The Role of Nutrition in the Management of Lower Extremity Wounds

Girish K. Patel
Department of Dermatology, University of Wales College of Medicine, Heath Park, Cardiff, UK

From 3000 BC, healers have understood the importance of nutrition in wound care and used nutritional supplements to aid healing. Many of the teachings from Hippocrates, the father of modern-day medicine, clearly state his firm belief that good health can be achieved through nutrition. In the early 1900s when advances in biochemistry were frequent, many of the essential constituents of nutrition were characterized, which formed the basis for many animal and human wound-healing experiments. This led to the discovery of vitamin C, zinc, and many other components essential for the orderly progression of healing. Modern-day research has concentrated on finding nutritional components that can enhance healing through supra-physiological doses, such as in the use of the amino acids arginine and carnitine. However, clinicians need to be aware that approximately 50% of patients admitted to the hospital are malnourished, requiring dietary supplementation; appropriate nutritional assessment and advice therefore should be an integral part of all wound management. This review provides an up-to-date commentary on the role of nutrition in wound care, with specific emphasis on lower limb wounds, from a historical perspective, and within it both the biomedical approach and current herbalist practices are considered.

Key words: wound healing, nutrition, ulcer and lower extremity wounds

The skin is the largest organ in the body; to maintain its structure and function, it requires a constant supply of metabolites that are directly derived from known nutrients. Many of the nutritional deficiency syndromes present with alterations in skin, some of which are associated with loss of skin integrity, and promote the presence of wounds. Wound healing per se is a complex process, involving hemostasis, inflammation, tissue proliferation, and remodeling, coordinated by multiple cytokines and growth factors, which are associated with increased metabolic activity. These processes are dependent on adequate tissue oxygenation, metabolic energy, protein synthesis, and multiple enzymatic reactions involving trace elements and vitamins.

Correspondence should be sent to: Dr Girish K. Patel, Honorary Clinical Tutor, Department of Dermatology, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN; e-mail: patelgk@cf.ac.uk.

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A holistic model of wound care should pay careful consideration to the nutritional requirements of all patients. Ideally, a dietician should assess all patients with wounds. Many observers have identified calorie, protein, vitamin, and essential minerals deficiencies among patients admitted to the hospital, many of whom have ongoing wounds or are about to undergo surgery.[1,2] Managing any deficiencies detected and then optimizing patients' nutrition with supplements may make the desired difference.

Our understanding of nutrition in wound healing is very far from complete. As science strives to understand the genome, it has yet to unravel the mysteries of the proteome, or the cellular metabolome; it is only by this approach that the importance of nutrition in wound healing can be unveiled.

HISTORICAL PERSPECTIVE

The translated works of Hippocrates (circa 30 BC) state that nutrition is important for maintaining health.[3] In the 1900s, during a period of rapid biochemical breakthrough, scientists identified many nutritional compounds essential for health. This also led to the discovery of many nutritional components essential for normal wound healing. In one of the earliest experiments in wound healing, Thompson et al demonstrated a tendency for wound dehiscence associated with diet-induced hypoproteinemia using a dog model of surgical wound repair.[4] Among the many advances that came during this period, the story pertaining to vitamin C is probably the most remarkable, as briefly outlined below.

Among the first descriptions of vitamin C deficiency, scurvy, came from the Portuguese sailor Vasco da Gama while traveling around the tip of Africa in 1498. Vasco da Gama observed swelling of the hands, feet, and gums among many of the sailors. The illness disappeared rapidly after the ship came ashore and the crew were able to consume fruits, including oranges. However, upon sailing again, the sickness reappeared after 10 weeks, this time causing old wounds to reopen, eventually leading to death. He wrote down that the ill sailors requested oranges. Indeed, Sir James Lancaster took bottles of lemon juice to prevent scurvy during his voyage to the East Indies in 1601.

In 1747, the Scottish physician James Lind conducted the first clinical trial among patients with scurvy and observed the rapid and dramatic effects of citrus fruit. Lind concluded that citrus fruits were the "most effectual remedies for distemper at sea."[5] Despite this and the efforts of Sir Gilbert Blane, it took the Admiralty until 1795 to approve taking citrus fruits for long sea voyages. The incidence of scurvy declined dramatically, flaring occasionally during the Great Potato Famine and the First World War.

