

Nutritional therapy in the treatment of pressure injuries: a systematic review

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Abstract

Objective: to review literature on the use of nutritional therapy in the treatment of pressure injuries. Methods: a systematic review of the PubMed, Lilacs and Scielo databases was performed, with studies in the English and Portuguese languages published in the last five years selected. Result: three articles that investigated the use of different doses of arginine, a mixture of amino acids and nutritional supplements enriched with arginine, zinc and antioxidants were analyzed. The studies found that there was a reduction in the area of wounds in the intervention groups, although the difference in size was not significant in all the articles. Conclusion: nutritional intervention should be considered an integral part of the treatment of pressure injuries. The use of certain nutrients may positively affect the healing process of such injuries. Due to the heterogeneity of the methodologies used, the small sample size and the range of intervention times and nutrients used, more scientifically rigorous studies are recommended to create an evidence based nutritional intervention model for the treatment of pressure injuries.

Keywords: Pressure Ulcer. Wound Healing. Nutrition Therapy. Diet Therapy.

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INTRODUCTION

Pressure ulcers (PU) are described as localized damage to the underlying skin and/or tissue, usually over a bony prominence. They may be related to medical equipment or other types of devices and are considered a global problem. They can be caused by prolonged and/or intense pressure or shear forces¹. In addition to worsening the quality of life of hospitalized patients, PU increase the length of hospital stays and the cost of treatment.

In recent years, the prevalence of pressure ulcers has increased due to the increased life expectancy of the population. One of the indicators of risk for the development of PU is the age factor, especially in patients aged 65 years or older. The non-healing of ulcers affects three to six million people from this age group, representing 85% of sufferers of such events^{3,4}. The occurrence of PU has been observed in 36% of elderly patients with hip fractures and in 10 to 35% of individuals at the time of admission to long-term care facilities (LTCF)4. In Brazil, a study performed in a LTCF for the elderly in Fortaleza found a mean prevalence of pressure ulcers of 18.8%. In Ribeirão Preto in the state of São Paulo, a study of adults and elderly persons receiving home care identified a prevalence of 21.7%⁶. In a study of patients living in an area covered by the Family Health Strategy (FHS) in Teresina, Piaui, where the majority (79.4%) of the sample were elderly, the prevalence of PU was 23.5%7.

Turning to the relationship between PU and nutrition, studies have indicated a low association between malnutrition and the development of PU and delayed healing. Low Body Mass Index values are associated with reduced body fat and, consequently, less protection against pressure in bony prominence areas8. A study of high risk and hospitalized individuals found that 29% of such patients were malnourished, and of these 17% developed PU over a four-week period, while only 9% of non-malnourished patients suffered such lesions in the same period³. A multi-center study conducted in several hospitals in Brazil from 2009 to 2011 indicated a prevalence of 16.9% of PU, and found that 52.4% of patients were malnourished. Fifteen years earlier, the Inquérito Brasileiro de Avaliação Nutricional Hospitalar (the Brazilian Hospital Nutritional Evaluation Enquiry) (IBANUTRI)

found that malnutrition was present in 48% of hospitalized patients⁹.

Nutritional therapy (NT) is recommended in cases of pressure ulcers where patients are unable to meet their nutritional needs by the conventional oral route¹⁰. The nutritionist is responsible for creating a dietary prescription based on nutritional diagnosis guidelines¹¹.

The healing process consumes energy, mainly through the use of carbohydrates in the form of glucose. In order for the body to avoid using proteins in this process, an adequate calorie supply is required.³. From 30 to 35 kcal/kg/day of energy and 1.2 to 1.5g/kg/day of proteins are recommended, in addition to 1 mL/kcal of fluid intake. In patients with more than one PU and/or very large lesions or major catabolic situations, as well as those who do not have other comorbidities, the supply of at least 1.5 g/kg/day can be considered. The use of formulas with a higher protein content and immunomodulatory nutrients has been recommended in the treatment of patients with PI¹⁰.

Several supplements for enteral nutritional therapy (ENR) and oral, nasogastric, nasoenteral or percutaneous (gastrostomy) nutritional supplementation have been commercially developed to prevent and treat PU. These formulas are mainly composed of protein, zinc, vitamin C, arginine and glutamine³.

The objective of the present study was to perform a literature review of the use of NT in the treatment of pressure ulcers.

