# The Influence of Vitamin C on the Outcome of Distal Radial Fractures

## A Double-Blind, Randomized Controlled Trial

Ingri Ekrol, MRCSEd, Andrew D. Duckworth, MSc, MRCSEd, Stuart H. Ralston, MD, FRSE, Charles M. Court-Brown, MD, FRCSEd(Orth), and Margaret M. McQueen, MD, FRCSEd(Orth)

*Investigation performed at the Edinburgh Orthopaedic Trauma Unit, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom*

**Background:** Vitamin C has been proposed to improve outcomes after a distal radial fracture by promotion of bone and soft-tissue healing and reduction of the prevalence of complex regional pain syndrome (CRPS). Our primary aim was to examine the effect of vitamin C on functional outcome after a distal radial fracture.

**Methods:** A total of 336 adult patients with an acute fracture of the distal aspect of the radius were recruited over a one-year period and randomized to receive 500 mg of vitamin C or placebo daily for fifty days after the fracture. The primary outcomes were the DASH (Disabilities of the Arm, Shoulder and Hand) score at six weeks and at one year. Secondary variables included complications, wrist and finger motion, grip and pinch strength, pain, and a CRPS score.

**Results:** There were no significant differences in patient or fracture characteristics between the treatment groups. There was no significant effect of vitamin C on the DASH score throughout the study period. At six weeks, patients in the vitamin C group with a nondisplaced fracture had a significantly greater wrist flexion deficit ($p = 0.008$) and pinch strength deficit ($p = 0.020$) and a greater rate of CRPS ($p = 0.022$), but there was no difference in the CRPS rate at any other time point. At twenty-six weeks, there was a higher rate of complications ($p = 0.043$) and greater pain with use ($p = 0.045$) in the patients with a displaced fracture treated with vitamin C. There was no significant difference in the time to fracture-healing.

**Conclusions:** This study demonstrated no significant difference at one year in the DASH score, other functional outcomes, the rate of CRPS, or osseous healing of nondisplaced or displaced distal radial fractures treated with vitamin C compared with placebo. We conclude that administration of vitamin C confers no benefit to patients with a displaced or nondisplaced fracture of the distal aspect of the radius.

**Level of Evidence:** Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

**Peer Review:** This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. It was also reviewed by an expert in methodology and statistics. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

The functional outcome after a fracture can be determined by the amount of associated soft-tissue injury. Vitamin C affects the soft tissues after a burn injury by stopping the progression of vascular permeability and reducing microvascular leakage of fluid and proteins[1-3]. It reduces lipid peroxidation[4], which increases capillary permeability by damaging the microvascular endothelial cells, and it influences the generation of vitamin E.

Animal studies have demonstrated that oxygen free radicals have an unfavorable effect on granulation tissue and fracture-healing[5]. Vitamin C improves fracture-healing both radiographically and histologically by accelerated callus formation[6,7], and it and reduces the skeletal muscle injury caused by compartment syndrome and ischemia-reperfusion injury[8,9]. A recent animal study demonstrated that subclinical deficiency of vitamin C resulted in callus with lower mechanical resistance and a lower

**Disclosure:** One or more of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of an aspect of this work. In addition, one or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

**TABLE I Inclusion and Exclusion Criteria for the Study***

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Age of at least 18 years | Inability to give informed consent |
| Acute unilateral nondisplaced or displaced distal radial fracture | Already taking vitamin C or multivitamin therapy |
| Extra-articular or minimally articular fracture that can be managed nonoperatively or operatively with external fixation or ORIF | Previous distal radial fracture on ipsilateral side |
| Ability to provide informed consent | Bilateral fractures |
| Ability to attend local follow-up | Articular displacement requiring ORIF |
| | Chronic renal impairment |
| | History of renal calculi |
| | History of glucose-6-phosphate dehydrogenase deficiency and hyperoxaluria |

*ORIF = open reduction and internal fixation.

histological grade[10], with vitamin C supplementation during the fracture-healing period decreasing this adverse effect.

Complex regional pain syndrome (CRPS) is one of the most devastating fracture complications and is associated with dysfunction of the sympathetic nervous system[11]. The primary inflammatory changes associated with generation of oxygen free radicals are thought to be caused by sympathetic microcirculatory disturbances[12]. Sympathetic overactivity has been implicated in the regional bone loss associated with CRPS[11,13]. The role of oxygen free radicals in the pathogenesis of CRPS has been investigated in a number of studies[11-13], with one study indicating that free radical scavengers improved the clinical picture[12]. A daily dose of 500 mg of vitamin C reduced the prevalence of CRPS after distal radial fracture in two randomized studies[14,15].

The null hypothesis of the present study was that vitamin C treatment following a fracture of the distal aspect of the radius would have no effect on functional outcome, as measured by the DASH (Disabilities of the Arm, Shoulder and Hand) score[16,17] at one year after injury. Our secondary aims were to assess whether vitamin C influenced the rate of complications, wrist and finger motion, grip and pinch strength, the prevalence of CRPS, or the time to healing after a distal radial fracture.

## Materials and Methods

The study was a prospective, randomized, double-blind controlled trial involving patients with a fracture of the distal aspect of the radius (EudraCT registration number 2005-003635-46). It was carried out over a one-year period at a large academic urban trauma center that manages over 1300 distal radial fractures per year. The primary outcome measure was the DASH score. The appropriate ethical and clinical trial committees authorized the study.

From June 2006 to July 2007, 336 adult patients (at least eighteen years of age) with an acute unilateral fracture of the distal aspect of the radius were recruited into the study. We included fractures that were extra-articular or minimally articular and that could be managed either conservatively in a cast or operatively with external fixation or open reduction and internal fixation. Patients were excluded if they were taking vitamin C or multivitamin therapy prior to the fracture, had a previous distal radial fracture on the ipsilateral side, had bilateral fractures, had articular displacement requiring open reduction and internal fixation, were unable to provide consent, or had chronic renal impairment (Table I). After informed consent, patients were randomized to receive either vitamin C or a placebo. The randomization was computerized and was stratified according to whether the fracture was nondisplaced or displaced. The fracture treatment was not altered for this study.

