EFFICACY OF A DISEASE-SPECIFIC NUTRITIONAL SUPPORT FOR PRESSURE ULCER HEALING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: *Objectives:* The aim of this systematic review was to summarize the evidence on the efficacy of high-calorie, high-protein nutritional formula enriched with arginine, zinc, and antioxidants (disease-specific support) in patients with pressure ulcers (PUs). *Methods:* Randomized controlled trials in English published from January 1997 until October 2015 were searched for in electronic databases (EMBASE, Medline, PubMed, and CINAHL). Studies comparing a disease-specific nutritional support (oral supplements or tube feeding) to a control nutritional intervention enabling the satisfaction of energy requirements regardless of the use of high-calorie formula or placebo or no support for at least 4 weeks were considered eligible. Study outcomes were the percentage of change in PU area, complete healing and reduction in the PU area ≥40% at 8 weeks, and the percentage of change in area at 4 weeks. *Results:* A total of 3 studies could be included in the meta-analysis. Compared with control interventions, formulas enriched with arginine, zinc and antioxidants resulted in significantly higher reduction in ulcer area (-15.7% [95%CI, -29.9, -1.5]; P=0.030; I2=58.6%) and a higher proportion of participants having a 40% or greater reduction in PU size (OR=1.72 [95%CI, 1.04, 2.84]; P=0.033; I2=0.0%) at 8 weeks. A nearly significant difference in complete healing at 8 weeks (OR=1.72 [95%CI, 0.86, 3.45]; P=0.127; I2=0.0%) and the percentage of change in the area at 4 weeks (-7.1% [95%CI, -17.4, 3.3]; P=0.180; I2=0.0%) was also observed. *Conclusions:* This systematic review shows that the use of formulas enriched with arginine, zinc and antioxidants as oral supplements and tube feeds for at least 8 weeks are associated with improved PU healing compared with standard formulas.

Key words: Pressure ulcers, malnutrition, nutritional support, healing, arginine.

Introduction

Pressure ulcers (PUs) are a major, albeit underestimated, health care problem around the world (1). Although prevalence varies across the different healthcare setting, PUs affect approximately 10–20% of patients and negatively affect patient's prognosis, medical resource use and healthcare costs (1-3).

Nutritional support has become a relevant strategy in the multidisciplinary care of patients with pressure ulcers (PUs) (4, 5). Malnutrition has been found closely linked to PUs (5-7) and, more important, studies have shown that PU patients are characterized not only by increased energy expenditures but also by the incapacity to cover their protein-calorie requirements (8). The importance of calories in PU healing has been adequately addressed by previous research and it is now recognized (5, 9-11). Accordingly, PU patients have increased energy requirements are often malnourished. Therefore, nutritional screening, assessment and support should be systematically considered.

International guidelines (4, 11, 12) have progressively recognized the role of nutritional support in the management of PU patients and a last edition has been released by the National Pressure Ulcer Advisory Panel (NPUAP), European Pressure Ulcer Advisory Panel (EPUAP) and Pan Pacific Pressure Injury Alliance (PPPIA). Specific recommendations on the amount of energy and proteins include the provision of at least 30-35 kcal/kg/day and 1.25-1.5 grams of protein/kg/day (11). Besides, based on the publication of different small trials (13-16), the role of supplementation with specific nutrients – arginine, zinc and antioxidants - involved in wound healing has been highlighted in the guidelines. However, these studies were at high risk of bias due to the small sample size and did not standardize for the protein and calorie content of the formula used. The independent role of these nutrients in the healing of PUs has been appropriately investigated in a recent high-quality trial (17). Interestingly, the secondary analysis of this trial's data has shown that the use of a disease-specific nutritional formula is also cost-effective (18).

