(median))	(Min-Max)- (Mean±SD(median))	(Min-Max)- (Mean±SD(median))	
Duration of immobilization (Day)		(14-45)-(36,21±7,52 (35))	(28-48)-(43,24±5,47 (45))	(14-48)-(37,08±7,65 (35))	¹ 0,000*
		n (%)	n (%)	n (%)	
Smoke status	Absent	259 (%86,9)	28 (%66,7)	287 (%84,4)	³ 0,002*
	Present	39 (%13,1)	14 (%33,3)	53 (%15,6)	
Diabetes	Absent	269 (%90,3)	33 (%78,6)	302 (%88,8)	² 0,030*
	Present	29 (%9,7)	9 (%21,4)	38 (%11,2)	
Vitamin C intake	Absent	144 (%48,3)	40 (%95,2)	184 (%54,1)	³ 0,000*
	Present	154 (%51,7)	2 (%4,8)	156 (%45,9)	

¹Mann Whitney U test²Fisher's Exact Test ³Continuity (Yates) Correction *p<0.05

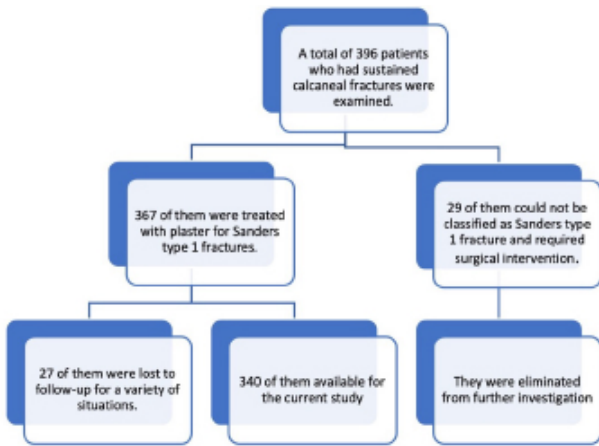


Figure 1. — The flowchart of the current study.

the current study’s major results indicate that long periods of immobility, female gender, and the absence of VC supplementation all increase the likelihood of developing CRPS. Moreover, comorbidities, including diabetes and smoking, have been shown to increase the prevalence of CRPS.

In a study by Riou C. et al.¹³, the incidence of CRPS was reported to be 13% in individuals who had surgery or were treated conservatively for foot bone fractures. Bullen et al.¹⁹ evaluated the rate of CRPS occurrence in patients they followed for lower extremity trauma and reported that 110 (36.6%) of 300 patients had at least one of the Budapest criteria in the three-month follow-up period. However, they stated that only one patient was considered positive for CRPS. They speculated that the

number of people with CRPS would be underreported during screening if the patients reported fewer symptoms when contacted by phone. Furthermore, their 3-month follow-up time was far shorter than our 12-month follow-up term (1 year). Recent reports put the rate at 4.36% for patients who have had foot and ankle surgery²⁰. In the present study, we found that the rate of CRPS development after calcaneal fractures was 12.4%. Since comorbidities including diabetes mellitus and smoking were not employed as exclusion criteria in the present research, it is likely that these factors, as well as differences in clinicians’ attitudes and the effects of long-term immobilization, contribute to the high prevalence of CRPS.

The study by Roh et al.²¹ on 477 patients who underwent surgery for a distal radius fracture found that high-energy traumas, comminuted fractures, and female gender all play a role in the development of CRPS. In a study comprising 218 patients who had surgery for a distal radius fracture, Beerthuisen et al.²² reported that intra-articular fractures, dislocations, and musculoskeletal comorbidities were related to the development of CRPS. Consistent with previous research, the present study indicated that the risk of developing CRPS was lower in male patients.

The question of whether one type of fracture is more likely to cause CRPS-1 is a topic of debate. Some research has shown no correlation between fracture type and the likelihood of developing CRPS-1²³, while other research has found that CRPS-1 is more common after more severe fractures²⁴. In the current study, those with Sanders Type 1 fractures, generally the

consequence of less severe traumas, were the inclusion cohort. To investigate the role of VC in influencing the development of CRPS and to assure homogeneity, only Sanders type 1 fractures have been examined in the current study.