METHODS

A systematic review of literature was conducted in August and September 2016 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology¹². To develop the research question the PICO acronym was used¹³: P - population and problem (adults and elderly persons with PU); I - intervention (use of nutrition therapy); C - comparison (no special formula, or different formulas, or use of specific nutrients and immunonutrients, or differences in composition and/or dosage); O - outcomes (partial or total healing, stability of total area, reduction of

exudate, reduction of devitalized tissues and others). The research question was: What NT was used to improve the healing of PU in adults and the elderly?

A search was carried out of bibliographic data on the PubMed, Lilacs and Scielo databases, selecting publications performed in the last five years in the English and Portuguese languages. The following descriptors from the Medical Subject Headings (MeSH) system were used: pressure ulcer, bed sores, bedsore, decubitus ulcer, pressure sore, wound healing, nutrition therapy, diet therapy together with the following from the Descriptors em Ciências da Saúde (Health Science Descriptors) (DeCS): pressure ulcer, decubitus eschar, healing, nutritional therapy, diet therapy, combined with Boolean operators (AND and OR).

The inclusion criteria were: randomized clinical trial design, studies involving humans, subject age over 18 years, oral or enteral diet administration route, and pressure ulcers only. Publications such as literature reviews, dissertations, theses, editorials and clinical guidelines and studies of injuries of other etiologies were excluded.

The studies were initially selected from their titles and abstracts after consulting the databases. They were then read in full in order to apply the predefined inclusion and exclusion criteria. For the extraction of data from the articles, an instrument was prepared containing the following information: authors, year of publication, study location, sample size, intervention, duration, results and outcome evaluation.

RESULTS

Following searches in the databases using the previously mentioned descriptors, 117 articles were found, with 98 in PubMed, 16 in Lilacs and 3 in Scielo. Eighteen studies were selected for a complete reading. The most common reasons for exclusion at this stage were: type of wound with etiology other than PU (3), non-randomized studies (2) and systematic reviews (7), parenteral route of administration (2), and TN used for objectives other than the healing of PU (1). In the end, three articles were included in this systematic review (Figure 1).

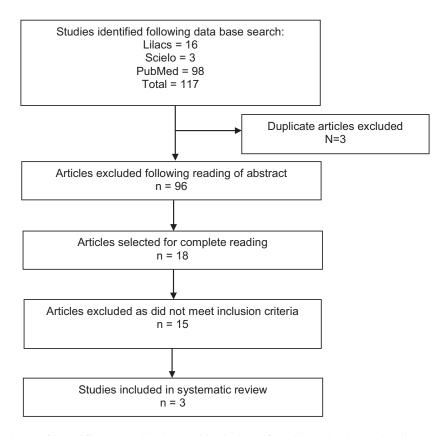


Figure 1. Flowchart of identification, selection and inclusion of studies. Distrito Federal, 2016.

The nutrients studied were: arginine, amino acid mixture [arginine, glutamine and beta-hydroxy-betamethylbutyrate (HMB)] and a formula enriched with zinc, arginine and antioxidants (Cubitan®). The mean age varied from 67.5±4.9 to 81.7±10.7 years and 246 patients participated in the study, 86 (35%) of whom were men and 160 (65%) of whom were women. Of the studies analyzed, one was performed in Australia¹⁴, one in Singapore¹⁵ and one in Italy¹⁶. The study by Leigh et al.¹⁴ did not receive any type of funding, while the study by Wong et al.¹⁵ was supported by Abbot Laboratories Pte Ltd and the authors declared there were no conflicts of interest. Cereda et al. 16 received financing from the Azienda Ospedaliera Universitaria Maggiore della Carità and declared that the source of the financial support had no role in the project or the undertaking of the study. All the studies described how randomization was performed.

In terms of sample losses, Leigh et al.¹⁴ described reasons such as death and collateral effects. The losses in the study by Wong et al.¹⁵ included pneumonia related death and aversion to the supplement. Cereda et al.¹⁶ described death, hospitalization, transference and the resistance of the participants to the treatment as reasons for losses.

All the studies performed nutritional and anthropometric evaluations. Two of the works^{14,15} used the Subjective Global Assessment (SGA) and the Body Mass Index (BMI). Leigh et al.¹⁴ classified 52% of the patients evaluated as malnourished. Wong et al.¹⁵ declared that 65% were malnourished or at risk of malnutrition. No significant alterations in weight were observed following the intervention in these two studies. The study by Cereda et al.¹⁶ evaluated only malnourished patients and used the BMI. The eight-week treatment resulted in an increase in body weight in both groups (p<0.001).