A 500-mg dose of vitamin C or a placebo was given daily for fifty days, starting on the day after the fracture. Compliance was monitored by counting the returned tablets and by an interview. There were no adverse reactions associated with the vitamin C use.

A dietary vitamin C intake score, based on a food frequency questionnaire, was recorded on enrollment in the study. This score is a semiquantitative tool designed for use in assessing the relation between dietary intake and chronic diseases[18]. It provides a baseline estimate of dietary intake of vitamins, including vitamin C. The treatment groups did not differ in terms of demographic or fracture characteristics, baseline DASH score, or dietary vitamin C score, confirming successful randomization (Table II).

### *Follow-up*

Clinical, functional, and radiographic evaluations were performed at two, six, twelve, twenty-six, and fifty-two weeks. The patient, the treating surgeon, the senior author (M.M.McQ.) who assessed radiographs for fracture-healing, and the dedicated research assistant who performed the follow-up assessments were all blinded to the randomization. Additional clinical and radiographic assessments were performed between these time points if clinically indicated.

Functional evaluations included the ability to perform activities of daily living, utilizing the DASH score as the primary outcome. A DASH score[17] and a Hospital Anxiety and Depression Score (HADS)[19] were recorded at baseline and at six, twelve, twenty-six, and fifty-two weeks, as anxiety and depression influence the DASH score[20-23]. For the baseline DASH score, patients completed the questionnaire to indicate their level of function immediately prior to injury. The HADS instrument is a screening questionnaire for depression and anxiety, consisting of fourteen questions with a maximum score of 42, and it is designed to detect the presence and severity of mild degrees of mood disorder. A score of 11 or higher indicates the probable presence of a mood disorder. Pain was assessed with use of a 10-cm visual analog scale (VAS) score. Patients marked the scale to indicate the degree of pain felt at rest and with use of the hand, with 0 being no pain and 10 being maximal pain.

Complications were recorded during each clinical evaluation; these consisted of loss of fracture reduction, paresthesia of the fingers, superficial wound or pin track infections in surgically treated patients, tendon injury, and symptoms or signs of CRPS. CRPS was clinically assessed with use of the Atkins criteria (neuropathic pain, vasomotor instability and abnormalities of sweating, swelling, loss of joint mobility, and joint and soft-tissue contractures)[11,24,25]. The presence of at least three criteria is required to establish a diagnosis of CRPS. Tenderness of the fingers was measured with use of a dolorimeter and was expressed as a ratio relative to the contralateral side[26]. The dolorimeter that was used measures pain tolerance with use of a pressure device, and the

**TABLE II Pre-Injury and Injury Demographics**

| | Displaced Fractures | | Nondisplaced Fractures | |
|---|---|---|---|---|
| | Vitamin C | Placebo | Vitamin C | Placebo |
| No. of patients | 94 | 92 | 75 | 75 |
| Age* *(yr)* | 58 ± 20 | 62 ± 18 | 51 ± 19 | 54 ± 21 |
| Male sex† | 27 (28) | 20 (22) | 17 (23) | 26 (35) |
| Occupation† | | | | |
| Sedentary | 15 (16) | 10 (11) | 17 (23) | 14 (19) |
| Light | 17 (18) | 15 (16) | 14 (19) | 9 (12) |
| Moderate | 12 (13) | 11 (12) | 15 (20) | 14 (19) |
| Heavy | 4 (4) | 0 (0) | 3 (4) | 5 (7) |
| Retired or unemployed | 46 (49) | 56 (61) | 26 (35) | 33 (44) |
| Injury mode† | | | | |
| Fall from standing | 72 (77) | 74 (80) | 56 (75) | 56 (75) |
| Fall from over 3 ft (1 m) | 9 (10) | 10 (11) | 7 (9) | 7 (9) |
| Road traffic accident | 9 (10) | 7 (8) | 6 (8) | 9 (12) |
| Other | 4 (4) | 2 (2) | 5 (7) | 3 (4) |
| HADS anxiety* | 5.6 ± 3.9 | 5.9 ± 4.3 | 5.5 ± 3.5 | 5.3 ± 2.9 |
| HADS depression* | 3.5 ± 3.5 | 3.9 ± 3.7 | 2.9 ± 2.8 | 2.7 ± 2.3 |
| AO/OTA type† | | | | |
| A2.1 | 1 (1) | 0 (0) | 32 (43) | 20 (27) |
| A3.2 | 47 (50) | 41 (45) | 11 (15) | 9 (12) |
| B1.1 | 1 (1) | 1 (1) | 13 (17) | 18 (24) |
| C2.1 | 14 (15) | 25 (27) | 5 (7) | 6 (8) |
| C3.2 | 16 (17) | 10 (11) | 1 (1) | 0 (0) |
| Other | 15 (16) | 15 (16) | 13 (17) | 22 (29) |
| Dorsal angle at injury*‡ *(deg)* | 15.1 ± 19.8 | 11.6 ± 19.0 | −5.2 ± 6.0 | −6.7 ± 6.2 |
| Shortening at injury*‡ *(mm)* | 3.2 ± 3.3 | 2.9 ± 3.0 | −0.2 ± 1.6 | 0.2 ± 1.4 |
| Carpal alignment at injury†‡ | 13 (16) | 16 (20) | 64 (95) | 66 (97) |
| Vitamin C score* | 4.0 ± 2.8 | 4.3 ± 2.8 | 4.2 ± 2.7 | 4.1 ± 2.6 |
| Pre-injury DASH score* | 9.2 ± 15.0 | 13.3 ± 18.4 | 7.6 ± 13.4 | 7.6 ± 13.8 |

*The values are given as the mean and the standard deviation. †The values are given as the number of patients, with the percentage in parentheses. ‡A small number of patients had missing data.

score is determined on the basis of when the patient feels pain. Swelling was assessed on the basis of hand volume, measured by water displacement when the hand was placed in a volumeter, and was expressed relative to the contralateral side.

