Nutrition therapy in the prevention and treatment of pressure ulcers

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Abstract

Pressure ulcers are serious problems within hospital and aged care settings and are associated with adverse health outcomes and high treatment costs. Because of a high incidence of pressure ulcers in the health system, attention is now being directed to not just preventing, but also more effectively treating them. Nutrition plays a fundamental part in wound healing, with malnutrition, dehydration and recent weight loss identified as independent risk factors for the development of pressure ulcers. While the optimal nutrient intake to promote wound healing is unknown, increased needs for energy, protein, zinc and vitamins A, C and E have been documented. There is reasonable evidence to show that nutritional support, mostly by high-protein oral nutritional supplements, is effective in significantly reducing the incidence of pressure ulcers in at-risk patients by 25%. Intervention studies using high-protein or specialised disease-specific nutritional supplements support a trend to increased healing of established pressure ulcers. Such specialised supplements are typically based on defined amounts of arginine, vitamin C and zinc. Mechanisms by which nutritional support can aid in pressure ulcer prevention and healing are likely related to addressing macro- and/or micro-nutrient deficiencies arising from either poor oral intake or increased nutrient requirements related to the wound healing process. With much more research still to be done in this area, nutrition support appears an efficacious and cost-effective adjunct to current medical and nursing approaches in the prevention and treatment of pressure ulcers.

Introduction

Pressure ulcers are serious and costly problems within the hospital and aged care settings. These ulcers are chronic conditions, in which the healing process is disrupted, often slowing or halting within the inflammatory or proliferative phases. Estimates of the prevalence and incidence of pressure ulcers vary, but it is recognised that high prevalence rates in both the acute and long-term settings contribute towards increased length of time spent in hospital, and increased morbidity and mortality rates [1].

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Pressure ulcers, also referred to as pressure sores, decubitus ulcers or bedsores, are defined as an area of localised damage to the skin and underlying tissue caused by pressure, shear force, friction, moisture, and/or a combination of these factors [2]. They develop from continuous pressure that affects cellular metabolism and impedes or obstructs capillary blood flow to the skin and underlying tissue, resulting in tissue ischaemia.

With aging populations and changes in the patterns of illnesses, the prevalence of pressure ulcers will escalate unless appropriate prevention, treatment and management plans are effected. The role of nutrition therapy in the prevention, treatment and management of pressure ulcers is one area that offers promise. This paper aims to review the current literature in order to assess the strength of evidence surrounding the role of nutrition therapy in the prevention and treatment of pressure ulcers.

Prevalence and incidence of pressure ulcers

Prevalence and incidence rates of pressure ulcers vary dramatically depending on the patient population and setting, as well as the definition used to categorise ulcers and the method of data collection used (e.g. direct examination of patients, patient self-reported or medical record audit); however, it is well recognised that most pressure ulcers develop within the hospital setting [3].

In Europe, the prevalence of pressure ulcers has been estimated at between 3-14%, rising to as high as 70% in elderly inpatients with orthopaedic problems [4, 5]. Incidence estimates within the European hospital setting vary between 1-5%, and increase to almost 8% in patients confined to bed or a chair for a period of time greater than 1 week [4]. Furthermore, in long-term healthcare facilities, it is estimated that 17-25% of patients will develop pressure ulcers [4,5]. In a review of articles published in the United States between 1990 and 2000, the National Pressure Ulcer Advisory Panel (NPUAP) reported pressure ulcer prevalence rates ranging from 10-18% in general acute care and up to 29% in home care [3]. Incidence rates over the same time period ranged between 0.4-38% in general acute care, 2.2-23.9% in long-term care, and 0-17% in home care patients [3]. In Australia, a state-wide point prevalence study found that 26.5% of patients in acute and subacute healthcare facilities had one or more pressure ulcers and that two-thirds of these ulcers were hospital acquired [6].

