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Practical aspects of nutritional support for wound-healing patients

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Abstract

Nutrition and metabolic support of acutely and chronically ill patients is an emerging branch of medicine that has direct applicability to wound healing. The occurrence of pressure ulcers is associated with malnutrition, as well as specific micronutrient deficiencies. A comprehensive approach is reviewed that involves nutritional assessment, selection of an appropriate route for nutrition support (enteral versus parenteral), prioritizing nitrogen retention over energy balance in stressed patients, micronutrient management, and incorporation of specialized nutritional pharmacologic interventions.

The issue of nutrition and wound healing applies to several specific scenarios in clinical medicine,

[MathJax]/extensions/MathZoom.js patient, but is also applicable to all patient popul at

for skin breakdown. At Mount Sinai Hospital in New York, an integrated approach has evolved between the Metabolic Support and Wound Healing teams to improve quality of life, shorten hospital stay, and decrease morbidity and mortality.

This collaborative approach is best exemplified in the care of chronically critically ill (CCI) patients in the respiratory step-down unit. The metabolic syndrome found among CCI patients includes (1) adult kwashiorkor-type malnutrition, (2) bone hyperresorption and vitamin D deficiency, (3) hypotestosteronemia in men, and (4) abnormal neuroendocrine function [1, 2, 3]. Skin breakdown, ulcerations, and wounds are common among CCI patients. The implementation of metabolic support in wound healing not only involves provision of protein and energy, but also manipulation of intermediary metabolism to induce anabolism, use of nutritional pharmacology, and management of metabolic complications.

Link between nutritional status and wound healing

In chronically hospitalized patients, the occurrence of pressure ulcers has been associated with nutritional status. The relative risk of developing a pressure ulcer in high-risk, malnourished patients was 2.1 times greater (95% confidence interval) compared with normally nourished patients [4]. In another study, 65% of severely malnourished nursing home patients had pressure ulcers, whereas no ulcers were detected in the mild to moderately malnourished or normally nourished nursing home patients [5]. Malnutrition is also associated with mortality in nursing home patients [6]. There are other risk factors that contribute to the development of pressure ulcers in hospitalized patients: immobility, hip fracture, dry skin, decreased dietary intake (especially protein), weight loss, hypoalbuminemia, lymphopenia, poor immune function, low zinc levels, fecal incontinence, diabetes mellitus, and stroke [7]. In spinal cord injury patients, those with pressure ulcers had lower serum prealbumin and albumin levels, as well as decreased cellular adhesion molecules, which participate in immunity and wound healing [8].

In a large prospective, randomized, controlled study of 672 critically ill patients treated with high-protein dietary supplements for 15 days, there was a reduction of pressure ulcer risk, compared with controls [9]. Eneroth et al [10] demonstrated the benefit of supplemental nutrition (as high as 2,098 kcal/day on average, for 11 days) on wound healing, but not mortality, in 24 transtibial amputees. Other small studies have demonstrated the benefit of higher-protein intake on pressure ulcer healing, supporting the practice that such patients ought to receive 1.2 to 1.5 g/kg per day

[11, 12] However, despite the rationality and scientific demonstration that nutr
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intervention can improve outcome in malnourished patients, some large studies have not been able to demonstrate this beneficial effect on mortality [\[\[13\]\]](#) or pressure ulcers [\[7, 14, 15, 16\]](#).

Diabetes has long been understood to be an independent risk factor for postoperative wound infection [\[\[17\]\]](#). A prospective study of 2,467 consecutive patients undergoing cardiac surgery demonstrated the efficacy of a perioperative continuous insulin infusion to achieve glycemic control <200 mg/dL and reduce the incidence of deep sternal wound infections [\[\[18\]\]](#). In fact, a recent study of critically ill patients demonstrated that insulin infusions producing tight glycemic control, <110 mg/dL, was associated with significantly reduced infection rates, morbidity, and mortality [\[\[19\]\]](#).

Chronic leg ulcers in the elderly have also been associated with diminished serum levels of certain micronutrients, such as vitamins A and E, carotenes, and zinc [\[\[20\]\]](#). Zinc deficiency has been associated with impaired wound healing, so it is not surprising that therapeutic zinc may be beneficial for wound healing [\[21, 22\]](#). However, overzealous zinc treatment can impair wound healing and induce a copper deficiency [\[\[22\]\]](#). Matrix metalloproteinases are neutral zinc-dependent endopeptidases that degrade extracellular matrix components and participate in wound healing [\[23, 24\]](#). During wound healing, matrix metalloproteinases are modulated by insulin, insulinlike growth factors [\[\[25\]\]](#), zinc availability and calcium availability, as determined by various proteins, such as calprotectin [\[\[26\]\]](#) and calmodulin [\[\[27\]\]](#).

Vitamin C is required for collagen synthesis and therefore plays a central role in wound healing. Conflicting data exist in the literature regarding the effect of ≥ 500 mg/day of vitamin C on pressure ulcer healing [\[28, 29\]](#). Vitamin A treatment is an effective intervention in patients with impaired wound healing and wound infections, especially while being treated with corticosteroids [\[30, 31\]](#). Vitamin E has unproven benefit in wound healing [\[\[32\]\]](#).

Clinical practice algorithms

During the initial evaluation of a patient with wound-healing issues, a nutritional assessment must be performed. Briefly, an unintentional loss of >10% usual body weight in the previous month, and/or a low serum albumin, defines a malnourished condition. Operationally, simple starvation or “marasmus” exists if the patient has lost >10% usual body weight and has a normal serum albumin. In this condition, low carbohydrate intake produces a low-insulin state with decreased energy expenditure and ketone production. Treatment consists of adequate nutrition support: 25 to 35

per day and 1.0 to 1.2 g/kg per day protein by means of oral, gastrostomy or jejunostomy
; [\[MathJax\]/extensions/MathZoom.js](#) ly, the majority of wound-healing patients manife is

inflammation, cytokine activation, and hypoalbuminemia, with or without weight loss depending on the extent of anasarca. This condition is termed “kwashiorkor-type” malnutrition and is associated with a higher in-hospital morbidity and mortality rate than patients with marasmus-type malnutrition [[33]]. In kwashiorkor-type malnutrition, cytokines have a plurality of effects on metabolism: (1) activation of the immune-neuroendocrine axis and counterregulatory hormones, (2) induction of lipolysis and muscle proteolysis, and (3) disinhibition of pyruvate dehydrogenase and inappropriately increased carbohydrate oxidation, energy expenditure, and substrate cycling [[34]]. The net effect of this dysmetabolism is the diminution of body cell mass and resultant visceral organ dysfunction and immune dysfunction. Treatment of kwashiorkor-type malnutrition is supportive: (1) ample protein to optimize nitrogen retention, (2) hypocaloric energy to avoid the refeeding syndrome, hepatopathy, and hyperinsulinemia, (3) correction of micronutrient deficiencies, and (4) nutritional pharmacologic interventions.

“If the gastrointestinal tract works, use it.” In a recent study by Lewis et al [[35]], a systematic review and meta-analysis of 837 patients in 11 randomized, controlled trials showed that enteral feeding within 24 hours after gastrointestinal surgery reduced the mean length of hospital stay and risk of infection. Traditionally, early enteral feedings may be held because of fears of inducing nausea and vomiting, and to protect the anastomosis. These results confirm an earlier study by Schroeder et al [[36]], in which early enteral feeds improve wound healing. If the patient can safely tolerate oral feedings, as determined by a speech pathology consultant to exclude aspiration, then a hospital diet incorporating patient preferences, along with appropriate nutritional supplements, should be ordered. A registered dietitian can both provide invaluable input into this prescription and perform calorie counting to assess adequacy. If oral intake is inadequate, then an enteral access device should be placed, preferably as an endoscopically or surgically positioned postpyloric feeding tube.

Semielemental feeds contain hydrolyzed protein as their nitrogen source and are differentiated from intact protein feeds (protein that has not been hydrolyzed) and elemental feeds (free amino acids as the sole source of nitrogen). Hypoalbuminemia may reflect the severity of active cytokine-mediated inflammation and chronic undernutrition, but it also contributes to gut edema and diarrhea and reflects impairment of proteins necessary for nutrient absorption [37, 38, 39]. Semielemental feeds are therefore recommended in those wound-healing patients who also have a serum albumin level <2.5 g/dL [[40]]. In critically ill patients after abdominal surgery, the use of a semielemental, versus an intact protein, enteral feed is associated with better amino acid absorption and insulin responses [[41]]. Semielemental feeds are associated with decreased stool output, compared with intact protein feeds, in critically ill patients [38, 42]. With early enteral nutrition support after trauma or

[MathJax]/extensions/MathZoom.js in 50% of patients receiving an elemental diet, 4 h

intact protein diet, but 0% on a semielemental diet [43, 44]. In critically ill and nursing home patients, improved visceral protein stores (albumin, transferrin, and retinol-binding protein) are induced with semielemental diets, compared with intact protein or elemental diets [41, 43, 45]. Moreover, a shorter hospital stay has been associated with semielemental feeds, compared with intact protein feeds, in trauma patients [43].

Several metabolic complications can result from enteral nutrition support. Tube feeding syndrome is a hypertonic dehydration state produced by overfeeding protein [46]. If there is inadequate free water administered as flushes (to meet the increased obligate renal free water excretion that accompanies urea formation and excretion), then the patient becomes hypernatremic. Treatment is simply to avoid hypertonic feeds and administer ample free water. Diarrhea can also induce a hypertonic dehydration and is typically osmotic, or the result of occult sorbitol in medications, although secretory causes, such as *Clostridium difficile* enterocolitis and bacterial overgrowth, are quite common. Diarrhea can markedly impair wound healing because of bacterial contamination, difficulty maintaining a clean dressing, malabsorption, and gastrointestinal protein losses. Empiric therapy consists of (1) reverting to a semielemental or dilute elemental feeding (for example, two-thirds strength Vivonex [Novartis, Basel, Switzerland] or FAA [free amino acids; Nestlé Clinical Nutrition, Glendale, CA]), (2) adding 10 mL kaolin-pectin (Kaopectate; Pfizer, New York, NY) and/or bismuth salicylate (Pepto-Bismol; Procter & Gamble, Cincinnati, OH) to each 500-mL bag of feeds, (3) taking cholestyramine, 1 packet, 2 to 4 times daily, and (4) using opioids, such as deionized tincture of opium or diphenoxylate HCl (Lomotil; Pfizer), octreotide, or pre-/probiotics.

Abnormal gut flora result from overgrowth of various enteric pathogens, such as *C difficile*, and produces disturbances of colonic salt and water resorption, nutrient absorption, and gas formation. Beneficial colonic anaerobic microflora salvage energy by means of bacterial fermentation of undigested carbohydrate and protein into short-chain fatty acids, which are trophic to colonocyte physiology. Beneficial genera include *Bifidobacterium* and *Lactobacillus*. Prebiotics are inulin and oligofructosaccharides, which serve to provide substrates for probiotic organisms. A 15-g/day dose of oligofructosaccharide or inulin leads to *Bifidobacterium* becoming the dominant genus in feces [47]. *Lactobacillus* GG (Culturelle; ConAgra Foods, Omaha, NE) treatment has been used successfully for the management of recurrent *C difficile* colitis [48].

In situations where patients are not able to meet the metabolic demands of wound healing with enteral feedings alone, parenteral nutrition support is initiated. Animal studies have indicated superiority of enteral nutrition over parenteral nutrition regarding wound-breaking strength, wound

in accumulation and type 1 (but not type 3) gene expression. However, these findings are not confirmed in humans [49]. One paradigm uses trophic enteral feeds with parenteral

nutrition so that, together, they fully meet the metabolic demands of the patient. Formulation of parenteral nutrition has been the subject of much controversy [\[50\]](#). For patients experiencing metabolic stress and manifesting signs of kwashiorkor-type malnutrition, a hyperproteic-hypocaloric approach has several advantages. High rates of amino acid infusion (up to 1.5 g/kg per day) are prescribed to meet the huge protein losses generated by wounds. Care must be taken not to create a hyperammonemic or severely azotemic state. Relatively low amounts of nonprotein calories (<20 to 25 total kcal/kg per day) in critically ill patients avoid the risk of overfeeding, without sacrificing benefit with regard to nitrogen balance [\[51, 52, 53\]](#). Regardless of the route of nutrient administration, tight glycemic control with subcutaneous and/or intravenous insulin should be achieved, as needed.

Micronutrient support of wound healing is accomplished by means of enteral and/or parenteral routes, as reviewed in [Table 1](#). Although certain nutrients play important roles in wound-healing physiology, the value of supplementing patients who are not deficient remains unproved.

Table 1 Micronutrition and nutritional pharmacology in wound healing

Nutrient	Dose
Arginine*	PO: 1–3 g/day
Ascorbic acid*	IV in PN: 100–200 mg/day; PO: 500–1,000 mg/day
Cyanocobalamin*	IV in PN: 25 µg/day; SC 1,000 µg/1–4 wk; PO: 250–1,000 µg/day
Glutamine	PO: 0.3–0.57 g/kg/day as 10–15-g doses
Growth hormone	SC: 0.03–0.1 mg/kg/day
<i>Lactobacillus</i> GG	PO: 1 capsule bid–tid
Molybdenum	IV in PN: 25 µg/day
Multivitamin*	IV in PN: 10 mL/day; PO: 1–2 qd
Oligofructosaccharide	PO: 1 capsule bid–tid
Oxandrolone	PO: 2.5–5.0 mg bid–qid

IM = intramuscularly; IV = intravenously; PN = parenteral nutrition; PO = orally; SC = subcutaneously.

* In addition to standard amounts in parenteral nutrition trace elements and multivitamins.

[Open table in a new tab](#)

Glutamine is a conditionally essential amino acid and may promote nitrogen balance [\[\[54\]\]](#), gut absorptive function [\[\[55\]\]](#), and immune function [\[\[56\]\]](#). Arginine is also a conditionally essential amino acid that improves wound healing and immune function [\[57, 58, 59\]](#). Ornithine α -tartrate is a precursor of glutamine, arginine, proline, and α -ketoisocaproate, and can regulate [\[MathJax\]/extensions/MathZoom.js](#) on of insulin and growth hormone, and improve \backslash h ϵ

[[60]]. If attempts at improving nitrogen retention are unsatisfactory, anabolic agents [[61]], such as intramuscular or transdermal testosterone enanthate [[2]], oral oxandrolone [62, 63, 64], or subcutaneous growth hormone [65, 66] can be considered, but their benefit regarding wound healing also remains unproved. It should be noted that systemic growth hormone therapy has been associated with a worse outcome among critically ill patients compared with controls [[67]]. Even topical essential fatty acids, insulin, and zinc, in addition to the commercially available growth factors, have demonstrated efficacy in wound healing in preliminary studies [68, 69].

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