# Nutrition and Pressure Ulcers

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## Introduction

For most health care professionals, the relevance of adequate nutrition for preserving skin and tissue viability and to promote tissue repair processes like wound healing is not in question. A good nutritional status reflects an overall healthy condition. Yet, little scientific evidence is available about the relation between nutrition and wound healing. Fortunately, in recent years more and more studies in this field are performed related to the problem of pressure ulcers (PUs).

In this chapter, after a short introduction on the relationship between nutritional status and PUs and on the general nutritional management of PU patients, attention will be paid to the assumed role of nutrients in preserving tissue viability and improving wound healing. Thereafter, the elements of adequate nutritional care as part of integrated PU-care will be discussed. Recommendations based on the most recent guidelines will be given for daily practice. Specific attention will be paid to the supplementation with high protein, arginine and micronutrients.

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M. Romanelli et al. (eds.), *Science and Practice of Pressure Ulcer Management*,
https://doi.org/10.1007/978-1-4471-7413-4_4

## Pressure Ulcers; the Possible Relation with Nutritional Status

Pressure ulcers (PUs), have affected humans in all times. They are one of the most costly and physically debilitating care problems and show a high prevalence and incidence in all health care sectors throughout the world. In addition, prevalence data are often higher in specific populations like, frail and disabled nursing home residents, patients receiving palliative care and patients in intensive care units [1–3].

PUs cause a great deal of discomfort for patients. They cause much pain, lead to a reduced quality of life, slow rehabilitation and delay hospital discharge. In addition they increase costs for hospitals, long-term care facilities and the community considerably. The cost-of-illness of pressure ulcers has been calculated to be at least 1% of the total Dutch health care budget and 4% of the UK respectively [4–7]. Therefore, addressing the overall management of PUs is nowadays a prominent national healthcare issue in many western countries.

The development of pressure ulcers depends on extrinsic and intrinsic risk factors. The most important and well known extrinsic risk factors are pressure, shear, friction and microclimate, which via complex and synergistic actions may lead to the formation of pressure ulcers. Intrinsic factors have an effect on tissue viability and consequently influence the pathophysiological response to mechanical loading and stress. Studies have found significant associations with age, sex, limited activity, care dependency, incontinence (bowel and bladder), acute disease (e.g. infection) and nutritional status. The relative influence of each of these intrinsic risk factors is still unclear [8].

Both poor nutritional intake and poor nutritional status have been shown to correlate with the development of PU as well as with protracted healing of wounds. Notwithstanding methodological shortcomings, cross-sectional and prospective studies suggest that there is a fairly strong correlation between malnutrition and the development of PUs [9–12]. Studies related to PUs have mostly focused on the relation between PUs and undernutrition and they have reported that 60–90% of PU patients are malnourished. Multivariate analysis of epidemiological data indicates that a poor nutritional status and related factors such as low body weight and poor oral food intake are independent risk factors for the development of pressure ulcers [13–15]. Moreover, many acute and chronically ill as well as elderly patients, at risk of PUs or with established PUs, suffer from undesired weight loss [16, 17]. A study from Shahin et al. 2010 studying the relationship between malnutrition parameters and pressure ulcers in German hospitals and nursing homes clearly established a significant relationship between the presence of pressure ulcers and undesired weight loss (5–10%) in hospitals and nursing homes. Inadequate and poor nutritional intake was strongly related to the presence of pressure ulcers in both health care settings as well [18]. Nonetheless, the relationship between malnutrition and PUs is likely bidirectional, being the basis of a vicious cycle. A PU is responsible for an increased inflammatory background which, in turn, causes an increase in energy requirements [19]. Accordingly, the inability of PU patients to meet protein-calorie needs is further emphasized (Fig. 4.1).

