



ORIGINAL ARTICLE

Treatment with supplementary arginine, vitamin C and zinc in patients with pressure ulcers: A randomised controlled trial

Katherine J. Desneves^a, Bree E. Todorovic^b, Ann Cassar^a,
Timothy C. Crowe^{b,*}

^aDepartment of Nutrition and Dietetics, Austin Health, Studley Road, Heidelberg 3084, Australia

^bSchool of Exercise and Nutrition Sciences, Deakin University, Burwood Hwy, Burwood 3125, Australia

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KEYWORDS

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Summary

Background & Aims: Nutrients putatively implicated in pressure ulcer healing were evaluated in a clinical setting.

Methods: Sixteen inpatients with a stage 2, 3 or 4 pressure ulcer randomised to receive daily a standard hospital diet; a standard diet plus two high-protein/energy supplements; or a standard diet plus two high-protein/energy supplements containing additional arginine (9 g), vitamin C (500 mg) and zinc (30 mg). Nutritional status measurements (dietary, anthropometric and biochemical) and pressure ulcer size and severity (by PUSH tool; Pressure Ulcer Scale for Healing; 0 = completely healed, 17 = greatest severity) were measured weekly for 3 weeks.

Results: Patients' age and BMI ranges were 37–92 years and 16.4–28.1 kg/m², respectively. Baseline PUSH scores were similar between groups (8.7±0.5). Only patients receiving additional arginine, vitamin C and zinc demonstrated a clinically significant improvement in pressure ulcer healing (9.4±1.2 vs. 2.6±0.6; baseline and week 3, respectively; *P*<0.01). All patient groups presented with low serum albumin and zinc and elevated C-reactive protein. There were no significant changes in biochemical markers, oral dietary intake or weight in any group.

Conclusions: In this small set of patients, supplementary arginine, vitamin C and zinc significantly improved the rate of pressure ulcer healing. The results need to be confirmed in a larger study.

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*Corresponding author. Tel.: +61 3 9251 7266; fax: +61 3 9244 6017.

E-mail address: tim.crowe@deakin.edu.au (T.C. Crowe).

Introduction

Pressure ulcers are areas of damage to the skin and underlying tissue that usually occur over bony protrusions such as elbows, heels and hips. While unrelieved pressure, shearing forces and friction account for the mechanical aetiology of pressure ulcers, many other conditions can also predispose an individual to pressure ulcers. Old age, uncontrolled diabetes, sepsis, neurological and vascular disease, spinal cord damage, malnutrition and trauma are all recognised risk factors for pressure ulcers.¹⁻³ Estimates of the incidence and prevalence of pressure ulcers in both acute and long-term settings vary widely with figures up to 30% commonly reported.⁴⁻⁹ In addition to the expensive financial costs of treating pressure ulcers, there are social costs to the individual including pain, discomfort, decreased mobility, loss of independence and social isolation. Furthermore, increased death rates have been observed consistently in elderly patients who develop pressure ulcers.¹⁰

Malnutrition, inadequate protein or poor energy intake and recent weight loss have been identified as independent risk factors for the development of pressure ulcers.¹¹⁻¹³ It has been shown that several indices of malnutrition are associated with developing pressure ulcers, with many investigators finding a relationship between wound healing and body weight, body mass index, low serum albumin and zinc and total protein levels.^{1,11,12,14-16} The role of nutrition of dietary intervention in modulating pressure ulcer development and healing is less clear. Some investigators have found that patients who receive extra nutritional support tend to develop fewer pressure ulcers and to heal existing pressure ulcers faster compared with patients who do not receive nutritional support.¹⁶⁻¹⁹ Furthermore, a number of studies have investigated the potential value of specific, single nutrients such as vitamin C and zinc in regulating wound healing and have found promising results.²⁰⁻²²

