The Interrelationship of Lean Body Mass and Nutrition in Wound Healing:

A Scientific Review

Abbott

Introduction: The Wound Healing Challenge Wounds and Healing

Wound care has become a clinical focus for several reasons, including regulatory compliance, financial issues, an increase in litigation claims, and the renewed importance of improving the quality of life for patients.

Wounds can result from a number of conditions. For example, surgical incisions, burns, and traumatic injuries are the result of acute conditions. If acute injuries are extensive or complicated by infection, they may require more time for resolution and become hard-to-heal; these types of wounds are also known as non-healing or difficult-to-heal wounds. In addition, people with chronic health conditions can develop other types of hard-to-heal wounds, such as venous leg ulcers due to poor circulation, diabetic foot ulcers, and pressure ulcers.[1] Hard-to-heal wounds fail to progress through an orderly sequence of repair in a timely fashion.[2]

Hard-to-heal wounds occur in the general population, but older individuals who are hospitalized or reside in long-term care facilities are at particular risk. Approximately 3.5% of the U.S. population older than 65 years has venous leg ulcers.[3] Of the 150 million people in the world with diabetes, at least 15% are expected to develop one or more foot ulcers in their lifetime, especially in their older years.[1] The prevalence of pressure ulcers among elderly people living in long-term care facilities exceeds 20% in the U.S. and Canada.[4,5] The prevalence of hard-to-heal wounds and the costs to manage them have continued to rise over time, despite increasing availability of advanced wound-care specialists and wound-healing centers.

Wounds and Healing

Normal wound healing

Wound healing begins as soon as the wound occurs. It is a complex interaction between epidermal and dermal cells, the extracellular matrix, and plasma-derived proteins; all of these activities are coordinated by an array of signaling molecules, including cytokines and growth factors.[6] The dynamic process of healing normal wounds is characterized by three overlapping phases—inflammation (Figure 1), proliferation (Figure 2), and remodeling (Figure 3).[6] Understanding the healing process is critical to the successful management of patients with wounds.[7]

Inflammation

Wound healing begins with clotting, which is also called hemostasis. Platelets, endothelial cells, and coagulation factors interact to stop bleeding and form a clot. Cells trapped within the fibrin clot, mainly platelets, release vasodilators and chemoattractants, including transforming growth factor-beta (TGF-ß) and platelet-derived growth factor (PDGF). These signaling molecules recruit neutrophils[8] which, in turn, trigger an inflammatory response[6] to clear the wound site of cellular debris.[9]

In the early inflammatory phase, neutrophils are the most prominent cell type in the wound. Neutrophils release enzymes and perform phagocytosis, thus beginning processes for breakdown and removal of bacteria and debris. Circulating monocytes are attracted to the wound site, ultimately maturing into macrophages responsible for finishing the cleanup process. Macrophages secrete proteases and clear dead cells, bacteria and expended neutrophils by phagocytosis. Macrophages also secrete substances that trigger production of cells important in the subsequent proliferative phase. As the wound site is cleared of damaged tissues and bacteria, the number of neutrophils and macrophages declines, thus ending the inflammatory phase and beginning the proliferative phase.

Figure 1: Inflammation, the first phase of wound healing.

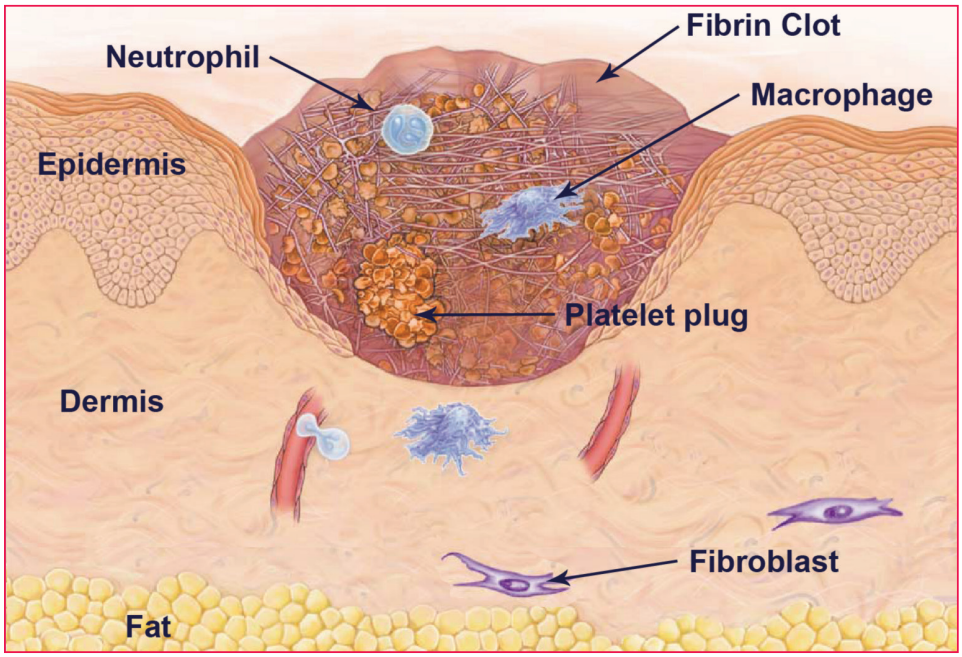


Figure with permission from the New England Journal of Medicine[10]

Inflammation is characterized by the following:

- Wound healing begins with hemostasis, or clotting
- Neutrophils break down bacteria and remove debris
- Monocytes arrive and mature into macrophages
- Macrophages finish the cleanup and stimulate needed cell production
- Fibroblasts enter, and the proliferation phase begins

Proliferation

The proliferation phase is characterized by buildup of connective tissue, starting with granulation tissue, which includes macrophages, fibroblasts, immature collagen, and blood vessels.[3]

Fibroblasts enter and proliferate in the wound site where they secrete collagen molecules, which are assembled into fibers and cross-linked into bundles, thus affording strength and structure to the wound. This newly-formed matrix is host to angiogenesis (development of new blood vessels), so that new vascular structures can deliver nutrients along with plasminogen activator and collagenase to the fibroblasts. Some fibroblasts differentiate into myofibroblasts, which bind to and draw the wound edges closer together, thereby reducing the size of the wound.[11] While new matrix is built, existing matrix around the wound margins is degraded by enzymes (i.e., metalloproteinases and plasminogen activators).[6] Activity of these enzymes is regulated to avoid excessive matrix degradation, which would weaken the structure of the repairing wound. In the final step of the proliferation phase, some keratinocytes migrate from the wound margins and divide until they form a contiguous epidermis, or surface layer of the skin. Other keratinocytes engulf or phagocytose debris. These keratinocyte-mediated changes, coupled with wound contraction, result in re-epithelialization and wound closure.[3,6] A scar forms when epithelialization is complete.