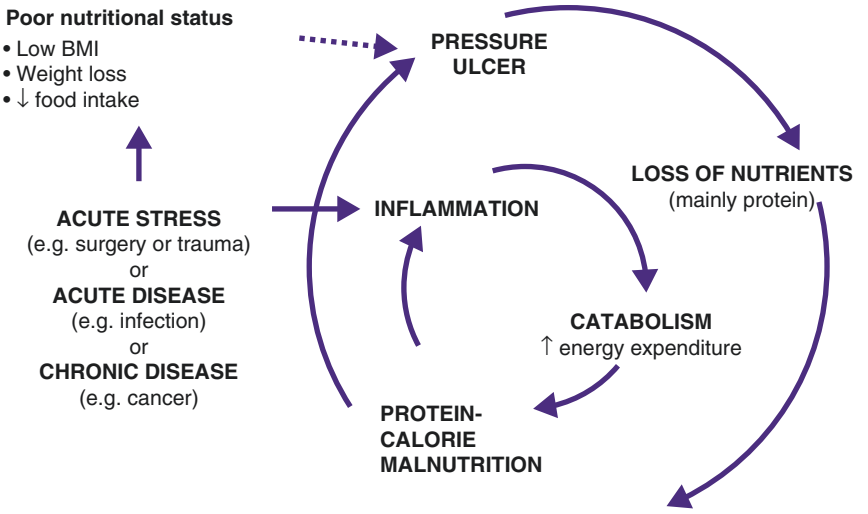


**Fig. 4.1** Inter-relationship between nutrition and pressure ulcers

Altogether, these findings underline the importance of adequate nutritional care in PU (prone) patients.

## Pressure Ulcers; Risk Assessment, Prevention and Treatment

To target PU preventive actions in the right way, risk assessment aimed at identifying susceptible patients is of utmost importance in daily clinical practice. PU risk assessment should be performed in a structured, multidisciplinary way and include activity, mobility, the skin's viability and moisture and nutritional status.

Next to clinical judgment, risk assessment can be supported by using a pressure ulcer risk assessment scale. There are several widely used risk assessment scales, such as the Waterlow pressure sore risk scale and the Braden scale, which consists of 6 items referring to sensory perception, skin moisture, activity, mobility, nutritional status and the extent of friction and shear forces [20, 21].

The advice is to incorporate one of such scales including the evaluation of the nutritional domain, structurally in the daily care process because this can can alert healthcare professionals to the possibility of pressure ulcers continuously.

## Pressure Ulcers; Prevention and Treatment in General

After establishing the risk of getting a PU or if a PU is diagnosed, preventive measures should be initiated.

Relevant preventive measures are:

– regular inspection of the skin together with the use of skin emollients to hydrate a dry skin;
– reduction of the duration and magnitude of pressure on vulnerable areas of the body by performing repositioning of at-risk patients in combination with the use of support surfaces, like mattresses seats and cushions;
– optimization of the patient's general health condition, including improvement of mobility and nutritional status.

In the case of a confirmed pressure ulcer, therapeutic measures must be taken directly, during the course of which the preventive measures remain in force.

Curative intervention consists primarily of appropriate wound care to encourage tissue repair as much as possible. In addition attention must be paid to the patient's general health status, the management of secondary infection, pain and psychosocial suffering and last but not least also to adequate nutritional care.

## Basic Aspects of Tissue Power and Wound Healing; the Assumed Role of Nutrients

To preserve tissue viability and to promote adequate wound healing, several endogenous factors play an important role, for instance the power of the body to preserve tissue homeostasis and tissue defence mechanisms including processes that generate an adequate inflammatory reaction as well as the defence response to deal adequately with acute tissue damage and to handle the subsequent bacterial burden of a wound and finally also the complex processes of tissue repair.

In this process nutrients play also a relevant role. Under here a short description of the most relevant nutrients is given.

### Calories by Carbohydrate, Fat and Protein

Carbohydrate, protein, and fat supply the energy source (kilocalories) for the body. The provision and consumption of adequate kilocalories supports collagen and nitrogen synthesis and healing and promotes anabolism by sparing protein from being used as an energy source. 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. It is also an essential part of cellular membranes, which is important for preserving tissue viability and for wound repair processes. Moreover, attention has recently being given to omega-3 essential fatty acids as potential modulators of the wound healing process [22]. Meats, fishes, eggs, dairy products, and vegetable oils represent resources of fat.

## Protein and Amino Acids

Protein is the only nutrient containing nitrogen and is composed of amino acids. Protein is important for tissue perfusion, preservation of the immune function, repair and synthesis of enzymes involved in wound healing, cell multiplication, collagen and connective tissue synthesis. Foods that provide all essential amino acids, such as meat, poultry, fish, eggs, milk products, and soybeans, are considered complete 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 32% nitrogen and has been shown to increase concentrations of hydroxyproline, which is an indicator of collagen deposition and protein in the wound site [23–25]. The role of arginine in wound healing will be described later.