Attempts to reproduce scurvy in an animal model were successful in 1907, when Axel Holst and Theodor Frölich developed the guinea pig model and showed that scurvy was a disorder of dietary deficiency. In 1912, the Polish Chemist Casimir Funk described the importance of certain nitrogen-containing compounds with an amine structure, which he called "vitamins," short for vital amines. Although the name *vitamins* has persisted, not all vitamins proved to be amines. In 1927, the Hungarian scientist Albert Szent-Györgyi unknowingly isolated vitamin C from oranges and cabbages. He later proved that the substance was in fact vitamin C and reported its effectiveness in preventing scurvy in guinea pigs.[6]

In 1939, Dr John Crandon investigated the effects of vitamin C deficiency on wound healing on himself. After 182 days abstaining from vitamin C, an old appendectomy scar began to disintegrate and a newly formed wound failed to heal, thus confirming the importance of vitamin C deficiency in wound healing.[7,8] It is now known that vitamin C is a specific cosubstrate for the enzymes 4-hydroxylase and lysyl hydroxylase, which are important in collagen synthesis.[9]

NUTRITIONAL NEEDS DURING WOUND HEALING

The nutritional requirements during wound healing may be considered on the basis of energy production (carbohydrates, fats, and occasionally proteins), protein synthesis and degradation (including amino acids), vitamins, and trace elements. However, the needs change over the course of the wound-healing process. Immediately after trauma, sepsis, and/or surgery, there is a hypercatabolic response that is then followed by an anabolic phase. Nutritional support should strive to minimize the effects of catabolism and meet the needs of the anabolic phase, preferably through the more effective enteral route.

Carbohydrates

Carbohydrates are composed of sugars, either as monosaccharides (single sugar units with the general formula $(CH_2O)_n$, where n is usually from 3 to 8) or polysaccharides (multiple sugar units combined together by a covalent glycosidic bond). Carbohydrates represent an important source of energy readily available for the body (Table 1). Ingested carbohydrates in our foods are broken down by the process of digestion, into smaller sugar subunits that are rapidly absorbed from the gut and taken up by the liver. In the liver, sugars are stored as simple polysaccharides, such as glycogen, which is composed of glucose. Thus, glycogen is a source of stored energy, which is rapidly converted to glucose on demand.

Monosaccharides released into the blood stream are able to enter the cell cytosol via a cell membrane transport receptor. Once in the blood stream, they convert into 2 pyruvates and energy, in the form of adenosine triphosphate and nicotinamide adenine dinucleotide phosphate, through a series of reactions called the glycolysis pathway. Furthermore, pyruvates pass into the mitochondria where they are converted into carbon dioxide, an acetyl group, and more energy. The resultant acetyl group binds to coenzyme A to form acetyl coenzyme A, which is a component of the citric acid cycle. The study of carbohydrates in wound healing has focused on the energy requirements for collagen synthesis and the adverse effect of diabetes.

The main determinant of energy requirement in an uncomplicated wound is assumed to be from collagen synthesis. Reducing the calorie intake can have detri-

Table 1. Energy Requirements for UK Adults

	Male (kcal/day)	Female (kcal/day)
<50 years old	2750-2550	2100-1900
>50 years old	2500-2100	1900-1810

NOTE: The energy requirement for a given individual should be adjusted for stress and activity.

mental effects on collagen synthesis, configuration, deposition, and remodeling.[10] It is estimated that 900 calories are required for each gram of collagen synthesis.[11] Thus, a wound 3 cm^2 in surface area and 1 mm depth would contain 10 mg of collagen and so require at least 9 Kcal. Hence, it is only large complicated wounds with the presence of a catabolic state (eg, burn injury or septicemia) that are likely to have a direct metabolic impact on energy requirements.

The impaired healing in diabetes is associated with a damped inflammatory response; this observation has both early and late features. Early in the wound-healing process, there is a reduced inflammatory response associated with a decreased leukocyte chemotaxis, thought to be caused by hyperglycemia leading to competitive inhibition of ascorbic acid membrane transport within inflammatory cells.[12] The impaired inflammatory response is associated with an increased incidence of wound infection.[13] During the later proliferative phase of wound healing, there is reduced fibroplasia, re-epithelialization, and endothelial activation.[14] The administration of ascorbic acid at the onset can reverse some of these effects; however, the most important dietary contribution to the management of wound care in diabetes is glucose control.[12,15]

Sugars are not only sources of energy. They can be covalently linked to lipids, glycolipids, or proteins to form glycoproteins. Glycolipids and glycoproteins are a fundamental component of the cell membrane.