Active range of motion of the distal radioulnar joint and of the wrist as a whole was measured with use of a standard full-circle goniometer. The recordings were made in triplicate to reduce intraobserver variability, and the mean values were noted. Flexion, extension, pronation, supination, and radial and ulnar deviation were each expressed as the percentage of the value for the contralateral side. Range of motion at the finger joints was measured with use of a goniometer and was expressed relative to the contralateral side. The range-of-motion deficit in each finger joint of the injured hand relative to that in the contralateral joint was determined, and these values were summed to calculate the total difference in finger motion.

Grip and pinch strength were measured with use of a JAMAR hand dynamometer (Patterson Medical) according to the guidelines for use issued by the American Society for Surgery of the Hand[27]. The mean of three recordings was calculated and recorded as a percentage deficit relative to the strength of the contralateral hand. The deficit was adjusted to allow for dominance, with a 10% increase in grip strength assumed for the dominant hand[28].

Radiographic evaluation consisted of standardized anteroposterior and lateral radiographs of the injured wrist as well as one set of radiographs of the contralateral wrist for comparison[29]. The dorsal angle, carpal alignment, and ulnar variance were measured manually with use of a protractor and a ruler. A fracture was defined as displaced if there was dorsal angulation of >10°, ulnar variance of >3 mm compared with the contralateral wrist, carpal malalignment[30], or any combination thereof[31]. Carpal malalignment was defined as failure of the long axes of the radius and capitate to intersect within the carpus on the lateral radiograph of the wrist[30]. The senior author classified the fractures with use of the AO/OTA classification[32]. Time to fracture-healing was assessed in a blinded fashion by the senior author as the time to bridging of three of four cortices, endosteal healing, and 75% organized trabecular bridging of the defect on both radiographic views[33,34]. Since healing was only assessed periodically at patient visits, the observed times at which healing was first seen are acknowledged to be an overestimate of the true times, but this should not have been biased between the treatment groups.

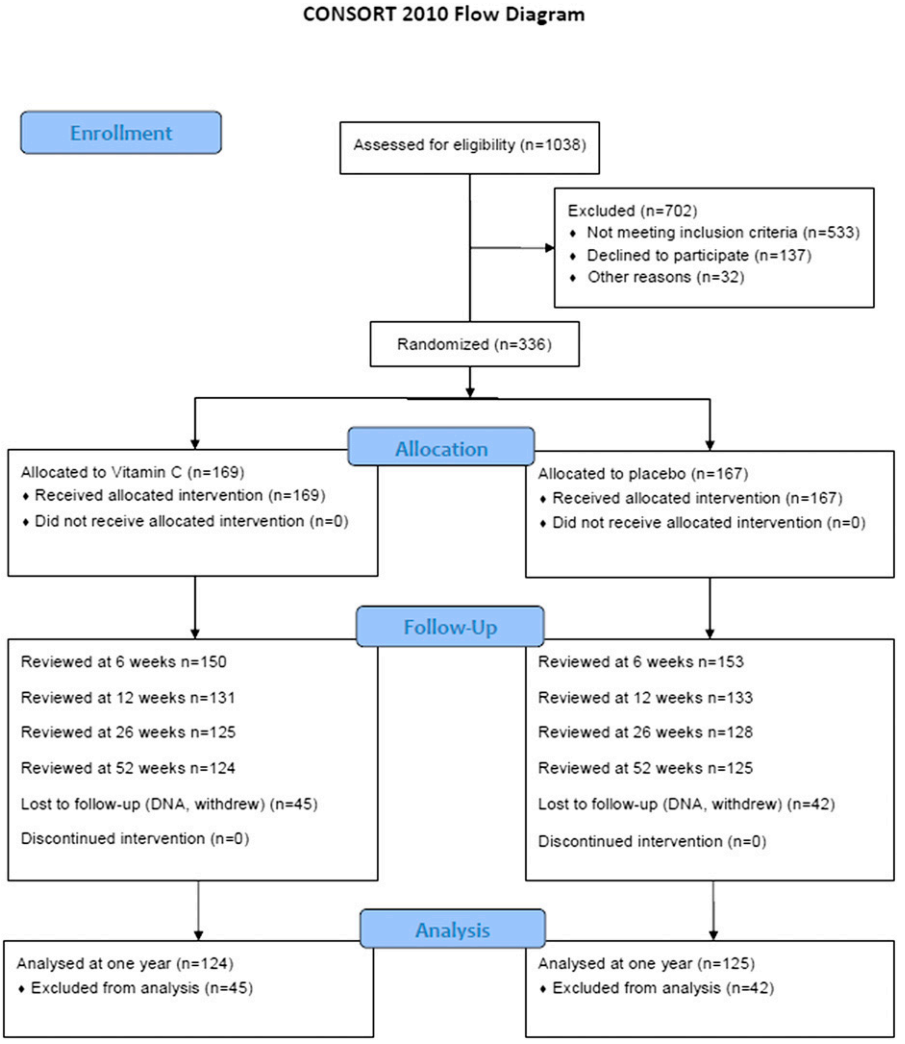


Fig. 1

CONSORT (Consolidated Standards of Reporting Trials) flow diagram showing recruitment and flow of participants through the trial. DNA = did not attend.

### *Statistical Methods*

The primary outcomes were the DASH score at six weeks (to assess the effect of vitamin C on the speed of recovery) and at one year (to assess the long-term effect). Secondary variables were complications; wrist and finger motion; grip and pinch strength; pain with use and at rest; water displacement (swelling); and the dolorimeter ratio CRPS score and HADS.

In a pilot study of thirty patients with a distal radial fracture who were evaluated at between six months and one year, the mean DASH score was 25 and the standard deviation was 17. A sample size of 300 would therefore provide high power (90%) to identify a true difference between the means of the randomized groups equal to 7 (0.4 standard deviation) as significant at the 5% level.