## Vitamins and Minerals

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. Hence a deficiency of vitamin C may prolong the healing time and contributes to reduced resistance to infection [9]. The required daily intake of vitamin C is achieved with the consumption of fruits and vegetables. Vitamin A and Vitamin E are fat soluble vitamins and the dietary intake comes from a variety of foods. Vitamin A acts as a stimulant during the wound healing process to increase collagen formation and promote epithelisation. 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 metabolizes protein, liberates vitamin A from storage in the liver, and assists in immune function. Copper is an essential mineral for collagen cross-linking. If deficiencies are suspected, suppletion can be provided for instance via multivitamins [26–28].

## Water

Water is distributed throughout the body in our intracellular, interstitial, and intravascular compartments and serves as the transport medium for moving nutrients to the cells and removing waste products. Water constitutes 60% of an adults body, thus being the most important nutrient for life. An 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. Individuals with draining wounds, diarrhoea, elevated temperature, or increased perspiration require additional fluids to replace fluid lost. Hydration needs are met from liquids plus the water content of food [29, 30].

## Adequate Nutritional Care as Part of Integrated PU-Care

To preserve a good tissue viability and tissue repair power in PU-(prone) patients adequate nutritional care as part of integrated PU care is required.

Under here, the essentials of this required nutritional care are described including the most important specific evidence based recommendations. The latter are based upon the most recent revised international guidelines of both the National Pressure Ulcer Advisory Panel (USA) and the European Pressure Ulcer Advisory Panel (NPUAP-EPUAP 2014) in which a specific nutritional part is incorporated.

In essence, the nutritional recommendations for prevention and treatment of PUs involve:

- recommendations to follow the basic nutritional cycle to achieve tailor-made nutritional care;
- recommendations on Calorie intake, Protein intake, Hydration, Vitamins and Minerals;
- New is a specific recommendation on the supplementation with high protein, arginine and micronutrients. This will be described in a separate part of this chapter, as mentioned before.

## 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 PUs (Fig. 4.2).

## Nutritional Screening

Unless the patient has a terminal illness, undernutrition is a reversible risk factor for pressure ulcer development, making early identification and management critical. Patients at risk of pressure ulcers or with PUs in which progress towards healing is not observed, often are in danger of undernutrition. Therefore, nutritional screening in patients at risk or with a PU should be completed at admission to a health care setting but also with each condition change or if a new ulcer occurs and/or progress towards healing is delayed [23, 31–33].

Healthcare organizations should have a policy on nutritional screening. Screening tools should be easy to use, validated, and reliable for the patient population served. Validated screening tools are widely used nowadays. The Mini-Nutritional Assessment (MNA) and the MNA short form were noted in a cross-sectional study by Langkamp-Henken et al. to have an advantage over using visceral protein when screening and assessing nutritional status [34]. The MNA-SF was revised to six questions and re-validated for adults 65 and older and has a 80% sensitivity and specificity and 97% positive predictive value of impaired nutritional status according