Figure 2: Proliferation, the second phase of wound healing.

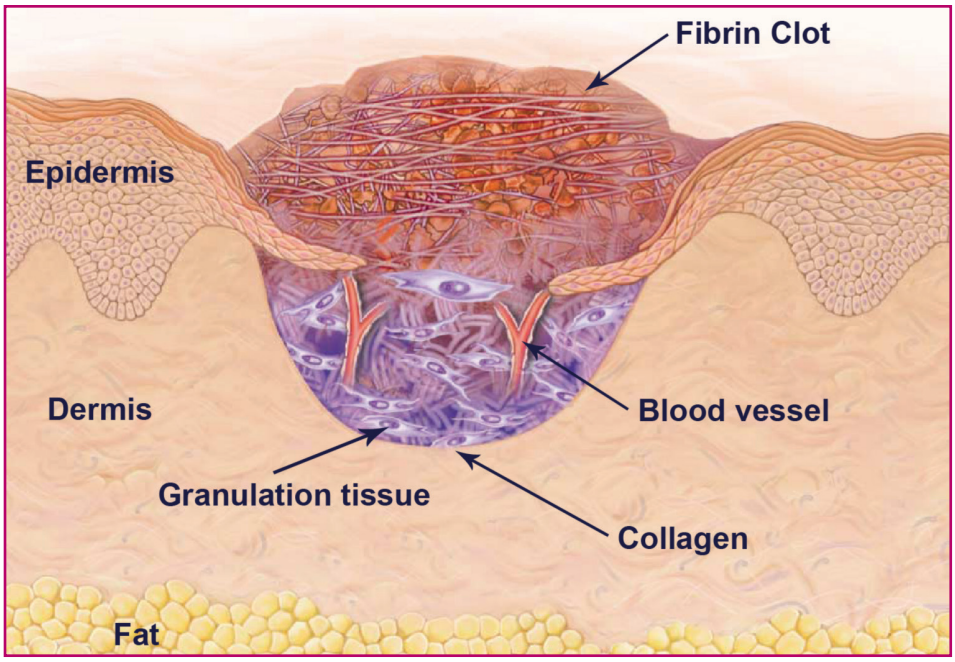


Figure with permission from the New England Journal of Medicine[10]

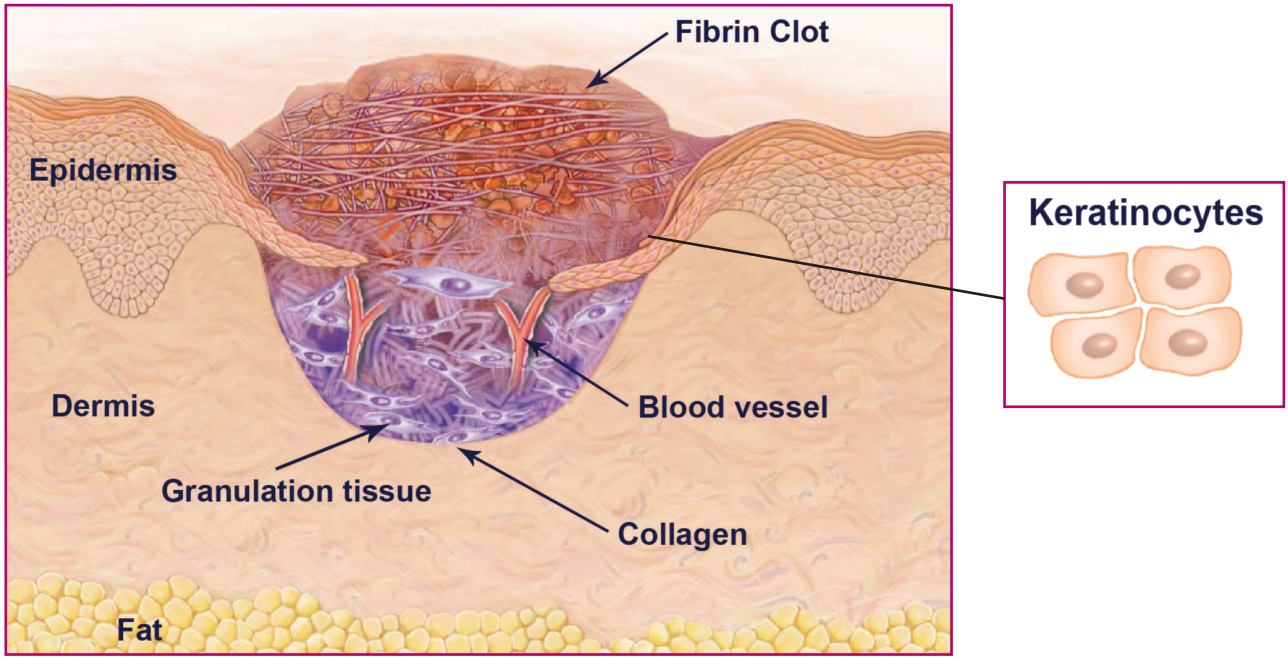
Proliferation is characterized by the following:

- Angiogenesis
- Connective tissue builds up as fibroblasts enter and secrete extracellular matrix proteins—collagen and fibronectin
- Keratinocytes migrate from the wound margins and divide until they form a contiguous epidermis
- Wound edges are drawn together (wound contraction)

Remodeling

Once the wound has closed, remodeling of the wound commences, a phase that can continue for an extended period of time.[6] Early, randomly-placed collagen is remodeled into a better-organized structure, providing greater tensile strength. Over time, cell content and blood flow in the scar tissue decreases. Remodeling concludes normal wound healing.

Figure 3: Remodeling, the final phase of wound healing.



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Remodeling is characterized by the following:

- Remodeling can continue for extended periods of time
- Collagen is remodeled into a better-organized structure to improve tensile strength
- Cell content and blood flow in scar tissue decreases as remodeling continues Remodeling concludes normal wound healing

Remodeling concludes normal wound healing.