Economic and social burden of pressure ulcers

Pressure ulcers place an enormous burden on both the patient and the healthcare system, and remain costly complications of health-related care. In addition to the expensive financial costs of treating pressure ulcers, there are social costs to the individual including pain, discomfort, decreased mobility, loss of independence and social isolation [4]. Furthermore, increased death rates have been observed in elderly patients who develop pressure ulcers [7]. A recent investigation into the burden of pressure ulcer associated mortality in the United States between 1990 and 2001 found pressure ulcers were reported as a cause of death among 114,380 persons, with nearly 80% of these deaths occurring in individuals aged 75 years or more [8]. From a quality of life perspective, pain, exudate, body image, wound healing and self-imposed social isolation are all issues of concern to patients, with local and systemic infections common, contributing towards increased hospitalisation rates [4].

The economic consequences of treating pressure ulcers are substantial, with the annual cost estimated to be £750 million in the United Kingdom and US$3 billion in the United States in 2003 [9]. A recent study in Australia estimated that each year 95,695 new pressure ulcer cases arise within the Australian public hospital system, incurring a mean cost of A$285 million [10]. These costs, however, are likely an underestimate as they do not take into account additional hospital nursing time, community-based nursing and physician costs, and loss of productivity for the patient and family.

Pathophysiology of pressure ulcers

There are four main factors implicated in the pathogenesis of pressure ulcers – pressure, shear force, friction and moisture, with pressure being the most important aetiological factor [2]. The aforementioned processes can be characterised into four progressive stages which indicate the severity of the pressure ulcer (Table 1).

Pressure

When the pressure between the plane of support (such as a mattress or chair) and a bony prominence (most commonly the sacrum or coccyx, hips, buttocks, elbows or heels) exceeds that of normal arterial capillary pressure, blood flow is reduced, resulting in ischaemia and hypoxia. Following ischaemia, anaerobic cellular metabolism leads to oedema and the start of the inflammatory process with blood and lymphatic occlusion. This process leads to the arrival of phagocytes and neutral leukocytes and the release of proteolytic enzymes and growth factors. The pressure ulcer proliferation begins with endothelial tissue damage that migrates to the next layer of skin, causing granulation tissue damage (pink or red with granular appearance). This is followed by slough (a yellow or white tissue), and finally the presence of necrotic tissue.

Shear force

Shear force is generated by the motion of bone and subcutaneous tissue relative to the skin, which is restrained from moving due to frictional forces (e.g. a patient slides down a bed). This acts to substantially reduce the amount of pressure required to occlude blood flow. In elderly patients, reduced elastin in the skin predisposes them to greater susceptibility to the adverse effects of shear force.

Friction

Friction opposes the movement of one surface against another, such as when a patient is pulled across a bed sheet, or as a result of ill-fitting prosthetic devices or footwear. Such

Table 1. Classification of pressure ulcers [2].

Stage	Characteristics
I	Non-blanchable erythema of intact skin. Discolouration of the skin, warmth, oedema, induration or hardness may also be used as indicators, particularly on individuals with darker skin
II	Partial thickness skin loss involving epidermis, dermis or both. The ulcer is superficial and presents clinically as an abrasion or blister
III	Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia
IV	Extensive destruction, tissue necrosis or damage to muscle, bone, or supporting structures with or without full thickness skin loss

frictional forces may lead to the formation of intraepidermal blisters, which may lead onto superficial skin erosions, which in turn initiate or accelerate pressure ulcer development.

Moisture

An excessively moist environment increases the adverse effects of pressure, shear force and friction in the development of pressure ulcers. Furthermore, moisture, as a result of perspiration, urinary or faecal incontinence, or excessive wound drainage, causes maceration of the surrounding skin, which can exacerbate the aforementioned factors.

Risk factors for pressure ulcer development

A number of risk factors have been identified for the development of pressure ulcers. Whilst unrelieved pressure, shear force and friction are the main aetiological factors, old age, uncontrolled diabetes, sepsis, neurological and vascular disease, spinal cord damage, malnutrition and trauma are all recognised risk factors for pressure ulcer development [4].