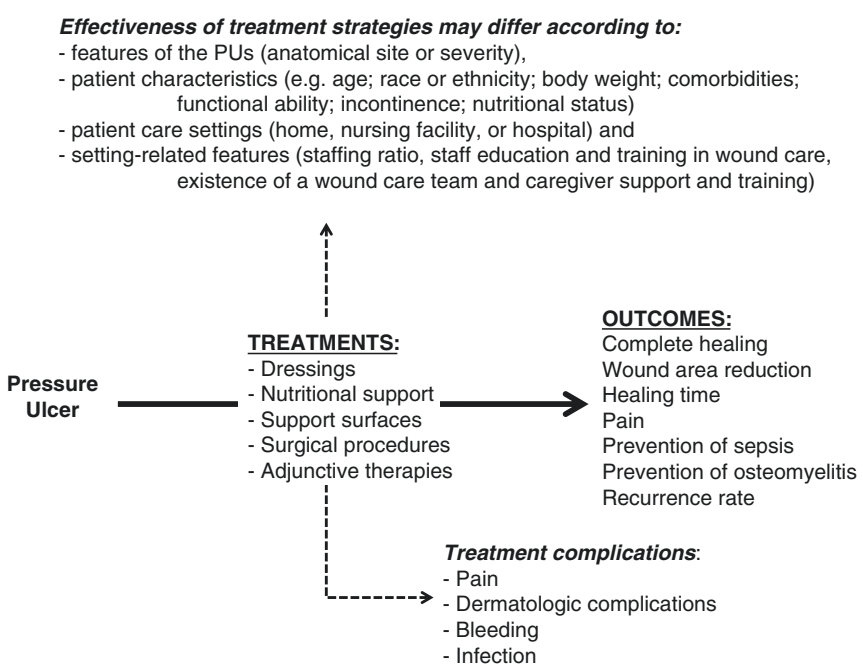


**Fig. 4.2** Workflow of treatment strategies [53]

to clinical judgement [35]. The Malnutrition Screening Tool (MUST) has been validated in acute care, long term care and the community and identifies those individuals underweight or at risk for undernutrition [36].

When the screening tool triggers nutrition as a point of necessary attention, timely referral to the appropriate professionals is critical. A subsequent nutritional assessment should be completed by a registered dietician who collaborates and communicates with the other members of the healthcare team including the speech therapist, responsible for screening, evaluating and treating swallowing problems, the occupational therapist who works to strengthen the patients' ability to feed themselves and the nursing staff whose responsibilities include monitoring the patient's acceptance of nutrition. The physician is responsible for the over-all care of the patient and ordering any treatments recommended by the team.

## Nutritional Assessment

The in-depth nutritional assessment 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, biochemical data and food-medication interactions; obtaining anthropometric measurements; and evaluation of visual signs of poor nutrition, oral status, chewing/swallowing ability, and/or diminished ability to eat independently.

Anthropometric measurements include height, weight and body mass index (BMI = weight [kg]/height [m] squared—[kg/m$^2$]). Obtaining an accurate height and weight is important, since 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. Special beds nowadays often are equipped with a device to weigh an immobile individual. The assessment of the weights status to determine the weight history and to identify significant weight loss >5% in the last 30 days or >10% in the last 180 days is very relevant because this places an individual at increased nutritional risk and has a negative effect on wound healing [37, 38]. Yet, an obese patient is also at risk for PU development and healing may be delayed when the diet consumed is inadequate in nutrients including protein. In patients unable to maintain the standing position height could be derived from knee-heel length through the use of appropriate and validated ethnic-specific equations [39, 40].

In addition a diet history should be performed to assess the adequacy of the total nutrient intake by determining the type, quantity and frequency of food usually consumed by the patient. A further nutrition focused clinical examination should explore signs of poor nutrition like changes in the hair, skin or nails, such as thin, dry hair, brittle nails or cracked lips. In addition also the patient's ability to eat normally and independently should be determined: individuals with missing or decayed teeth or ill-fitting dentures often reduce their intake of difficult to chew protein foods, thus restricting their caloric intake and increasing the chance for weight loss. Moreover, individuals with swallowing problems, dysphagia or disabilities that cause dependency on others for eating and drinking, may become dehydrated and lose weight. All these conditions may lead to an increased PU risk and can negatively affect wound healing.

Analysis of current laboratory values is also a component of the nutritional assessment, but not a very important one. Biochemical assessment data must be used with caution because values can be altered by hydration, medication, and changes in metabolism. There is not one specific laboratory test that can expressly determine an individual's nutritional status. Serum hepatic proteins including albumin, prealbumin and transferrin may not correlate with the clinical observation of nutritional status [41, 42].

Serum concentrations of these laboratory parameters may not be markers of malnutrition or caloric repletion, but instead may be indicators of morbidity severity and risk of mortality.

## Nutritional Intervention

After the nutritional assessment, an individualized nutritional care plan should be developed for patients at risk of or with a PU. Caloric, protein, fluid and vitamin/mineral requirements should be individualized and increased or decreased, depending on the assessed requirements of the patient.