Conditions and Diseases that Affect Wound Healing

If a wound does not progress through the normal stages of healing in a timely manner, it may result in a wound that is hard-to-heal. Hard-to-heal wounds lack anatomic and functional integrity, so they heal slowly or do not heal at all. These wounds remain in the inflammatory or proliferative phase, allowing the excessive accumulation of extracellular matrix components, which in turn may lead to the premature degradation of collagen and growth factors.[12] Various factors, both local and systemic, are known to impede wound healing; wound infection and nutritional deficiencies are common contributors (Table 1). Less common factors include local or distant cancers, use of certain anti-cancer drugs, and genetic healing abnormalities.[1]

Table 1: Factors Commonly Involved in Hard-to-Heal Wounds[1,2]

Local Factors	Systemic Factors
Wound Infection Ischemia Venous insufficiency Mechanical trauma (i.e., pressure) Tissue maceration Presence of a foreign body	Nutritional deficiencies (i.e., deficiencies of proteins, vitamins, minerals) Chronic diseases (i.e., diabetes mellitus, renal disease) Advanced age and general immobility Smoking

Chronic diseases, such as diabetes and chronic kidney disease, are noteworthy because by impacting metabolic processes they affect wound healing. Control of diabetes is important for proper wound healing.[13-15] The dialysis patient population, which has a high incidence of diabetes, vascular disease and related complications, is also at increased risk for non-healing wounds. The chronic exposure of tissues to hyperglycemia appears to result in a variety of complications, including microvascular problems of neuropathy, retinopathy, and nephropathy, and the macrovascular complications of stroke, coronary artery, and peripheral vascular disease. Any of these complications can contribute to wounds that are difficult to heal.

The Role of Lean Body Mass in Health

Maintenance of lean body mass (LBM) is a key to good health. LBM includes all body tissue, except fat, and accounts for approximately 75% of normal body weight.[16] Muscle is the largest component of LBM and comprises 50% to 60% of LBM by weight.[16] LBM is maintained by the appropriate balance of protein synthesis and protein breakdown.[17] Because muscle plays a central role in protein metabolism[16, 17] in the absence of adequate nutrient intake, muscle is the principal repository of protein and amino acids used in protein synthesis.[16, 17] Maintenance of muscle mass is essential to support whole-body protein metabolism, wound healing, physical strength, organ function, skin integrity, and immune function.[18]

Loss of protein from LBM generally results in complications associated with involuntary weight loss.[19] The progressive and generalized loss of LBM, called sarcopenia, is a syndrome recently characterized by the presence of both low muscle mass and either low muscle strength or low physical performance.[20] Sarcopenia can develop in younger individuals, although it mainly occurs in older adults.[20] Sarcopenia affects as many as 30% of adults older than 60 years of age and 50% of those older than 80 years.[21,22] The process underlying the loss of LBM begins around 30 years of age and normally continues unabated.[22-26]

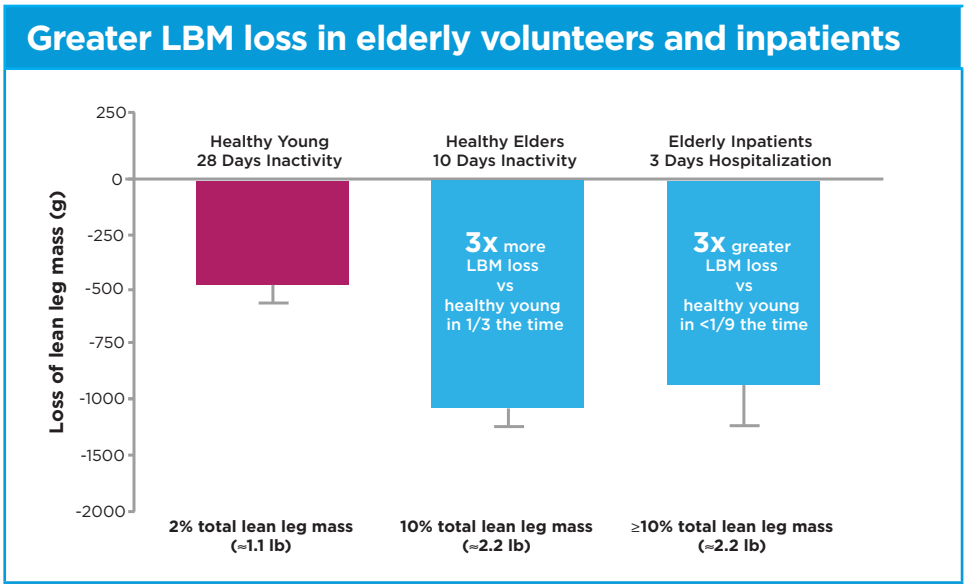
- At 30 years of age, weight gain begins to be preferentially accrued as fat instead of muscle
- After 40 years of age, LBM loss can occur as much as 8% per decade
- After 70 years of age, that rate of LBM loss may increase to 15% per decade

Chronic conditions, such as cancer, non-healing wounds, HIV/AIDS, chronic obstructive pulmonary disease, and congestive heart failure are also associated with loss of LBM.[16, 27]

Ilness and injury can cause or accelerate LBM loss, as was shown in three separate studies. In healthy young people, bed rest alone can lead to 2% to 3% loss in skeletal muscle in the leg.[28,29] With illness or injury, the loss of LBM

increases to as much as 10%, with even greater LBM loss in older adults.[28,29] Healthy younger adults were confined to bed for 28 days; healthy elderly adults, for 10 days; and elderly inpatients, for 3 days.[29] All healthy volunteers consumed the RDA for protein; the elderly inpatients did not.[32] LBM loss was measured in elderly inpatients after 3 days of hospitalization (Figure 4).[29]

Figure 4. LBM loss associated with bed rest or hospitalization in healthy younger adults, healthy elderly, and hospitalized elderly patients[29]



Adapted with permission from Paddon-Jones[29]

Loss of LBM can be debilitating, impacting immune function, wound healing and overall body function.[16] In older adults, loss of lean mass compromises physical strength, functionality, and energy, thereby increasing fatigue and the risk for falls and fractures. In addition, loss of LBM weakens the immune system, increases susceptibility to illness and infection, compromises healing, and reduces the ability to recover from surgery, illness, or disease.[16,27,30-33]

Documented consequences of LBM loss in older adults include:[16,22,30]

- **Frailty**—reduced ability to walk, climb stairs, rise from a chair, and carry a load
- **Physical disability**—3- to 4-fold greater risk, independent of age, gender, obesity, ethnicity, socioeconomic status, chronic morbidity, and health behaviors
- **Loss of independence**—reduced ability to cope with major illness and limited capacity to participate in activities due to diminished aerobic capacity
- **Depression**—due to loss of independence
- **Increased mortality**—due to infections, falls, pneumonia, etc.

Individuals of all ages can be impacted by loss of LBM as illustrated in Table 2.