Indeed, the grade of evidence and strength of recommendations depend on the evaluation of several factors associated with the quality of published trials: the risk of bias, consistency of results across the available studies, precision of the results, directness, and likelihood of publication bias, dose-response, and strength of the association, as well as plausible confounders influencing the efficacy. Accordingly, the conduction of meta-analysis is justified (19, 20) as it reasonably enables clarifying the efficacy of available treatments. To better evaluate the role of disease-specific formulae in the healing of PUs, we conducted a systematic review and meta-analysis of studies investigating the efficacy of a high-calorie nutritional support enriched with specific micronutrients and comparing it

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Table 1
Characteristics of the studies included in quantitative synthesis

Reference	Country; setting	Study size (active / control)	Malnutrition(%)	Study duration (weeks)	Active intervention [energy ; proteins]	Control intervention [energy and proteins]	Method used in outcome assessment	Results * - Mean difference in reduction in area at 8 weeks (%) - Reduction in area ≥40% at 8 weeks (n) - Complete healing at 8 weeks (n) - Mean difference in reduction in area at 4 weeks (%)
Cereda, 2009	Italy (multi-center); long-term care institutions	N=30 (15/15)	90%	12	Oral: standard oral diet + 2 specific ONS § per day Tube: specific formula # (1000 mL/day) + standard formula as necessary [30 kcal/kg/day; 1.5 g/kg/day]	Oral: standard oral diet + 2 standard ONS/day Tube: standard and high-protein formula as necessary [29.5 kcal/kg/day; 1.2 g/kg/day]	Tracing the perimeter onto sterile, transparent block paper and counting the blocks	-24.4% (95%CI, -37.5, -11.3) ‡ Active, n=10; Control, n=8 Active, n=2; Control, n=0 -6.5% (95%CI, -22.8, 9.8) ‡
Van Anholt, 2010	Multi-country; hospitals and long-term care institutions	N=43 (22/21)	0%	12	Standard oral diet + 3 specific ONS § per day [not reported]	Standard oral diet + 3 bottles of non-caloric placebo/day [not reported]	Measuring the maximum length and width of the ulcer with a ruler and assuming the surface area of the ulcer has an ellipse form	7.3% (95%CI, -18.7, 33.2) † Active, n=15; Control, n=15 Active, n=6; Control, n=5 -1.6% (95%CI, -26.7, 23.5) †
Cereda, 2015	Italy (multi-center); long-term care institutions and home-care services	N=200 (101/99)	100%	8	Standard oral diet + 2 specific ONS § per day [27.5 kcal/kg/day; 1.5 g/kg/day]	Standard oral diet + 2 isocaloric, isonitrogenous ONS/day [27.0 kcal/kg/day; 1.5 g/kg/day]	Tracing the perimeter onto sterile, transparent paper and using the VISITRAKTM system (resolution 0.1 cm2; precision of -0.2%–3.3%)	-18.7% (95%CI, -31.8, -5.7) ‡ Active, n=71; Control, n=54 Active, n=17; Control, n=10 -10.2% (95%CI, -27.0, 6.5) ‡

Abbreviations: ONS, oral nutritional supplements; 95%CI, 95% confidence interval; * According to multiple imputation of missing outcomes; ‡ Estimates adjusted for pressure ulcer (PU) area at baseline, PU stage, setting of care, and recruiting center.; † Estimates adjusted for pressure ulcer (PU) area at baseline, PU stage, and recruiting center; § Approximate additional amount of specific nutrients per each ONS: arginine 3 g; zinc, 4 mcg; copper, 600 mcg; manganese, 1.2 mg; selenium, 40 mcg; vitamin E, 30 mg; vitamin C, 200 mg; # Approximate additional amount of specific nutrients per 1 litre of formula: arginine 8.5 g; zinc, 8 mcg; copper, 200 mcg; manganese, 0.5 mg; selenium, 40 mcg; vitamin E, 60 mg; vitamin C, 250 mg.

to a control one providing an adequate amount of calories and proteins.

Methods

The review was conducted following the indications of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (21).

Search Strategy

Two investigators (EC, JN) independently conducted an electronic literature search using EMBASE, Medline, PubMed, and CINAHL. The selection was limited to English-language publications made from January 1997 (year of introduction of wound-specific nutritional formula) until October 2015. Any disagreement was resolved by consensus with a third author (RC). A description of the strategy used in the identification of potentially relevant publication is provided in the Supplementary Appendix. Reference lists of included articles and of those relevant to the topic were also reviewed.

Study Selection

We included only randomized, clinical trials that: 1) addressed the efficacy of a high-calorie disease-specific nutritional support compared to a control nutritional intervention enabling the satisfaction of energy requirements, regardless of the use of high-calorie formula or placebo or no support; 2) included patients with PUs; 3) and lasted at least 4 weeks. A disease-specific support was defined as any type of intervention providing micronutrients putatively involved in the healing process (e.g. arginine, zinc and antioxidants). A study duration of 4 weeks was chosen following recent reviews that suggested that efficacy of nutritional support could not be adequately evaluated for short-term interventions (5, 22).