The nutritional intervention strategy always tries to focus first on improving normal oral nutritional intake. Yet, despite many daily efforts on this, for instance by taking into account individual preferences on foods and drinks and by improving

mealtime ambiance, it is known that many patients with PUs cannot meet their nutritional demands via normal intake only [19]. Therefore, the incorporation of fortified foods and/or oral nutritional supplements (ONS) into the treatment plan should be determined. Fortified foods include commercial products, such as cereal, soup, cookies, or dairy products enriched with additional calories and protein or enriched menu items. When normal oral intake is inadequate, 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 [43–45]. ONS in addition to the regular diet should be preferably consumed in between meals, because then they do not affect normal intake negatively.

In any case, it is not sufficient to prescribe only. Compliance to intervention must be monitored and food and fluid intakes reviewed periodically.

## Recommendations on Calorie Intake, Protein Intake, Hydration, Vitamins and Minerals

The consistent research made in the last 15 years in the field of "nutrition and PU" has brought the incorporation into international guidelines of a chapter dedicated to the improvement of nutritional care [46]. The statements included are primarily oriented on how to adjust the intake of calories, proteins, vitamins, minerals and water in patients both having or at high risk of developing PUs. It is interesting to note that the evidence collected substantially refers to an adult population and, although pediatric patients may be at high risk of skin breakdown and nutritional derangements, high-quality research still needs to be conducted in this segment of the population. A summary of recommendations and the related strength of evidence is presented in Table 4.1.

### Energy Intake

In patients assessed to be at risk of malnutrition, nutritional intervention should be tailored to achieve an energy intake of 30–35 kcal/kg of body weight daily. This applies to both adults having or at risk of developing PUs. In any case, starting from this general statement, the provision should be individualized based on underlying medical conditions, weight changes and weight status. Those being underweight or having experienced unintended weight loss may need additional energies. Accordingly, disease-related dietary restrictions should be reconsidered under medical control when they have a negative impact on nutrients and fluid intake. In line with this, the use of fortified foods and/or high-calorie, high-protein ONS between meals should always be considered when estimate requirements are difficult to cover with oral diet. In patients at high risk of developing due to acute-stress conditions (e.g. surgery) the use of ONS has been demonstrated to reduce the occurrence of new PU of about 25% and it is strongly recommended [47].

**Table 4.1** Recommendations and strength of evidence for "Nutrition in Pressure Ulcer Prevention and Treatment" from NPUAP-EPUAP 2014 Guidelines [46]

| Statement | Strength |
|---|---|
| *Nutrition screening* | |
| – Screen nutritional status for each individual at risk of or with a pressure ulcer:<br>• at admission to a health care setting;<br>• with each significant change of clinical condition; and/or<br>• when progress toward pressure ulcer closure is not observed | C |
| – Use a valid and reliable nutrition screening tool to determine nutritional risk | C |
| – Refer individuals screened to be at risk of malnutrition and individuals with an existing pressure ulcer to a registered dietitian or an inter-professional nutrition team for a comprehensive nutrition assessment | C |
| *Nutrition assessment* | |
| – Assess the weight status of each individual to determine weight history and identify significant weight loss (≥5% in 30 days or ≥10% in 180 days) | C |
| – Assess the individual's ability to eat independently | C |
| – Assess the adequacy of total nutrient intake (food, fluid, oral supplements and enteral or parenteral nutrition) | C |
| *Care planning* | |
| – Develop an individualized nutrition care plan for individuals with or at risk of a pressure ulcer | C |
| – Follow relevant and evidence-based guidelines on nutrition and hydration for individuals who exhibit nutritional risk and who are at risk of pressure ulcers or have an existing pressure ulcer | C |
| *Energy intake* | |
| – Provide individualized energy intake based on underlying medical condition and level of activity | B |
| – Provide 30–35 kcal/kg body weight for adults at risk of a pressure ulcer who are assessed as being at risk of malnutrition | C |
| – Provide 30–35 kcal/kg body weight for adults with a pressure ulcer who are assessed as being at risk of malnutrition | B |
| – Adjust energy intake based on weight change or level of obesity. Adults who are underweight or who have had significant unintended weight loss may need additional energy intake | C |
| – Revise and modify/liberalize dietary restrictions when limitations result in decreased food and fluid intake. These adjustments should be made in consultation with a medical professional and managed by a registered dietitian whenever possible | C |
| – Offer fortified foods and/or high calorie, high protein oral nutritional supplements between meals if nutritional requirements cannot be achieved by dietary intake | B |
| – Consider enteral or parenteral nutritional support when oral intake is inadequate. This must be consistent with the individual's goals | C |
| *Protein intake* | |
| – Provide adequate protein for positive nitrogen balance for adults assessed to be at risk of a pressure ulcer | C |
| – Offer 1.25–1.5 g protein/kg body weight daily for adults at risk of a pressure ulcer who are assessed to be at risk of malnutrition when compatible with goals of care, and reassess as condition changes | C |
| – Provide adequate protein for positive nitrogen balance for adults with a pressure ulcer | B |