The elderly are at an increased risk of developing pressure ulcers, with a cumulative incidence for pressure ulcers of a Stage II severity or higher being estimated at 12.9% in elderly people hospitalised for periods of up to 8 weeks for an acute event [11]. However, it is not old age itself that predisposes an individual to pressure ulcers, but rather problems common in the elderly that are associated with pressure ulceration. Hip fractures, faecal and urinary incontinence, smoking, dry skin, chronic systemic conditions, malnutrition and terminal illnesses all compound pressure ulcer development [4]. In addition to contributing towards immobility, acute or chronic illnesses increase metabolic rate and oxygen demand, thus compromising tissue healing ability [4]. Sensory impairment, due to neuropathies or spinal cord injury, can also diminish the ability to perceive pain and discomfort associated with prolonged pressure, leading to a reduced frequency of repositioning.

Malnutrition, inadequate protein or poor energy intake and recent weight loss have been identified as independent risk factors for the development of pressure ulcers [12, 13]. It has been shown that several indices of malnutrition are associated with the risk of developing pressure ulcers, with many investigators finding a relationship between wound healing and body weight, body mass index, low serum albumin and zinc and total protein levels [13-17]. Prospective studies comparing pressure ulcer development in nourished and malnourished patients show a higher incidence of pressure ulcers in the latter patients, thus arguing for a case of nutrition support in this patient group [18].

Nutrition in the prevention of pressure ulcers

Meticulous pressure care is the mainstay of prevention and treatment of pressure ulcers. And, while medical nutrition therapy is recognised as playing an important adjunct role in the prevention of pressure ulcers, there has been a lack of quality evidence-based research into this area, with current nutrition recommendations generally based on small studies and expert opinions [19].

In 2005, Stratton *et al.* [20] conducted a systematic review and meta-analysis investigating the clinical benefits of nutritional support in patients at risk of developing pressure ulcers, specifically focusing on the effects of oral and enteral nutritional support in their prevention. Five randomised control trials were included in the analysis, four investigating oral nutritional support [17, 21-23] and one investigating enteral nutritional support [24]. All trials involved elderly patients who were hospitalised for a range of serious underlying medical conditions, and nutritional support was provided (according to the randomisation allocation) regardless of the patient's current nutritional status. Oral nutrition support included either standard or high-protein supplements, while in two of the studies the supplements were also enriched with arginine [21, 22].

The analysis revealed that the provision of nutritional support (either oral or enteral) significantly reduced the incidence of pressure ulcers by approximately 26% (odds ratio 0.74, 95% CI 0.62-0.88) in high-risk patients when compared to patients receiving standard care [20]. As the studies included in the analysis were all randomised controlled trials, confidence in the findings is supported by the results of the individual trials. Whilst none of the individual study results reached the level of statistical significance, all reported a decreased incidence of pressure ulcers as a result of nutritional support, suggesting that the lack of significance was due to small sample sizes. In addition, as most of the studies were short-term (2-4 weeks), a longer timeframe would likely benefit outcomes, as restoration of nutritional status, especially in those who are malnourished, is a slow process [25]. The broad inclusion criteria of elderly patients, irrespective of their underlying medical condition or nutritional status, make the results applicable to a wider proportion of hospital and community patients considered to be at risk of pressure ulcer development.

The likely mechanisms by which nutritional support assists in the prevention of pressure ulcers is unknown; however, it is believed to be associated with an improvement in nutritional intake and therefore nutritional status [20]. An improvement in nutritional status along with associated weight gain would increase soft-tissue 'padding' over bony prominences, helping to distribute pressure on underlying tissues over a wider area, reducing the risk of blood flow occlusion. Furthermore, skin condition would be improved, increasing its resistance to the effects of pressure, shear force and friction [20]. In addition, the extra fluid consumed as a result of nutritional support may reduce the incidence of dehydration – an independent risk factor for pressure ulcer development [26].

Nutrition in the treatment of pressure ulcers

The optimal nutrient intake to promote the healing of pressure ulcers is unknown, with current recommendations based on limited studies of heterogeneous design. Energy and protein, arginine and micronutrients (vitamins A and C and zinc) are all important in the wound healing process and current recommendations tend to focus on these particular nutrients [27-30]. While it appears intuitive that these aforementioned nutrients play an important part in the wound healing process, current published research only provides limited guidance as to the optimal combination, dose and duration of these nutrients either alone or in combination. The following section attempts to provide insights as to the likely degree of benefit of these nutrients as part of a regimen of nutritional support to aid the healing of pressure ulcers.