Recent research has focused on the use of arginine to enhance wound healing and prevent pressure ulcer development. Arginine, a dietary conditionally essential amino acid, has been shown to possess numerous unique and potentially useful pharmacologic effects.²³ Arginine functions as a substrate for protein synthesis, collagen deposition, cell proliferation, T-lymphocyte function and promotes positive nitrogen balance.²⁴ It is also the biological precursor for nitric oxide, which has potent vasodilatory, antibacterial and angiogenic properties.²⁴ Investigations using a standardised wound model, measuring hydroxyproline synthesis

in artificial wounds as an index of new collagen synthesis and deposition, have found that subjects who are supplemented daily with arginine showed a significantly enhanced rate of collagen production compared to control subjects.^{25,26}

Strong preliminary results have shown a tendency for improved pressure ulcer healing in a small number of patients with severe cognitive impairment supplemented with a high-protein, high-kilojoule supplement enriched with arginine, zinc and antioxidant vitamins for 15 days.¹⁸ More recently, a study found an improved rate of healing of advanced pressure ulcers following 3 weeks supplementation with a commercial supplement containing additional arginine, zinc and antioxidants.¹⁹ Interestingly, use of a defined arginine-containing nutritional supplement was not beneficial in preventing the incidence of pressure ulcers in a randomised group of patients with hip fractures, suggesting that the benefits of arginine supplementation may be during the wound healing process.¹⁷

There is a paucity of well-designed trials using appropriate control groups and relevant clinical outcomes which examine the efficacy of supplemental nutrients on the healing of pressure ulcers. This study aims to investigate the nutritional status of patients diagnosed with pre-existing pressure ulcers and to determine whether nutrients putatively implicated in pressure ulcer healing (arginine, vitamin C and zinc) will improve the rate of pressure ulcer healing.

Materials and methods

Patients

Sixteen inpatients from Austin Health (Melbourne, Australia) with either a stage 2, 3 or 4 pressure ulcer were recruited for the study in order of admission to the wards. Initial staging was completed by the nurse referring the patient to the study dietitian. Pressure ulcers were staged according to the Australian Wound Management Association Clinical Practice Guidelines.²⁷ Patients were selected from aged care or spinal injury wards as these wards were previously found to possess a high prevalence of pressure ulcers (unpublished observations).

Individuals with a clinical suspicion or diagnosis of osteomyelitis were excluded as osteomyelitis can cause skin ulcers that have a different aetiology to pressure ulcers. Also excluded were patients with diabetes mellitus, individuals receiving enteral or

parenteral nutrition support or individuals prescribed hydroxyurea or greater than 10 mg of steroids/day as these factors all inhibit wound healing.

Written informed consent was obtained from the patient or from next of kin for patients with dementia or communication difficulties. The study was approved by both the Deakin University Human Research Ethics Committee and the Austin Health Human Research Ethics Committee.

Study design

Patients were randomly assigned into one of three dietary treatment groups: Diets A–C for 3 weeks. The randomisation process was as follows: over the 6-month recruitment period, patients were allocated to a dietary treatment group in the order that they were recruited. The sequence of dietary treatment allocation was determined before the beginning of the study by sorting a list of random numbers (generated using a computer program) in numerical order. Before sorting the list of random numbers, each of the numbers was linked to a dietary intervention group.

Diet A was the standard hospital diet. Diet B was the standard hospital diet plus two tetrapaks of a high-protein, high-energy supplement providing an additional 2100 kJ (500 kcal), 18 g protein, 0 g fat, 72 mg vitamin C and 7.5 mg zinc (Resource[®] Fruit Beverage; Novartis, MN, USA). Diet C was the standard hospital diet plus two tetrapaks of a defined arginine-containing supplement supplying an additional 2100 kJ (500 kcal), 21 g protein, 0 g fat, 500 mg vitamin C, 30 mg zinc and 9 g of arginine (Resource[®] Arginaid[™] Extra; Novartis, MN, USA). At 0, 1, 2 and 3 weeks, assessment was made of the patients' weight, blood biochemistry and pressure ulcer severity.