When necessary, we contacted authors asking for further information when data could not be meta-analyzed (e.g. no mean difference in the reduction in PU area or no data on complete healing were provided), 2) or other relevant information was missing (e.g. estimate boundaries).

Data Extraction

Two authors (EC, JN) independently extracted data from the selected studies on a standardized record form. Any disagreement was resolved by consensus with a third author (MR). The following information were extracted: 1) study population characteristics; 2) country; 3) clinical setting in which the study was performed; 4) duration and type of interventions; 5) efficacy outcomes.

Outcomes

The primary outcome was the percentage of change in ulcer area at 8 weeks. Secondary outcome measures included: a reduction in the area of 40% or greater and complete healing at 8 weeks; the percentage of change in the area at 4 weeks.

Risk of Bias Assessment

Assessment of bias was performed using the Cochrane Collaboration criteria (23). Accordingly, the following issues were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and differences in baseline features between treatment arms. Risk of bias was independently graded by two reviewers as follows: low risk, high risk, and unclear risk. Any discrepancies between raters were resolved through consensus. Finally, authors of included articles were contacted to obtain additional information on unclear reporting.

Statistical Analysis

The meta-analysis was performed using the software Comprehensive Meta-Analysis, version 2.2.064 (Biostat, Englewood, NJ - http://www.meta-analysis.com/index.php), establishing the level of significance at a 2-tailed $P<0.05$.

For continuous end points (the percentage of reduction in area at 8 and 4 weeks) we computed the pooled mean difference between interventions using fully-adjusted estimates. However, for categorical outcomes (reduction in the area ≥ 40% and complete healing at 8 weeks) risk ratios were calculated using the number of events. For all the outcomes we pooled estimates calculated using according to the multiple imputation of missing outcomes. All estimates were provided along with 95% confidence interval (95%CI).

Results

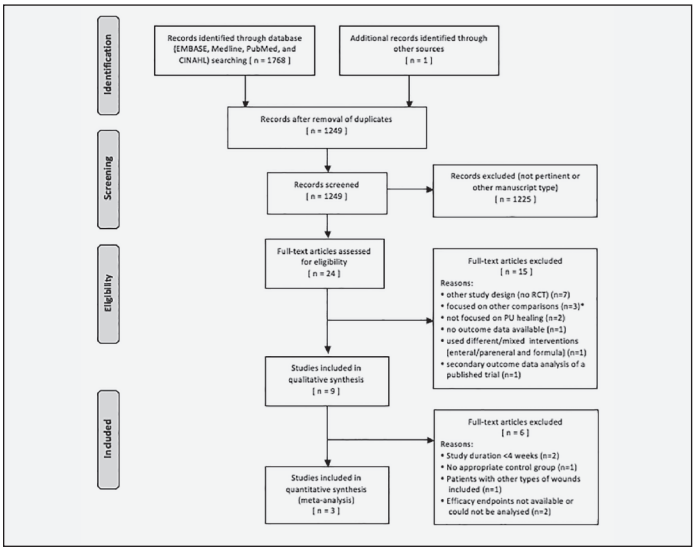
The search identified 1249 non duplicate potentially eligible studies. After excluding 1225 papers through title and abstract review, 24 full text articles were examined. Altogether, 9 studies were included in the qualitative synthesis and 3 in meta-analysis (Figure 1) (15-17). A description of the articles excluded (13,14,24-27) is provided in the Supplementary Table 1. Particularly, study were excluded due to the following reasons: short duration (n=2) (14, 29); outcome data not available (n=2) (13, 24); inclusion of patients with different types of chronic wounds (n=1) (26); lack of a control group (n=1) (25).

