Promising effects of arginine-enriched oral nutritional supplements on wound healing

Introduction
Nobody would argue against the importance of adequate nutrition to preserve skin and tissue viability and to promote tissue repair processes such as wound healing. A good nutritional status generally reflects a healthy condition and adequate body power. However, there is little scientific evidence about the relationship between nutrition or nutritional intervention and wound healing, and most studies that have been performed to date are related to the problem of pressure ulcers (PUs).1

This article first addresses the assumed role of nutrients in wound healing, and then relevant aspects of the nutritional cycle. Finally, some recent studies with an arginine-enriched oral nutritional supplement in PU healing will be described because they represent important nutritional research in this area.

BASIC ASPECTS OF WOUND HEALING AND THE ASSUMED ROLE OF NUTRIENTS
The wound healing process involves several stages, including phases of blood coagulation, inflammation, migration and proliferation of defence and repair cells, remodelling of tissue structure, and scar formation and maturation. Several endogenous factors play an important role in promoting this process, for example the power of the body to generate adequate inflammation as well as the defence response to deal adequately with the bacterial burden of the wound. Nutrients also play a relevant and important role in this process. Carbohydrate, protein, and fat provide the energy source (kilocalories) for the body. The provision and consumption of adequate kilocalories supports collagen and nitrogen synthesis and promotes anabolism by sparing body protein from being used as an energy source.3

Fat
Fat is the most concentrated source of kilocalories, transports the fat-soluble vitamins (A, D, E, K), and provides insulation under the skin and padding to bony prominences. Moreover, fat is an essential component of cellular membranes, which are also important for preserving tissue viability and for wound repair processes. Meats, eggs, dairy products, and vegetable oils represent dietary sources of fat.1

Protein and Amino Acids
Protein is composed of amino acids and is the only nutrient containing nitrogen. Protein is important for tissue perfusion, preservation of immune function, repair and synthesis of enzymes involved in wound healing, cell multiplication, and collagen and connective tissue synthesis.2

Foods that provide all essential amino acids, such as meat, poultry, fish, eggs, milk products, and soybeans, are considered complete proteins. The body requires an adequate supply of the essential amino acids plus enough nitrogen and energy to synthesise the other amino acids. Legumes, grains, and vegetables provide nonessential proteins.
During period of stress or trauma such as injury and wound healing, certain amino acids, such as arginine and glutamine, become conditionally essential.

L-Arginine is composed of 32% nitrogen and has been shown to increase the concentration of hydroxyproline, an indicator of collagen deposition and protein, at the wound site.\(^3\) Faster wound healing has been described in non-malnourished patients with stage III-IV PUs who received an oral nutritional supplement (ONS) containing arginine, protein, zinc, ascorbic acid, and vitamin E.\(^5\)

**Water**

Water is distributed throughout the body in intracellular, interstitial, and intravascular compartments and serves as the transport medium for moving nutrients to the cells and removing waste products. Fluids are solvents for minerals, vitamins, amino acids, glucose, and other small molecules, thus enabling them to diffuse into and out of cells. Individuals with draining wounds, diarrhoea, elevated temperature, or increased perspiration require additional fluids to replace the fluid lost.\(^6\) Water constitutes 60% of an adult's body. The elderly individual generally has an increase in body fat and a decrease in lean body mass, resulting in a decrease in the percentage of water stored. This decrease in body water, coupled with a diminished sense of thirst, places the elderly at particular risk for dehydration.\(^7\) Hydration needs are met from liquids plus the water content of food, which accounts for 19% to 27% of the total fluid intake of healthy adults.\(^8\)

**Vitamins and Minerals**

The role of micronutrients in promoting wound healing is debatable.\(^1\)

Ascorbic acid (vitamin C), a water-soluble vitamin, is a cofactor with iron during the hydroxylation of proline and lysine in the production of collagen. Therefore, a deficiency of vitamin C may prolong the healing time and contribute to decreased resistance to infection.\(^9\) The required daily intake of vitamin C is achieved through the consumption of fruits and vegetables. Mega doses of ascorbic acid have not resulted in accelerated pressure ulcer healing.\(^10\)

Vitamin A and Vitamin E are fat-soluble vitamins and dietary intake of these vitamins comes from a variety of foods. Vitamin A acts as a stimulant during the wound healing process to increase collagen formation and promote epithelisation. High doses of Vitamin A are not recommended without consultation with a physician. Vitamin E acts as an anti-oxidant and the required intake can easily be met with food and/or a multivitamin unless a deficiency is confirmed.

Zinc, a cofactor for collagen formation, also enhances metabolism of protein, liberates vitamin A from storage in the liver, and assists in immune function. Unless a deficiency is confirmed, elemental zinc supplementation is not recommended for individuals with wounds such as pressure ulcers.\(^11,12\) Copper is a mineral that is essential for collagen cross-linking. Zinc and copper compete for the same binding site on the albumin molecule, thus high serum zinc levels interfere with copper metabolism and can induce copper deficiency.\(^13,14\) If deficiencies are suspected, a multivitamin with minerals may be appropriate.

