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Review article

Arginine-enriched oral nutritional supplementation in the treatment of pressure ulcers: A literature review

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ABSTRACT

Purpose: Pressure ulcers are a common, potentially mortal complication to disease, care and treatment for patients of all ages with mobility impairments. In addition, pressure ulcers not always heal straightforward because of multiple intrinsic factors e.g. undernutrition and extrinsic factors e.g. inadequate nutrition that may influence the healing process.
The aim of this descriptive review is to investigate the treatment effect of arginine-enriched oral nutritional supplementation in pressure ulcers.
Results: The included studies, seven RCTs and four CTs, were published between January 2001 and October 2015, and conducted in different settings: hospital, long-term care/care homes and home care. The duration of follow-up of the studies varied from 2 weeks to complete healing and the sample size varied from 16 to 245 patients aged from 37 to 92 years and with pressure ulcer stages II, III or IV. The wound-specific oral nutritional supplementation contained 3–9 g of arginine. The main outcome measures were complete healing, time needed for complete wound closure, reduction in wound surface area, nursing time, and the number of dressings used. Ten out of eleven studies showed a beneficial effect of the arginine-enriched oral nutritional supplementation on the healing of pressure ulcers.
Conclusions: This review shows that there is substantial evidence supporting the positive effect of nutritional supplementation with additional protein, arginine and micronutrients to promote pressure ulcer healing. Currently, there is only one large study (N = 200) with level 1 evidence. It may be postulated that at least one extra comparable level 1 study is needed to draw firm conclusions on the importance of key nutrients in complete pressure ulcer healing.

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1. Introduction

Pressure ulcers (PUs) are a common, potentially mortal complication to disease, care and treatment for patients of all ages who are bed- or wheel-chairbound. In addition, pressure ulcers not always heal straightforward because of multiple intrinsic and extrinsic factors that may influence the healing process.

Wound-healing complications are a significant clinical problem for patients and care professionals with a considerable socioeconomic burden for health care policy [1–3]. Undernutrition, inadequate nutrition and unintentional weight loss have been identified as independent risk factors not only for the development of PUs but also for delayed wound healing [4–6]. In this article, the focus is on nutritional factors related to PUs. Indeed, many patients at risk of or with PUs show a compromised nutritional status [5]. These patients often show either a reduced nutritional intake, an increased nutritional need that they can not meet, or an abnormal loss of nutrients [7,8]. Since several nutrients play a physiological role in wound healing, extra supplementation of these nutrients, e.g. via sip-feed/oral nutritional supplement (ONS) may improve wound healing. Then, providing ONS in addition to regular food intake seems a logical strategy to be integrated in daily PU care. Protein-enriched ONS showed beneficial effects in wound healing [4]. More recently, research has focussed more on wound-specific ONS, namely arginine-enriched ONS. Arginine holds a key position in the cellular functions and interactions that occur during inflammation and immune responses [9,10]. Arginine has been shown to enhance wound strength and collagen deposition in artificial wounds in rodents and humans [11–13]. Arginine improves protein anabolism and cellular growth, is a donor of nitric oxide which increases blood flow to the wound area and acts as an immune response mediator [14] and increases the release from the bone marrow of endothelial progenitor cells [15] which are directly involved in new blood vessels and tissue regeneration.

The aim of this descriptive review is to investigate the treatment effect of arginine-enriched ONS in PUs.

2. Method

2.1. Search strategy

Potentially relevant articles were obtained by performing a search in four electronic databases (EMBASE, Medline, PubMed, and CINAHL) from January 1997 until October 2015. The start date of the search period was based on the introduction of one of these wound-specific ONS. The language selection was limited to English language.

The following search terms were combined with OR and AND:
"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]) OR Cubitan[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]

where * denotes truncated terms.

2.2. Study selection

Initially, the literature search was broad and focused on scientific studies performed with enriched nutrition. Subsequently, the search was narrowed. Articles were eligible for inclusion if they met the following inclusion criteria: 1) written in English; 2) randomised clinical trial (RCT) or clinical trial (CT); 3) intervention studies in patients with primarily PUs, using a sip-feed/ONS enriched with arginine. In the first phase, all retrieved potentially relevant articles were reviewed based on their title. In the second phase, based on abstract assessment, potentially relevant articles/studies were excluded if they were either a review, a congress report or comments, had another outcome than wound healing, did not use ONS, did not involve PUs, did not contain arginine, and were not treatment studies. In the third phase, after removal of the duplicates, we checked the reference lists of the included articles and retrieved reviews, and the Cochrane Library to achieve the final selection of relevant articles.