Table 2. Regardless of age or cause, LBM loss compromises immune function and affects all organs[16]

Complications increase with greater LBM loss		
% Loss of total LBM	Complications*	% Mortality
10	Impaired immunity, increased infection	10
30	Decreased healing, weakness, infection, thinning of skin	30
20	Too weak to sit, pressure ulcers, pneumonia, wound healing stops	50
40	Death—usually due to pneumonia	100

*In the absence of preexisting LBM loss.
Adapted from Demling.[16]

The Role of Nutrition in the Healing Process

Nutrition and hydration, along with routine wound care, are critical to tissue integrity and are important factors in the care of wounds and the prevention and healing of pressure ulcers. Research has shown a strong relationship between wound healing and nutritional status,[11,34-41] and malnutrition is a major risk factor for pressure ulcer development.[36] Studies have demonstrated that involuntary weight loss, low weight status, low albumin levels, and low body mass index (BMI) also are associated with pressure ulcer development and poor healing.[34-38,42] One study found that calorie and protein intake was lower for long-term care residents who developed pressure ulcers than for those who did not.[43] Horn et al.[4] showed that, in more than 1500 long-term care residents, those who had experienced significant weight loss and eating problems were more likely to develop pressure ulcers, while residents receiving nutritional intervention (e.g., use of oral nutritional supplements and tube feeding for more than 21 days) were less likely to develop pressure ulcers.[4]

The Role of Specific Nutrients in Skin Integrity and Healing

Increased protein intake is often emphasized in patients with non-healing wounds. However, adequate intake of one nutrient alone does not prevent pressure ulcer formation or facilitate healing. Sufficient calories, protein, fluid, and essential vitamins and minerals are all required for preventing and treating pressure ulcers and other wounds (Table 3).

Table 3: Specific nutrients for skin integrity and healing

Nutrient	Role in Skin Integrity and Healing	Dietary Recommendation	Benefit
Calories	Energy source	30–35 kcal/kg body weight[44,45]	Provide energy; preserve lean body mass (LBM)
Protein	Tissue maintenance and repair	1.25–1.5 g/kg body weight[44,45]	Builds LBM
Fluid	Normal cell function and tissue integrity, adequate blood volume and circulation, and nutrient and oxygen supply to tissues	3.7 L (125 fl oz, approx. 13 cups) for males >19 years old **OR** 2.7 L (91 fl oz, approx. 9 cups) for females >19 years old **OR** 30–35 mL/kg body weight. Increase by an additional 10–15 mL/kg if patient is on air-fluidized bed[46]	Supports wound repair
Vitamins and Minerals		Daily multivitamin/mineral supplement[45]	
Vitamin A	Cellular differentiation and proliferation; Collagen synthesis; Immune function; Epithelial development	Supplement above RDA if deficient. RDA=900 μg/day for males; 700 μg/day for females; UL=3000 μg/day[47]	Supports wound strength and healthy new tissue
Vitamin C	Connective tissue and collagen synthesis	Supplement above RDA if deficient. RDA=90 mg/day for males; 75 mg/day for females; UL=2000 mg/day[48]	Supports wound strength
Vitamin E	Antioxidant	Supplement above RDA if deficient. RDA=15 mg/day for males and females; UL=1000 mg/day[48]	Quenches free radicals and helps maintain membrane integrity
Zinc	Cellular growth and replication	Supplement above RDA if deficient. RDA=11 mg/day for males; 8 mg/ day for females; UL=40 mg/day[47]	Supports growth of healthy new tissue
Arginine	Regulates many metabolic and physiologic functions involved in wound healing and tissue repair	17–24 g/day have shown benefits in wound healing	Supports protein synthesis needed for wound healing
Glutamine	Tissue repair and cell proliferation	0.57 g/kg is the daily suggested maximum	Supports protein synthesis and offsets muscle glutamine depletion
HMB	May inhibit breakdown of LBM	3 g CaHMB, along with arginine and glutamine, support collagen deposition	Helps maintain and rebuild lean body mass

RDA: Recommended Daily Allowance
UL: Tolerable Upper Intake Level

Calories

Calories provide the body with energy. If sufficient calories are not consumed, weight loss occurs in the form of adipose tissue and lean body mass loss. Weight loss is associated with an increased risk of pressure ulcers.[49]

If the body does not have the calories it needs for energy, it will use protein and lean body mass for its energy source. Calorie needs should be assessed carefully, and adequate calories should be provided so that protein can be used for tissue maintenance and repair, and not for energy.

The National Pressure Ulcer Advisory Panel (NPUAP), the European Pressure Ulcer Advisory Panel (EPUAP) and the Pan Pacific Pressure Injury Alliance (PPPIA)[45] have provided guidelines for determining calorie needs for patients with pressure ulcers.[45] Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline. Emily Haesler (Ed.). Cambridge Madia: Osborne Park, Western Australia: 2014. These guidelines recommend providing 30 to 35 kcal/kg body weight per day for malnourished persons who have a pressure ulcer. It is reasonable to use this same calorie recommendation for persons with other types of wounds or who are at risk of pressure ulcer development, but it is important to remember that calorie needs are individualized and vary for each person based on specific needs and conditions.

Protein

Protein provides amino acids, which are the building blocks of the body. Protein is needed for tissue maintenance and repair. Insufficient intake of protein is associated with pressure ulcer development,[43,50] and a high-protein intake is important for wound healing.[45,51]

The NPUAP, EPUAP and PPPIA guidelines recommend 1.25–1.5 g/kg body weight per day for patients with pressure ulcers who are malnourished.[45] As with calories, it is reasonable to also use this recommendation for persons with other types of wounds or who are at risk of pressure ulcer development. Increasing protein intake in adults beyond 1.5 g/kg per day may not increase protein synthesis and may cause dehydration.[52]

Amino Acids

There is an exchange between body protein (i.e., all the protein in tissues and the circulation) and the free amino acid pool (i.e., amino acids dissolved in body fluids). Free amino acids are derived from protein turnover, which is a continual process, dietary intake, and *de novo* synthesis of dispensable amino acids in the cell. Amino acids are lost via excretion, oxidation and non-protein pathways.[53]

The conditionally indispensable amino acids (also commonly known as conditionally essential amino acids) are defined as amino acids that require a dietary source when endogenous synthesis cannot meet metabolic needs. The requirement for these amino acids varies according to the specific condition, but it is known that catabolic stress increases the need for the conditionally indispensable amino acids.[53] Table 4 lists the amino acids according to the current classifications in the human diet.