Study and Patient Characteristics

The characteristics of the studies meta-analyzed are summarized in Table 1. The trials (15-17) included a total of 273 participants (disease-specific, N=138; control, N=135); they were all multicentre, mainly conducted in a long-term care setting and substantially of good quality (Table 2) although for two studies (15, 16) it was necessary to retrieve additional information (random sequence generation [2 studies] and allocation concealment [1 study]) from the authors to fully evaluate the risk of bias. They included old patients (age at baseline assessment >70 years) with moderate-severe PUs (stage II, III and IV). In two trials participants were characterized by a severe impairment of nutritional status (15, 17), while in one malnutrition was listed among exclusion criteria (16). Finally, two studies were focused exclusively on patients able to drink oral nutritional supplements while in one study 65% of participants were tube-fed (15). In all the studies a nutritional formula enriched with arginine, zinc and antioxidants from the same industry was used.

Figure 1

Flow diagram of systematic review of literature



* compared different (non disease-specific) protein-calorie regimens (n=3)

Study outcomes

For all the trials fulfilling inclusion criteria for quantitative synthesis it was possible to collect data on the outcomes considered. In primary analysis, based on all trials, the use of a disease specific nutritional support was associated with a significantly higher reduction in ulcer area (Figure 1) and a higher proportion of participants having a 40% or greater reduction in PU size at 8 weeks (Table 3). Besides, we observed a nearly significant difference in complete healing at 8 weeks and the percentage of change in the area at 4 weeks with

Table 2
Risk of bias of RCTs included in quantitative synthesis

Reference	Evaluation of the study based on	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of patients and outcome assessors (performance and detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Differences in baseline characteristics between arms
Cereda, 2009	Manuscript review	↑	?	↑	↑	↑	More patients with multiple PUs in the disease-specific group
	Request to the authors	↑	↑	↑	↑	↑	
Van Anholt, 2010	Manuscript review	?	?	↑	↑	↑	None
	Request to the authors	↑	↑	↑	↑	↑	
Cereda, 2015	Manuscript review	↑	↑	↑	↑	↑	None
	Request to the authors	↑	↑	↑	↑	↑	

Risk of bias - rating: ↑ low; ↓ high; ?, unclear.

Table 3
Secondary efficacy end points

END POINT	Analysis #	Disease-specific		Control		Treatment effect [95%CI]	P-value	Heterogeneity (I^2 [P-value])
		Total (N)	Events (N) *	Total (N)	Events (N) *			
Reduction in area ≥40% at week 8 ‡	Primary	138	96	135	77	1.72 [1.04, 2.84]	0.033	0.0% [0.520]
	Sensitivity	116	81	114	62	1.94 [1.13, 3.34]	0.016	0.0% [0.883]
Complete healing at week 8 ‡	Primary	138	25	135	15	1.72 [0.86, 3.45]	0.127	0.0% [0.655]
	Sensitivity	116	19	114	10	1.95 [0.87, 4.37]	0.106	0.0% [0.482]
Difference in percentage of reduction in ulcer area at week 4 †	Primary	138	--	135	--	-7.1% [-17.4, 3.3]	0.180	0.0% [0.847]
	Sensitivity	116	--	114	--	-8.3% [-19.6, 3.2]	0.156	0.0% [0.751]

Abbreviations: 95%CI, 95% confidence interval; * According to multiple imputation of missing outcomes; ‡ Odds ratio (95%CI) [disease-specific vs. control]; † Mean difference (95%CI) [disease-specific vs. control]; # Primary analysis was based on estimates from all studies, while sensitivity analysis was limited to those from trials including malnourished participants

no heterogeneity (I2=0.0% for all). These findings were substantially confirmed by sensitivity analysis (Table 3) refitted on studies including malnourished patients (15, 17). Particularly, in respect to the primary outcome we observed an increase in the pooled effect size with no heterogeneity (Figure 1).

Publication Bias

Visual inspection of funnel plots showed that publication bias was unlikely.