Fats

Fats are composed of various fatty acids. Fatty acids molecules consist of a long hydrocarbon chain (which is hydrophobic) and an acidic carboxyl group (which is extremely hydrophilic and reactive). Almost all fatty acids in cells are covalently linked to other molecules through their carboxylic acid group. Fatty acids are either saturated, if they have no double bonds between the carbon atoms, or unsaturated because of the presence of double bonds between carbon atoms. The presence of a double bond creates a kink within the hydrocarbon tail, which prevents unsaturated fatty acids from being so closely packed together.

The fats in food are digested into fatty acids, which are readily absorbed through the gastrointestinal mucosa by binding to membrane-associated lipoproteins. These are then transported to the liver via the portal circulation coupled to various proteins and converted to triplets called triglycerides. Triglycerides are then stored in the body's fatty areas within lipocytes. Triglycerides become liberated into the circulation when there is a need for a sustained energy source. Triglycerides enter into the cell by endocytosis and are converted to fatty acids. Within the mitochondria, fatty acids combine with coenzyme A to form fatty acyl CoA, which is utilized within the citric acid cycle to provide aerobic cellular energy. Each fatty acid is able to produce 6 times more energy than the equivalent glucose.

In addition, fatty acids are also constituents of the cell membrane and hormones and are mediators of inflammation. The importance of essential fatty acids was elucidated by Burr and Burr in 1929, who showed that rats fed a fat-free diet developed scaly skin and tail necrosis,[16,17] a phenotype that could be reversed by linoleic acid.[18] Linoleic acid cannot be synthesized from other dietary constituents and in the body is converted to arachidonic acid, which is used to synthesize leucotrienes and prostaglandins; absence of linoleic acid selectively inhibits prostaglandin synthesis.[19] Studies on humans conducted at the outset of parenteral feeding revealed that an absence of linoleic acid from the diet results in serum values falling below detectable levels within 2 weeks; however, clinical features take between 2 and 7 months to develop.[18] The typical skin findings were diffuse erythema, dryness, and scaling, with disruption of the skin barrier function. Caldwell observed an increase in capillary fragility, brittle nails, and impaired wound healing.[20] Hulsey also found delayed healing of partial thickness burn wounds.[21] These findings were confirmed in a study of full thickness wounds, which showed that topically applied arachidonic acid could reverse the effects on healing.[22]

More recently, studies have examined the role of omega 3 fatty acids supplementation, which has anti-inflammatory properties through modulating the arachidonic acid pathway.[23] The use of omega 3 supplementation has gained favor among patients with ischemic heart disease; however, diets rich in omega 3 fatty acids are associated with impaired wound healing.[24] Diets rich in omega 3 fatty acids are associated with wounds with reduced tensile strength in rats; this effect is most pronounced after the wound has healed and may be related to an adverse effect on wound maturation.[24]

Proteins

Proteins are composed of amino acids (Table 2). Amino acids are characterized by the presence of a carboxyl and an amino group that are bound to a single carbon atom (called the alpha-carbon). The chemical variety comes from additional side chains attached to the alpha-carbon; in mammals, there are 20 common amino acids. Humans have lost the ability to make essential amino acids, through evolution, and rely upon consumption of organisms that continue to make them. Nine of these essential amino acids that cannot be synthesized from other dietary ingredients are threonine, methionine, lysine, valine, leucine, isoleucine, histidine, phenylalanine, and tryptophan. Amino acids join head to tail, by a peptide bond, to form peptides; longer peptide chains are called polypeptides or proteins. The presence of amino acid side chains and the differing ends of the protein give rise to differing polarities and unique 3-dimensional structure.

Collagen is the major structural protein in animals; about one third of the body's protein is collagen. Almost three quarters of the protein in the skin is collagen. Collagen imparts tensile strength and flexibility to the skin. Hence, it is arguable that collagen defects provide the molecular explanation for several types of skin conditions, including nutritional deficiencies.