Energy and protein

Increased energy and protein intakes are typically promoted for patients with pressure ulcers, with recent recommendations by the European Pressure Ulcer Advisory Panel (EPUAP) advocating a minimum of 30-35kcal per kg body weight per day and 1-1.5g protein per kg body weight per day [29]. These guidelines for energy and protein intake are in agreement with previously published figures of 30-35kcal/kg and 1.25-1.5g protein per kg by the Agency for Health Care Policy and Research (AHCPR) [30]. While there is a strong case to argue for additional energy and protein to aid in pressure ulcer healing, there is little in the way of definitive trials that support these recommendations, nor to provide for a graded approach to energy and protein supplementation according to the severity of the pressure ulcer, nor to assess the extent of malnutrition if present. A country-by-country review of nutrition recommendations for pressure ulcers showed a large degree of heterogeneity in recommendations for the nutritional management of pressure ulcers, though concluded that adequate energy and protein in the range specified by the EPUAP may accelerate the healing of pressure ulcers [31].

Protein is required for all stages of the wound healing process, including fibroblast proliferation, collagen synthesis, angiogenesis and immune function. Current recommendations for protein intake to promote pressure ulcer healing (when combined with adequate energy to prevent protein being used as an energy substrate) are based on achieving positive

nitrogen balance, although exact requirements are difficult to assess and are likely dependent on the severity of the wound, metabolic stress from comorbidities, as well as nitrogen losses from draining wounds and fistulae [28].

One small study involving 28 malnourished nursing home residents with existing pressure ulcers, found an improved rate of wound healing in those receiving supplemental nutritional formulas containing 24% protein over 8 weeks compared to patients randomised to formulas containing 14% protein [12]. In a subset of patients with Stage IV pressure ulcers, wound healing was correlated with dietary protein intake, but not with higher energy intakes. A similar benefit on pressure ulcer healing with higher protein intakes was seen in a small study with 12 institutionalised elderly patients who were tube-fed formula containing either 16% or 25% protein [32]. The group receiving the higher protein (equivalent to 1.8g protein per kg body weight) demonstrated close to a two-fold greater rate of healing than those randomised to lower protein (equivalent to 1.2g protein per kg body weight). Despite the small sample sizes and several methodological issues of these aforementioned studies, there appears to be a tendency for increased protein intake to improve the healing rate of pressure ulcers, though additional research is needed to support these findings.

Of interest, a recent 8-week double-blinded randomised controlled trial using a commercially available collagen protein hydrolysate supplement examined its benefit on pressure ulcer healing (as measured by PUSH tool, Pressure Ulcer Scale of Healing) in 89 long-term aged care residents with existing Stage II, III or IV pressure ulcers [33]. The nutritional supplement was given as a 45mL dose containing 15g of the collagen hydrolysate. There was a statistically significant greater improvement in PUSH score in the intervention group compared with the placebo group (60% vs 48% reduction respectively; $P<0.05$). These findings add to the rationale for higher protein intake recommendations in patients with pressure ulcers.

Arginine

There is considerable interest in the potential therapeutic role of arginine to enhance wound healing and prevent pressure ulcer development. Arginine, a dietary conditionally essential amino acid, has been shown to possess numerous unique and potentially useful pharmacologic effects [34]. Arginine functions as a substrate for protein synthesis, collagen deposition, cell proliferation, T-lymphocyte function and promotes positive nitrogen balance [35]. It is also the biological precursor for nitric oxide, which has potent vasodilatory, anti-bacterial and

angiogenic properties – all important processes in wound healing [35]. Based on normal protein intakes, habitual arginine intake of an average diet is 5-6g/day, although one study in elderly nursing home residents with pre-existing pressure ulcers reported a much lower dietary arginine intake of between 2.4-3.3g/day [36]. While arginine is not essential for normal growth and development, it is considered essential in times of metabolic stress and poor oral intake [35, 37]. As pressure ulcers can be described as chronic inflammatory conditions, and frequently exist in malnourished individuals with poor oral intake, it is thought that supplemental arginine may play an important role in pressure ulcer healing [35].