Daily energy requirements were calculated in the study by Leigh et al.¹⁴ using the Schofield equation. Protein requirements were based on the recommended daily dose for subjects with PU, according to the National Pressure Ulcer Advisory Panel (1.2-2g/kg of body weight)¹⁷. Wong et al.¹⁵ used from 30-35 kcal/kg of body weight and 1.2-2 g/kg of body weight of protein, according to the stage of the

pressure ulcer. Cereda et al. ¹⁶ multiplied the result of the Harris-Benedict formula by a correction factor of 1.2 for physical activity and a PU stress factor of 1.1. Daily protein requirements were set at an intake of 1.5 g/kg of body weight.

To evaluate the ulcer, one study¹⁶ used the Visitrak tool¹⁸ while the other two^{14,15} employed the Pressure Ulcer Scale for Healing (PUSH)¹⁹. The primary outcome in the study by Leigh et al.¹⁴ was the healing rate of the PU. Wong et al.¹⁵ did not describe the outcome of the methodology, but also evaluated the healing of the ulcers using the PUSH tool. Cereda et al.¹⁶ describes a primary outcome of the reduction of the ulcer area at eight weeks, and secondary outcomes that included a reduction in area of 40% or more; full healing at eight weeks, and percentage change in area within four weeks.

Regarding the pressure ulcers themselves, Leigh et al.14 found that 74.2% were classified as grade II (n=23) and 32.3% were located in the sacral region (n=10). Of the 34 ulcers found by Wong et al.15, 47.1% (n=16) were classified as grade IV and half were found in the sacral region. Cereda et al.16 obtained similar results: 40% of the PU were grade IV (n=80) and 64% were located in the sacral region (n=128). Following the intervention, Leigh et al.14, who evaluated different doses of arginine, found a reduction in PUSH scores in the two groups (p<0.001), although there were no significant differences in the healing rates between the groups (p=0.991). Wong et al.¹⁵ used a mixture of amino acids and found similar results, but observed that the improvement in viable tissues was significantly higher in the experimental group (p=0.02). Cereda et al.16 found that the use of a formula enriched with zinc, arginine and antioxidants resulted in a greater reduction in the area of the PU (60.9%) than the standard formula (45.2%).

One bias associated with the study by Leigh et al. ¹⁴ was that it did not feature an active control group (for ethical reasons), and the authors questioned whether the healing rates would be different from the normal healing rates of PU. The sample size was small. In the study by Wong et al. ¹⁵ the determination of viable tissue was based on examination of the site and the

retrospective analysis of photographs of sores, which may have led to bias in data interpretation. Both the time period and the survey size were small. When hospital discharge occurred, control of the use of the mixture (intervention) was via the verbal reports of the relatives. The study by Cereda et al. ¹⁶ featured only malnourished patients.

Chart 1 shows the characteristics of the studies found.

Chart 1. Randomized clinical trials selected, describing authors, location, number of patients, intervention and results found. Distrito Federal, 2016.

Author/ year of publication	Study location	Sample (intervention/ control)	Intervention	Duration	Results/evaluation of outcome
Leigh et al. 2012	acute care and rehabilitation hospital/ Australia	23 patients (12/11)	Standard hospital diet (SHD) + 9g de arginine - two sachets vs SHD + 4.5 g de arginine - one sachet. Each sachet contained 4.5g of arginine, 4g of carbohydrate, 155mg of vitamin C and 40.5mg of vitamin E.	3 weeks	There was a reduction in the initial PUSH scores of the two groups $(8.9\pm0.7 \text{ vs } 8.1\pm1.0 \text{ for } 4.5 \text{ g and } 9.0 \text{ g of arginine}$ groups, respectively, $p=0.507$). Although this reduction was significant ($p<0.001$) there was no difference in the healing rates of the two treatment groups ($p=0.991$). There was no significant difference in healing rates based on arginine dosage ($p=0.393$).
Wong et al. 2014	Acute care hospital / Singapore	23 patients (11/12)	Recommended diet for PU + 2 sachets of placebo (carbohydrate, calcium, flavoring) vs Recommended diet for PU + 2 sachets of a mixture of amino acids [7g of L-arginine, 7g of L-glutamine, 7.9g of carbohydrate, 1.5g of beta-hydroxybeta-methylbutyrate (HMB), 200mg of calcium and orange flavoring].	2 weeks	The PUSH scores were significantly reduced in the two groups: the experimental 9.63 ± 1.09 (CI 95%, 7.31 to 11.94 , $p<0.001$) and the placebo 10.63 ± 1.06 (CI 95%, 8.37 to 12.88 , $p=0.009$). However, there was no overall difference in the PUSH scores of the two groups. The improvement in the viable tissue of the experimental group was significantly greater ($p=0.02$), 43.1% (from 42.8 ± 6.6 to 85.8 ± 4.5) compared to 25.93% (from 57.2 ± 7.4 to 83.1 ± 5.0) in the placebo group.