Proteins are maintained in a constant state of turnover; their degradation results in nitrogen excretion, which can be measured. Thus, the quantity of nitrogen in proteins can be calculated and compared to that excreted, the nitrogen balance. In a surgical or burn wound setting, nitrogen balance during the first 4 weeks can be used to evaluate the total protein requirement; though for greater accuracy, losses based on the size of the open wound should also be included in the assessment[25]:

<10% body surface area = 0.02 g nitrogen/Kg/day
10%-30% body surface area = 0.05 g nitrogen/Kg/day
>30% body surface area = 0.12 g nitrogen/Kg/day

In rodent experiments on severe protein malnutrition, wounds were associated with increased risk of infection, decreased collagen deposition, and reduced tensile strength.[26,27] Although essential amino acid deficiency is uncommon, researchers have recently investigated the potential benefits of super-physiological doses of specific amino acids to enhance wound healing.[28,29] The 2 amino acids that have shown most promise are arginine and glutamine.

Arginine is a precursor for proline during collagen synthesis, and after injury there is a rapid decrease in the body stores.[30] It is important in maintaining positive nitrogen balance, stimulating T lymphocyte function, release of growth factors, and generation of nitric oxide.[31] Two studies to date have studied the effects of arginine supplementation (17-25 g/day) in human wound healing and noted increased collagen deposition in adults and elderly.[28,29]

Table 2. Protein Requirements for UK Adults

	Males (g/day)	Females (g/day)
Adult	55-53	45-46

Glutamine is important in gluconeogenesis and an important precursor for the synthesis of nucleotides. In vitro and in vivo animal studies show that it is able to enhance neutrophil killing and stimulate the release of growth hormones, and it is a potent antioxidant (in the glutathione form).[32] Supplemental glutamine has been advocated for the treatment of wounds[33]; however, the true benefit remains to be established.[34]

Vitamins

As mentioned earlier, the term *vitamins* was a misnomer, first proposed by the Polish Chemist Casimir Funk upon discovery of vitamin C in 1911 (Table 3). These fundamental compounds cannot be synthesized de novo by humans. Although there is limited synthesis of vitamin-like nutrients, they too are derived mostly from the diet. Vitamins are classically subdivided into water-soluble vitamins (thiamine [B_1], riboflavin [B_2], pyridoxine [B_6], nicotinic acid, pantothenic acid, biotin, folic acid, B_{12}, and C), fat-soluble vitamins (A, D, E, and K), and vitamin-like nutrients (inositol, choline, carnitine, alpha lipoic acid, and coenzyme Q; Table 4). Water-soluble vitamins and vitamin-like nutrients are important constituents of coenzymes, whereas the function of fat-soluble vitamins is more varied. In an individual with malnutrition, supplementation with all the vitamins and vitamin-like nutrients should be considered as important. In addition to the extensive description of vitamin C in wound healing, studies have identified a significant and potential therapeutic role for vitamins A, E, and K.

Vitamin A has 3 forms within the body. The alcohol form, retinal, can be reversibly oxidized to retinal and the isomeric irreversible aldehyde retinoic acid (which can present as 9-cis retinoic acid or 13-cis retinoic acid). Each metabolite has a specific receptor, and this may explain why vitamin A has many functions within the body. Retinal, which is also isomeric, is converted

Table 3. Vitamins Are Essential Dietary Compounds That Serve Multiple Different Processes Within the Body. They Can Be Subdivided Into Water or Fat Soluble

Vitamin	Type	Physiology	Disease	Recommended Daily Dietary Supplement
Thiamine [Vitamin B_1]	Water soluble	Thiamine pyrophosphate is the essential coenzyme involved in the actions of enzymes that catalyze cleavage by decarboxylation, in particular, alpha-ketoacids such as pyruvate during carbohydrate metabolism.	Deficiency causes beri-beri, which may manifest with weakness, constipation, peripheral neuropathy, depression, and cardiomyopathy	Male 0.9-1.1 mg/day Female 0.8 mg/day
Riboflavin [Vitamin B_2]	Water soluble	Vitamin B_2 is incorporated into the redox coenzymes, referred to as flavoproteins, flavin adenine mononucleotide, and flavin adenine dinucleotide. These coenzymes participate in dehydrogenation, oxygenation, and oxidization of a variety of substrates including glucose, amino acids, and fatty acids.	Deficiency causes photophobia, angular stomatitis, chelitis, glossitis, and anemia	Male = 1.3 mg/day Female = 1.1 mg/day
Niacin and nicotinamide [Vitamin B_3]	Water soluble	Nicotinamide gives rise to 2 coenzymatic forms, nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$), which are important reducing agents. NAD^+ and $NADP^+$ are essential electron carriers within the mitochondrial respiratory chain. Niacin is able to cause peripheral vasodilatation and reduce very-low-density lipoprotein synthesis.	Deficiency results in pellagra, which is characterized by diarrhea, dermatitis, and dementia	Male = 16-18 mg/day Female = 12-14 mg/day
Pantothenic acid [Vitamin B_5]	Water soluble	Pantothenic acid is an important component of coenzyme A, thus has a central function in the citric acid cycle.	Deficiency is exceptionally rare	Adult = 5 mg/day
Pyridoxine, pyridoxal, pyridoxamine, and their phosphates [Vitamin B_6]	Water soluble	Vitamin B_6 is an important component of more than 100 coenzymes. Each of these coenzymes is itself able to participate in many reactions, for example, pyridoxal-5-phosphate is involved in many reactions involving amino acids including decarboxylation, racemization, elimination, and aldolization.	Vitamin B_6 deficiency is rare; in adults it presents with normocytic anemia	Male = 1.5-1.4 mg/day Female = 1.2 mg/day
Biotin	Water soluble	Biotin is the essential coenzyme for carboxylation involving bicarbonate as the carboxylation agent.	Deficiency may resemble zinc deficiency; in addition, there is neurological disturbance	Adult = 30 µg/day