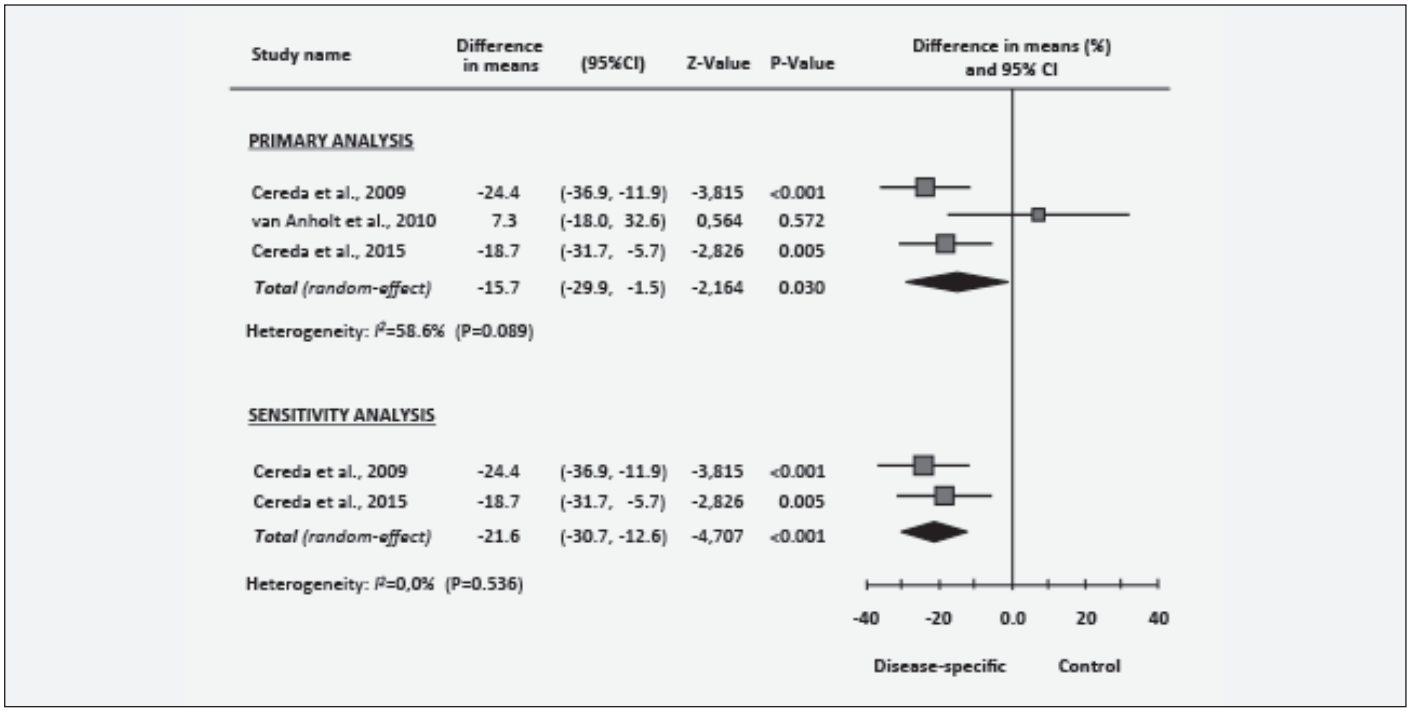
Discussion

Despite the wide availability of nutritional formulae, many of which are marketed for specific disease conditions, there is limited evidence supporting their efficacy and use in clinical practice (28-30). This is an important issue as these formula are usually more expensive than standard ones. Our meta-analysis reasonably supports as Grade A evidence for the use of a disease-specific formula enriched with arginine, zinc and antioxidants in the nutritional support of PU patients. Accordingly, it strengthens the recent recommendations included in the NPUAP-EPUAP-PPPIA international guidelines released in 2014 (11). Interestingly, the use of this formula has been found to be also cost-effective, as it enables reducing the intensity of local care (18).

Results on efficacy are consistent with and expand those of a previous meta-analysis (31) reporting a trend to improved healing from the use of a disease-specific formula. Unfortunately, the analysis was based on the findings of small trials (13-16, 26) and did not consider those of the OligoElement Sore Trial (OEST), a large trial with a low risk of bias specifically addressing the independent role of specific nutrients in wound healing (18). Arginine is a semiessential amino acid contributing to protein anabolism (e.g collagen synthesis), cellular growth. As a donor of nitric oxide, it can also increase tissue blood flow, improve immune response and induce the mobilization of endothelial progenitor cells from

Figure 2

Forest plot of the percentage of change in ulcer area at 8 weeks in participants receiving disease-specific vs control nutritional support. In the plots, the squares indicate point estimates of effect (mean difference), with the size of the square representing the weight attributed to each study and the horizontal bars indicating 95%CI. Sensitivity analysis is based on studies including malnourished participants



the bone marrow. Zinc is an important co-enzyme of enzymes involved in protein and DNA synthesis, immune function, and cellular proliferation. Antioxidants are also relevant in any chronic inflammatory condition. Particulalry, vitamin C plays an important role in cellular immunity, fibroblast proliferation and the synthesis of collagen (32, 33). Previous trials were not able to demonstrate a positive effect for these single micronutrients and the failure was likely due to the lack of concomitant energy supply (17, 31).