to be continued

continued from Chart 1

Author/ year of publication	Study location	Sample (intervention/ control)	Intervention	Duration	Results/evaluation of outcome
Cereda et al. 2015	Long term care facilities and home care services / Italy	200 malnourished patients (101/99)	Standard oral diet (SOD) + 400ml/day of oral nutritional supplement (ONS) vs SOD + 400ml/day of ONS with similar values of calories and proteins, enriched with zinc, arginine and antioxidants (vitamin C, E).	8 weeks	Primary outcome: the use of the formula enriched with zinc, arginine and antioxidants resulted in a greater reduction in the area of the PU, 60.9% (CI 54.3% to 67.5) than in the control formula, 45.2% (38.4% to 5.0%). Secondary outcome: 69.9% (CI 59.5% to 79.9%) of patients in the intervention group exhibited a reduction of 40% or more in the size of the PU in eight weeks, compared to 54.1% (CI 42.7% to 65.5%) in the control group (odds ratio [OR], 1.98 [CI 1.12 to 3.48]; p=0.018). A complete cure at 8 weeks was more common in the experimental group (16.9% [CI 8.2% to 25.6%]) than in the control formula group (9.7% [CI 2.1% to 17.3%]), but the difference was not significant (OR 2.16 [CI 0.88 to 5.39]; p=0.097). No significant differences were found in the reduction of the lesion area at 4 weeks (10.2% [CI 6.5% to 27.0%]; p=0.149).

DISCUSSION

The objectives of nutritional therapy in patients with pressure ulcers include the promotion of tissue regeneration and the facilitating of the healing process²⁰. The main nutrients used in the studies were arginine, beta-hydroxy-beta-methylbutyrate, zinc and antioxidants. Other substances were also included in the supplements used, such as glutamine, selenium, copper and vitamin C¹⁴⁻¹⁶.

Carbohydrates participate in phagocytic activity, cell proliferation and fibroblastic function, with recommended levels around 50% to 60% of the energy substrate. Proteins participate in neovascularization,

fibroblast proliferation, collagen synthesis, and leukocyte production and migration²⁰.

The main immunonutrients used in enteral formulations for the treatment of pressure lesions are arginine, glutamine and amino acids, which exercise a substrate function in the biochemical pathways responsible for mediating collagen synthesis and immune response. Arginine is a substrate for ornithine, nitric oxide and proline, which results in vasodilation, synthesis and collagen deposition, as well as being a conditionally essential amino acid, necessary during the active growth phases and in the healing process, diabetes and stress situations. Glutamine is the most abundant free amino acid in

the body. Classified as a non-essential amino acid, its synthesis, in critical situations of metabolic stress, does not meet the demand required by the organism. Glutamine has been shown to be important in healing as it is related to collagen synthesis and the proliferation of inflammatory cells^{3,21,22}.

Beta-hydroxy-beta-methylbutyrate supplementation is associated with an increase in muscle mass and may inhibit muscle proteolysis and modulate protein turnover. A quantity of 3g/day can increase the formation of collagen, stimulating wound healing¹⁵.

Zinc, copper and selenium also appear to be beneficial to the healing process. Zinc is a cofactor for the formation of collagen, granulation and epithelial tissue, has an antioxidant function and is important for protein synthesis. Copper participates in the cross-linking reactions of collagen, elastin and the elimination of free radicals^{3,23}. Selenium is required for the functioning of the glutathione system, responsible for the management of inflammation induced by oxidative stress²⁴. Vitamin C acts on the formation of collagen and the functioning of neutrophils and macrophages in the inflammatory phase. It also acts as a reducing agent, protecting copper and iron from oxidative damage, as well as participating in all the healing stages^{23,24}.

