

Review Article

The Potential Role of Specific Amino Acids, Vitamins, and Zinc Oral Supplementation as Support Strategies for the Management of Chronic Wound

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The oral supplementation with some amino acids (such as arginine, glutamine and Hydroxy-Methylbutyrate - HMB), vitamins and zinc could contribute to accelerate the healing process in subjects with chronic wounds such as pressure sores. In this mini review we summarized the rational and the evidences available regarding the possible role of some nutrients supplementation in the management of chronic wounds. In particular we focused on clinical data available for arginine, HMB, glutamine, vitamins and Zn oral supplementation. Several studies suggested that these foods could promote the recovery of muscle mass and the reconstruction of damaged tissue (e.g in patients with pressure sores, ulcers, sarcopenia and burns). Food supplements containing all these components are commercially available. These products could be useful in the management of subjects with or at risk of Pressure Ulcers (PUs). In addition, these formulas can be us as integrations in the treatment of sarcopenic subjects, a condition that could be associated to PUs. The use of specific oral nutritional formula not only could allow a better healing of PUs, but also can reduce the costs of healthcare system. In these respects, controlled clinical trials are warranted to confirm the efficacy of this supplementation strategy.

Keywords: Pressure ulcers; Wound healing; Food supplement; Protein malnutrition

Introduction

The skin is an organ responsible for numerous processes in human body (e.g. protection, thermal regulation, vitam D synthesis). Skin possesses different repair processes to counteract severe skin damages [1]. However, the repair processes could be limited in presence of chronic wounds. Chronic wounds include vascular ulcers, diabetic ulcers, and pressure ulcers. Pressure ulcer is defined by National Pressure Ulcer Advisory Panel as "localised injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear" [2]. Pressure ulcers are classified based on severity and level of tissue injury in different grades: from Grade 1 (persistent non-blanching erythema) to Grade 4 (the damage is extended to the underlining bone, tendon, or joint capsule) [3,4]. The overall prevalence of Pressure Ulcers (PUs) across European countries is 13.7% [5]. The factors re-

sponsible for pressure sore are different such as vascular diseases, loss of sensory stimuli, reduce mobility, fecal and urine incontinence, and malnutrition. Patients with reduce activity/mobility present the highest risk of developing a PU. Indeed, sarcopenia increases the risk of pressure ulcers [6]. Sarcopenia is defined as the loss of muscle mass and muscle strength. These conditions, along with a decreased immune function, can lead to impaired wound healing [7]. PUs significantly affects the quality of life of patients, increase morbidity and mortality and is associated with high costs for the individuals and health care system [8]. In this contest the prevention and management of PU is essential and required a multidisciplinary approach. The management of underlying causes and comorbidities (e.g. diabetes, deep vein thrombosis, chronic kidney disease, coronary artery disease, heart failure) is required; in addition, different

preventive intervention are available such as various support surfaces, frequent changes of position, and an appropriate local wound care (adequate dresses, cream and management of incontinence). Patients with PUs required also an appropriate psychosocial support; indeed, these subjects suffer of pain and the disease impacts on their normal activities [9,10].

A relevant role in PU management is also specific nutritional supplement strategies. There are some evidences that the incidence and severity of PUs is negatively correlate with poor nutrition [4,11,12]. On the other hand, there is no clear evidence on improve PU healing with nutritional supplements [4]. However, there is a consensus that nutrition is an important factor, cited in numerous guidelines such as the reference guide from the European Pressure Ulcer Advisory Panel (EPUAP) [3,13,14]. Patients with chronic wounds are often in catabolic rate, showing an increased need for energy and macronutrients (such as proteins), therefore an optimization in protein and total caloric intake is important [10,15]. An increase protein intake (1.25 to 1.5g/kg/day) promotes healing [10,16,17]. In addition, in presence of adequate quantities of proteins and calories, some authors suggesting to considered arginine and glutamine supplementation. There is some evidence of improved healing, evaluated measuring surrogate outcomes, after the supplementation with arginine compared to a standard hospital diet. Micronutrients deficiency may have a significant impact on wound healing. Some micronutrients such as vitamin C and zinc, are usually supplemented to promote healing, although their efficacy has not to be conclusive demonstrated [4,10]. In addition, the water-soluble vitamins and some minerals are important cofactors for some metabolic reactions. Therefore, the nutrition supplementation could represent an important tool in the prevention and management of PUs. In presence of an adequate ingestion of proteins and energy, the supplementation with some amino acids (such as arginine, glutamine and hydroxymethylbutyrate), vitamins and zinc could contribute to accelerate the wound healing process. In this mini review the possible role of some nutrients in the management of chronic wounds was further explored. In particular, we focused on clinical data available for arginine, HBM, glutamine, vitamins (A, B, and C) and Zn supplementation. The data are summarized in Table 1.

Table 1: Nutrients and the possible role of their supplementation in the management of chronic wound.

Nutrient	Mechanism of action
Arginine	<ul style="list-style-type: none"> - Protein anabolism; - Cellular growth and proliferation; - Improve the production of nitric oxide (responsible for vasodilatation, secretion of growth hormones and growth factors and immune response mediator).
Glutamine	<ul style="list-style-type: none"> - Cellular division (enterocytes and leukocytes); - Key role for the immune system.
HMB	<ul style="list-style-type: none"> - Proteolysis inhibition and protein turnover modulation.
Vitamins (e.g. Vitamin A, Vitamins B, and Vitamin C)	<ul style="list-style-type: none"> - Cellular proliferation; - Collagen synthesis stimulation; - Immune system stimulation.
Zn	<ul style="list-style-type: none"> - Cell growth; - Protein synthesis; - Anti-inflammatory activity; - Anti-microbial activity.

Arginine

Arginine has many functions in human organism that could be correlated with wound healing processes [18]. It is involved in protein synthesis and induce the release of growth hormone, prolactin, and insulin. Is therefore indirectly involved in polyamines synthesis, responsible for cell division, differentiation, and growth [18]. Arginine is a precursor of proline and hydroxyproline, which are important for the synthesis of collagen. Arginine represents the substrate of Nitric Oxide synthase (iNOs), which converts arginine to Nitric Oxide (NO). Nitric oxide, a known immune response mediator, also plays a central role in skin repair improving the vasodilatation and stimulating the secretion of growth hormones and insulin-like growth factor [18]. The human body is able to synthesize arginine, however in presence of a stressful state and insufficient nutritional intake, arginine supplementation could be suggested for adequate muscle and connective tissue growth. The effect of oral arginine supplementation in pressure ulcers has been evaluated. Different *in vivo* human trials (including open trials and randomised clinical trials) were conducted, enrolling in total 645 patients with PUs (stages II, III or IV) [19]. In these trials the protein-enriched oral nutritional supplementation was consumed one to three times/day and contained 3–9g of arginine/dose, until a maximum of 18g arginine/day. The majority of the considered studies supported the positive effect of nutritional supplementation with additional protein, arginine and micronutrients on PU healing. To confirm the role of arginine Cereda et al. observed that a nutritional formula enriched with proteins, arginine, zinc, and vitamin C was able to accelerate the rate of PU healing, compared to a standardized formula with a similar protein content [20]. Leigh et al. evaluated the effect on PUs healing of two different daily doses of arginine (4.5g and 9g) in 23 hospital patients. Both doses significant decreased the PUs severity (reduction in PU area and Pressure Ulcer Score for Healing) without differences between the two dosages considered. Therefore, the authors concluded that a lower dosage of arginine could be sufficient to increase the PU healing [21]. On the other hand, in a meta-analysis conducted by Cheshmeh et al. was reported that higher doses of arginine supplement had a greater effect on reducing the probability of PU development [22]. In conclusion, there are some evidences of improved healing with an arginine enriched mixed nutritional supplements containing other micronutrients (such as vitamin C and Zn) compared with standard diet. Although other studies are necessary to confirm the role of arginine supplementation alone, it seems to represent an important key nutrient in pressure ulcer healing.

Glutamine

Glutamine is a conditionally essential amino acid [23]; it can be synthesized by human body however during stress conditions its level may be depleted. Glutamine represents a fuel source for cells with rapid turnover (e.g. enterocytes, epithelial cells, fibroblasts, macrophages, and lymphocytes) and plays a key role for the immune system [24]. Glutamine is known to play a regulatory role in different cellular processes including: metabolism, cell integrity, protein synthesis and extracellular matrix synthesis. Indeed, glutamine is able to stimulate the synthesis of collagen representing a precursor of proline and hydroxyproline residues [25]. Two studies observed a faster wound healing rates in severe burns after enteral glutamine supplementation [26,27]. Although no specific studies have been conducted on wound healing for pressure ulcer patients and glutamine supplementation alone, some amino acids mix-

ture (containing β -hydroxy β -methylbutyrate, arginine and glutamine), may improve tissue viability and overall wound conditions in patients with PU [23,28].

Hydroxy-Methylbutyrate

Hydroxy-Methylbutyrate (HMB) is a metabolite of leucine, an essential amino acid. HMB, inhibiting proteolysis and modulating protein turnover, it is associated with muscle mass increment and collagen synthesis. Therefore, it could stimulate the wound-healing processes [23]. The supplementation of amino acids mixture (containing HMB, arginine and glutamine) has been reported to improve wound healing processes [23,29]. In these studies, is difficult to identify the direct effect of the active ingredients. However, in a study conducted by Chang et al., a diet with HMB was compared with other available enteral nutrition. A significant reduction in mortality and pressure ulcers were observe in HMB group compared to the control group [30].