Pressure ulcer care

To control for extraneous variables, pressure ulcer care including turning schedules, bed and mattress type and dressings were kept constant during the 3-week study period and according to standard ward practice. Each patient was on a 2-hourly turning regimen, had a dynamic air mattress on their bed and a gel cushion for when sitting out of bed. Other interventions occurred as per the Pressure Ulcer Prevention Strategies tool and equipment flow charts implemented across all campuses of Austin Health on January 27, 2004. Choice of dressing remained dependent on depth of wound, amount of exudate, position of the wound,

whether infection was present and type of tissue in the wound base.

Pressure ulcer measurements

An independent person (Clinical Nurse Consultant), blinded to the dietary treatment, conducted the assessment of the pressure ulcers using the PUSH tool (Pressure Ulcer Scale for Healing).²⁸ The PUSH tool was developed by the National Pressure Ulcer Advisory Panel as a quick and reliable tool to monitor the change in pressure ulcer status over time. The tool is based on (1) an analysis of research literature to identify critical parameters commonly used to monitor pressure ulcer healing and (2) a statistical analysis (i.e. principal component analysis) of existing research databases on pressure ulcer monitoring and (3) a national retrospective validation study. The PUSH tool has a sub-score for (a) wound length and depth; (b) exudate amount and (c) tissue type. The sub-scores were then added together to give a PUSH total score on a scale of 0 (completely healed) to 17 (greatest severity). A comparison of total scores measured over time provided an indication of the improvement or deterioration in pressure ulcer healing.

Assessment of dietary intake

A food and fluid record was completed daily for all subjects for the 3-week period. A 24-h dietary recall was used to cross check intake daily and monitor compliance with the diet. Analysis of the food record used the Australian Food and Nutrient Database (AusNut) compiled in 1999 by Food Standards Australia and New Zealand.²⁹ The arginine content of the patients' diet was determined manually using an Australian database listing the amino acid composition of food items.³⁰ Patients' daily energy requirements were estimated using the Schofield equation with an appropriate activity/injury factor.³¹ Protein requirements were based on the recommended daily allowance for individuals with pressure ulcers as decided by the National Pressure Ulcer Advisory Panel.²⁸

Anthropometry

Weight of the patients was taken on the day of commencing the study and weekly during the 3-week study period. Weight was measured using standard ward scales. For all patients, knee height was measured as an estimate for stature as many of the patients had severe spinal curvature or were unable to stand. Knee height was measured with a

calliper consisting of an adjustable measuring stick with a blade attached to each end at a 90° angle. A standard formula for men and women was used to estimate stature from knee height.³²

Blood biochemistry

A full blood examination, liver function tests, urea and electrolytes, transthyretin (also known as thyroxine-binding pre-albumin), C-reactive protein (CRP), serum zinc and serum vitamin C were assessed prior to commencing the study and weekly over the study period. Serum albumin is a common measure of long-term nutritional status; however, is not very sensitive to short-term changes in protein status due its half-life of 14–20 days. Transthyretin is a more sensitive index of protein status and responds more rapidly to dietary treatment than serum albumin due to its half-life of 2 days.³²

Statistical analysis

Within-group changes in pressure ulcer size and severity (PUSH score) were evaluated using the Friedman test with between-group comparisons evaluated using the Mann–Whitney *U*-test. Differences in baseline measures (age, weight, dietary intake and BMI) were tested by one-way ANOVA. Repeated-measures ANOVA testing was used to calculate differences between weight changes and biochemical parameters over the study period. An alpha error of $P < 0.05$ was used to determine statistical significance in all analyses. Data was analysed using SPSS statistical software (version 11.5). Results were presented as means \pm SEM.

Results

Baseline characteristics

Sixteen patients were sequentially recruited for the study over a period of 6 months. Age, gender, weight, BMI, initial staging and location of pressure ulcer and medical diagnosis of patients randomised to each diet group are presented in Table 1. Patients' age and BMI ranges were 37–92 years and 16.4–28.1 kg/m², respectively. Patients randomised to Diet C had a significantly lower BMI compared to patients allocated to Diet B. Twelve of the 16 patients presented with Stage 2 pressure ulcers. Three of the 16 patients (one from each of the three dietary intervention groups) did not have assessments performed in the final week 3 of the

study as one patient was discharged (from Diet C) and two died (from Diets A and B) after completion of their assessment at week 2.

Anthropometry

Over the 3-week study period, there were no significant changes or fluctuations in patients' body weight irrespective of which dietary intervention they were randomised to. In fact, there was a slight, non-significant, trend for weight to increase in each group with an average of 1.2, 0.4 and 1.1 kg gained by patients randomised to Diets A–C, respectively. Patients were evenly matched for weight at baseline between each group with no significant differences between treatment groups seen over the 3-weeks. For the 3 patients that had either died or were discharged after week 2, weight measured at week 2 was carried forward to week 3 to allow inter-group weight comparison.

Pressure ulcer assessment

Fig. 1 shows the change in pressure ulcer severity as measured by the PUSH tool. PUSH score was similar among all three diet intervention groups at baseline (8.7 ± 1.0 , 8.0 ± 0.5 and 9.4 ± 1.2 ; Diets A–C, respectively; NS). For patients randomised to Diet C, there was a significant improvement from baseline PUSH score (9.4 ± 1.2) at both week 2 (4.4 ± 1.5 ; $P < 0.05$) and week 3 (2.6 ± 0.6 ; $P < 0.01$). Furthermore, PUSH score at week 3 for the Diet C group was significantly lower than both Diets A and B (7.0 ± 1.5 and 6.0 ± 1.2 ; Diets A and B, respectively; $P < 0.05$). Patients randomised to Diet A (control) showed a small, but significant, improvement in pressure ulcer healing at week 3 (8.7 ± 1.0 vs. 7.0 ± 1.5 ; week 0 and week 3, respectively; $P < 0.05$). No significant change in PUSH score over the 3 weeks was seen for patients on Diet B. In terms of fold change, patients on Diet C showed an approximate 2.5-fold greater improvement in pressure ulcer healing after 3 weeks compared to the other two diet groups.

Dietary intake and adequacy

Table 2 shows the average daily dietary intake of energy, protein, arginine, vitamin C and zinc of patients over the 3-week period based on analysis of food and fluid records. There were no significant differences in patients' energy and protein intake between the three diets. As would be expected, patients randomised to Diet C consumed significantly more arginine, vitamin C and zinc than other

Table 1 Description and clinical characteristics of patients randomised to each diet group.

| | Diet A | Diet B | Diet C |
|--|----------|----------|-----------|
| Number of patients | 6 | 5 | 5 |
| Age (years) | 63.0±9.9 | 75.6±5.9 | 83.2±1.1 |
| Body Mass Index (kg/m ²) | 24.4±1.0 | 25.6±0.8 | 20.6±1.5* |
| Weight (kg) | 63.0±2.6 | 68.8±5.8 | 59.5±8.7 |
| <i>Gender</i> | | | |
| Male | 4 | 3 | 3 |
| Female | 2 | 2 | 2 |
| <i>Diagnosis</i> | | | |
| Dementia | | 1 | |
| Cerebrovascular accident | 3 | 1 | 2 |
| Spinal cord injury | 1 | | 1 |
| Parkinson's disease | | | 1 |
| Chronic cardiac failure | | 2 | |
| Fractured bones | 1 | 1 | 1 |
| Pressure ulcers (alone) | 1 | | |
| <i>Initial stage of pressure ulcer</i> | | | |
| Stage 2 | 4 | 5 | 3 |
| Stage 3 | 2 | | 1 |
| Stage 4 | | | 1 |
| <i>Pressure ulcer location</i> | | | |
| Heel | 2 | 2 | 1 |
| Sacrum | 1 | 1 | 3 |
| Perineal | 1 | | |
| Ischium | | 1 | 1 |
| Ankle | 1 | 1 | |
| Toe | 1 | | |

Data presented as mean ± SEM. *P < 0.05 (compared to Diet B group).

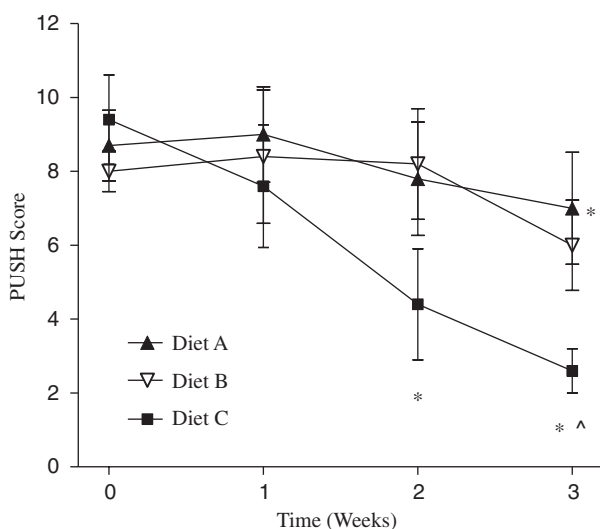


Figure 1 Change in patients' PUSH score over the study period with different dietary interventions. The ranges for PUSH scores at baseline were 6–12 (Diet A), 7–10 (Diet B) and 5–12 (Diet C). Week 3 PUSH score ranges were 3–11 (Diet A), 4–9 (Diet B) and 1–4 (Diet C). Data presented as mean ± SEM. *P < 0.05 (compared to Week 0); ^P < 0.05 (compared to Diet A or B).

patients owing to the nutrient formulation of the commercial supplement.

Based on patients' actual dietary intake, comparison was made to estimated daily energy and protein requirements (Table 2). Patients randomised to Diets A or B consumed 20% and 15% significantly fewer kilojoules, respectively than their estimated requirements (P < 0.05). Patients on Diet B only consumed 63% of their estimated protein requirements (P < 0.05) while patients on Diet A or C consumed 79% and 92%, respectively of their estimated protein requirement (non-significant difference).

Blood biochemistry

Baseline measurements of most indices of blood biochemical nutritional status did not differ greatly between each group with the exception of albumin levels of patients on Diet B which were significantly lower compared with patients randomised to Diet A or C (Table 3). At baseline, serum albumin and zinc

were below the normal range while CRP was elevated in all three diet groups. Transthyretin and serum vitamin C concentrations at baseline were within the normal range. There were no significant changes in any of the aforementioned biochemical markers over the 3 weeks with albumin and zinc consistently remaining low and CRP remaining elevated. Despite supplementation, serum zinc levels did not increase significantly from baseline to week 3 in Diet C. Vitamin C levels showed a trend for improvement from baseline to week 3 in patients consuming Diet C; however, this did not reach statistical significance.

On average, full blood examination, liver function tests (with the exception of albumin), urea and electrolytes showed little variation from the normal range while no significant changes in any of these parameters over the 3 weeks were observed (data not shown).

Dietary compliance

Compliance of consumption of the nutritional supplements was 94%. Supplement compliance was calculated by dividing the actual number of

Table 2 Average daily dietary intake over the study period with comparison to estimated daily energy and protein requirements.