2.3. Data extraction

Data from the included articles were extracted by two independent investigators (JN and EC). For each paper we extracted also data about authors, publication year, study size and design, participant characteristics (age and PU stage), nutritional intervention and its duration (in weeks), and outcome measures. Study authors were contacted if necessary.

3. Results

3.1. Results of the selection process

The initial search strategy yielded 1545 potentially relevant articles. Based on title, 1464 articles were excluded because they did not meet the inclusion criteria. Thereafter, 81 abstracts were scrutinised. Forty-eight of them were excluded because being a review, congress report or comments, having other outcomes, not solely PU, not related to sip-feed/ONS and/or PU and/or arginine and/or treatment. Then, thirthy-three full text publications remained for review. Finally, after removal of duplicates, checking the reference lists of the included articles, the reference lists of retrieved reviews [4,16–18], and the Cochrane Library [19], eleven clinical studies were included in the review. The flow chart of the selection process is depicted in Fig. 1.

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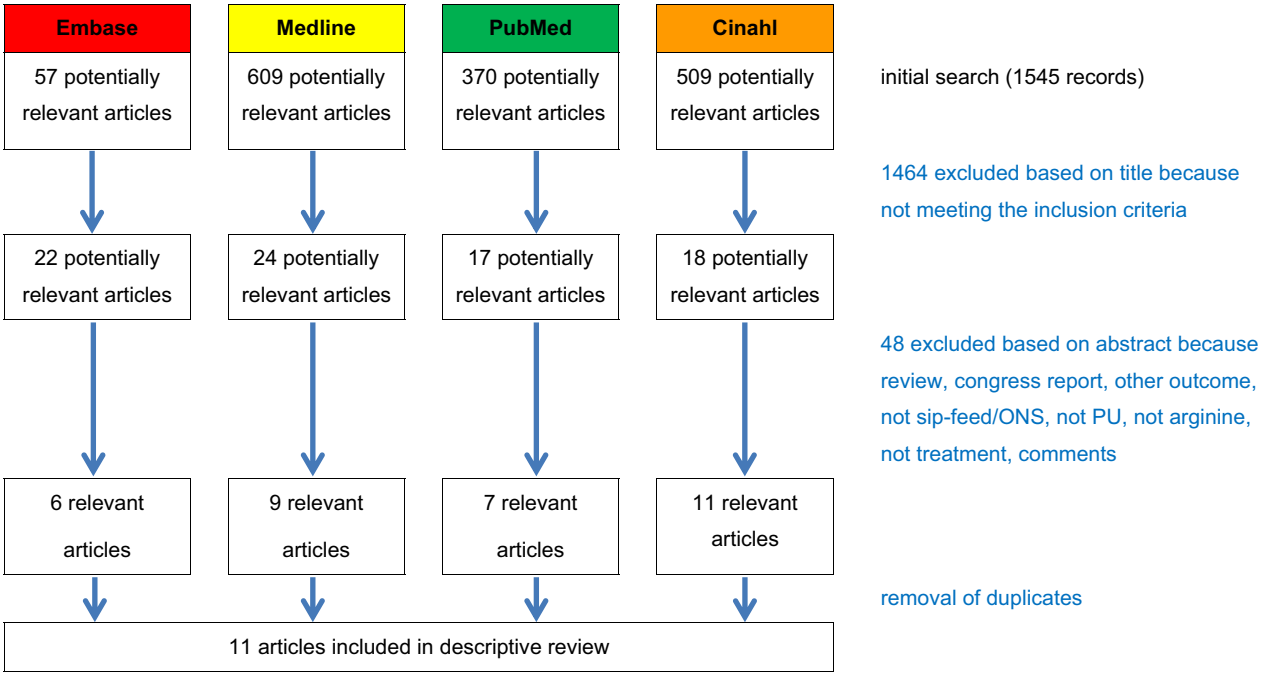

Fig. 1. Flow chart of the selection process of the literature.