Investigations using a standardised wound model (which measured hydroxyproline synthesis in artificial wounds as an index of new collagen synthesis and deposition), found that participants supplemented with arginine at doses of 17g and 24.8g/day for 2 weeks showed a significantly enhanced rate of collagen production compared to control participants, with no reports of adverse events [38, 39]. While such studies provide an important insight to the potential role of arginine in the wound healing process, the clinical model used provides only a proxy measure of wound healing, and direct studies in a clinical setting examining pressure ulcer healing have yet to be performed using oral arginine supplementation in isolation.

Of interest, one study found that in elderly nursing home residents with existing pressure ulcers, oral arginine at doses of 8.5g or 17g/day (provided as a syrup) was orally and metabolically well tolerated [36]. The study was limited as it did not assess the size or severity of the pressure ulcer itself; however, the results were promising in the sense that arginine supplementation at pharmacologic doses were found to be well tolerated by the elderly – a high-risk group for pressure ulcers. Clinical trials in which patients with established pressure ulcers were provided with arginine in combination with other nutrients are discussed below.

Micronutrients

Numerous studies have been conducted examining the role of dietary intervention in the form of vitamin and mineral supplementation in modulating pressure ulcer development and healing. Zinc and vitamin C are two of the most commonly used nutrients in dietary interventions, as both of these nutrients play an important role in the wound healing process [28]. Vitamin C aids wound healing by increasing collagen synthesis, neutrophil function and angiogenesis [40]. Collagen production also serves to produce a barrier to pathogens. Zinc is an essential trace mineral that is required for cellular growth and replication; zinc deficiencies are thought to affect wound healing by decreasing protein and collagen synthesis [40].

A randomised controlled study published in 1974 examined the effects of ascorbic acid on the healing of pressure ulcers in 20 surgical patients [41]. In patients randomised to ascorbic acid supplementation (500mg twice daily for 1 month), there was an 84% reduction in pressure ulcer area compared to a mean reduction of 43% in the control group (P=0.005). While the results from this study were interesting, a larger-scale study involving 88 patients from nursing homes with one or more pressure ulcers randomised to 500mg ascorbic acid twice daily for 12 weeks or control (20mg ascorbic per day) could not reproduce a similar benefit on wound healing [42].

Although results from supplementation studies appear equivocal, baseline vitamin C status may be an important factor in ascribing a clinical benefit to vitamin C supplementation on wound healing, with deficient individuals potentially benefiting more from supplementation. Of note, in the aforementioned study by ter Riet [42], baseline vitamin C levels were similar in both groups of patients, and were indicative of an adequate oral vitamin C intake before commencement of the trial. As vitamin C assays are expensive and not routinely performed, and vitamin C supplementation is both cheap and presents little risk to the patient at doses up to 500mg/day, then supplementation can be recommended for most patients. The AHPCR guidelines currently recommend vitamin C supplementation at levels up to 10-times the recommended dietary allowance for those patients with suspected deficiency [30].

Unlike vitamin C supplementation which has some clinical evidence to support its use in patients with pressure ulcers, evidence for similar use of zinc supplements is considered weak [29]. Few studies of any methodological strength have been performed to support the benefit of routine zinc supplementation in the healing of pressure ulcers [40, 43]. In fact, caution has been advised against the use of high-dose zinc supplements (>40mg/day) as they have been linked to impaired copper status (which can impact on collagen cross-linking), gastrointestinal disturbances, reduced immunity and altered lipid profiles [28, 44].

Further, measurement of serum zinc levels are unhelpful as, while poor oral intake may explain a low zinc level, acute infection or inflammation (as would exist in pressure ulcer wounds) can give rise to low zinc readings as zinc is redistributed from the plasma to the liver [45]. Furthermore, as zinc is transported by albumin, low albumin levels may impact on measurable serum zinc levels. Unless overt deficiency exists, there appears little evidence or rationale for zinc supplementation in patients with pressure ulcers.