Table 4: Classification of amino acids in the human diet.[53]

Indispensable	Dispensable	Conditionally Indispensable	Precursors of Conditionally Indispensable
Histidine	Alanine	Arginine	Glutamine /glutamate, asparate
Isoleucine	Aspartic acid	Cysteine	Methionine, serine
Leucine	Asparagine	Glutamine	Glutamic acid / ammonia
Lysine	Glutamic acid	Glycine	Serine, choline
Methionine	Serine	Proline	Glutamate
Phenylalanine		Tyrosine	Phenylalanine
Threonine			
Tryptophan			
Valine			

Specific amino acids, particularly arginine and glutamine, may also be beneficial for healing.

Arginine

Arginine is a conditionally essential amino acid, meaning that it is made by the body in sufficient quantities under usual conditions but a dietary source becomes necessary during periods of growth or healing. Arginine regulates metabolic and physiologic functions that support wound healing and tissue repair.[54] Supplemental arginine has resulted in improved markers of wound healing, including greater protein and hydroxyproline (an amino acid precursor present in collagen) in the wound bed, enhanced T-lymphocyte function, and promotion of positive nitrogen balance.[55-57] Many of these data have been obtained from studies in healthy human volunteers[55-57] over short periods using doses between 7 and 25 g of arginine per day.[56-58] In general, these data suggest that when the usual oral diet is supplemented with arginine for two weeks, there is benefit in healing and immune function.[55,56] The current guidelines for the prevention and treatment of pressure ulcers, suggests supplementation of arginine for adults with pressure ulcers.[45] Therefore, supplemental arginine may be a beneficial component of care for healing.

Glutamine

Glutamine is also a conditionally essential amino acid in certain circumstances such as tissue injury.[59] It is important for tissue repair and is used by inflammatory cells within wounds for cell proliferation.[60] Lymphocytes, macrophages, and intestinal cells depend on glutamine as a fuel source. Thus, when the body's immune system is mobilized because of severe illness or infection, the need for glutamine is increased. This increased demand may reduce blood glutamine concentration, which in turn mobilizes muscle glutamine stores. Loss of muscle glutamine negatively affects new muscle protein synthesis.[59] Supplemental glutamine has been used to offset muscle glutamine depletion and replete muscle glutamine levels. In addition, glutamine may stimulate collagen synthesis, vital to growth of new tissue.

Amino Acid Metabolite

ß-hydroxy-ß-methylbutyrate (HMB)

HMB is a naturally occurring metabolite of the essential amino acid leucine, and has been shown to attenuate muscle proteolysis or breakdown and modulate protein turnover.[60] If supplied in the diet in sufficient quantity, HMB can help protect muscle from stress-related damage. This effect has been shown for several stressors, including various types of strenuous exercise and in certain disease states associated with muscle wasting, such as AIDS and cancer, as well as in older adults. Other mechanisms of action of HMB in reducing muscle loss are currently under investigation.

HMB is a metabolite of leucine, a branched-chain essential amino acid consumed from dietary sources.[61] A 70-kg person produces 0.2 to 0.4 g of HMB daily; this quantity may not be sufficient to support metabolic needs during times of stress and healing.[61, 62] Leucine regulates protein synthesis and helps maintain nitrogen balance, an indicator of the availability of protein for the body's use.[63,64] HMB is the active metabolite of leucine that regulates protein synthesis in muscle cells.[65]

HMB exerts its effects through protective, anti-catabolic mechanisms and has been shown to directly influence protein synthesis.[66] HMB has been shown to:

- stabilize the muscle cell membrane[61]
- modulate protein degradation[67-69]

Stabilization of the muscle cell membrane

Cholesterol plays a crucial role in the structure of the cellular membrane, reducing susceptibility to rupture during stretching. As a substrate for cholesterol synthesis in the muscle cell, HMB contributes to the strengthening of the cell membrane. In this way, HMB helps stabilize the muscle cell membrane to keep the muscle cell intact.[61]

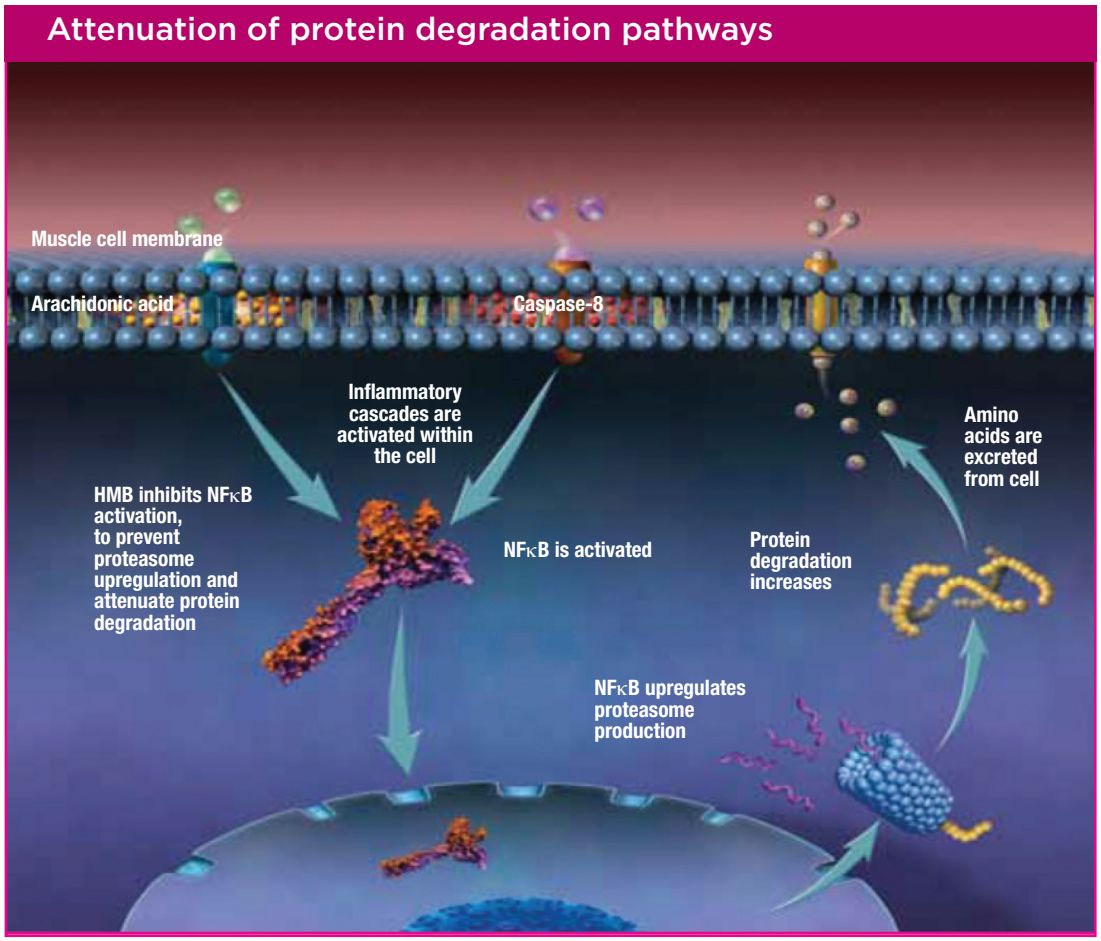
Modulation of protein degradation

LBM loss associated with chronic disease, acute illness, cancer, and chronic wounds is the result of increased circulation of inflammatory cytokines or signaling factors that increase protein degradation.[67, 69-71]

For example:

HMB interrupts two pathways that promote protein degradation in skeletal muscle cells (Figure 5). Although initiated by these different signaling factors, both pathways result in the activation of a regulator that promotes protein degradation, namely, nuclear factor kappa B (NFκB).

Figure 5. HMB selectively inhibits intracellular inflammation to attenuate protein degradation[72-75]



HMB Clinical Research with/without Glutamine and Arginine

HMB (ß-hydroxy-ß-methylbutyrate) has been extensively studied in healthy adults, alone and in combination with amino acids, as an adjunct to exercise to help improve body composition and performance. A review of 20 human-research publications support the effectiveness of HMB in:[66]

- decreasing delayed onset of muscle soreness and markers of muscle damage
- increasing lean body mass (LBM) without fat gain
- increasing various markers of performance, including LBM and strength

These studies also demonstrated a favorable safety profile for HMB supplementation and support a daily effective dose of 3g per day.[66] Additional randomized controlled studies have been conducted in populations that have increased risk related to loss of LBM. In these studies, HMB alone or in combination with arginine and glutamine or lysine effectively:

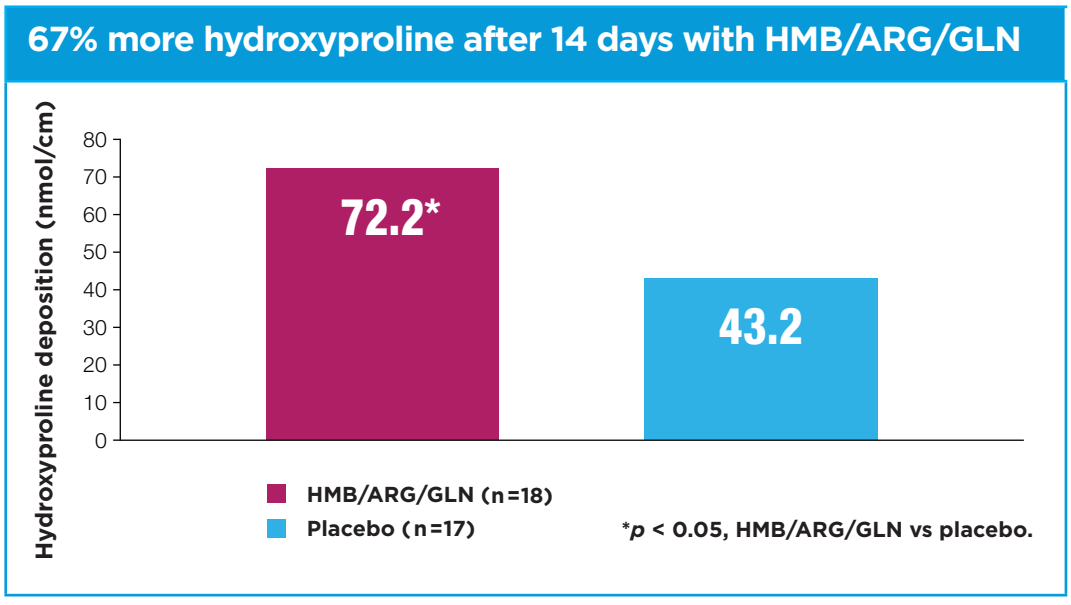
- improved nitrogen balance in critically injured adult patients[76]
- improved body composition and functionality in healthy elderly men and women[77,78]
- increased LBM in patients with stage IV cancer and AIDS-associated wasting[64,79]

Enhanced wound healing in older volunteers

Of related interest is the impact of a combination of HMB, arginine, and glutamine on an experimentally induced wound.[80] This combination of nutrients significantly increased collagen deposition at the wound site. In a 14-day randomized, controlled, double-blind study, two small, sterile polytetrafluoroethylene (PTFE) tubes were implanted subcutaneously into the deltoid region of 35 healthy elderly volunteers (mean age: 75.4 years). The volunteers received 2 daily doses of an amino acid mixture totaling 3g HMB, 14g arginine, and 14g glutamine (HMB/ARG/GLN, n=18) or an isonitrogenous isocaloric mixture of nonessential amino acids (placebo, n=17). The tubes were removed after 7 and 14 days for evaluation of collagen matrix deposition, evidenced by hydroxyproline accumulation (collagen matrix enhances wound strength and integrity).[80]

After 14 days, hydroxyproline content was 67% greater ($p<0.05$) with HMB/ARG/GLN compared to placebo, indicating significantly greater collagen deposition (Figure 6). The authors concluded that oral administration of HMB/ARG/GLN significantly enhanced collagen synthesis in healthy elderly volunteers and would provide a safe nutritional means for increasing wound repair.[80]

Figure 6. HMB/ARG/GLN produced significantly greater collagen deposition vs placebo after 14 days in elderly volunteers[80]

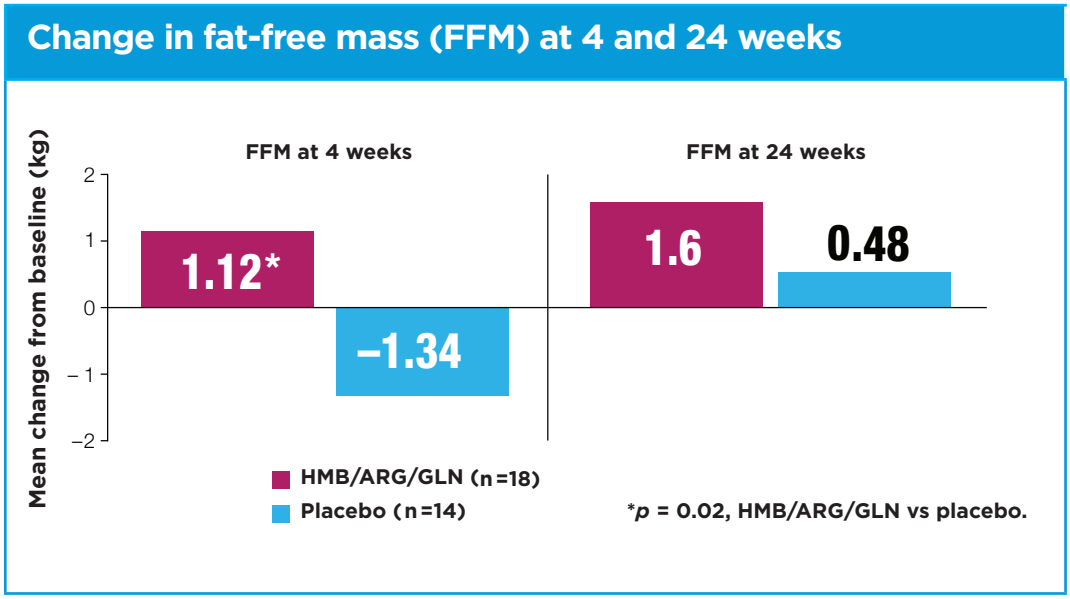


Reversing LBM loss due to cancer or AIDS

HMB in combination with arginine and glutamine significantly increased LBM in patients with advanced cancer. A 24-week randomized, double-blind, placebo controlled study evaluated the effects of 3g/day of calcium HMB in combination with 14g/day of L-arginine and 14g/day of L-glutamine (HMB/ ARG/GLN; n=18) or an isonitrogenous mixture of nonessential amino acids (n=14) in patients with stage IV solid tumors who had lost ≥5% overall weight.[64] Daily supplementation with the HMB nutrient mixture increased weight gain and LBM in these cancer patients. Benefits were seen as early as 4 weeks after starting HMB/ARG/GLN and maintained throughout the 24 weeks of nutritional therapy (Figure 7). With HMB/ARG/GLN, the majority of weight gain was LBM, whereas with placebo, patients who gained weight gained only fat:[64]

- Change in body weight at 4 weeks: +0.95 kg with HMB/ARG/GLN, –0.26 kg with placebo
- Change in LBM at 4 weeks: +1.12 kg with HMB/ARG/GLN, –1.34 kg with placebo (p=0.02)
- Change in LBM at 24 weeks: +1.60 kg with HMB/ARG/GLN, +0.48 kg with placebo

Figure 7. Patients with stage IV tumors gained significantly more fat-free mass after 4 weeks of HMB compared with those who received placebo[64]



Baseline LBM was not reported.

In another study, HMB in combination with arginine and glutamine significantly improved weight and LBM and provided immune benefits in patients with AIDS. An 8-week randomized, double-blind, placebo- controlled study evaluated the effects of a nutrient mixture containing 3g calcium HMB, 14g L-glutamine, and 14g L-arginine (HMB/ ARG/GLN; n=34) or a maltodextrin placebo (n=34) in AIDS patients with documented weight loss of ≥5% within the previous 3 months.[79] Patients taking the HMB mixture gained significantly more weight in 8 weeks than did patients taking the placebo mixture, and the weight gained with HMB/ARG/GLN was primarily LBM[79] (Figure 8):

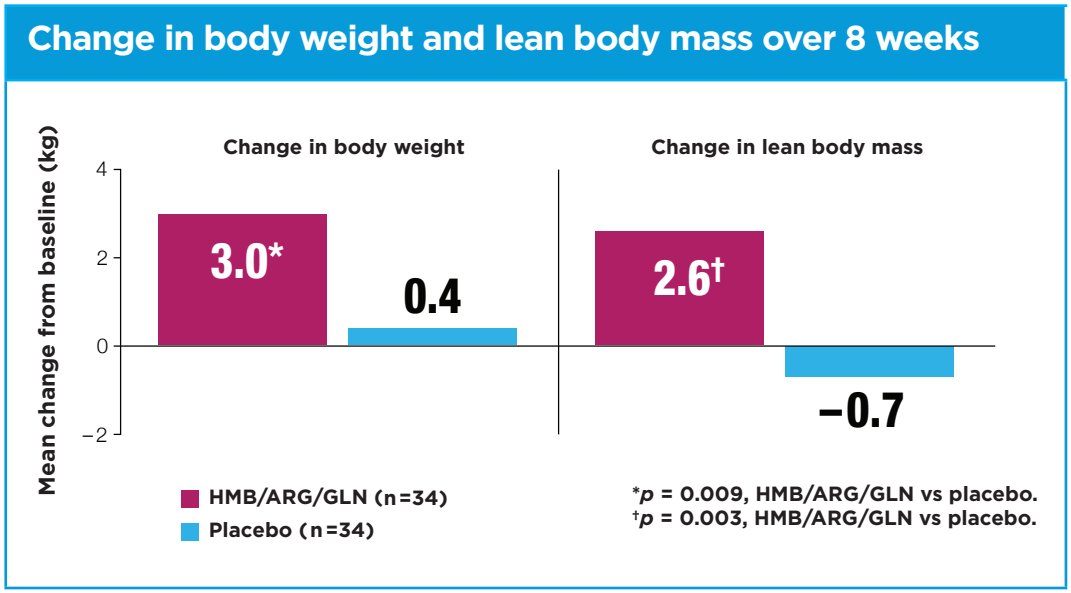
- Mean change in body weight at 8 weeks: +3.0 kg with HMB/ARG/GLN, +0.4 kg with placebo (p=0.009)
- Mean change in LBM at 8 weeks: +2.6 kg with HMB/ARG/GLN, –0.7 kg with placebo (p=0.003)
- Percent of patients gaining >0.5 kg LBM: 70% with HMB/ARG/GLN, 40% with placebo

HMB/ARG/GLN also provided significant improvements in immune status for these AIDS patients. Total circulating lymphocyte counts and HIV viral load improved significantly in patients receiving the HMB mixture; improvements in lymphocyte count were primarily reflected in CD3 (p=0.01 vs placebo) and CD8 (p=0.02 vs placebo) subsets:[79]

- Change in total circulating lymphocyte count: +0.29 x 10^3 cells/mm^3 with HMB/ARG/GLN, –0.31 x 103 cells/mm^3 with placebo
- Significant increases in CD3 and CD^8 counts with HMB/ARG/GLN vs placebo (p=0.01 and p=0.02, respectively); nonsignificant increase in CD4 with HMB/ARG/GLN vs placebo (p=0.10)
- Placebo-corrected change in HIV RNA with HMB/ARG/GLN: –0.7 log copies/mL (p=0.007 vs placebo)