**Table 4.1** (continued)

| Statement | Strength |
|---|---|
| – Offer 1.25–1.5 g protein/kg body weight daily for adults with an existing pressure ulcer who are assessed to be at risk of malnutrition when compatible with goals of care, and reassess as condition changes | B |
| – Offer high calorie, high protein nutritional supplements in addition to the usual diet to adults with nutritional risk and pressure ulcer risk, if nutritional requirements cannot be achieved by dietary intake | A |
| – Assess renal function to ensure that high levels of protein are appropriate for the individual | C |
| – Supplement with high protein, arginine and micronutrients for adults with a pressure ulcer Category/Stage III or IV or multiple pressure ulcers when nutritional requirements cannot be met with traditional high calorie and protein supplements | B |
| *Hydration* | |
| – Provide and encourage adequate daily fluid intake for hydration for an individual assessed to be at risk of or with a pressure ulcer. This must be consistent with the individual's comorbid conditions and goals | C |
| – Monitor individuals for signs and symptoms of dehydration including change in weight, skin turgor, urine output, elevated serum sodium, and/or calculated serum osmolality | C |
| – Provide additional fluid for individuals with dehydration, elevated temperature, vomiting, profuse sweating, diarrhea, or heavily exuding wounds | C |
| *Vitamins and minerals* | |
| – Provide/encourage individuals assessed to be at risk of pressure ulcers to consume a balanced diet that includes good sources of vitamins and minerals | C |
| – Provide/encourage an individual assessed to be at risk of a pressure ulcer to take vitamin and mineral supplements when dietary intake is poor or deficiencies are confirmed or suspected | C |
| – Provide/encourage an individual with a pressure ulcer to consume a balanced diet that includes good sources of vitamins and minerals | B |
| – Provide/encourage an individual with a pressure ulcer to take vitamin and mineral supplements when dietary intake is poor or deficiencies are confirmed or suspected | B |

## Protein Intake

Recommendations on how to manage protein intake are incorporated into guidelines in strong connection with those pertaining energy intake. Indeed, there could be no protein anabolism and new tissue synthesis in absence of energy supply. In agreement with other international society guidelines, the advised protein target is 1.25–1.5 g/kg per day. As proteins represent the building bricks of new tissues and patients at risk of or suffering from PUs are typically of advanced age, the recommendation for 0.8 g/kg body weight for a healthy adult is considered inadequate. Again, specific restrictions associated with comorbid status should be taken into account and eventually reconsidered based on current clinical conditions. Usual diet should be improved accordingly and the use of high-calorie, high-protein ONS is strongly recommended in those not able to meet estimated requirements, particularly in presence of a high risk of developing PU due to acute-stress conditions.

### Hydration

Although recommendations are all of low-grade, water remains undoubtedly the most important nutrient being it essential for the maintenance of blood tissue flow and a cofactor for most enzymatic reactions. Minimum daily requirements are set to 30 mL/kg/day or 1 mL/kcal of energy intake. It should be considered that foods generally account only for 20% of total fluid needs. Patients with dysphagia are more likely to experience difficulties in meeting their needs. Nonetheless, daily requirements should be individualized according to comorbid conditions and the presence of factors potentially responsible for imbalance such as elevated temperature, vomiting, profuse sweating, diarrhea, or heavily exuding wounds.

### Vitamins and Minerals

As already reported, patients with PUs or at risk of developing PUs are frequently unable to meet protein-calorie requirements. Accordingly, deficits in micronutrients are more likely to occur. Oral diet should be a good source also of these and the use of supplements should always be considered when dietary intake is poor and deficiencies are confirmed or even suspected. This applies to both patients having a PU or at risk of it.

