Nutritional support in the treatment and prevention of pressure ulcers: An overview of studies with an arginine enriched Oral Nutritional Supplement

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KEYWORDS
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Abstract
Under-nutrition, inadequate protein or poor protein and energy intake and unintended weight loss have been identified as independent risk factors for the development of pressure ulcers. Providing oral nutritional supplements (ONS) in addition to regular food intake seems a logical way to replenish body shortages of macro- and micronutrients as well as to supply extra nutrients for the preservation of skin tissue, strengthening of tissue resistance, and promoting tissue repair. To examine the effect of nutritional intervention in pressure ulcer care, clinical studies performed with a specific ONS enriched with arginine, vitamin C and zinc were reviewed. Six clinical studies that were performed with the specific ONS, identified via electronic and conference databases, were included in the review. Four studies examined the effects of the specific ONS in patients with pressure ulcers, while two studies examined the effects of the specific ONS in patients at high risk of developing pressure ulcers. The reviewed practice-based studies with the specific ONS specifically developed for patients with pressure ulcers show positive effects of this ONS on pressure ulcer healing and the ONS might potentially reduce the risk of developing pressure ulcers.
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Introduction
Pressure ulcers are a common and costly problem in all health care institutions. Under-nutrition and
protein-energy malnutrition are commonly observed in institutionalised elderly and in patients admitted to hospitals [1–3]. A combination of immobility, loss of lean body mass comprising muscle and skin — as well as challenges to the immune system increases the risk of pressure ulcers by 74% [4]. Malnutrition, inadequate or poor protein and energy intake and recent weight loss have been identified as independent risk factors for the development of pressure ulcers [5]. Common causes of malnutrition in the elderly include decreased appetite, dependence on help for eating, impaired cognition and/or communication, poor positioning, frequent acute illnesses causing poor absorption or gastrointestinal losses, decreased thirst response, psycho-social factors such as isolation and depression, monotonity of the diet, and higher nutrient requirements along with the physiological demands of age, illness and impairment [4]. Malnutrition has been found to delay pressure ulcer healing and increase the risk for developing (chronic) pressure ulcers [6]. Furthermore, malnourished patients at risk of pressure ulcers or with established pressure ulcers often have problems in fulfilling their nutritional needs with normal food intake. Providing an oral nutritional supplement (ONS) and even an ONS specifically developed for patients with pressure ulcers in addition to regular diet is a logical way to replenish shortages of macro- and micronutrients and to supply extra nutrients for preserving skin tissue, strengthening of tissue resistance, and promoting tissue repair [7–9]. To examine the effect of a specific nutritional intervention in pressure ulcer healing, clinical studies performed with a specific ONS enriched with arginine, vitamin C and zinc for the healing of pressure ulcers were reviewed.

The specific ONS reviewed is a Food for Special Medical Purposes (European Commission Directive 1999/21/EC, 25 March 1999) for the dietary management of pressure ulcers and provides nutrients that are believed to be important in the wound healing process containing 20 g protein of which 3 g arginine, 250 mg vitamin C, 38 mg vitamin E, 9 mg zinc, and other micronutrients with 250 kcal per 200 ml serving (6.8 fl. oz). Protein deficiency adversely affects pressure ulcer healing by blunting the fibroblastic response, neo-angiogenesis, collagen synthesis and wound remodelling processes [10]. The ONS is enriched with arginine, because arginine appears to favourably influence pressure ulcer healing by affecting microvascular and perfusion changes, enhancing collagen production via proline synthesis [11,12]. Arginine is classified as a nonessential amino acid that becomes aconditionally essential substrate in stressed adults. Arginine has been shown to enhance wound strength and collagen deposition in artificial incisional wounds in rodents and humans [11,12]. Furthermore, the ONS contains vitamin E, C and zinc, all ingredients that have been described to support pressure ulcer healing [7].

Methods

The search was focused specifically on studies performed with the specific ONS (Cubitan®, Nutricia Advanced Medical Nutrition, The Netherlands). Studies were identified by searching electronic databases from the year that the product was launched (1997) through 31 October 2008 including the databases PubMed, EMBASE, The Cochrane Library and reference lists of retrieved articles, and conferences databases including the European Society for Parenteral and Enteral Nutrition (ESPEN), American Society for Parenteral and Enteral Nutrition (ASPEN), the European Pressure Ulcer Advisory Panel (EPUAP) and the Advanced Wound Care and Wound Healing Society Spring Meeting (SAWC/WHS). To ensure all studies with the specific ONS were retrieved, search terms included: decubitus, pressure sore*, pressure ulcer*, bed sore*, nutrition*, enteral*, oral*, supplement*, sip, feed, liquid, formula*, protein, arginine, zinc, Vitamin C, ascorbic acid, Vitamin E, antioxida*, Cubitan. No restrictions were placed on studies with regard to type of comparator (e.g. routine care, nutritional support, dietary advice), year of publication, language (providing an English abstract was available) and source. One reviewer (EM) selected potentially relevant articles based on literature search. These articles were independently screened by two other reviewers (JS, HH).

Results

The search retrieved six clinical studies that were performed with the specific ONS mentioned in this review as ONS-pu (pu = pressure ulcers). An overview of the included studies is depicted in Tables 1 and 2.

Treatment — open-label studies

The first open-label study was performed in 10 Spanish hospitals in which 39 patients with grade II, III or IV pressure ulcers received the ONS-pu 2—3 times daily for 3 weeks in addition to standard care [13]. The mean age of the study population was 74.7 ± 12.9 years and a large proportion of the
Table 1  Treatment studies with the specific ONS included in the review.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benati et al. [15]</td>
<td>RCT, parallel groups</td>
<td>16 cognitively impaired elderly inpatients with pressure ulcers aged 72–91 y</td>
<td>2 times ONS-pu daily for 15 days vs. standard hospital diet (treatment A) and high-protein formula (treatment B)</td>
<td>Treatment B and C had more effect on PU healing than A</td>
<td>Stage of ulcers not reported. The data were provided only graphically.</td>
</tr>
<tr>
<td>Frias Soriano et al. 2004 [13]</td>
<td>CT, single group</td>
<td>39 elderly inpatients with pressure ulcers grade III–IV; mean age 75 y</td>
<td>2–3 times ONS-pu daily for 3 weeks, along with their normal diet or enteral feed and standard pressure care</td>
<td>After 3 wks median PU area reduced from 23.6 ± cm² to 19.2 ± cm² (P &lt; 0.001)</td>
<td>Pressure ulcer healing was assessed with the Pressure Sores Status Tool (PSST).</td>
</tr>
<tr>
<td>Heyman et al. [14]</td>
<td>CT, single group</td>
<td>245 long-term care residents with grade II–IV pressure ulcers; mean age 82 y</td>
<td>2–3 times ONS-pu daily for 9 weeks, along with their normal diet or enteral feed and standard pressure care</td>
<td>Average PU area reduced from 1580 ± 3743 mm² to 743 ± 1809 mm² (P &lt; 0.0001).</td>
<td>Amount of exudation was assessed subjectively.</td>
</tr>
<tr>
<td>Cereda et al. [16]</td>
<td>RCT</td>
<td>28 Institutionalised elderly with grade II–IV pressure ulcers</td>
<td>15 subjects were prescribed standard nutrition (hospital diet or standard formula; protein: 16% of total calories) and 13 received standard diet plus 2 servings of the ONS-pu</td>
<td>After 12 wks both groups had improved PU healing compared to baseline (P &lt; 0.0001)</td>
<td>Difference mean PUSH score after 12 wks: ONS-pu group −6.1 ± 2.7, control group (−3.3 ± 2.4; P &lt; 0.05)</td>
</tr>
</tbody>
</table>

Reduction surface area: ONS-pu −1140.9 ± 669.2 mm², control group −571.7 ± 391.3 mm² (P < 0.05)

Abbreviations: RCT = randomised-controlled trials; CT = clinical trial; ONS-pu = Oral Nutritional Supplement specifically designed for patients with pressure ulcers; PU = pressure ulcer.
No pressure ulcers present at start of the study

PU incidence of stage II: supplemented group 4 J.M.G.A. Schols et al.

No pressure

PU incidence: placebo group was 59%, supplement group 55% (difference: 0.037; 95% CI: 0.23)

18.4%, placebo group 27.5% (difference: 0.091; 95% CI: 0.073; P = 0.25; Q = 0.345)