Outcomes in each pair of randomized treatment groups were compared with use of the chi-square test for binary variables and with use of either the Mann-Whitney or two-sample t test for quantitative variables (depending on the distribution of the variable). Multiple logistic or linear regression was used to investigate the effect of other prognostic factors on outcomes and to provide estimates of the efficacy of vitamin C after adjustment for these factors. In particular, analysis of covariance was used to adjust the comparison of later DASH scores for the values at earlier times to examine patterns of change over time in the two treatment groups. Intention-to-treat analyses of the primary outcome measure with use of the last-observation-carried-forward (LOCF) method were also performed at twelve, twenty-six, and fifty-two weeks.

### *Source of Funding*

This study was funded by the Chief Scientist's Office for Scotland and the Scottish Orthopaedic Research Trust into Trauma (SORT-IT).

## Results

Of the 336 patients entered into the study, 186 had a displaced fracture and 150 had a nondisplaced fracture. Half of each cohort was randomized to receive the vitamin C capsules, and the other half received the placebo capsules (Fig. 1). The mean patient age was fifty-six years, and 73% were female (Table II).

Management of the fractures involved conservative treatment with a cast for six weeks in 252 patients (including seventy-eight who required manipulation under anesthesia) and surgical treatment in eighty-four (including forty-one who had undergone a prior manipulation). The surgical treatment consisted of open reduction and internal fixation with a volar plate (n = 31), a dorsal plate (n = 1), or both (n = 1); nonbridging external fixation (n = 39); bridging external fixation and Kirschner wires (n = 9), Kirschner wire fixation (n = 2); or percutaneous screw fixation (n = 1).

**TABLE III Outcomes at Six Weeks**

| Outcome | Displaced Fractures | | | Nondisplaced Fractures | | |
|---|---|---|---|---|---|---|
| | Vitamin C, N = 80 | Placebo, N = 86 | P Value | Vitamin C, N = 70 | Placebo, N = 67 | P Value |
| DASH score* | 40 ± 18 | 42 ± 17 | 0.74 | 32 ± 20 | 29 ± 21 | 0.42 |
| Complications† | 20 (25) | 24 (28) | 0.77 | 7 (10) | 6 (9) | 1.00 |
| Range-of-motion deficit* *(%)* | | | | | | |
| Wrist flexion | 57 ± 20 | 59 ± 15 | 0.42 | 54 ± 23 | 42 ± 32 | 0.008 |
| Wrist extension | 51 ± 27 | 50 ± 28 | 0.83 | 30 ± 18 | 33 ± 21 | 0.47 |
| Supination | 36 ± 33 | 32 ± 30 | 0.43 | 17 ± 20 | 13 ± 21 | 0.21 |
| Pronation | 24 ± 29 | 18 ± 22 | 0.11 | 12 ± 19 | 9 ± 15 | 0.29 |
| Total finger difference* *(deg)* | 137 ± 141 | 177 ± 149 | 0.07 | 70 ± 91 | 64 ± 103 | 0.69 |
| Grip deficit* *(%)* | 79 ± 17 | 79 ± 18 | 0.98 | 55 ± 28 | 51 ± 26 | 0.44 |
| Pinch deficit* *(%)* | 61 ± 23 | 63 ± 21 | 0.42 | 42 ± 27 | 31 ± 24 | 0.020 |
| Pain at rest* | 2.1 ± 2.4 | 2.1 ± 2.4 | 0.95 | 1.3 ± 2.1 | 1.2 ± 1.9 | 0.88 |
| Pain with use* | 5.1 ± 2.7 | 4.7 ± 2.8 | 0.34 | 3.6 ± 2.9 | 3.5 ± 2.6 | 0.94 |
| Hand volume difference* *(mL)* | −16 ± 54 | −14 ± 35 | 0.73 | −2 ± 37 | −12 ± 33 | 0.08 |
| Dolorimeter ratio* | 0.78 ± 0.24 | 0.75 ± 0.31 | 0.47 | 0.91 ± 0.20 | 0.89 ± 0.22 | 0.45 |
| CRPS score* | 3.3 ± 2.0 | 3.5 ± 2.6 | 0.70 | 2.7 ± 2.7 | 2.0 ± 1.9 | 0.09 |
| CRPS > 3†‡ | 33 (42) | 35 (42) | 1.00 | 27 (40) | 13 (20) | 0.022 |
| HADS anxiety* | 5.1 ± 4.0 | 5.2 ± 3.8 | 0.88 | 4.9 ± 4.0 | 4.3 ± 3.1 | 0.42 |
| HADS depression* | 3.5 ± 3.0 | 4.2 ± 3.5 | 0.14 | 2.9 ± 3.0 | 2.4 ± 2.4 | 0.26 |

*The values are given as the mean and the standard deviation. †The values are given as the number of patients, with the percentage in parentheses. ‡Four patients had missing data.

### *Functional Outcome*

At six weeks, 303 patients returned for follow-up (Table III). The remaining thirty-three patients were younger than those who attended but were similar with regard to displacement, sex, recalled preoperative DASH score, and vitamin C score. No significant differences between the treatment groups were found in the cohort with a displaced fracture ($p > 0.05$); the mean DASH score was 40 in the vitamin C group and 42 in the placebo group. In the cohort with a nondisplaced fracture, patients in the vitamin C group had significantly greater deficits in wrist flexion ($p = 0.008$) and in pinch strength ($p = 0.020$).

The Appendix and Table IV show the functional outcome results at twelve weeks ($n = 264$), twenty-six weeks ($n = 253$), and fifty-two weeks ($n = 249$). At one year, 74% of the 336 patients returned for review, including 73% (124) of the vitamin C group and 75% (125) of the placebo group.

No significant effect of vitamin C on the DASH score was found at any time point ($p = 0.19$ to $0.82$). As anticipated on the basis of the lesser severity of the injury, the DASH score at six weeks was lower in the cohort with a nondisplaced fracture (32 in the vitamin C group and 29 in the placebo group). The DASH score improved gradually over time in all four groups. At one year, the mean DASH score in the cohort with a nondisplaced fracture was 8 in both treatment groups. The mean DASH score in the cohort with a displaced fracture was poorer, 17 in the vitamin C group and 15 in the placebo group, but the treatment groups did not differ significantly ($p = 0.36$).