## Promising Effects of Arginine Enriched Oral Nutritional Supplements on Wound Healing

Finally, there is high-quality, high-strength evidence that specific micronutrients such as arginine, as well as zinc and antioxidants, can exert an additional benefit to PU healing. A specific recommendation has been recently included in the upcoming (2014) edition of the NPUAP-EPUAP guidelines and rated as a grade-B evidence (see Table 4.1).

However, based on recent data—adding to those previously collected—the strength is going to increase further (grade-A) as the additional value of these micronutrients is likely to be independent of that of proteins and calories. Nonetheless, these macronutrients must always be provided to promote new tissue synthesis in this category of patients that in fact should be considered malnourished by definition. Furthermore, it is noteworthy that no effect was found for each of these nutrients when provided alone and only the combination of them within a high-energy support is likely responsible for a positive effect on healing.

A preliminary suggestion for the beneficial use of nutritional formula enriched with arginine, zinc and antioxidants dates back to 2001 [48]. After that date three small randomized and controlled trials were published [49–51]. The main limitations of these studies were the small sample size, the inclusion of specific groups of patients and the lack of control for calorie and protein support among intervention groups (Table 4.2). However, the first study by Cereda et al. [50] was able to show an effect of enriched formula in patients primarily fed by enteral route, while the study by van Anholt et al. [51] demonstrated the effectiveness in non-malnourished patients.

**Table 4.2** Randomized trials evaluating the efficacy of a nutritional formula enriched with arginine, zinc and antioxidants on the healing of PUs [46]

| Study | Participants (N) | Study duration | Intervention | Endpoint | Summary of results | Limitations | Risk of bias |
|---|---|---|---|---|---|---|---|
| Benati et al. [48] | Cognitively impaired elderly inpatients (N = 16) | 2 weeks | High-protein supplement enriched with AZA vs. high-protein support vs. routine care | Pressure Ulcer Status Tool | Patient treated with the enriched formula appeared to experience higher improvement | Very small study; results were provided only graphically; short duration | High |
| Desneves et al. [49] | Inpatients (N = 16) with Stage II–IV PU | 3 weeks | Standard hospital diet + oral formula enriched with AZA vs. standard diet | PUSH score | Improved rate of healing | Very small study; sub-optimal randomization; short duration | High |
| Cereda et al. [50] | Long-term care (N = 28) residents with Stage II–IV PU of recent onset | 12 weeks | High-calorie, high-protein protein support enriched with AZA vs. high-calorie, normal-protein support | PU area and PUSH score | Difference in ulcer area significant by week 8; difference in PUSH score significant by week 12 | Small study; mainly tube-fed patients | Moderate |
| Van Anholt et al. [51] | Non-malnourished PU patients (N = 43) with a Stage III and IV PU from hospitals and long-term care | 8 weeks | High-calorie, high-protein support enriched AZA vs. non-caloric placebo | PU area, PUSH score, nursing time duration, number of dressings | Significant difference in all the endpoints considered | Small study; only non-malnourished patients able to drink ONS; control group treated with a non-caloric placebo | Moderate |
| Cereda et al. [52] | Malnourished PU patients (N = 200) with a Stage II–IV PU from long-term care or home-care services | 8 weeks | High-calorie, high-protein oral support enriched with AZA vs. an isocaloric, isonitrogenous formula | PU area, complete healing, number of dressings and wound infections | Significant difference in ulcer area | Only malnourished patients able to drink ONS; setting of care | Low |

*AZA* arginine, zinc and antioxidants, *ONS* oral nutritional supplements, *PU* pressure ulcer, *PUSH* pressure ulcer scale for healing

The shortcomings of previous studies have been recently overcome in the Oligo-Element Sore Trail (OEST) [52]. This large (N = 200) randomized (1:1), double-blind, controlled trial compared a high-calorie, high-protein nutritional formula enriched with arginine, zinc and antioxidants with an active isocaloric, isonitrogenous control formula confirming that a disease-specific support improves PU healing, with a 20% higher reduction in PU area after 8 weeks of intervention. Accordingly, although in PU patients with normal gut function and unable to meet energy needs by normal food the use of a high-calorie, high-protein support—by either oral or enteral route—is recommended, additional supplementation with specific nutrients (arginine, zinc and antioxidants) results in improved healing. The use of this formula is therefore to be considered whenever and wherever possible.

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