Table 2 Preventive studies with the specific ONS included in the review.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hommel et al. [17]</td>
<td>CT, two groups</td>
<td>420 hip fracture patients undergoing surgery; patients aged 85 year or older: ONS-pu 80.4 ± 10.3 y; control group 81.5 ± 10.5 (n.s.)</td>
<td>The intervention group (n = 210) received the ONS-pu twice daily postoperatively until hospital discharge (median 11 days)</td>
<td>At discharge total amount of PU: control group 50 ulcers in 43 patients, intervention group 28 ulcers in 21 patients (P = 0.009) Total number of patients with hospital-acquired PU: control group 39 patients, intervention group 19 patients (P = 0.007) PU incidence: placebo group was 59%, supplement group 55% (difference: 0.037; 95% CI: −0.16; −0.23) PU incidence of stage II: supplement group 18.4%, placebo group 27.5% (difference: 0.091; 95% CI: −0.073; −0.25; P = 0.345)</td>
<td>No pressure ulcers present at start of the study</td>
</tr>
<tr>
<td>Houwing et al. [18]</td>
<td>RCT, double blind, parallel groups</td>
<td>103 patients with hip fractures at risk for pressure ulcers. Mean age: ONS-pu 81.5 ± 0.9 y; placebo group 80.5 ± 1.3 (n.s.)</td>
<td>After surgery, patients received 2 times daily the ONS-pu (n = 51) or a non-caloric, placebo (n = 52) for 4 weeks or until discharge (median: 10 days)</td>
<td>Time of onset of PU: supplement group 3.6 ± 0.9 days, placebo group 1.6 ± 0.9 days; P = 0.09</td>
<td>No pressure ulcers present at start of the study</td>
</tr>
</tbody>
</table>

Abbreviations: RCT = randomised-controlled trials; CT = clinical trial; ONS-pu = Oral Nutritional Supplement specifically designed for patients with pressure ulcers; PU = pressure ulcer.
sometimes left at least half the ONS or refused one or more daily serving; Poor — the patient usually left at least half of the ONS or refused one or more daily serving. The study showed that the average intake of the ONS recorded was 2.3 ± 0.56 servings per day, which is indicative of good concordance. This is substantiated by the fact that eight out of 10 patients did not complain about being prescribed three servings per day. In addition, 86 patients (35%) indicated excellent self-reported concordance and 115 patients (47%) very good concordance; the remaining 44 patients reported insufficient (10%) and poor concordance (8%). Importantly, 9 out of 10 health care professionals reported they would continue to use the ONS in the future as part of pressure ulcer care in their long-term care facility.

**Treatment — randomised-controlled studies**

The first randomised-controlled study (2001) was performed in a small number of patients ($N=16$) with severe cognitive impairment with a Mini Mental State Examination score of 15 or lower. The study examined the effects on pressure ulcer healing with the Pressure Sore Status Tool between three groups that received standard hospital diet (not specified in the publication); a standard diet plus high-protein formula or the ONS-pu for 15 days, respectively [15]. All patients lay on an alternating air pressure mattress and pressure ulcer treatment was standardised (not specified in the publication). The results were presented graphically and showed a tendency for a more pronounced pressure ulcer healing in patients supplemented with the ONS-pu compared to a high-protein formula or standard hospital diet.

Interestingly, Cereda et al. [16] recently performed a 12-week follow-up randomised-controlled trial with the same ONS-pu in a long-term care setting. Twenty-eight Institutionalised elderly with grade II, III or IV pressure ulcers with less than one month history were studied and received nutritional support of 30 kilocalories/kg/day. 15 subjects were prescribed standard nutrition (hospital diet or standard enteral nutrition formula containing 16% of total calories as protein) and 13 received the disease-specific nutrition (standard diet plus 2 servings of the ONS-pu). After 12 weeks both groups had significant improvement in pressure ulcer compared to baseline as measured with the Pressure Ulcer Scale for Healing (PUSH) score and pressure ulcer surface area ($p<0.0001$; repeated-measures ANOVA). Treatment with ONS-pu was, however, associated with a significantly higher rate of healing. The difference in mean PUSH score in the ONS-pu study group ($-6.1±2.7$) was significantly decreased at 12 weeks compared to the control group ($-3.3±2.4$; $P<0.05$). At week 8 the reduction in surface area was significantly higher in the ONS-pu group compared to the control group ($-1140.9±669.2\,\text{mm}^2$ vs. $-571.7±391.3\,\text{mm}^2$; $P<0.05$), with a significantly higher mean reduction in occurrence of pressure ulcers (57% vs. 33%; $P<0.02$). Based on these results the authors concluded that disease-specific nutritional support
of pressure ulcer-patients with an ONS, enriched with protein, arginine, zinc and vitamin C, should be preferred to a standard protocol for improving the rate of pressure healing.