3.2. Characteristics of included studies

All eleven studies, seven RCTs and four CTs, were published between January 2001 and October 2015, and conducted in different settings: hospital, long-term care/care homes and home care. The duration of follow-up of the studies varied from 2 weeks to complete healing and the sample size varied from 16 to 245 patients. In total 645 patients participated in these 11 studies and their age varied from 37 to 92 years. They all had PUs with stages II, III or IV. The wound-specific ONS servings varied from one to three times per day, and contained 3–9 g of arginine per ONS. A variety of outcome measures were object of investigation: complete healing, time needed for complete wound closure, healing rate or the percentage of patients with complete wound closure, partial healing assessed via PU area (length × width), the Pressure Sores Status Tool (PSST) [20] with a total score ranging from 13 (best condition) to 65 (worst condition) or the Pressure Ulcer Score for Healing (PUSH) [21–23] with a total score ranging from 0 (best

Table 1
Characteristics of included studies.

1st Author	Follow-up	Sample size	Mean age (range)	PU-stage	Study type	Nutritional intervention serving/day, arginine/ONS	Comparison	Outcome measurement
Benati [24]	2 wks	N = 16	–(72–91)	–	RCT	specific ONS©, 2x, 3.75g	high-protein formula or normal hospital diet	PSST score
Frias Soriano [28]	3 wks	N = 39	75	III-IV	CT	specific ONS©, 2–3x, 3g	no ONS	complete healing/ PU area
Desneves [30]	3 wks	N = 16	73(37–92)	II-III-IV	RCT	specific ONS ω, 2x, 9g	standard hospital diet or standard + protein-enriched ONS	PUSH score
Heyman [29]	9 wks	N = 245	82	II-III-IV	CT	specific ONS©, 1–3x, 3g	no ONS	complete healing/ PU area
Cereda [25]	12 wks	N = 10	82	II-III-IV	RCT	specific ONS©, 2x, 6g	standard hospital diet	PU area/ PUSH score
Brewer [32]	until healed	N = 35*	51	II-III-IV	CT	specific ONSω, 2x, 9g	no ONS (historical control)	healing rate/ time for closure
van Anholt [27]	8 wks	N = 43*	75	III-IV	RCT	specific ONS©, 1–3x, 3g	non-caloric control ONS	PU area/PUSH score, nursing time, number of dressings
Chapman [33]	until healed	N = 34	47	II-III-IV	CT	specific ONS ω, 2x, 4.5g	ceased consuming specific ONS ω	PUSH score
Leigh [31]	3 wks	N = 23*	(31–92)	II-III-IV	RCT	specific ONS1ω, 1x, 4.5 g specific ONS2ω, 1x, 9.0g	standard hospital diet (historical control)	PU area/PUSH score/healing rate
Wong [34]	2 wks	N = 23	77	II-III-IV	RCT	specific ONSδ, 2x, 7g	standard nutritional care	PU area/ PUSH score
Cereda [26]	8 wks	N = 200**	81	II-III-IV	RCT	specific ONS©, 2x, 6g	isocaloric, isonitrogenous ONS	complete healing/ PU area

* = non-malnourishe.
** = malnourished.
© = Cubitan®, Nutricia.
ω = Resource Arginaid®Nestlé Health Science.
δ = Abound™, Abbott.

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condition) to 17 (worst condition), the percentage of PUs experiencing a reduction in area ≥40%, nursing time, and the number of dressings used.

Six out of the eleven studies, four RCTs, Benati et al. (single-blinded) [24], Cereda et al. (single-blinded, multicenter) [25], Cereda et al. (double-blinded, controlled, multicenter) [26], and van Anholt et al. (double-blinded, placebo-controlled, multicenter, multicountry) [27], and two uncontrolled, open label, multicenter CTs, Frias Soriano et al. [28] and Heyman et al. [29], reported on the same ONS (Cubitan®, Nutricia) and all showed a beneficial effect of the arginine-enriched ONS on the healing of PUs.

Four studies, two double-blinded controlled RCTs, Desneves et al. [30] and Leigh et al. [31], and two CTs, Brewer et al. (open-label, historical controlled) [32] and Chapman et al. (open-label, observational) [33], reported on another arginine-enriched ONS (Resource Arginaid®, Nestlé Health Science) and they also showed beneficial effects on the healing of PUs.

Finally, the RCT of Wong et al. (placebo controlled, multicenter) [34] did not show positive effects on the healing of PUs.