According to research conducted by Jacques Hernigou and colleagues²⁵, individuals who have had foot or ankle fractures and have been immobilized with plaster for more than 41 days and/or who drink alcohol have an increased possibility of developing CRPS. In our research, we did not ask about alcohol usage, but we did find that those who developed CRPS had substantially longer plaster time values than individuals who did not develop CRPS ($p:0.000$; $p<0.05$).

The incidence of CRPS was shown to be considerably higher among smokers in a retrospective study conducted by HS An et al. on 53 trauma patients admitted for treatment²⁶. Nicotine usage, caffeine intake, and smoking all enhance the likelihood of developing CRPS, based on a study conducted retrospectively by C. Hsu et al.²⁷. In the present study, patients with CRPS were observed to have a significantly higher prevalence of smoking compared to those without CRPS ($p:0.002$; $p<0.05$). Furthermore, an increased risk of CRPS was shown to relate to high levels of haemoglobin A1c and diabetes mellitus in a study of 200 participants²⁸. Among our participants in the current study, those with CRPS seemed to have a considerably higher rate of diabetes ($p:0.030$; $p<0.05$).

Studies have shown that VC may prevent the damage to membrane lipids and the microcirculation caused by reactive oxygen species¹⁴. VC supplementation has shown benefit in preventing CRPS-I in many studies, but also with inconsistent outcomes. A recent meta-analysis revealed that VC intake may help prevent CRPS-I following lower limb injuries²⁹. Jacques Hernigou suggests taking VC daily to lessen the likelihood of developing CRPS following foot and ankle surgery²⁵. In a cohort of 392 patients who had foot and ankle surgery done by Jean-Luc Besse¹⁴, 9.6% developed CRPS. He also stated that CRPS was not related to factors like age, gender, or trauma severity. He claimed that the likelihood of developing CRPS was decreased by consuming 500 milligrammes of VC daily and that the disease was more common in those who were overweight or used antidepressants. Disorders such as anxiety, high cholesterol, depression, diabetes, and hyperuricemia all contribute to an increase in oxidative stress and free radicals. The inflammatory response, vascular permeability, neuropeptide (substance P) release, and tissue damage may all be exacerbated or initiated by free radicals. Studies have shown that

free radical scavengers such as N-acetylcysteine, dimethyl sulfoxide, mannitol, and VC reduce CRPS symptoms³⁰. Many antioxidants have been advocated for the treatment of CRPS on the basis that local inflammation in CRPS causes the production of free oxygen radicals³¹. VC, however, is the only antioxidant medication with current evidence for preventing CRPS following limb surgery, and hence it is routinely administered peri-operatively. The incidence of CRPS was shown to be considerably reduced in patients treated for ankle fractures who were given 500 mg of VC daily and 50 days of preventive therapy, based on a randomized, placebo-controlled study including 875 patients³². Based on a meta-analysis conducted by Ishith Seth et al.³³, prophylactic use of 500 mg of VC daily for 50 days significantly reduced the risk of developing CRPS, and there was no significant difference between the VC group and the placebo group with respect to functionality, pain scores, or complications. Despite conflicting recommendations, most experts agree that a daily 500-1000 mg VC pill used as a preventative treatment for 40-50 days is effective¹⁸.

VC's impact on CRPS, a complication that might arise after the treatment of foot and ankle fractures, has only been studied in a small number of papers¹⁴. VC is an effective preventative therapy for CRPS after foot and ankle surgery since it is well-known to be safe, inexpensive, and easily obtainable³⁴. Patients diagnosed with CRPS in the current study were shown to have a considerably lower VC usage rate (4.8% vs. 51.7%, respectively) than those without the disorder.

As with all retrospective chart review studies, the data presented is limited. First, the data were not collected prospectively in a standardized manner. Second, data for each variable was not available in all charts, and therefore, reported percentages may be a misrepresentation of actual values. Third, the studied patient population consisted only of patients treated in a tertiary clinic based in Elazig, Turkey. Also, different follow-up protocols by different clinicians in the clinic affect standardization.

CONCLUSION

In conclusion, the most significant determinants preventing the development of CRPS in patients followed up retrospectively for calcaneal fractures are male gender, a short immobilization period, and notably VC supplementation. In this respect, prospective studies comparing different treatment protocols on more patients would be more beneficial.

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Ethics approval: The study was approved by the local institutional ethical review board of the Firat University Medical Faculty Ethics Committee (2022/15-37).

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