Preventive studies

Furthermore, a recent quasi-experimental study at the University Hospital in Lund investigated the effects of integrated extra care (including specific nutritional intervention) in relation to nutritional status and pressure ulcers in 420 hip fracture patients undergoing surgery (210 intervention group; mean age 80.4 ± 10.3 y, 210 standard care group; mean age 81.5 ± 10.5 y). Patients aged 65 year or older in the intervention group who had no pressure ulcers before surgery received the ONS-pu twice daily postoperatively until hospital discharge (median 11 days). There were fewer patients with a hospital-acquired pressure ulcer when the ONS-pu was given twice a day postoperatively compared to the control group [17]. At discharge, there were 50 ulcers in 43 patients in control group vs. 28 ulcers in 21 patients in the ONS-pu group (P = 0.009).

Another study examining the potential preventive effect of ONS-pu was done in 103 patients with hip fracture at risk for pressure ulcers undergoing surgery (mean age: ONS-pu 81.5 ± 0.9 y; placebo group 80.5 ± 1.3; n.s.) [18]. Immediately after surgery patients received 2 times daily ONS-pu (n = 51) or a non-caloric placebo (n = 52) for 4 weeks or until discharge (median: 10 days). Regarding patients’ concordance with the prescribed product intake, approximately 75% of the patients consumed 75% or more of their daily dose. The study demonstrated that the incidence of pressure ulcers in the placebo group was 59%, which was slightly higher than in the supplement group (55%) but not statistically significant (difference: 0.037; 95% CI: −0.16–0.23). Additionally, the incidence of pressure ulcer of stage II was 9% (difference: 0.091; 95% CI: −0.073–0.25) lower in the supplemented (18.4%) than the placebo group (27.5%), but this did not reach statistical significance (P = 0.345). Time of onset, however, showed a trend (P = 0.09) towards a later onset of pressure ulcers in the supplement (3.6 ± 0.9 days) than the placebo group (1.6 ± 0.9 days).

Discussion

Malnutrition, dehydration and catabolism all play a role in the development and healing of pressure ulcers [6]. Therefore, medical nutritional therapy is imperative for the prevention and treatment of pressure ulcers. Consequently, the role of nutrition in pressure ulcer care has been included in several international guidelines such as the nutritional guideline of the European Pressure Ulcer Advisory Panel [19], and in national guidelines such as the pressure ulcer management guideline of the National Institute for Health and Clinical Excellence [20]. Although the role of nutrition in pressure ulcer care is steadily being recognized and guidelines focus on nutrition and nutritional supplementation for patients with pressure ulcers, nutritional supplementation is not yet part of standard care [21]. The current practice-based studies with the ONS specifically developed for patients with pressure ulcers, show positive effects on pressure ulcer healing and a potential preventive effect in patients at high risk of developing pressure ulcers. Although the studies described in this review support the use of ONS pressure ulcer healing, it should be mentioned that these and other nutritional intervention studies reported in the literature [22] are limited in size, which might affect the acceptability of results. Other limitations in nutrition research in pressure ulcers include the design of the studies, the variable patient population, and methodological flaws as there is no golden standard to measure pressure ulcer healing [10]. Moreover, most studies are not randomised-controlled trials and most studies are small and have a short duration. In addition, the (small) sets of patients with pressure ulcers or pressure ulcer-prone patients often are very heterogeneous and the variables 'standard' treatment regimes and 'standard' care differ considerably. Consequently, more randomised clinical studies are required in addition to studies on the experiences by health care professionals and patient case reports [1,23]. Health care practitioner endorsement is of crucial importance to ensure implementation and use of nutrition as part of pressure ulcer care. This is in accordance with a recent study of Meijers et al. [21] who performed a cross-sectional study in 363 hospitals, nursing homes, and home care organizations in the Netherlands, Germany, and the United Kingdom. They showed that nutritional screening and intervention in pressure ulcer care were conducted significantly more frequently in institutions where a nutritional guideline was implemented and used, compared with institutions without a guideline.

Interestingly, the large open intervention study of Heyman et al. [14] demonstrated that 9 out of 10 health care professionals that participated in the study reported they would continue to use the ONS-pu as part of pressure ulcer care in their long-term care facility. Furthermore patients’
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Conclusions

The reviewed clinical trials with the specific ONS specifically developed for patients with pressure ulcers show positive effects on pressure ulcer healing and might potentially reduce the risk of developing pressure ulcers. The largest open-label study revealed that the disease-specific ONS was well tolerated resulting in a high concordance with product prescription and was well appreciated by health care professionals [14]. Importantly, a randomised-controlled trial that is currently running with this ONS will provide more evidence-based data regarding the role of this disease targeted ONS in the healing of pressure ulcers.

Conflict of interest

EM is employee of Danone Research – Centre for Specialised Nutrition (formerly Numico Research).

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References