Specialised nutrition support

Although there appears a foundation for additional energy, protein, arginine, vitamin C and zinc supplementation,

the optimal mix of nutrients to promote the healing of pressure ulcers is unknown. The role of nutrition support in patients with existing pressure ulcers using disease-specific formulations is an emerging area of interest, and perhaps provides the greatest insight into potential nutrition interventions that may be effective in accelerating pressure ulcer healing.

Five studies to date have been published that have evaluated the efficacy of enteral nutrition support on the healing of existing pressure ulcers versus routine care [5, 17, 46-48]. A randomised controlled trial of 495 elderly long-term care patients (14.1% with existing pressure ulcers) investigated the effect of nutritional support (200mL liquid supplement twice daily; providing in total 16g protein, 16g lipid and 1680kJ) on the development and healing of pressure ulcers over 26 weeks [17]. In the intervention group, 51% of ulcers healed and 42% were improved, compared with 30 and 41% respectively in those patients receiving routine care, although none of the differences reached statistical significance. However, the results from the study provided some suggestive evidence for a role of nutrition support in pressure ulcer healing.

Of the additional four published studies, all shared the commonality of evaluating specialised disease-specific nutrition supplements containing supplemental arginine at up to 9g per day [5, 46-48]. A controlled trial of 39 patients with a Stage III or IV pressure ulcer given an oral supplement containing arginine, vitamin C and zinc (mean intake 5.7g arginine, 475mg vitamin C and 17.1mg zinc) for 3 weeks found a 29% reduction in median wound area, and a decrease in necrotic tissue and exudate [46]. However, a major deficiency of the trial was the absence of a control group, with healing rates compared against historical controls from studies investigating the effect of dressing types or supplemental protein on wound healing. While the results are interesting and appeared to show a greater benefit in wound reduction when compared to the rate of wound healing from different historical control groups, it was not possible to ascribe a defined benefit to the nutritional supplement due to the lack of randomisation and the issue of no appropriate comparable control group.

A study of similar design (open label, non-randomised and no placebo group) in 245 patients with Stage II, III or IV pressure ulcers and using the same nutritional supplement as used in the prior study, found a statistically significant 53% reduction in pressure ulcer area after 9 weeks [47]. Again, lack of any comparable control group makes the interpretation of the study's findings difficult.

Two studies of similar design provide the best available evidence so far for specialised nutritional support in the healing of pressure ulcers. Studies by Benati *et al.* [5] and Desneves *et al.* [48] evaluated a defined arginine, zinc and vitamin C containing nutritional supplement against routine care or traditional nutritional support.

The study by Benati *et al.* used a pressure sore status tool to track changes in pressure ulcer healing of 16 inpatients with severe cognitive impairment who were randomised to oral nutrition support or a control diet for 2 weeks. Results from the study were only presented in graphical form, with the authors concluding that there was a "tendency of improving wound healing" in patients randomised to nutrition support, with the greatest benefit seen in those patients randomised to the specialised nutritional supplement with additional arginine (7.5g/day), zinc (25mg/day) and antioxidants. However, the study had many deficiencies with a lack of reporting in the paper of the staging of the pressure ulcers, nutritional compliance, anthropometric data and exclusion criteria. Furthermore, the timeframe of the study of 2 weeks was unlikely to be expected to be able to show clinically significant improvements in wound healing.

The final study examining a role for specialised nutritional support in the healing of pressure ulcers used a similar study design to that of Benati *et al.* [5] and examined the role of an oral supplement containing arginine, vitamin C and zinc (providing in total 21g protein, 2100kJ, 9g arginine, 500mg vitamin C and 30mg zinc), against a traditional nutritional supplement (providing in total 18g protein, 2100kJ, 72mg vitamin C and 7.5mg zinc), or a standard hospital diet for a period of 3 weeks [48].