There was a strong correlation between the DASH score at six, twelve, twenty-six, and fifty-two weeks and the baseline HADS (see Appendix). For the cohort with a displaced fracture, the DASH score correlated equally well with the HADS anxiety and depression subscores. For the cohort with a nondisplaced fracture, the DASH score correlated most strongly with the HADS depression subscore.

### *Complications*

Complications were assessed in 311 patients. In the nondisplaced fracture cohort, the prevalence of CRPS at six weeks was significantly higher in the patients treated with vitamin C ($p = 0.022$) (Table III). These patients also reported significantly greater pain with use at one year ($p = 0.011$) (Table IV), but there were no differences between the pain scores of the two treatment groups at the earlier time points. For the displaced fracture cohort, there were no differences in the prevalence of CRPS between the treatment groups throughout the follow-up period. However, at twenty-six weeks, the vitamin C group in this cohort had significantly more complications ($p = 0.043$) and greater pain with use ($p = 0.045$) (see Appendix).

### *Radiographic Outcomes and Fracture-Healing*

At six and twenty-six weeks, the nondisplaced fracture cohort had significantly greater radial shortening in the placebo group

**TABLE IV Outcomes at Fifty-two Weeks**

| Outcome | Displaced Fractures | | | Nondisplaced Fractures | | |
|---|---|---|---|---|---|---|
| | Vitamin C, N = 70 | Placebo, N = 68 | P Value | Vitamin C, N = 54 | Placebo, N = 57 | P Value |
| DASH score* | 17 ± 20 | 15 ± 16 | 0.36 | 8 ± 12 | 8 ± 15 | 0.82 |
| Complications† | 21 (30) | 13 (19) | 0.22 | 6 (11) | 4 (7) | 0.67 |
| Range-of-motion deficit* *(%)* | | | | | | |
| Wrist flexion | 21 ± 20 | 24 ± 21 | 0.42 | 13 ± 13 | 12 ± 15 | 0.66 |
| Wrist extension | 9 ± 15 | 7 ± 16 | 0.40 | 2 ± 11 | 2 ± 12 | 0.98 |
| Supination | 5 ± 12 | 3 ± 10 | 0.30 | 0 ± 2 | 0 ± 3 | 0.23 |
| Pronation | 3 ± 14 | 1 ± 9 | 0.56 | 0 ± 0 | 0 ± 1 | 0.21 |
| Total finger difference* *(deg)* | 18 ± 62 | 22 ± 67 | 0.66 | 6 ± 51 | 11 ± 47 | 0.55 |
| Grip deficit* *(%)* | 23 ± 18 | 19 ± 22 | 0.26 | 9 ± 19 | 8 ± 21 | 0.85 |
| Pinch deficit* *(%)* | 7 ± 22 | 6 ± 22 | 0.80 | 1 ± 22 | −2 ± 22 | 0.53 |
| Pain at rest* | 0.9 ± 1.8 | 0.9 ± 1.5 | 0.88 | 0.5 ± 1.4 | 0.3 ± 0.8 | 0.33 |
| Pain with use* | 2.0 ± 2.5 | 1.6 ± 2.0 | 0.34 | 1.6 ± 2.4 | 0.7 ± 1.2 | 0.011 |
| Hand volume difference* *(mL)* | 3 ± 30 | 1 ± 22 | 0.64 | 3 ± 22 | 1 ± 16 | 0.54 |
| Dolorimeter ratio* | 0.97 ± 0.09 | 0.98 ± 0.11 | 0.80 | 0.99 ± 0.15 | 0.97 ± 0.08 | 0.57 |
| CRPS score* | 1.3 ± 2.0 | 1.4 ± 2.2 | 0.89 | 0.7 ± 1.3 | 0.6 ± 1.2 | 0.45 |
| CRPS > 3† | 11 (16) | 11 (16) | 1.00 | 3 (6) | 3 (5) | 1.00 |
| HADS anxiety* | 4.7 ± 4.0 | 4.5 ± 4.0 | 0.86 | 4.3 ± 3.9 | 3.3 ± 3.1 | 0.15 |
| HADS depression* | 2.8 ± 3.2 | 2.7 ± 3.5 | 0.86 | 1.9 ± 2.2 | 1.8 ± 2.2 | 0.97 |

*The values are given as the mean and the standard deviation. †The values are given as the number of patients, with the percentage in parentheses.

**TABLE V Radiographic Outcomes and Time to Fracture-Healing**

| Outcome | Displaced Fractures | | | Nondisplaced Fractures | | |
|---|---|---|---|---|---|---|
| | Vitamin C | Placebo | P Value | Vitamin C | Placebo | P Value |
| Dorsal angle deficit* *(deg)* | | | | | | |
| At 2 wk | 0.3 ± 9.7 | 1.7 ± 10.5 | 0.38 | −3.9 ± 7.9 | −6.4 ± 8.5 | 0.08 |
| At 6 wk | 1.2 ± 11.3 | 1.6 ± 12.0 | 0.87 | −3.0 ± 9.2 | −5.9 ± 9.4 | 0.08 |
| At 26 wk | 1.3 ± 11.0 | 1.5 ± 12.5 | 0.92 | −3.1 ± 9.2 | −5.4 ± 10.2 | 0.22 |
| Radial shortening* *(mm)* | | | | | | |
| At 2 wk | 0.6 ± 1.9 | 0.9 ± 1.9 | 0.42 | 0.2 ± 1.7 | 0.5 ± 1.4 | 0.24 |
| At 6 wk | 1.1 ± 1.9 | 1.4 ± 2.1 | 0.30 | 0.3 ± 1.6 | 0.9 ± 1.6 | 0.037 |
| At 26 wk | 1.4 ± 2.9 | 1.6 ± 2.3 | 0.64 | 0.2 ± 1.6 | 0.9 ± 1.6 | 0.028 |
| Carpal alignment† | | | | | | |
| At 2 wk | 65 (84) | 54 (71) | 0.07 | 59 (92) | 58 (89) | 0.78 |
| At 6 wk | 57 (77) | 49 (68) | 0.30 | 59 (90) | 55 (87) | 0.33 |
| At 26 wk | 56 (79) | 47 (71) | 0.31 | 49 (94) | 50 (88) | 0.40 |
| Time to healing* *(d)* | 47 ± 10 | 48 ± 13 | 0.42 | 39 ± 7 | 42 ± 13 | 0.23 |