The present meta-analysis has shown that nutritional support should be at least 8-week long and primarily directed to malnourished patients as these reasonably more likely to be characterized by low values of several nutrients. Although van Anholt et al. have reported a significant difference in PU healing over time (faster improvement in the initial phases of the study with a reduction in the intensity of care) in non-malnourished patients, at 8 weeks the reduction in PU area appeared to be comparable to that obtained in the placebo group (16). Interestingly, this was the only trial – among those included in quantitative synthesis – in which a significant difference in protein-calorie support between treatment arms was present. Besides, a less accurate method of assessment of ulcer area was used and not description of how pressure (a key estrinsic factor for PU) was managed (e.g. mattresses/overlays, repositioning protocol, etc...). It is also worth mentioning that the study was stopped before reaching the estimated sample size due to unavailability of non-malnourished patients. In agreement with this, the OEST study has found that about 90% of PU patients are malnourished (17). Therefore, PU patients are likely malnourished and nutritional support should be systematically considered.

The following limitations are acknowledged. First, despite using multiple database we searched only for English-language full-text articles. Second, only 3 high-quality trials have been included in the present meta-analysis. Other studies have considered the use of a disease-specific nutritional support in PU patients (13, 14, 24-27). Although they did not fulfill criteria for inclusion in quantitative synthesis they have all shown a positive effect of supplementation with nutrients playing a role in wound healing (arginine + different combination of other nutrients) on mixed healing outcomes (Pressure Ulcer Scale for Healing [PUSH]; complete healing; time to complete healing; improved tissue viability). On the other hand, the limited number of studies included in quantitative synthesis highlights the important methodological limitations in this research area. Besides, we cannot exclude that multiple separate micronutrient supplements provided in combination with a high-calorie, high-protein formula have the same effectiveness of a all-in-one oral nutritional supplement. Third, complete healing is an important outcome in wound care. However, most available studies did not consider a support until complete healing and have included it as a secondary

outcome measure. Besides, it should be recognized that all available trials were underpowered. Finally, at least another large confirmatory trial is probably required to provide definite conclusions and recommendations in this area.

In conclusion, the use of disease-specific formulas enriched with arginine, zinc and antioxidants as oral supplements and tube feeds for at least 8 weeks are associated with improved PU healing compared with standard formulas. The use of this formula should be preferred to that of high-calorie, high-protein ones whenever available. Future studies should consider an evaluation of its use in patients with other types of wounds.

Conflict of Interest Disclosures: The Authors certify that there are no affiliations with, or involvement in, any organization or entity that has a direct financial interest in the subject matter, or material, discussed in the manuscript. Dr. Cereda reports having received (not for the present study and before 2010) consultancy and speaker honoraria and investigator grants from the "Fondazione Grigioni per il Morbo di Parkinson", the Fondazione IRCCS Policlinico San Matteo and Nutricia Italia.

Author Contributions: Dr. Cereda had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Cereda, Schols. *Acquisition of data:* Cereda, Neyens, Caccialanza, Rondanelli, Schols. *Statistical analysis and interpretation of data:* Cereda, Schols. *Drafting of the manuscript:* Cereda. *Critical revision of the manuscript for important intellectual content:* Cereda, Neyens, Caccialanza, Rondanelli, Schols. *Obtained funding:* Cereda, Schols. *Administrative, technical, or material support:* Cereda, Neyens, Schols. *Study supervision:* Schols. *Additional Contributions:* The authors wish to thank Dr Jennifer S Hartwig for assistance in editing the manuscript.

Ethical standard: The study did not required the approval of the Ethics Committee.