(continued)

Table 3 (continued)

Vitamin	Type	Physiology	Disease	Recommended Daily Dietary Supplement
Folic acid	Water soluble	Folic acid is essential for the formation of tetrahydrofolate and its derivatives, which act as substrates to maintain formaldehyde and formate in nontoxic forms.	Pernicious anemia	Male = 200 µg/day Female = 200 µg/day
Cobalamin [Vitamin B_{12}]	Water soluble	Vitamin B_{12} is essential for hematopoiesis, myelination of nerves, and nucleic acid synthesis. The coenzymes are able to transfer methyl groups.	Pernicious anemia	Male = 1.5 µg/day Female = 1.5 µg/day
Ascorbic acid [Vitamin C]	Water soluble	Vitamin C is a major antioxidant and is involved in protein synthesis.	Scurvy	Male = 40 µg/day Female = 40 µg/day
Vitamin A	Fat soluble	Retinoic acid (a derivative of vitamin A) is an important skin developmental hormone.	Hypo-vitaminosis A is characterized by severe xerophthalmia, follicular papules, xerosis of mucous membranes	Male = 700 µg/day Female = 600 µg/day
Vitamin D	Fat soluble	Vitamin D_3 has an important role in calcium homeostasis.	Osteomalacia	Individuals over 65 years = 10 µg/day
Vitamin E	Fat soluble	This is an important antioxidant, in particular, protecting against lipid oxidation.	Deficiency causes disorders of reproduction, hemolysis, spinocerebellar disease, capillary leakage, and cardiomyopathy	Individuals = 12-30 IU/day
Vitamin K	Fat soluble	Vitamin K is necessary for the synthesis of 4 plasma proteins, 2 thrombotic factors (protein C and protein S), and bone matrix proteins (osteocalcin and matrix Gla-protein).	Hemorrhagic disease in newborn	Adults 65-80 µg/day

from trans-retinal to cis-retinal upon exposure to light. This in turn results in a conformational change in rhodopsin within the rod photoreceptor of the eye and initiation of a visual response. Hence, retinal is important for vision, in particular, night vision.

In the skin, the retinoic acid form of vitamin A is necessary for normal growth and differentiation of the skin epidermis. Within the epidermal cells, retinoic acid isomers are able to bind to intracellular retinoic acid receptors (α, β, and γ) as well as the retinoid X receptors. Retinoid receptors activation results in a change in the cellular response to extracellular signaling pathways, involving prostaglandins, vitamin D, thyroid hormone, and corticosteroids. Hence, supplemental vitamin A has been shown to improve wound healing in dietary deficiency[35,36] but also by moderating the adverse effects of corticosteroids,[37,38] cyclophosphamide,[39] irradiation,[36] and diabetes.[40] In these latter situations, the improved wound healing observed with the addition of vitamin A has been associated with an increase in collagen deposition and macrophage influx and activation. In vitro studies that examined the effect of adding vitamin A into fibroblast culture have demonstrated increased collagen synthesis and epidermal growth factor receptor expression, respectively. In severe injury, which is often associated with a hypercortisolemic state, it has been suggested prophylactic daily treatment, vitamin A 25,000 IU, can help wound healing.[41,42]