| | Diet A | Diet B ^a | Diet C ^a |
|------------------------------------|-------------------------|-------------------------|---------------------------|
| Energy (kJ) | 6473 ± 650 [#] | 6138 ± 439 [#] | 6688 ± 274 |
| Est. energy requirements (kJ/day) | 8100 ± 672 | 7160 ± 558 | 6780 ± 589 |
| Protein (g) | 69.6 ± 8.2 | 60.8 ± 6.1 ⁺ | 74.4 ± 4.6 |
| Recommended protein intake (g/day) | 88.2 ± 3.6 | 96.2 ± 8.2 | 80.5 ± 14.0 |
| Arginine (g) | 3.5 ± 1.1 | 4.4 ± 1.7 | 10.4 ± 0.2 [*] |
| Vitamin C (mg) | 110.7 ± 37.0 | 123.5 ± 13.5 | 573.9 ± 13.7 [*] |
| Zinc (mg) | 8.7 ± 0.8 | 13.7 ± 0.7 [^] | 37.1 ± 0.5 [*] |

^aAnalysis for Diets B and C includes contribution made by the nutritional supplements. Data presented as mean ± SEM. [#]*P* < 0.05 (compared to estimated energy requirements); ⁺*P* < 0.05 (compared to recommended protein intake); ^{*}*P* < 0.05 (compared to Diet A or B); [^]*P* < 0.05 (compared to Diet A).

Table 3 Changes in biochemical indices of nutritional status over the study period for each dietary intervention group.

| | Baseline | Week 1 | Week 2 | Week 3 | Reference range |
|----------------------|-------------------------|-------------------------|-------------------------|--------------|-----------------|
| <i>Diet A</i> | | | | | |
| Albumin (g/l) | 31.5 ± 2.3 | 33.7 ± 2.5 | 31.8 ± 2.4 | 33.6 ± 2.6 | 36–48 |
| Transthyretin (mg/l) | 212.2 ± 16.2 | 231.8 ± 31.2 | 214.0 ± 13.0 | 221.0 ± 30.8 | 180–360 |
| Zinc (μmol/l) | 10.6 ± 1.5 | 10.6 ± 1.1 | 11.1 ± 1.8 | 9.8 ± 1.0 | 11–19 |
| Vitamin C (μmol/l) | 38.3 ± 15.2 | 47.7 ± 14.6 | 43.2 ± 13.2 | 52.8 ± 10.5 | 26–85 |
| CRP (mg/l) | 23.9 ± 11.5 | 29.4 ± 14.3 | 34.3 ± 14.6 | 23.7 ± 14.6 | 1.6–8.7 |
| <i>Diet B</i> | | | | | |
| Albumin (g/l) | 24.4 ± 1.9 [*] | 26.0 ± 1.8 [*] | 24.4 ± 2.1 [*] | 25.8 ± 2.4 | 36–48 |
| Transthyretin (mg/l) | 200.0 ± 22.6 | 247.2 ± 42.6 | 198.5 ± 24.6 | 224.1 ± 29.7 | 180–360 |
| Zinc (μmol/l) | 9.7 ± 0.4 | 8.8 ± 0.7 | 8.9 ± 0.7 | 9.3 ± 0.3 | 11–19 |
| Vitamin C (μmol/l) | 47.8 ± 24.2 | 34.4 ± 14.8 | 79.8 ± 45.4 | 41.7 ± 15.5 | 26–85 |
| CRP (mg/l) | 42.9 ± 13.5 | 70.9 ± 54.6 | 66.1 ± 32.3 | 46.4 ± 20.7 | 1.6–8.7 |
| <i>Diet C</i> | | | | | |
| Albumin (g/l) | 30.6 ± 1.1 | 32.0 ± 0.9 | 31.4 ± 0.9 | 34.3 ± 2.9 | 36–48 |
| Transthyretin (mg/l) | 237.0 ± 36.6 | 213.9 ± 20.6 | 232.1 ± 24.5 | 259.2 ± 27.5 | 180–360 |
| Zinc (μmol/l) | 9.2 ± 1.1 | 9.5 ± 0.9 | 9.7 ± 0.7 | 9.4 ± 0.5 | 11–19 |
| Vitamin C (μmol/l) | 68.4 ± 18.6 | 99.5 ± 18.2 | 79.4 ± 14.6 | 107.0 ± 17.8 | 26–85 |
| CRP (mg/l) | 20.2 ± 13.5 | 17.0 ± 8.9 | 17.8 ± 13.8 | 17.3 ± 11.6 | 1.6–8.7 |

Data presented as mean ± SEM. ^{*}*P* < 0.05 (compared to Diet A or C).

full supplement tetrapaks consumed by patients in Groups B and C by the total number of tetrapaks that were provided to be consumed over the 3 weeks (i.e. 2 tetrapaks/day for 3 weeks).