**THE NUTRITIONAL CYCLE**

Screening and assessment of nutritional status followed by adequate nutritional intervention should be part of the prevention and treatment plan for patients at risk for (chronic) wounds.\(^1\)

Pressure ulcers are a representative example of such wounds.

The 'why' of this statement is clearly revealed by the literature related to PUs, which are used as an example here. The essentials, however, also apply to other types of wound such as chronic venous leg ulcers, arterial leg ulcers, and diabetic foot ulcers, in which nutritional care is additional to other disease-specific interventions.

**Nutritional status and PUs**

Whether a patient develops a PU depends on both extrinsic and intrinsic factors. Important extrinsic factors (coming from outside the patient) are pressure, friction, and shear forces.\(^15\)

Intrinsic (patient-related) factors affect tissue viability and therefore the tissue response to mechanical loading.

A number of intrinsic factors have been described in the literature. An adequate nutritional status is one of the most important intrinsic factors, and also one that can be readily influenced.\(^16,17\)

Poor nutritional intake and poor nutritional status have both been identified as key risk factors for pressure ulcer development and protracted wound healing. Notwithstanding methodological shortcomings, cross-sectional and prospective studies suggest a fairly strong correlation between undernutrition and pressure ulcer development.\(^18-21\) Moreover, it appears that many acutely or chronically ill patients and elderly patients who are at risk of pressure ulcer development or have established pressure ulcers suffer from undesired weight loss.\(^22-26\)
Nutrition Screening
Unless the patient has a terminal illness, undernutrition is a reversible risk factor for pressure ulcer development and early identification and management is therefore critical. Individuals at risk for wounds like pressure ulcers are often also in danger of undernutrition, so nutritional screening should be completed in such cases.2,27 Healthcare organisations should have a policy on nutrition screening and its frequency. Since individuals frequently move from one health care setting to another, the screening results must be documented and communicated from one care setting to another.2,28 Screening tools should be quick, easy to use, validated, and reliable for the patient population served.29 Validated screening tools are widely used in Europe. In a cross-sectional study by Langkamp-Henken et al., the Mini-Nutritional Assessment (MNA) and the MNA short form (SF) were noted to have an advantage over the use of visceral protein when screening and assessing nutritional status.30,31 The MNA-SF, which was revised to six questions and re-validated for adults 65 and older, has 80% sensitivity and specificity and 97% positive predictive value according to clinical status.32 The Malnutrition Screening Tool (MUST) has been validated in acute care, long-term care, and the community setting, and identifies individuals who are underweight or at risk for undernutrition.33

When the screening tool indicates nutritional deficits, timely referral to the appropriate professionals is critical. The nutrition assessment should be completed by a registered dietician who collaborates and communicates with other members of the healthcare team, including the speech therapist who is responsible for screening, evaluating, and treating swallowing problems; the occupational therapist who works to strengthen the patient’s ability to feed themselves; and the nursing staff, whose responsibilities include monitoring the patient’s acceptance of nutrition. The physician is responsible for the overall care of the patient and ordering any treatments recommended by the team.

Nutrition Assessment
The in-depth nutrition assessment that is performed in individuals with a screening result that points towards undernutrition is a methodical process of obtaining and interpreting data in order to make decisions about the basis of nutrition-related problems. The assessment includes interpretation and analysis of medical, nutritional, and biochemical data and food-medication interactions; obtaining anthropometric measurements; and evaluation of visual signs of poor nutrition, such as oral status, chewing/swallowing ability, and/or diminished ability to eat independently.1

Diet History: The diet history includes consultation with the patient and/or caregivers to determine the type, quantity, and frequency of food normally consumed by the patient. One should consider any factors that may influence the patients’ decision about nutrition.

Nutrition-Focused Clinical Examination: The interdisciplinary team, including the dietician, should examine the individual for physical signs of undernutrition and protein depletion, as evidenced by changes in the hair, skin, or nails such as thin, dry hair, cracked lips, or brittle nails. Individuals with missing or decayed teeth or ill-fitting dentures often reduce their intake of protein foods that are difficult to chew, thus restricting their caloric intake and increasing the chance for weight loss. Moreover, individuals with swallowing problems or dysphagia may become dehydrated, lose weight, and develop pressure ulcers. Loss of dexterity and/or the ability to self-feed is a risk factor that often results in poor oral intake. All of these conditions negatively affect wound healing.

Anthropometrics: Anthropometric measurements include height, weight, and body mass index (BMI). Obtaining an accurate height and weight is important, because these values are the basis for calculating body mass index (BMI) and caloric requirements.