Table 4. Other Compounds Important for Homeostasis and Dependent on Dietary Intake at Times of High Utilization

Inositol	Is essential in the metabolism of phosphatidylinositol, which provides structural support to membranes
Choline	Choline is a component of lecithin, an important constituent of plasma membranes
Carnitine	Carnitine is important in shuttling long-chain fatty acids into the mitochondria
Alpha lipoic acid	Alpha lipoic acid is a coenzyme within the Kreb cycle and a potent antioxidant
Coenzyme Q	This is an essential component of the mitochondrial electron transport chain and is therefore important in cellular energy production

The potential benefits of improving wound healing through supplemental doses of vitamins D, E, and K over and above their requirements for homeostasis remains to be determined. Vitamin E maintains and stabilizes membrane integrity. In addition, vitamin E is reported to protect against oxidative stress, an effect that may be deemed beneficial for the management of lower leg ulcers caused by primary inflammatory diseases, for example, pyoderma gangrenosum.[39,42] However, results with supplemental vitamin E in conventional wound-healing studies have failed to demonstrate benefit; therefore, its role remains unclear. Vitamin K is an essential nutrient for the production of coagulation factors II, VII, IX, and X. These clotting factors are essential in thrombus formation; deficiency is associated with a propensity for hemorrhage. However, supplemental treatments, beyond maintaining homeostasis, have not proven beneficial in wound healing.

Trace Elements

In addition to the vitamins, a number of inorganic compounds are essential for maintaining skin integrity and are potential therapeutics for lower extremity wounds. Often very small amounts are required for homeostasis (Table 5); in addition to the detrimental effects of dietary deficiency, dietary excess can be harmful.

Zinc is one of the oldest medicinal treatments known; it is described in Egyptian papyrus tablets more than 3000 years old for topical treatment of skin disease. In 1934, Todd et al realized zinc was essential for the normal reproduction, development, and growth of rats.[43] Zinc metalloenzymes, of which there are more than 50 examples in mammals, are involved in synthesis of DNA and RNA. Six zinc-based enzymes are involved in glycolysis. Zinc is essential for the normal maturation of the epidermis, a process referred to as terminal differentiation.[44,45] Moynahan and Barnes in 1973 described a congenital disorder caused by zinc deficiency, acrodermatitis entropathica, characterized by a reversible triad consisting of dermatitis, diarrhea, and alopecia.[46]

Zinc deficiency is reported to delay wound healing.[47] In original studies on postsurgical wounds following pilonidal sinus excision, patients treated with zinc supplementation healed faster.[48] However, studies in animals failed to demonstrate improved wound healing with zinc-supplemented diets.[49] Despite this, advocates suggest zinc supplementation should be used preoperatively even in otherwise normal individuals to accelerate wound healing after surgery.[50] Human studies in lower leg ulceration treated with zinc supplementation have yielded conflicting results.[51-53] A recent systematic Cochrane review concluded that in the absence of low serum zinc, zinc supplementation offers no benefits to the healing of venous/ischemic leg ulcers.[54] Determination of serum zinc levels made with great care to avoid sample contamination and hence false positive results may reveal zinc deficiency and hence help to preselect those who may benefit from zinc supplementation.[55]

Magnesium is a cofactor for many enzymatic reactions, including collagen synthesis, an assay that is often used to assess wound healing.[39] Similarly, copper is a cofactor in protein synthesis, and it too may be deemed essential for wound healing.[40] Iron is required for hydroxylation of proline and lysine; both amino acids are essential for collagen synthesis. It is likely that many other trace elements are involved in wound healing. However, it remains to be determined if supplemental doses can enhance healing.

Herbal Remedies

In 1996, sales of dietary "herbal" supplements rose by 9% over the previous year and reached over £5 billion.[56] Herbal alternative therapies are common, particularly among patients with chronic painful conditions. It is important to realize that many patients find them helpful, even though there may be a lack of good clinical trials to support their use. For some herbal remedies, there is concordant acceptance, such as the use of carnitine supplementation (see later). A brief description of some herbs is afforded below.

Table 5. Mineral Requirements for UK Adults

	Calcium (mg/day)	Phosphorus (mg/day)	Magnesium (mg/day)	Sodium (mg/day)	Potassium (mg/day)	Chloride (mg/day)	Iron (mg/day)	Zinc (mg/day)	Copper (mg/day)	Selenium (μg/day)	Iodine (μg/day)
Adult	1000-700	775-550	300-270	1600	3500	2500	14.8-8.7	7-9.5	1-1.2	60-75	140

Patients with peripheral arterial disease may be taking hawthorn, garlic, ginger, tumeric, and/or cayenne as advised by a herbalist. Hawthorn is reported to have antioxidant properties, whereas the others are believed to reduce thrombosis by interfering with platelet function and lowering lipid levels. Extra-virgin olive oil,[57] fish oils,[57] vitamin C,[58] and vitamin E[59,60] have all been shown in studies to reduce atherogenesis, though the clinical benefit to patients remains to be determined. Meta-analysis of ginkgo[61] and garlic[62] studies in peripheral arterial disease has demonstrated improved claudication distances. Carnitine is an endogenous cofactor that enhances carbohydrate metabolism and reduces the accumulation of toxic metabolites from anaerobic exercise, possibly by stimulating mitochondrial fatty acid metabolism. As such, it is used widely by athletes and has demonstrated efficacy in peripheral arterial disease. Oral supplements of carnitine (2 g daily taken over 6 months) led to increases in claudication distance[63,64]; however, this benefit appears to be restricted to those with severe peripheral vascular disease.[65]

Patients with diabetic foot ulcers and peripheral arterial disease often have coexisting peripheral neuropathy. Neuropathic symptoms are notoriously difficult to control. Progression of peripheral neuropathy may be impeded by improved glycemic control. For existing peripheral neuropathy, alpha-lipoic acid, an endogenously produced sulfur-based antioxidant, if taken for up to 7 months has been shown to improve symptoms.[66]

For the management of venous leg ulcers, herbalists recommend horse chestnut seed extract, which has been proven to reduce edema, pain, and pruritus in a number of clinical studies.[67] Although it remains to be demonstrated in a clinical trial, it is believed by many herbalists that the use of the arnica flowers (*Arnica Montana L*) can reduce muscle aches associated with chronic venous insufficiency.[68] Occasionally, topical witch hazel is used as an astringent.

INCREASED NUTRITIONAL REQUIREMENT

Malnutrition: The Immediate Period

Calorie intake following serious injury needs to be high. The calorie-to-nitrogen ratio needs to mirror the changes in nitrogen balance. Thus, during the early weeks, it should be 120-150:1, increasing to 200-225:1 as the nitrogen balance moves from negative to positive. The correct supplementation of amino acids, vitamins, essential fatty acids, and minerals is implicit in any modern-day regimen. However, the needs for these constituents may vary per patient, dependent on their prior nutritional status.

In medical and surgical wards in Europe and North America, it was found that almost half of the patients admitted show some degree of malnutrition.[69,70] Although the proportion of patients affected may vary based on the setting and assessment methods,[69,70] malnutrition remains a current problem. Furthermore, it appears that the effects of malnutrition on wound healing are more pronounced if there is malnutrition within the immediate period prior to wounding.[71] It is often possible, particularly with surgical patients, to optimize the nutritional status prior to wounding as well. For malnourished individuals, correction of the nutritional state 7 days prior surgery can significantly improve postoperative wound healing and reduce the rate of other complications, including mortality.[72] Otherwise well-nourished individuals who have been subject to a period of malnutrition may also benefit from preoperative nutritional support.[73,74] Greater than 10% weight loss in the immediate preoperative period is associated with delayed healing and graft take in patients with burn wounds.[25]

Infection

The nutritional requirements in serious infection are greatly increased to improve healing and maintain immune function. Sepsis is often associated with a hypercatabolic state, which is associated with greater protein degradation-to-synthesis ratio. During the treatment of sepsis, dietary supplements should aim to minimize the catabolic effect.

ASSESSMENT OF NUTRITIONAL STATUS AND NEEDS

Assessment of nutritional status can be used to define nutritional need and monitor progress; however, there is no single standard approach for nutritional assessment.[75] The key components of any nutritional assessment include identification of patients likely to benefit from nutritional support, identification and assessment of the severity of malnutrition, determination of the level of the patient's needs and objective outcomes, definition of the key parameters and the basis for further intervention, and the approach to monitor the patient. The nutritional assessment should take into consideration the pathological consequences of the disease, present physical state, current dietary intake, and biophysical/chemical measurements.