*The values are given as the mean and the standard deviation. †The values are given as the number of patients, with the percentage in parentheses.

compared with the vitamin C group (p = 0.037 and 0.028) (Table V). No other radiographic differences were found between the treatment groups in either cohort throughout the follow-up period. The time to fracture-healing did not differ between the treatment groups in either cohort (p = 0.42 and 0.23).

## Discussion

This study demonstrated no significant difference in functional outcome at one year between patients treated with vitamin C or a placebo after either a nondisplaced or displaced distal radial fracture. The condition of soft tissues influences functional loss, disability, and overall outcome after a fracture of the distal aspect of the radius[35]. Vitamin C is an important reducing agent that binds harmful free radicals[6]. Although other studies have suggested a beneficial effect of vitamin C, both in animal models and in patients with a distal radial fracture[2,4,8,9,14,15], we found no difference in the DASH score, other functional outcomes, occurrence of CRPS, or fracture-healing with vitamin C treatment in patients with a distal radial fracture.

The majority of fractures in the study occurred in middle-aged to elderly women, and they were predominately low-energy injuries similar to those in previous epidemiological studies[36,37]. As would be expected, the DASH scores were poorer in the displaced compared with the nondisplaced fracture cohort throughout the study period and improved gradually over time. Our primary focus was on the effect of vitamin C in the individual fracture cohorts (patients with a displaced fracture and those with a nondisplaced fracture); we performed only a limited analysis of the two cohorts combined. At one year, the DASH score in the nondisplaced fracture cohort had returned to its pre-injury level of 8; the value in the displaced fracture cohort was 16, slightly poorer than the normative level of 10 for the general population[16]. Similar trends have been shown in other studies of distal radial fractures[38-41]. Jaremko et al. reported a mean DASH score of 24 at six months in seventy-four patients over the age of fifty years who had been treated nonoperatively for a range of distal radial fracture types[42]. This was poorer than the DASH scores for nondisplaced and displaced fractures at six months in the present study. At one year, the only outcome that demonstrated a significant difference between treatment groups was pain with use in the nondisplaced fracture cohort, which was greater in patients treated with vitamin C; all other outcome parameters were comparable. Given the normative DASH scores, the relevance of this finding is unknown and it is possible that the difference was due to chance.

We did demonstrate a strong correlation between the DASH score at each time point and the baseline HADS; anxious or depressed patients tended to score worse on the DASH. This is consistent with other studies that have demonstrated that female sex, employment status, depression, catastrophic thinking, and kinesiophobia are predictive of the DASH score[20,22,23]. However, the two randomized groups in the present study were balanced with respect to all parameters, including the HADS, at baseline; thus, we do not believe that the conclusions were biased by this association. Throughout the study period, grip strength and range-of-motion measures (except at six weeks) did not differ significantly between the treatment groups. The normative functional results at one year indicate that nondisplaced fractures of the distal aspect of the radius are relatively benign injuries that recover well, without functional deficits. The displaced fracture cohort had greater mean deficits in functional outcomes, particularly in wrist flexion and strength, but these also gradually improved over time. Wilcke et al. showed that reduced grip strength and range of motion correlated with a poorer DASH score in seventy-eight patients with a distal radial fracture[43].

Our study showed no differences in the time to fracture-healing between the treatment groups. In the nondisplaced fracture cohort, there was significantly more radial shortening in the placebo group than in the vitamin C group at both six and twenty-six weeks. Although this might suggest that the fracture took longer to heal in patients treated with placebo, allowing more subsidence, there was no significant difference in the healing time between the two treatment groups. One limitation of our study is that it was not powered to determine a difference in the time to fracture-healing between groups, and a study with larger numbers might have revealed a difference. Furthermore, the method used to determine the time to fracture-healing may lead to an error, as it is an estimate.

Studies have indicated enhanced fracture-healing following vitamin C administration in animals with gene mutations that render them unable to produce their own vitamin C[10]. In the developed world, vitamin C deficits are rare except among certain groups such as the elderly, alcoholics, and smokers[44]. In the present study, the dietary vitamin C scores revealed no clinical vitamin C deficits. However, to our knowledge it has not been determined whether a subclinical vitamin C deficit has any effect on fracture-healing. The absence of an effect of vitamin C supplementation on fracture-healing in the present study could be explained if acceleration of fracture-healing is observed only when supplements are given to a vitamin C-deprived population.

The study demonstrated no significant reduction in the prevalence of CRPS at one year in patients with either a displaced or nondisplaced fracture who were treated with vitamin C compared with placebo. There was a significantly greater prevalence of CRPS at six weeks in the vitamin C group in the nondisplaced fracture cohort, with the only significantly greater pain with use found at one year in this group. Since this may be a type-I error, the importance of this finding is unknown, and further work may be warranted. It is possible that the greater pain with use experienced by these patients at one year was related to the greater prevalence of CRPS at six weeks, although it would be expected that the other outcome parameters at one year would further reflect this. Our findings contrast with the findings of Zollinger et al., who performed two randomized studies of patients with distal radial fractures. In the first trial, they found the prevalence of CRPS to be lower in the patients who received vitamin C (7%) compared with the placebo group (22%) at one year[15]. That study included only fractures that were treated conservatively, implying a less severe range of fractures than those in the present study or in other previous studies[45,46], yet the CRPS rate in the placebo group at one year was unusually high. In the present study, the prevalence of CRPS was lower in patients with a nondisplaced fracture. In the

second multicenter trial by Zollinger et al., which included both conservatively and operatively treated fractures, the reported CRPS prevalence was 2.4% in the vitamin C group compared with 10% in the placebo group at one year, as established on the basis of a telephone interview or inquiry letter[14]. In that study, all adult patients with fractures of one or both wrists were included, exclusion criteria were not clear, and patients who had already been taking vitamin supplements were included. The present study had a higher dropout rate of 26% and a compliance rate of 84%. It showed no difference in the prevalence of CRPS between treatment groups in either the nondisplaced fracture cohort (6% and 5%) or the displaced fracture cohort (15% and 16%) at one year.