Sixteen patients with Stage II, III or IV pressure ulcers were randomised to the three dietary treatment groups. Only patients receiving additional arginine, vitamin C and zinc demonstrated a clinically significant improvement in pressure ulcer healing, with a reported 2.5-fold statistically significant greater rate of healing as assessed by the PUSH tool. Interestingly, in terms of dietary intake of both the hospital diet only and nutritional supplement groups, there were no differences in intake between the groups in terms of protein and energy, with the only significant difference being a greater arginine, vitamin C and zinc intake in those patients receiving the specialised nutritional supplement. There were also no significant changes in weight or biochemical markers in any group, while all patient groups presented with low serum albumin and zinc and elevated C-reactive protein levels.

With much more research still to be done in this area, results from these initial studies using specialised nutritional supplements look promising considering the strong biochemical rationale for supplemental arginine, vitamin C and zinc in patients with pressure ulcers.

Future directions

Despite the limited research to date, pressure ulcers represent the most well-studied chronic wound model when evaluating the efficacy of nutrition in the prevention and management of wounds. Unlike pressure ulcers where a rationale for dietary recommendations to assist healing has some clinically relevant published studies to support them, there is a dearth of nutritional intervention studies lending support for nutritional supplementation in the treatment of diabetic foot ulcers. Diabetic foot ulcers, particularly neuroischaemic foot ulcers, have some similarities in their aetiology and pathogenesis to pressure ulcers, hence this area of nutrition research could benefit from further investigation.

Diabetic foot ulcers are a common consequence of diabetes; they occur as a result of the vascular and neurological complications associated with the disease [49], as well as opportunistic infections and inadequate wound healing [50]. The most recent prevalence estimates suggest that between 4-10% of individuals with diabetes have foot ulcers [49].

In diabetes, nitric oxide synthesis is reduced in the wound environment and, as arginine is the only substrate for nitric oxide synthesis, it has been hypothesised that arginine supplementation could enhance wound healing by augmenting nitric oxide production [51, 52]. While the effect of arginine supplementation on wound healing in diabetes has mostly been studied in diabetic rodent models, initial results appear promising [51, 53, 54]. These rodent studies using artificial wounds as a model of healing have typically used arginine doses at the level of 1g per kg body weight per day which resulted in greater collagen production and wound tensile strength in animals rendered diabetic, with a concomitant restoration of nitric oxide levels to normal levels.

Little in the way of human studies using clinically relevant models examining the effect of arginine supplementation on diabetic foot ulcers have been conducted. While not constituting an oral supplementation study, a pilot study using a topical arginine preparation has shown improved blood flow and temperature to the feet of individuals with diabetes, though it is unclear if this translates into reduced foot ulcers or improved healing of existing ulcers [55]. One study of 33 patients with diabetes and existing foot ulcers found that, of the 11 patients randomised to receive 10mM arginine subcutaneously daily at the site of the wound, eight reached full wound healing and three demonstrated close to full healing, while those not treated with arginine showed a deterioration of their ulcer with several requiring some form of lower-limb amputation [56]. Because of the defined diet-disease relationship and some promising preliminary studies, randomised controlled trials examining oral arginine supplementation or even subcutaneous arginine injection at the site of the wound in the healing of diabetic foot ulcers would be of great interest.

Conclusion

Mechanisms by which nutritional support can aid in pressure ulcer prevention and healing are likely related to addressing macro- and/or micro-nutrient deficiencies arising from either poor oral intake or increased nutrient requirements related to the wound healing process. There is reasonable evidence to show that nutritional support, mostly by high-protein oral nutritional supplements, is effective in reducing the incidence of pressure ulcers in at-risk patients. Results from intervention studies using specialised nutritional supplements support a trend to increased healing of pressure ulcers using disease-specific formulas.

While current studies are limited in sample size and heterogenous study design, the possibility of significantly enhanced pressure ulcer healing using defined amounts of arginine, vitamin C and zinc appears to exist, although confirmatory studies are required to support current clinical evidence. Novel and effective treatments that can reduce the severity and incidence of pressure ulcers would be of great benefit in improving the quality of care for many patients. A 'nutrition solution' that is cheap, safe and efficacious would be an ideal adjunct to current medical and nursing approaches in the prevention and treatment of pressure ulcers.

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