The main characteristics of the 11 included studies are summarized in Table 1.

3.3. Efficacy of arginine-enriched ONS per included study

A summary of the studies included is presented in Table 2.

In the studies of Benati et al. [24], Frias Soriano et al. [28], Heyman et al. [29], and Cereda et al. [25], the same specific 200 ml high calorie-high protein, arginine- and micronutrient-enriched ONS was used, and all studies showed significant positive effects of this ONS on pressure ulcer healing (respectively decreased PSST score, decreased PU area or completely healed or decreased PUSH score).

Desneves et al. [30] showed statistically significant improved wound healing (decreased PUSH score) with supplementary arginine, vitamin C and zinc in 16 hospitalized patients with PUs.

The study of van Anholt et al. [27] showed statistically significant accelerated PU healing (decreased PU area/PUSH score) and decreased wound care intensity (fewer dressings required per week and less time spent per week on changing the dressings) in non-malnourished patients.

Brewer et al. [32] and Chapman et al. [33] showed that arginine supplementation of 9 g daily may be associated with statistically significant improved PU healing (respectively healing rate/time for closure and decreased PUSH score) in patients with spinal cord injury (SCI).

Leigh et al. [31] compared different daily dosages of arginine (4,5 g and 9 g) for healing PUs in 23 hospital patients. There was a statistically significant decrease in PU severity (decreased PU area/PUSH score) over time but without evidence of a dose-response relationship. Since both different dosages arginine-enriched ONS showed a similar clinical benefit in PU healing, the authors concluded that an increased PU healing can already be achieved with a lower dosage of arginine.

Wong et al. [34] concluded that the use of a specialised amino acid (arginine and glutamine mixture) did not appear to reduce wound size and PUSH score but may improve tissue viability in 2 weeks.

The most recent and large OligoElement Sore Trial (OEST) of Cereda et al. [26], showed with statistical significance that the additional provision of arginine, zinc, and antioxidants within a high-calorie, high-protein nutritional support is independently responsible for improved PU healing (decreased PU area/proportion of patients experiencing a reduction in wound surface area (WSA) ≥40%) in malnourished patients. Particularly, at 8 weeks, the mean WSA reduction in the group receiving the PU-specific ONS was 61% compared with 45% in the control group receiving an isocaloric-isonitrogenous ONS (mean adjusted difference, 19% [CI, 6–32%]).

4. Discussion

Based on the results of 10 (6 RCTs and 4 CTs) out of the 11 included clinical studies, this review shows that there is substantial evidence supporting the positive effect of nutritional supplementation with additional protein, arginine and micronutrients to promote PU healing. Conversely in the study of Wong et al. [34], the use of an arginine-enriched ONS did not reduce WSA further. Although RCTs provide more evidence than CTs, overall, the included RCTs showed some flaws especially regarding the small sample sizes, the use of an acceptable control formula or

Table 2
Overview of the effect of an arginine-enriched ONS.

1st Author (year of publication)	Study conclusion	P values
Benati [24]	The results showed a tendency for a more pronounced PU healing in patients supplemented with a specific ONS enriched with arginine compared to a high-protein formula or to normal hospital diet.	not available
Frias Soriano [28]	Treatment with a specific arginine-enriched ONS improved the PU healing rate.	$p < 0.001$
Desneves [30]	ONS enriched with arginine, vitamin C and zinc demonstrated a statistically significant improvement in the PU healing rate compared to standard hospital diet or standard hospital + protein-enriched ONS.	$p < 0.01$
Heyman [29]	A high-protein ONS enriched with arginine, vitamin C, vitamin E and zinc significantly reduced the mean PU area in long-term nursing home residents.	$p < 0.0001$
Cereda [25]	Compared to standard hospital diet, treatment with a specific ONS enriched with arginine, zinc, and vitamin C was associated with a statistically significant higher rate of PU healing.	$p = 0.042$
Brewer [32]	ONS enriched with arginine significantly improved the time-to-healing in PU patients compared to historical control patients.	$p < 0.05$
van Anholt [27]	Specific oral nutritional supplementation enriched with arginine accelerated healing of PUs and decreased wound care intensity in non-malnourished patients compared to a non-caloric placebo.	$p \leq 0.016$
Chapman [33]	A wound-specific ONS demonstrated the potential to shorten the full PU healing time compared to ceased consuming specific ONS.	$p < 0.001$
Leigh [31]	Similar clinical benefits on PU healing (a two-fold improvement in the healing rate) can be achieved with a lower dosage of arginine and compared to standard hospital diet.	$p < 0.001$
Wong [34]	Compared to standard nutritional care, the use of specialised amino acid mixture does not appear to reduce wound size and PUSH score but may improve tissue viability after 2 weeks.	$p = 0.002$
Cereda [26]	Among malnourished PU patients, 8 weeks of supplementation with an oral nutritional formula enriched with arginine, zinc, and antioxidants statistically significant improved PU healing compared to an isocaloric, isonitrogenous control ONS.	$p = 0.017$