Discussion

The results of this nutrition intervention study suggested an improved rate of pressure ulcer healing over 3 weeks when supplemental arginine, vitamin C and zinc is added to the diets of aged care and spinal patients. Only one previous study has attempted to evaluate the effectiveness of these supplemental nutrients in a randomised controlled trial in a clinical setting.¹⁸ Results from this aforementioned study were promising as improved pressure ulcer healing over 15 days was seen in patients receiving additional energy (2100 kJ/day), arginine (7.5 g/day), zinc (25 mg/day) and antioxidants; however, statistical analysis was not performed and results were presented as preliminary data only. A study investigating the effectiveness of supplemental arginine, vitamin C and zinc in 39 patients with a stage 3 or 4 pressure ulcer found a 29% reduction in wound area after 3 weeks; however, reported healing rates were compared against historical controls from studies investigating the effect of dressing types or supplemental protein on wound healing.¹⁹ The results from our study build on these preliminary research studies, and provide evidence for the efficacy of supplemental nutrition in aiding pressure ulcer healing. Of note was the magnitude of healing of pressure ulcers in the patient group consuming the specialised arginine-containing supplement which equated to an approximate 2.5-fold greater improvement in pressure ulcer healing after 3 weeks compared to the other two diet groups.

Patients with pressure ulcers may require higher protein diets and more energy than other bedridden patients.³³ Our study found that many patients were not consuming the recommended daily intakes for energy (Diets A and B) and protein (Diet B) and this may have impacted on the rate of pressure ulcer healing. Our study suggests that using a defined supplement aimed at pressure ulcer healing helped to ensure an adequate nutrition intake, which may have been a defining difference between the groups. Interestingly, dietary analysis of oral food intake (which excluded the contribution made by the supplements) found that patients randomised to the supplement groups (Diets B and C) consumed significantly fewer kilojoules than

the control group. We speculate that the supplements had an effect on satiety even though no instruction was given that the patients needed to consume the supplements at defined meal times; hence the supplements were unintentionally acting to replace some of the patients' oral food intake.

One noteworthy finding from this study was that almost all patients enrolled consistently had low levels of serum albumin and zinc and elevated CRP. Many studies have found a relationship between low serum albumin and the risk of development of pressure ulcers and impaired pressure ulcer healing.^{8,11,12,16} Whilst serum albumin may be a good biochemical marker for identifying patients at risk of developing pressure ulcers, it is not very sensitive to short-term changes in protein status due to its long half-life of 14–20 days hence it may take longer than 3 weeks to see changes with nutritional intervention.³² As an adjunct to using serum albumin as a biochemical marker of nutritional status, transthyretin was measured as it is more sensitive to short-term changes in protein status due to its half-life of 2 days.³⁴ Transthyretin levels of patients at the commencement of the study were found to be normal which may suggest that patients in this study were not severely 'malnourished' or 'diseased' although one deficiency of our study was that screening for malnutrition was not performed at the outset. Most patients in this study were admitted for rehabilitation secondary to their illness (such as cerebrovascular accident, fractured bones or spinal cord injury) so whilst these patients were unwell, they may not necessarily have been malnourished.

Zinc supplementation is often promoted as aiding in wound healing yet evidence for its efficacy is far from conclusive.^{22,35} In our study, serum zinc was found to be low in all patient groups whilst no changes were observed in serum levels over the study period despite significant supplementation in Diets B and C groups. While poor oral intake may explain the low zinc levels, acute infection or inflammation can give rise to low zinc readings as zinc is redistributed from the plasma to the liver.³² Furthermore, as zinc is transported by albumin, low albumin levels may impact on the measurable serum zinc levels. Interestingly, vitamin C levels were within the normal range throughout the study and did not change significantly. One study at least has found that supplemental vitamin C (500 mg twice daily) increased leukocyte ascorbic acid levels and accelerated pressure ulcer healing²⁰; however, another study found no benefit on the healing rate of pressure ulcers in a randomised trial in nursing home patients supplemented with 500 mg of vitamin C daily.²¹

Despite improvements in pressure ulcer size and severity in many of the patients, there were no significant changes in patients' weight. As the study period was only 3 weeks, it can be argued that this was not long enough to see significant changes in weight in either direction. Furthermore, as no significant weight changes were observed, it is entirely possible that the calculation of energy needs overestimated the impact of the injury/stress factor applied to the energy requirement equation. Mean BMI at baseline for all patient groups was within the normal range; however, mean BMI of patients on Diet C (20.6 kg/m²) was lower than the other groups (24.4 and 25.6 kg/m²; Diets A and B, respectively) whilst this same group was also older (83.8 cf. 63.0 and 75.6 yr). The possibility does arise that patients randomised to Diet C were more likely to receive benefit from nutritional supplementation on the healing rate of their pressure ulcers as they represented a more 'at risk' group due to their greater risk of malnutrition by virtue of being elderly and having a low-normal BMI. While a relationship between low BMI and the development of pressure ulcers has been observed by other researchers,^{12,14–16,36} how BMI can impact on healing rate once a pressure ulcer is formed is not known.

One deficiency of the current study is the limited sample size. Even though achieving statistical significance with small sample sizes requires large differences to be observed (which we demonstrated), issues of normal biological variation cannot be discounted. Nevertheless, findings from this study do support previous research whilst a plausible physiologic mechanism exists to support the application of supplemental arginine, vitamin C and zinc in pressure ulcer healing. Nonetheless, our results do need confirmation with larger patient numbers and also benefit would be gained in following all patients until complete pressure healing is achieved. The majority of patients in the study presented with Stage 2 pressure ulcers (75%). Estimates of the length of time to healing for Stage 2 pressure ulcers are between 12 and 16 weeks with Stages 3 and 4 ulcers requiring substantially longer treatment.^{37,38} Based on our data, linear regression analysis to determine time-to-healing (designated as a PUSH score of zero) indicated that patients on Diet A or B would require 15.6 and 14.8 weeks, respectively to completely heal their pressure ulcers. Patients on Diet C would be expected to demonstrate full healing after only 5 weeks. This conforms to a close to 3-fold improvement in the expected time-to-healing by using supplemental arginine, vitamin C and zinc if the pressure ulcers of all patients continued to heal at the rates demonstrated.

Whilst healing of pressure ulcers is important, prevention of these ulcers is the first option. There is a lack of research aimed at finding the optimal diet for prevention of pressure ulcers. Future studies may incorporate the use of supplemental arginine, vitamin C and zinc in patients at high risk of developing pressure ulcers to examine the efficacy in prevention. We excluded patients with diabetes and osteomyelitis due to potential confounding issues; however, future research on the role of supplemental nutrition on pressure ulcer healing in these patient groups would also be of interest.

Conclusions

Preventive therapy in patients at risk of developing pressure ulcers, and nutritional treatment of patients with pressure ulcers, have the benefits of reducing patient suffering and prolonged hospitalisation. The added cost of nutritional support for patients with pressure ulcers represents only a small component of their management care plan. The possibility of enhanced pressure ulcer healing using defined amounts of additional arginine, vitamin C and zinc could significantly reduce the costs associated with the management of pressure ulcers as well as decrease patient pain and discomfort.

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