Supplementary Appendix

Search terms used in literature review

"nutrition[MeSH Terms]) OR enteral*[MeSH Terms]) OR oral*[MeSH Terms]) OR supplement*[MeSH Terms]) OR feed[MeSH Terms]) OR sip[MeSH Terms]) OR liquid[MeSH Terms]) OR formula*[MeSH Terms]) OR protein[MeSH Terms]) OR arginine[MeSH Terms]) OR zinc[MeSH Terms]) OR vitamin C[MeSH Terms]) OR ascorbic acid[MeSH Terms]) OR vitamin E[MeSH Terms]) OR antioxida*[MeSH Terms]))"
AND
"decubitus[MeSH Terms]) OR pressure ulcer[MeSH Terms]) OR pressure sore[MeSH Terms]) OR bed sore[MeSH Terms])"
AND
«1997/01/01»[Date - Publication]: «2015/10/01»[Date - Publication]
AND
«English»[Language]

* truncated terms.

Supplementary Table 1

Characteristics of the randomized trials undergoing qualitative review and excluded from quantitative synthesis

Reference	Duration	Sample size	Experimental intervention [servings/day (n)]	Comparison	Reason of exclusion
Benati, 2001	2 weeks	N=36	Normal hospital diet + wound-specific ONS* [2]	Normal hospital diet or diet + high-calorie/high-protein ONS	Data on wound healing were presented only graphically (only for 16 patients); short duration; data not available
Desneves, 2005	3 weeks	N=16	Standard hospital diet + wound-specific ONS § [2]	Standard hospital diet or diet + high-calorie/high-protein ONS	Short duration; a significant imbalance in baseline features was also present
Benati, 2012	12 weeks	N=50	Home standard tube feeding + specific supplements # [2]	Home standard tube feeding	Data not available
Leigh, 2012	3 weeks	N= 23	Standard hospital diet + wound-specific ONS § [1 vs. 2]	No comparison	Lack of a control group receiving standard high-calorie ONS
Bauer, 2013	8 weeks (4 weeks of support + 4 weeks of best wound and nutrition care)	N=24	Oral diet + wound-specific ONS § [2]	Oral diet + standard high-calorie ONS	Patients with different types of chronic wounds were included and pooled in the analysis
Wong, 2014	2 weeks	N= 23	Normal hospital diet + standard high-calorie ONS + specific supplements # [2]	Normal hospital diet + standard high-calorie ONS	Short duration

Abbreviations: ONS, oral nutritional supplement; * , Cubitan®, Nutricia (high-calorie formula enriched with wound-specific nutrients [arginine, zinc and antioxidants]) ; § , Resource Arginaid®, Nestlé Health Science (high-calorie formula enriched with wound-specific nutrients [arginine, zinc and vitamin C]) ; # , AboundTM, Abbott (calorie-free supplement containing wound-specific nutrients [arginine, glutamine and β-hydroxy β-methylbutyrate]) ; Reference list: 1. Benati G, Delvecchio S, Cilla D, Pedone V. Impact on pressure ulcer healing of an arginine-enriched nutritional solution in patients with severe cognitive impairment. Arch Gerontol Geriatr Suppl. 2001;7:43-7. 2. Desneves KJ, Todorovic BE, Cassar A, Crowe TC. Treatment with supplementary arginine, vitamin C and zinc in patients with pressure ulcers: a randomised controlled trial. Clin Nutr. 2005 Dec;24(6):979-87. 3. Benati G, Gasparoni R, Coppola D. Supplementation with arginine, glutamine and β-hydroxy β-methylbutyrate (βHMB) can improve pressure ulcer healing, reduce pain and frequency of dressing changes, improving costs. Clin Nutr Suppl. 2012; 7(1):269. 4. Leigh B, Desneves K, Rafferty J, Pearce L, King S, Woodward MC, Brown D, Martin R, Crowe TC. The effect of different doses of an arginine-containing supplement on the healing of pressure ulcers. J Wound Care. 2012 Mar;21(3):150-6. 5. Bauer JD, Isenring E, Waterhouse M. The effectiveness of a specialised oral nutrition supplement on outcomes in patients with chronic wounds: a pragmatic randomised study. J Hum Nutr Diet. 2013 Oct;26(5):452-8. 6. Wong A, Chew A, Wang CM, Ong L, Zhang SH, Young S. The use of a specialised amino acid mixture for pressure ulcers: a placebo-controlled trial. J Wound Care. 2014 May;23(5):259-60, 262-4, 266-9.

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