In conclusion, the present study demonstrated no benefit of vitamin C supplementation on the functional outcome or fracture-healing in patients with either a nondisplaced or displaced distal radial fracture.

## Appendix

eA Tables showing the outcomes at twelve and twenty-six weeks and the correlations between the HADS subscores at presentation and the DASH score at each time point are available with the online version of this article as a data supplement at jbjs.org. ■

Ingri Ekrol, MRCSEd
Andrew D. Duckworth, MSc, MRCSEd
Charles M. Court-Brown, MD, FRCSEd(Orth)
Margaret M. McQueen, MD, FRCSEd(Orth)
Edinburgh Orthopaedic Trauma Unit,
Royal Infirmary of Edinburgh,
51 Little France Crescent,
Edinburgh EH16 4SU,
United Kingdom.
E-mail address for A.D. Duckworth: andrew.duckworth@yahoo.co.uk

Stuart H. Ralston, MD, FRSE
Rheumatic Disease Unit,
Institute of Genetics and Molecular Medicine,
University of Edinburgh,
Western General Hospital,
Edinburgh EH4 2XU,
United Kingdom

## References

**1.** Matsuda T, Tanaka H, Shimazaki S, Matsuda H, Abcarian H, Reyes H, Hanumadass M. High-dose vitamin C therapy for extensive deep dermal burns. Burns. 1992 Apr;18(2):127-31.

**2.** Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. Arch Surg. 2000 Mar; 135(3):326-31.

**3.** Edgar DW, Fish JS, Gomez M, Wood FM. Local and systemic treatments for acute edema after burn injury: a systematic review of the literature. J Burn Care Res. 2011 Mar-Apr;32(2):334-47.

**4.** Matsuda T, Tanaka H, Yuasa H, Forrest R, Matsuda H, Hanumadass M, Reyes H. The effects of high-dose vitamin C therapy on postburn lipid peroxidation. J Burn Care Rehabil. 1993 Nov-Dec;14(6):624-9.

**5.** Göktürk E, Turgut A, Bayçu C, Günal I, Seber S, Gülbas Z. Oxygen-free radicals impair fracture healing in rats. Acta Orthop Scand. 1995 Oct;66(5):473-5.

**6.** Sarisözen B, Durak K, Dinçer G, Bilgen OF. The effects of vitamins E and C on fracture healing in rats. J Int Med Res. 2002 May-Jun;30(3):309-13.

**7.** Yilmaz C, Erdemli E, Selek H, Kinik H, Arikan M, Erdemli B. The contribution of vitamin C to healing of experimental fractures. Arch Orthop Trauma Surg. 2001 Jul;121(7):426-8.

**8.** Kearns SR, Daly AF, Sheehan K, Murray P, Kelly C, Bouchier-Hayes D. Oral vitamin C reduces the injury to skeletal muscle caused by compartment syndrome. J Bone Joint Surg Br. 2004 Aug;86(6):906-11.

**9.** Kearns SR, Moneley D, Murray P, Kelly C, Daly AF. Oral vitamin C attenuates acute ischaemia-reperfusion injury in skeletal muscle. J Bone Joint Surg Br. 2001 Nov;83(8):1202-6.

**10.** Alcantara-Martos T, Delgado-Martinez AD, Vega MV, Carrascal MT, Munuera-Martinez L. Effect of vitamin C on fracture healing in elderly Osteogenic Disorder Shionogi rats. J Bone Joint Surg Br. 2007 Mar;89(3):402-7.

**11.** Atkins RM, Duckworth T, Kanis JA. Features of algodystrophy after Colles' fracture. J Bone Joint Surg Br. 1990 Jan;72(1):105-10.

**12.** van der Laan L, Goris RJ. Reflex sympathetic dystrophy. An exaggerated regional inflammatory response? Hand Clin. 1997 Aug;13(3):373-85.

**13.** Oyen WJ, Arntz IE, Claessens RM, Van der Meer JW, Corstens FH, Goris RJ. Reflex sympathetic dystrophy of the hand: an excessive inflammatory response? Pain. 1993 Nov;55(2):151-7.

**14.** Zollinger PE, Tuinebreijer WE, Breederveld RS, Kreis RW. Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study. J Bone Joint Surg Am. 2007 Jul; 89(7):1424-31.

**15.** Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. Lancet. 1999 Dec 11;354(9195):2025-8.

**16.** Hudak PL, Amadio PC, Bombardier C; The Upper Extremity Collaborative Group (UECG). Development of an upper extremity outcome measure: the DASH (Disabilities of the Arm, Shoulder and Hand) [corrected]. Am J Ind Med. 1996 Jun;29(6): 602-8.

**17.** Gummesson C, Atroshi I, Ekdahl C. The Disabilities of the Arm, Shoulder and Hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. BMC Musculoskelet Disord. 2003 Jun 16;4: 11. Epub 2003 Jun 16.

**18.** Hernández-Avila M, Romieu I, Parra S, Hernández-Avila J, Madrigal H, Willett W. Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City. Salud Publica Mex. 1998 Mar-Apr;40(2):133-40.

**19.** Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70.

**20.** Ring D, Kadzielski J, Fabian L, Zurakowski D, Malhotra LR, Jupiter JB. Self-reported upper extremity health status correlates with depression. J Bone Joint Surg Am. 2006 Sep;88(9):1983-8.