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placebo and the differences regarding nutritional care in the control groups. Moreover, other external and internal factors than nutrition, known to influence pressure ulcer healing are not adequately described in some of the studies e.g. repositioning, mattresses, medical status, infection, comorbidity and mobility. In addition we can mention the fact that among the studies, the outcome measures were rather heterogeneous which hampered to measure an overall healing tendency.

A potential flaw also may be the inclusion of malnourished patients, despite the fact that many PU patients in reality are in a bad nutritional status. In this case, the positive effects on wound healing might be attributed to the improved nutritional status after use of the ONS with a subsequent positive effect on wound healing.

With respect to these flaws, we report that there is currently only one large study (N = 200) with level 1 evidence [26]. The strength of this multicenter, randomised, double-blinded, placebo-controlled study was that specific micronutrients were given within the content of appropriate nutritional care and both control and intervention groups received a similar high-protein, high-calorie support to promote new tissue synthesis. In addition, a secondary analysis of the OEST study's data has recently demonstrated the value of this disease-specific nutritional support as a cost-effective intervention able to reduce the overall costs of local PU care [35].

It may be postulated that at least one extra comparable level 1 study is needed to draw firm conclusions, because, based on the other included studies, it is not possible yet to draw definitive conclusions due to their insufficient scientific quality. Nonetheless, the results of the OEST study were largely confirmatory of those of a pilot trial [25] in which in addition to arginine, zinc and antioxidants only a small difference in protein support between treatment arms was present (1.2 vs. 1.5 g/kg/day).

That way, some issues can be raised: 1) complete wound closure should be the primary clinical outcome in wound healing-related research (rather than improved healing), 2) malnutrition in patients must be addressed first to enable insight in the direct effect of a specific ONS on wound healing, and 3) the overall cost-effectiveness of PU treatment should be involved much more often.

This review might have some limitations. Despite the effort of the authors to conduct a sensitive search strategy, other potentially relevant studies may not have been retrieved.

4.1. Implications for practice

PUs are a well-recognised problem, with an aetiology that is multifactorial and not solely a consequence of pressure or, broadly, extrinsic factors [36]. Intrinsic factors must be considered as well. Poor nutritional status is one of these. Actually, it can and must be influenced because most PU patients are malnourished and fail to meet their nutritional requirements via normal oral food intake [8,37]. Many of these patients therefore require additional nutritional support to reduce the possibility of PU development, or to support PU healing [17,38,39]. Nowadays, several nutritional supplements are available: protein-enriched ONS and wound-specific ONS, e.g. the protein-, arginine- and micronutrient-enriched ONS to improve wound healing. In the meantime, the use of both of these ONS is acknowledged by the guidelines of the NPUAP, EPUAP and PPPIA [36] and should therefore be part of adequate nutritional care for PU patients.

4.2. Recommendations for future research

In a review by the Swedish Council on Health Technology Assessment (SBU), the apparent difficulties to assess studies on pressure ulcer healing were described [40]. This was mainly due to the fact that numerous internal and external factors, influencing healing were insufficiently described in most studies. One recommendation was to review data from register-studies where applicable.

In addition to the findings of this review, there is an urgent need for more level 1 studies (RCT) on the importance of key nutrients in complete wound healing with a longer follow-up period (needed to stabilise nutritional status and subsequently improve complete wound healing). A meta-analysis on the use of nutritional support with an arginine-enriched formula is also needed. Last but not least, future studies also need to assess the clinical and economic impact of arginine supplementation in patients with other types of (chronic) wounds e.g. diabetic foot ulcers, arterial leg ulcers, and venous leg ulcers.

Conflict of interest

All authors declare no conflict of interest.

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