The majority of participants in the studies were elderly, as illustrated by the advanced average age. Elevated age is considered a risk factor for the development of PU, probably due to changes in the skin and subcutaneous tissue of the elderly during the aging process, making it more fragile and susceptible to pressure, friction and shear forces. There was a predominance of females, characterizing what literature describes as "the feminization of old age", a phenomenon that also occurs in Brazil²⁶.

A systematic review by Pedroni et al.²⁷ evaluated the impact of malnutrition on the development and severity of PU and revealed, through eight studies, that the risk of developing pressure ulcers is higher in malnourished patients. Four studies showed that the severity of malnutrition increases the likelihood of having more severe PU or a greater number of lesions. Another study observed that pressure ulcers and their severity were directly associated with malnutrition, finding that 98% of those with

PU of severity greater than or equal to grade II were malnourished²⁸. Nutritional status interferes directly with tissue repair. Malnutrition is related to inadequate wound healing, decreased fibroblast production, neoangiogenesis and collagen synthesis, as well as reduced tissue remodeling capacity¹⁰.

Leigh et al.¹⁴ observed that well-nourished patients displayed greater improvement in healing rates than malnourished patients, although the difference was not significant (p = 0.057). Wong et al.¹⁵ and Cereda et al.¹⁶ did not evaluate the relationship between healing rate and nutritional status.

A recent systematic review on the use of argininecontaining supplements found that such substances resulted in a significant improvement in PU healing in malnourished patients and those with normal nutritional status²⁹. Another study observed that the PU of patients who received the arginine-enriched supplement were significantly smaller than those of the control group (p < 0.016). The PUSH score in the intervention group was significantly lower than control (p < 0.033) in the eighth week³⁰. The study which evaluated different doses of arginine in this systematic review found a significant reduction in PU severity over time (p < 0.001), with no evidence of differences in healing rate between the two doses of arginine (p = 0.991). The authors suggest that a 4.5g dose of arginine per day may promote a similar benefit in healing to a 9g dose¹⁴. Wong et al.¹⁵ concluded that the use of specialized amino acids does not appear to reduce wound size and PUSH scores, but may improve tissue viability after two weeks. In both studies the follow-up time was short, with three and two weeks respectively.

In a previous study performed by Cereda et al.³¹ which featured the application of a formula enriched with arginine, zinc and antioxidants for 12 weeks, the differences between the interventions were statistically significant in terms of the area of the PU in week 8 (p <0.05) and in the PUSH score at week 12 (p <0.05). In a more recent study, NT effectively improved the healing of PU (p <0.001) in both groups, with a larger area in the intervention group at the eighth week¹⁶.

This systematic review presented some limitations, as the sample sizes of the studies included were small, ranging from 23 to 200 subjects. The

studies employed different outcomes, nutritional assessment, proportion of areas and tissue evaluation tools (Visitrak, PUSH), and follow-up times, ranging from two to twelve weeks.

CONCLUSION

The therapeutic benefits of nutrition should be encouraged by multi-professional teams. Nutritional intervention should be considered an integral part of the treatment of pressure ulcers. The evaluation of the nutritional status of patients is recommended, as is ensuring adequate energy and protein intake as recommended by current guidelines.

Several studies have pointed to the presence of certain nutrients that can positively affect the healing process of pressure ulcers. The evidence of supplementation with arginine and other amino acids is generally favorable, but is confused by the addition of other nutrients in available commercial preparations and by the fact that the study periods involved have been relatively short.

The use of nutritional supplements enriched with arginine, zinc and antioxidants effectively aided the healing of PU in malnourished patients, although they may have a different effect on patients with adequate nutritional status.

More scientifically rigorous studies with standardized interventions and more participants are needed to create an evidence-based nutritional intervention model for the treatment of PU.

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ERRATUM

In the review article "Nutritional therapy in the treatment of pressure injuries: a systematic review", published in the Revista Brasileira de Geriatria e Gerontologia v. 20, n. 4, p. 562-570, 2017, DOI: http://dx.doi.org/10.1590/1981-22562017020.160195, the names of two of the authors in reference 18 on P. 570 are incorrect.

Instead of Eberhardta, TD, Kesslera, M the reference should read Eberhardt, TD, Kessler, M.