**21.** Calderón SA, Zurakowski D, Davis JS, Ring D. Quantitative Adjustment of the Influence of Depression on the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire. Hand (N Y). 2010 Mar;5(1):49-55. Epub 2009 Jun 3.

**22.** Jenkins PJ, Watts AC, Duckworth AD, McEachan JE. Socioeconomic deprivation and the epidemiology of carpal tunnel syndrome. J Hand Surg Eur Vol. 2012 Feb; 37(2):123-9. Epub 2011 Sep 15.

**23.** Das De S, Vranceanu AM, Ring DC. Contribution of kinesophobia and catastrophic thinking to upper-extremity-specific disability. J Bone Joint Surg Am. 2013 Jan 2;95(1):76-81.

**24.** Atkins RM, Duckworth T, Kanis JA. Algodystrophy following Colles' fracture. J Hand Surg Br. 1989 May;14(2):161-4.

**25.** Atkins RM. Complex regional pain syndrome. J Bone Joint Surg Br. 2003 Nov; 85(8):1100-6.

**26.** Atkins RM, Kanis JA. The use of dolorimetry in the assessment of post-traumatic algodystrophy of the hand. Br J Rheumatol. 1989 Oct;28(5):404-9.

**27.** American Society for Surgery of the Hand. The hand: examination and diagnosis. New York: Churchill Livingstone; 1983.

**28.** Crosby CA, Wehbé MA, Mawr B. Hand strength: normative values. J Hand Surg Am. 1994 Jul;19(4):665-70.

**29.** Ng CY, McQueen MM. What are the radiological predictors of functional outcome following fractures of the distal radius? J Bone Joint Surg Br. 2011 Feb; 93(2):145-50.

**30.** McQueen MM, Hajducka C, Court-Brown CM. Redisplaced unstable fractures of the distal radius: a prospective randomised comparison of four methods of treatment. J Bone Joint Surg Br. 1996 May;78(3):404-9.

**31.** van der Linden W, Ericson R. Colles' fracture. How should its displacement be measured and how should it be immobilized? J Bone Joint Surg Am. 1981 Oct;63(8):1285-8.

**32.** Marsh JL, Slongo TF, Agel J, Broderick JS, Creevey W, DeCoster TA, Prokuski L, Sirkin MS, Ziran B, Henley B, Audigé L. Fracture and dislocation compendium – 2007: Orthopaedic Trauma Association Classification, Database and Outcomes Committee. J Orthop Trauma. 2007 Nov-Dec;21(10 Suppl):S1-133.

**33.** Uhthoff HK, Rahn BA. Healing patterns of metaphyseal fractures. Clin Orthop Relat Res. 1981 Oct;160:295-303.

**34.** Kristiansen TK, Ryaby JP, McCabe J, Frey JJ, Roe LR. Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound. A multicenter, prospective, randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am. 1997 Jul;79(7):961-73.

**35.** Kozin SH, Wood MB. Early soft-tissue complications after fractures of the distal part of the radius. J Bone Joint Surg Am. 1993 Jan;75(1):144-53.

**36.** Sigurdardottir K, Halldorsson S, Robertsson J. Epidemiology and treatment of distal radius fractures in Reykjavik, Iceland, in 2004. Comparison with an Icelandic study from 1985. Acta Orthop. 2011 Aug;82(4):494-8.

**37.** Ruch D, McQueen MM. Distal radius and ulna fractures. In: Bucholz RW, Heckman JD, Court-Brown CM, Tornetta P, editors. Rockwood and Green's fractures in adults. 7 ed. Philadelphia: Lippincott, Williams & Wilkins; 2010. p 831-80.

**38.** Knight D, Hajducka C, Will E, McQueen M. Locked volar plating for unstable distal radial fractures: clinical and radiological outcomes. Injury. 2010 Feb;41(2): 184-9. Epub 2009 Oct 12.

**39.** Rozental TD, Blazar PE, Franko OI, Chacko AT, Earp BE, Day CS. Functional outcomes for unstable distal radial fractures treated with open reduction and internal fixation or closed reduction and percutaneous fixation. A prospective randomized trial. J Bone Joint Surg Am. 2009 Aug;91(8):1837-46.

**40.** Wei DH, Raizman NM, Bottino CJ, Jobin CM, Strauch RJ, Rosenwasser MP. Unstable distal radial fractures treated with external fixation, a radial column plate, or a volar plate. A prospective randomized trial. J Bone Joint Surg Am. 2009 Jul; 91(7):1568-77.

**41.** Abramo A, Kopylov P, Tagil M. Evaluation of a treatment protocol in distal radius fractures: a prospective study in 581 patients using DASH as outcome. Acta Orthop. 2008 Jun;79(3):376-85.

**42.** Jaremko JL, Lambert RG, Rowe BH, Johnson JA, Majumdar SR. Do radiographic indices of distal radius fracture reduction predict outcomes in older adults receiving conservative treatment? Clin Radiol. 2007 Jan;62(1):65-72.

**43.** Wilcke MK, Abbaszadegan H, Adolphson PY. Patient-perceived outcome after displaced distal radius fractures. A comparison between radiological parameters, objective physical variables, and the DASH score. J Hand Ther. 2007 Oct-Dec;20(4): 290-8; quiz 299.

**44.** Falch JA, Mowé M, Bøhmer T. Low levels of serum ascorbic acid in elderly patients with hip fracture. Scand J Clin Lab Invest. 1998 May;58(3):225-8.

**45.** Dijkstra PU, Groothoff JW, ten Duis HJ, Geertzen JH. Incidence of complex regional pain syndrome type I after fractures of the distal radius. Eur J Pain. 2003; 7(5):457-62.

**46.** Atkins RM, Tindale W, Bickerstaff D, Kanis JA. Quantitative bone scintigraphy in reflex sympathetic dystrophy. Br J Rheumatol. 1993 Jan;32(1):41-5.