The causes of the lower extremity wounds and their treatment will have a direct impact on nutrient requirement, loss, or absorption. To illustrate this point, consider pyoderma gangrenosum, an idiopathic inflammatory disease associated with an aggressive form of ulceration, which is often associated with an underlying disease. The ulcer in pyoderma gangrenosum may be large, secondarily infected, or associated with fever, all of which increase the calorie and protein intake necessary. Furthermore, if associated with underlying ulcerative colitis, then there may be direct consequences on nutrient losses through diarrhea and foods from the gut. In such cases, parenteral feeding may be necessary to support the nutritional requirements. Finally, high-dose corticosteroids are often used in the treatment of pyoderma gangrenosum and will have an impact on wound healing, bone mineralization, and fat distribution.

The physical appearance of the patient may provide clues of nutrient depletion. For example, there may be emaciation, weakness, apathy, confusion, edema, and breathlessness. Rarely, but noteworthy, are clinical features of specific essential vitamin or mineral deficiency syndromes, such as osteomalacia or zinc deficiency. Malnutrition is not an infrequent finding in elderly patients, particularly those with pressure ulceration; a history of current intake, the factors influencing intake, and the duration of inadequate intake need to be considered. For a given individual, there may be a complex mix of problems and circumstances that have led to malnutrition. It is only when all of these issues are clearly elucidated that effective prevention measures can be instituted.

Calculation of the nitrogen balance and tests to measure plasma proteins (eg, transferrin or thyroxine-binding prealbumin), plasma urea, grip strength, and mid-arm muscle circumference[76] may be used as indirect measures of protein needs of the patient. Fat stores are measured by assessing triceps skin fold thickness[77] and body mass index.[78] In addition, body water can be measured through fluid balance charts, biochemistry tests, the presence of edema or ascites, and bioelectrical impedance.[79]

After the nutritional status and needs of the patient have been evaluated, the next step is to estimate normal and supplemental nutritional requirements for energy, protein, fluid, electrolytes, and micronutrients. Decisions are based on clinical judgment as much as on raw calculations. Dietary reference ranges provide a foundation upon which such estimates can be calculated, and they provide normalized ranges available for energy, proteins, minerals, and vitamins based on age and sex, and they are available for many countries. But these reference ranges do not take into account the nutritional status of the specific patient or his or her additional requirements. Several mechanisms have been developed to help calculate requirements based on the patient's circumstances; precise details are provided in the *Manual of Dietetic Practice*.[80]

DISCUSSION

The aim of this article was to review the role of nutrition in lower extremity wounds. The article has examined the development of our knowledge of nutrition and the evidence available relating to some aspects. A holistic model of wound care should include dietetic intervention for every patient. Despite the fact that lower extremity wounds are the majority of the burden of chronic wound care, the knowledge of nutritional needs is developed from studies of surgical (acute) wounds and some animal models. Despite the efforts of clinician scientists and basic scientists, our understanding of this topic is far from complete at present. We know that many nutritional deficiencies involving carbohydrates, essential fats, amino acids, vitamins, and minerals have clear detrimental effects on wound healing. Moreover, certain nutrients in greater doses than physiologically necessary can further enhance healing, even in the absence of deficiency.

Nutritional assessments of patients with lower leg wounds should include a history of the immediate period prior to onset, so that nutritional needs can be accurately assessed. Although these findings are based on surgical and burn injury patients, they should be easily extrapolated to more conventional lower limb wounds. The nutritional status in the immediate period prior to surgery is important in determining outcome, and when possible surgery should be postponed to optimize the preoperative nutritional status.

Used appropriately, nutritional intervention can make the difference in healing a wound and so represents best practice. However, injudicious use of high doses of nutritional supplements can be harmful. It is only through careful study that effective treatments can be identified but, more important, safety issues addressed.

THE FUTURE

It is important to examine beneficial and other effects of nutrition on lower extremity wound healing. A clear outline of the role of each nutrient during the wound-healing process may seem distant, although advances in proteomics made possible by better imaging techniques may lend itself to wound healing studies. A technique in point is positron electron tomography (PET), in which a 3-dimensional isotope imaging system is used to accurately chart the presence of a short-lived radionucleotide tracer in the host either over a period of time or over a physiological process. This may permit studies of perfusion of water into a wound using oxygen 15 isotope or glucose uptake using an FDG (fluorine^{18} deoxyglucose) PET scan. These discoveries have great potential for studying wounds and for improving our understanding of their management and prevention.

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