Vitamins

Some micronutrients, such as vitamins B and C, become deficient at old age [31] and their supplementations could have an interesting role in pressure ulcer healing. Vitamin A plays stimulatory activity on immune system, contributes to maintain epithelial integrity, and stimulate collagen synthesis. Vitamin C exerts a role in fibroblast maturation and collagen formation. Both vitamins A and C could have a role in wound healing process [32].

Vitamins B are water soluble vitamins involve in different process, they promote cells proliferation and muscle tone, improve metabolic rate, and stimulate immune and nervous systems. Vitamins B deficiency, in particular Vitamin B1 (thiamine) deficiency, could be involved in many disorders characterized by skin manifestation and could weaken wound healing process [33].

Zinc

Zn is an essential element; it is an important cofactor of numerous enzymatic reactions involved in cell growth and protein synthesis [34]; therefore, it could play an important role in wound healing process. Zn also exerts anti-inflammatory and anti-microbial effects [31]. Zinc is usually supplemented to promote healing, although their efficacy has not to be conclusive demonstrated [4,10]. Delayed in wound healing have been associated to zinc deficiency. Although there are no evidences that supported the positive effect of Zn on wound healing in absence of deficiencies, the assessment of Zn state is not easy, therefore the routine supplementation of this micronutrients for PU patients at high risk for zinc deficiency is usual in clinical practice.

Conclusions

Pressure ulcers are an important healthcare issue, that affect the quality of life of patients and is associated with a significant economic burden. Different factors could contribute to the development of PUs, among which malnutrition and sarcopenia. Although there is no clear evidence that nutritional intervention reduce the development of PU, due to the limitations associated to the *in vivo* studies, difference guidelines, include the guideline by the European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel, and Pan Pacific Pressure Injury Alliance, recommends use of a high-protein, high-calorie oral nutrition supplement fortified also with arginine and other

antioxidants to treat adults with grade 2 or greater pressure injury and who are malnourished or at risk of malnutrition [14]. Recent ESPEN guidelines suggested that in patients with bed-sore specific amino acids such as arginine, glutamine, and β hydroxy β methylbutyrate can be added to oral/enteral foods to improve and accelerate the wound healing process [35]. These amino acids have also shown positive effects in the framework of sarcopenia [36]. Different products suitable for this kind of patients are available on the market; a food for special medical purposes containing essential amino acids, arginine, glutamine, HMB, vitamins B, and Zn has been recently commercialized*. Its components could counteract different factors involved in the pathogenesis of PUs or chronic wounds (Figure 1).

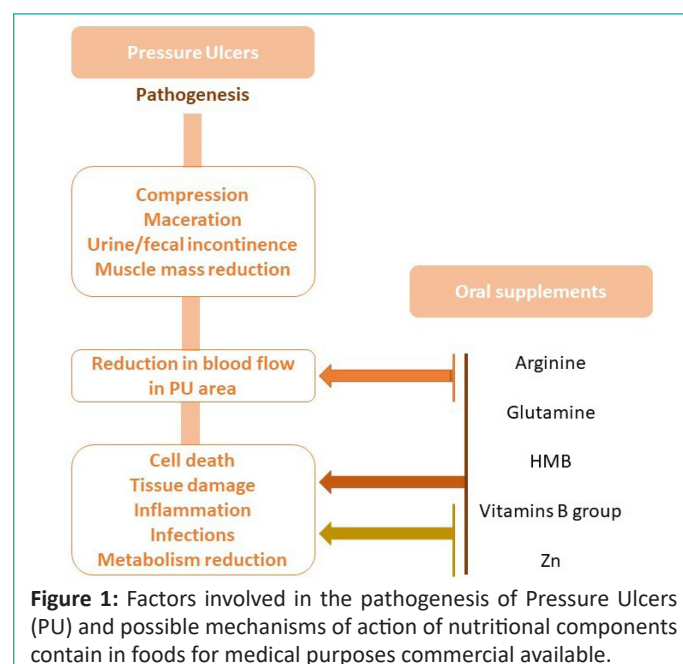


Figure 1: Factors involved in the pathogenesis of Pressure Ulcers (PU) and possible mechanisms of action of nutritional components contain in foods for medical purposes commercial available.

These foods could promote the recovery of muscle mass and the reconstruction of damaged tissue (e.g in patients with pressure sores, ulcers, sarcopenia and burns). Nutrition plays a key role in the prevention, treatment, and management of PU and correlate pathologies (e.g. sarcopenia). Patients with pressure ulcers/injuries generally required a high-calorie and high-protein intake. In addition, the use of specific oral nutritional formula containing amino acids and micronutrients could contribute and improve the would haling processes. In conclusion, nutritional intervention not only could allow a better healing of PUs and/or preventing their formation, but also could reduce the costs of healthcare system [37]. Further controlled trial evaluating the efficacy of specific oral supplementation with these components are warranted.

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