Individuals should be weighed on a calibrated scale, at the same time of the day, and wearing the same amount of clothing. Specialty beds often are equipped with a device to weigh an immobile individual. Significant weight loss places an individual at increased nutritional risk and has a negative effect on wound healing. Several studies support the theory that unintentional weight loss of 5% in 30 days or 10% in 180 days is a predictor of mortality in the elderly.34-37 Moreover, an obese patient is also at risk for PU development and healing may also be delayed in such patients when the diet consumed is inadequate in nutrients including protein.

Biochemical Data: Analysis of current laboratory values is one component of the nutrition assessment, but not a very important one. Biochemical assessment data must be used with caution because values can be affected by hydration, medication, and changes in metabolism. There is no single specific laboratory test that can expressly determine an individual’s nutritional status. Serum levels of hepatic proteins including albumin, prealbumin (transthyretin), and transferrin may not correlate with the clinical observation of nutritional status.38 In fact, studies indicate that hepatic proteins correlate with the severity of illness rather than with nutritional status.39-41
Nutrition Intervention
Ultimately, the nutrition assessment will lead to a nutrition diagnosis, followed by the necessary nutritional support. Early nutrition intervention and subsequent monitoring of the nutrition plan can reverse poor outcomes associated with undernutrition and promote healing. Caloric, protein, and fluid requirements should be individualised and either increased or decreased, depending on the assessed requirements of each patient. Furthermore it should be determined when fortified foods and/or ONS should be incorporated into the treatment plan. Fortified foods include commercial products, such as cereal, soup, cookies, or dairy products enriched with additional calories and protein, or enriched menu items.

Of course, the nutritional intervention strategy always tries to focus first on improving normal oral nutritional intake. However, despite many daily efforts towards this goal, for example by taking into account individual preferences for foods and drinks and improving mealtime ambiance, it is known that many patients with chronic wounds like PUs cannot meet their nutritional demands via normal intake only.

When normal oral intake is inadequate to promote healing, enteral or parenteral nutrition is considered if it is consistent with the individual’s goal. When the gut is functioning, enteral feeding via oral nutritional supplements in addition to the diet or total tube feeding is the preferred route.

Research supports the theory of providing ONS to reverse undernutrition, prevent PU occurrence, and promote PU healing. ONS given in addition to the regular diet should be preferably consumed between meals so that it does not negatively affect normal intake.

ARGININE-ENRICHED ORAL NUTRITIONAL SUPPLEMENTS AND PRESSURE ULCER HEALING – WHAT’S KNOWN?
Considering nutritional intervention and the prevention of PUs, adequate nutrition, meaning the intake of adequate amounts of protein and energy, seems to reverse the common underfed status of PU-prone patients and protect against ulcer formation. With regard to nutrition and healing of PUs, there is a gradual accumulation of evidence indicating that meeting the patient’s calorie and protein requirements improves the rate of wound healing. Intake of supplements or tube feeding with a high content of protein has been described to improve the rate of wound healing.

Particularly interesting are studies performed with arginine-enriched nutritional supplements. Benati et al. tested a PU-specific nutritional supplement that was high in energy and protein and enriched with arginine, vitamin C, and zinc, and found a positive effect on wound healing. Subsequently, these findings were confirmed in an open multicentre study conducted in Belgium and Luxembourg (n=245 patients) and in a small randomised controlled trial (n=28 patients) including several tube-fed patients.

In the CUBE study, a randomised controlled trial (n=43 patients), van Anholt et al. observed significantly faster wound healing in non-malnourished patients (aged between 18 and 90, with a normal BMI and no undesired weight loss) with stage III or stage IV pressure ulcers who received the same oral nutrition as controls, but supplemented with arginine, protein, zinc, ascorbic acid, and vitamin E.

Robust evidence for the independent role of these specific micronutrients within a high-calorie, high-protein oral nutritional support came recently from the large (n=157), randomised, and controlled OligoElement Sore Trial (OEST). In this multicentre study, Cereda and collaborators found that, in malnourished patients with stage III or stage IV pressure ulcers, an 8-week supplementation with an oral formula enriched with arginine, zinc, and antioxidants resulted in faster healing (increased by 20%) than an isocaloric-isonitrogenous control nutritional support. Both the CUBE study and the OEST trial additionally found a positive cost effect, because in both studies significantly fewer wound dressings were used in the intervention group with less overall nursing time required for dressing changes. This finding is very relevant at a time when awareness of the costs of health care has become increasingly important.

ARGININE ENRICHED ORAL NUTRITIONAL SUPPLEMENTS AND HEALING OF OTHER TYPES OF CHRONIC WOUNDS – WHAT’S KNOWN?
Arginine-enriched nutritional supplements may also have a positive effect on the healing of other types of chronic wounds, such as venous leg ulcers, arterial leg ulcers, and diabetic foot ulcers. However, at the present time there are only case reports on these applications. Therefore, more research in this field should be performed.

CONCLUSION
Nutrition is a key element in the prevention and treatment of patients with (chronic) wounds such as pressure ulcers. Nutritional care has to be incorporated into integrated and multidisciplinary wound care performed by a dedicated professional team.
References:


Additional references on nutrition and wound healing in general:
