Nutrition and Wound Healing

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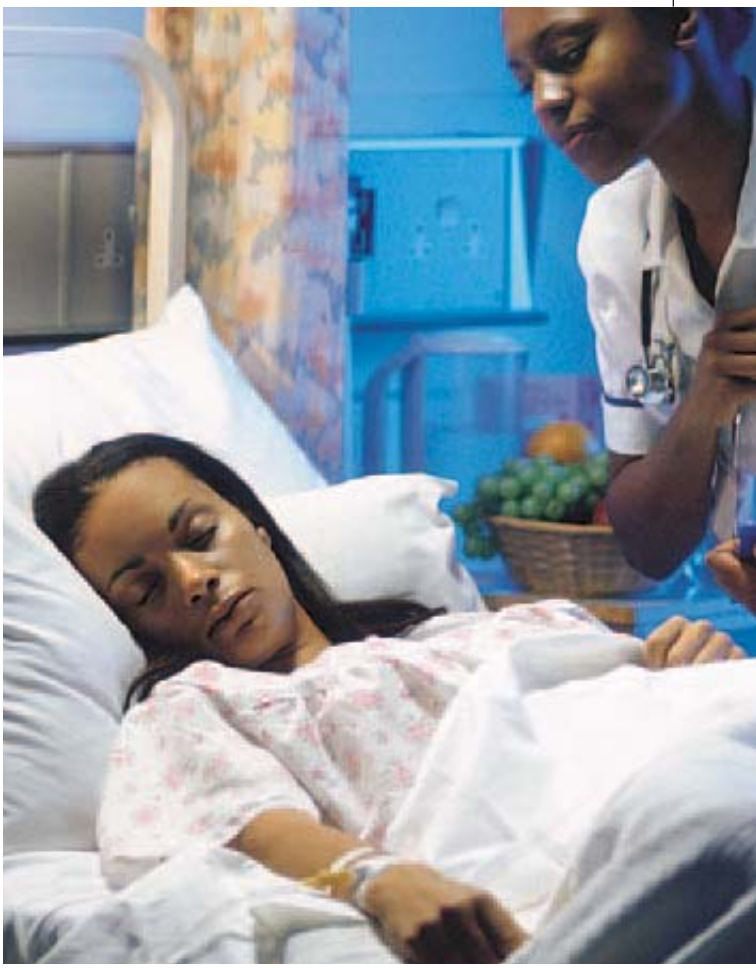
Wounds serve as a source of morbidity and mortality due to associated tissue inflammation and infection (Figure 1). Systemic infection and inflammation through the release of cytokines and other mediators may lead to sepsis, multi-system organ failure and death. Optimal wound healing is important from many perspectives, including the prevention of bacterial colonization, as well as contractures and scar formation, which can have cosmetic and functional consequences.

Wound healing involves a complex sequence of events that begins with the inflammatory phase, followed by vasoconstriction to initiate clot formation and then vasodilation secondary to factors such as histamine and prostaglandins. This results in the accumulation of fluid and leukocytes. In the proliferative phase, the presence of lactic acid, ascorbic acid and growth factors stimulate fibroblasts, which produce collagen, provided there is an adequate supply of oxygen, vitamin C, iron, copper and pyridoxal. The final phase is the maturation phase where the wound contracts and is strengthened by increased collagen cross-linking and remodeling.

The importance of nutrition is seen with decreased wound healing in individuals with protein-energy malnutrition. Malnourished patients



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Summary

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- Wounds serve as a source of morbidity and mortality due to associated tissue inflammation and infection.
- Malnourished patients have decreased collagen formation, as compared with normally nourished patients.
- It is important to consider the patient's nutritional status prior to intervention.
- Protein requirements increase with the presence of a wound due to requirements for protein synthesis.
- Patients should consume approximately 55% to 60% of their calories in the form of carbohydrates. This ensures enough carbohydrate calories are provided to spare protein from being oxidized for energy.
- Fat is important in wound healing because it provides linoleic and linolenic acids, which are essential fatty acids needed for cell membranes.
- Ensuring optimal hydration status is an important part of the nutritional care of a patient with wounds, especially in the elderly.
- Oral intake with high-protein, high-calorie foods or supplements is usually sufficient to promote wound healing.

have decreased collagen formation, as compared with normally nourished patients.[1]

Wound healing is influenced by other factors besides nutrition, including the age of the patient, wound care, pressure on the area, surgical intervention (debridement), presence of metabolic disturbances (*i.e.*, hyperglycemia), edema, infection and medications (*i.e.*, anticoagulants and immunosuppressive drugs, including steroids) (Table 1).[2] It is important the etiologic factors responsible for the wound are treated concomitantly with nutritional intervention to achieve optimal outcomes.

Nutritional Assessment

It is important to consider the patient's nutritional status prior to intervention. An underweight individual with a body mass index (BMI) of less than 20 kg/m^2 can be at the same nutritional risk as an obese patient (BMI greater than 30 kg/m^2), since the intake of protein, vitamins and minerals may also be low in obese individuals. Recent involuntary weight loss from one's ideal body weight also can increase the risk of compromised nutritional status.

Protein

Protein requirements increase with the presence of a wound due to requirements for synthesis of protein and to replace protein lost through the wound exudate. Patients should be encouraged to consume between 1.2 g and 1.5 g of protein/kg of ideal body

weight, or approximately 20% of their total daily calories in the form of protein. This is an increase from 0.8 g of protein/kg of ideal body weight, which is required for healthy adults. Tolerance should be assessed by monitoring fluid status and renal function indices, such as blood urea nitrogen and serum creatinine levels.[3]

Serum albumin, the most abundant plasma protein, has long been used as an index of visceral protein status to determine adequate protein intake. Due to albumin's long half-life of 20 days and its key role in maintaining oncotic pressure, it is affected more by changes in the intravascular space than by the nutritional status of the patient. Albumin is a negative acute-phase protein, which is often low during the inflammatory phase of healing due to down-regulated hepatic protein synthesis.

It is possible to have severely undernourished individuals with an albumin within the normal range due to a compensatory decrease in degradation. It is recommended, therefore, to monitor transferrin or pre-albumin levels with a shorter half-life of eight and two days, respectively, and that respond more quickly to changes in nutritional status.

During wound healing, protein synthesis increases at the wound site. If there is a deficiency of amino acids, protein synthesis may be impaired. It has been shown that, during wound healing, the amino acid arginine can become conditionally essential. A dose of 17 g to 24 g of supplemental arginine has been shown to improve both collagen formation and wound healing.[4] Although arginine is present in a variety of protein-rich foods, the amount is not sufficient to provide 17 g/day to 24 g/day. Supplements have been developed that provide 4.5 g of arginine per serving. The effect of supplemental arginine on wound healing, however, remains equivocal.

Figure 1. A 21-year-old patient with toxic epidermal necrolysis (TEN).

Kirk reported increased wound hydroxyproline content, increased insulin-like growth factor levels and increased lymphocyte proliferation in a study of 30 healthy elderly volunteers randomized to receive 17 g/day of arginine or a placebo.[5] Langhamp-Henken, however, found supplemental arginine of 8.5 g/day or 17 g/day did not enhance mitogen-induced lymphocyte proliferation in a study of 33 nursing home residents with pressure ulcers.[6]

Carbohydrate

Patients should consume approximately 55% to 60% of their calories in the form of carbohydrates. This ensures enough carbohydrate calories are provided to spare protein from being oxidized for energy.

Insulin resistance and hyperglycemia, either due to inactivity, aging or obesity, is a common finding in elderly patients. It has been shown that, in addition to glycosylation of hemoglobin, elevated blood glucose

Table 1

Factors Affecting Wound Healing

- Nutrition
- Age of the patient
- Wound care
- Pressure on the area
- Surgical intervention (debridement)
- Presence of metabolic disturbances, such as hyperglycemia
- Edema
- Infection
- Medications, such as anticoagulants and immunosuppressive drugs, including steroids

can result in glycosylation of various immunoglobulins and lymphocytes, which impairs their function.[7] Chronic hyperglycemia also can impair the transport of vitamin C into cells, including leukocytes and fibroblasts, and inhibits proliferation of fibroblasts.[8,9]

These studies support the clinical observations of impaired wound healing in patients with diabetes, and indicate the importance of euglycemia in reducing morbidity and mortality. It is recommended, therefore, that glycosylated hemoglobin (HgbA1C) be obtained as an indication of glucose control over the preceding two to three months. If the value is above the normal range of 4% to 6%, the patient would benefit from improved glucose control.

Fat

Fat is important in wound healing because it provides linoleic and linolenic acids, which are essential fatty acids needed for cell membranes, in addition to fat soluble vitamins. Vegetable oils such as corn, safflower and soybean oil are high in linoleic acid, an omega-6 fatty acid. This is metabolized to arachidonic acid, and is a precursor for series 2 prostaglandins, which are pro-inflammatory and immunosuppressive. Linolenic acid, an omega-3 fatty acid, is found mainly in fish and to a lesser extent in canola oil. It is a precursor for series 3 prostaglandins, which are anti-inflammatory, immune-enhancing and have vasodilating properties.[3] It is recommended patients consume approximately 20% to 25% of their calories from fat to ensure adequate energy intake.

Fluids

Ensuring optimal hydration status is an important part of the nutritional care of a patient with wounds. In the elderly, dehydration is the most common fluid disturbance and is associated with decreased urine output, elevated body temperature, constipation and skin turgor changes. It also can affect biochemical values, resulting in inaccurate assessments.[10] Patients should consume 30 mL of fluid/kg of actual body weight, meaning a 70-kg person should consume 2.5 L of fluid per day.[10]

Vitamins and minerals

Vitamin C is an essential co-factor in the synthesis of collagen and in maintaining immune function. It continues to be important after the wound has healed, because wounds are more metabolically active and previously healed scars can break down in states of vitamin C deficiency.[8] It is usually recommended patients with chronic wounds consume up to 500 mg of vitamin C per day to ensure tissue saturation. Although, the dietary reference intake for healthy adults has been increased to 75 mg/day in females and 90 mg/day in males from the previously recommended 60 mg/day, the tolerable upper limit of 2,000 mg/day should not be exceeded in order to avoid adverse effects.[11]

Vitamin A promotes wound healing by increasing fibroblast differentiation, collagen synthesis, wound strength and by reducing infection.[2] Vitamin A supplements have been used to counteract the catabolic effects of steroids on wound healing. They also have been used by malnourished patients with gastrointestinal tract dysfunction who are undergoing surgery. Assessment of vitamin A status is difficult, however. Most of the vitamin A in the body is stored in the liver, and plasma measures, such as serum vitamin A and retinol levels, only reflect vitamin A status when the liver stores are severely depleted or excessively high.[12]

There is no evidence to suggest supplemental *vitamin E* improves wound healing. In fact, wound healing is delayed and the beneficial effects of vitamin A on wound healing are reduced when an excessive amount of vitamin E is given.[2] Vitamin E is often used topically by lay individuals to improve the cosmetic outcome of burns and wounds. In a double-blind study of 15 patients with healed wounds after skin cancer removal, however, topical vitamin E did not improve the cosmetic appearance of scars. Furthermore, it led to contact dermatitis in 33% of the patients.[13]

Vitamin K is required as a co-factor for clotting factors and is normally produced by bacteria in the large intestine. If the patient is taking antibiotics, however, endogenous vitamin K production may be limited. This can lead to deficiency, which can result in uncontrolled bleeding and impaired

wound healing.[2] It is important to monitor the prothrombin time (PT), also called the international normalized ratio (INR). PT will increase with vitamin K deficiency, severe diarrhea/vomiting, anticoagulants, liver disease, hypervitaminosis A, alcohol consumption and dehydration. PT will decrease with enteritis, medications (*i.e.*, steroids and digitalis) and excess vitamin K. Vitamin K should not be given to patients on warfarin, as it is an antagonist to the therapeutic effects of warfarin.

Ensuring optimal hydration status is an important part of the nutritional care of a patient with wounds.

Zinc deficiency can impair wound healing. The elderly often are at increased risk of zinc deficiency due to poor intake and absorption.[14] Zinc sulfate contains 23% zinc, and 110 mg provides 25 mg of elemental zinc with approximately 20% to 40% of ingested zinc being absorbed. Excess zinc, however, can impair wound healing by interfering with both iron and copper metabolism. In a Cochrane systematic review of six randomised controlled trials, there was some evidence that oral zinc supplements might improve healing of venous ulcers, but only in those with a low serum zinc level at baseline.[15] In a study of children with severe protein-energy malnutrition, high doses of zinc supplements (6 mg/kg body weight) were associated with increased mortality. Due to the potential for adverse effects of zinc on copper status, immune function and gastrointestinal tolerance, patients with wounds should not receive routine zinc supplements in excess of the tolerable upper limit of 40 mg/day, without measuring plasma zinc levels to assess zinc status.[14,16]

Iron is required for hydroxylation of proline and lysine in collagen synthesis. Severe anemia can impair wound healing through reduced peripheral circulation and oxygenation of the wound site. Severe anemia also causes a reduction in the bactericidal activity of leukocytes.[2] It is recommended that serial measures of hemoglobin, mean cell volume and serum iron are monitored regularly.

Copper is an important nutrient in wound healing, as it is a co-factor for many enzymes, including lysyl oxidase involved in cross-linking of collagen and elastin. If a patient is suspected of being deficient in copper, a serum ceruloplasmin level should be obtained before supplementation in excess of the recommended dietary allowance of 900 µg/d or the tolerable upper limit of 10,000 µg/d.[16] It should be noted that copper deficiency can be due to excessive zinc supplementation.[17]

Route of Nutrient Delivery

Oral intake with high-protein, high-calorie foods or supplements is usually sufficient to promote wound healing. Patients who are unable to meet their energy and protein requirements orally, and who have a functioning gastrointestinal tract, require enteral supplementation. Tube feeding by nasogastric or percutaneous endoscopic gastrostomy routes, or by jejunostomy to reduce aspiration, can be administered nocturnally to enhance mobility and allow oral intake during the day. Enteral nutrition, not parenteral nutrition, is the preferred route of nutrient delivery to prevent villus atrophy and reduce infectious complications.[3]

Other Therapeutic Factors

In addition to nutrients, growth factors have an important role in modulating the wound healing response. Transforming growth factor-beta (TGF-ß) is a local and circulating cytokine that

can enhance wound healing.[18] Hirshberg reported in a 16-week, randomized, placebo-controlled pilot study of 14 patients with chronic, non-healing ulcers, that daily topical application of TGF-ß resulted in a significantly increased rate of wound healing during the early phases of wound healing.[19] Excessive TGF-ß, however, can lead to excessive fibrosis and the formation of hypertrophic scars.[20]

Interferons (IFNs) have been used as antifibrogenic factors to modulate the excessive production of extracellular matrix associated with dermal fibroproliferative disorders. IFNs work by reducing Type 1 collagen messenger ribonucleic acid (mRNA) and histamine levels.[20] Research in guinea pigs support the use of a dermal cream containing IFN-alpha 2b for treatment of hypertrophic scars.[21]

Conclusion

Wound healing is a complex process that requires adequate intake of protein, carbohydrates, fat, vitamins and minerals for tissue repair. Nutrient deficiencies can impair wound healing and impact the recovery and morbidity of patients. Clinicians need to be aware of the nutritional and metabolic factors affecting wound healing and what preventive and corrective therapies can be used to optimize wound healing. CME

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