HMB/ARG/GLN was well-tolerated by patients with HIV and did not alter hepatic enzyme profiles or indicators of kidney function. All study patients were on multiple combination antiretroviral therapies, without apparent interference from HMB/ARG/GLN.[79]

Figure 8. Changes in body weight and fat-free mass in patients with AIDS: HMB/ARG/GLN vs placebo[79]



Building LBM in older volunteers

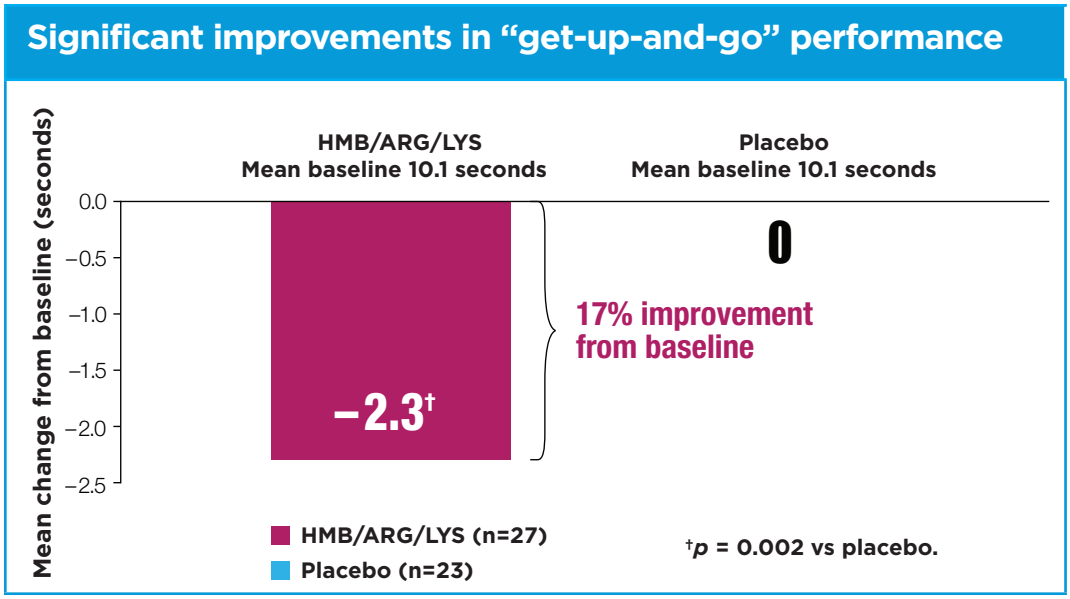
In older women HMB, in combination with arginine and lysine, significantly increased protein synthesis and improved body composition, strength, and functionality. A 12-week randomized, double-blind, placebo-controlled study compared the effects of once-daily administration of a nutrient mixture containing 2g calcium HMB, 5g arginine, and 1.5g lysine (HMB/ARG/LYS; n=27) or a placebo drink (an isocaloric drink of maltodextrin and ascorbic acid, n=14; or isocaloric isonitrogenous mixture containing nonessential amino acids and ascorbic acid, n=14) in elderly women (mean age 76.7 years). Participants were normotensive or had controlled hypertension, had normal blood glucose or controlled diabetes, and were not receiving active treatment for liver or kidney disease.[4] The rate of protein synthesis increased approximately 20% in women taking HMB/ARG/LYS in comparison to

placebo (p=0.03) with 12 weeks of HMB-containing therapy. Body composition improved significantly with HMB/ARG/LYS, evidenced by a substantial increase in LBM:[78]

- Mean change in LBM from baseline: +0.7 kg with HMB/ARG/LYS, 0 kg with placebo (p=0.08)
- Change in fat mass and percentage of body fat: 0% in both treatment groups
- Change in average limb circumference (arm, forearm, and thigh combined): +0.4 cm with HMB/ ARG/LYS, –0.3 cm with placebo (p=0.03)

Significant improvements were seen in functionality with HMB/ARG/LYS compared with placebo. "Get-up-and-go" performance* improved 17% (a decrease of 2.3 seconds from baseline) vs. no change with placebo (p=0.002).

Figure 9. Elderly women who received HMB/ARG/LYS showed significant improvement in functionality ("get-up-and-go" performance) at 3 months[78]



Across studies, supplementation with this HMB nutrient mixture has not been associated with any adverse indicators of health.

Summary: Impact of HMB, Arginine, and Glutamine on LBM and Wound Healing

Table 5: Impact of HMB, arginine, and glutamine on LBM and wound healing

HMB—A normal constituent of muscle
If supplied in sufficient quantity, HMB can help protect muscle from stress-related damage.[60] Published studies with HMB have shown the following benefits: * Building of LBM[60] * Decrease in muscle breakdown[81] * Increase in protein synthesis[82]
Arginine—A conditionally essential amino acid
Helps support wound healing and protein synthesis. Benefits of supplemental arginine include: * Promotion of wound healing[55,56] * Support of collagen/protein synthesis[56] * Enhanced immune function[55,56]
Glutamine—A conditionally essential amino acid
Helps support the immune system and protein synthesis. Benefits of supplemental glutamine include: * Stimulation of collagen synthesis[83,84] * Support of immunity[85] * Support of gut integrity[86]

Selected Vitamins and Minerals

Various vitamins and minerals have been studied to examine their effects on wound healing. Nutritional deficiencies have been associated with pressure ulcer development and impaired wound healing. Therefore, clinicians often supplement intake of vitamins and minerals thought to be especially important for wound healing. The NPUAP, EPUAP and PPPIA guidelines recommend a daily multivitamin and mineral supplement if deficiencies are confirmed or suspected.[45] Additional vitamins and minerals routinely supplemented in persons with wounds or pressure ulcers are vitamins A, C and E, and zinc. This practice is most beneficial for persons with confirmed or suspected nutritional deficiencies.

Vitamin A

is a fat-soluble vitamin important for cellular differentiation and proliferation. Vitamin A has a role in collagen synthesis, the immune system, and epithelial development.[25] Studies indicate that vitamin A plays a role in wound healing by increasing collagen synthesis and epithelialization.[87] Vitamin A deficiency may result in delayed wound healing and an increased susceptibility to infections.[87] Studies of vitamin A supplementation for wound healing have been done with doses that range from 25,000 to 50,000 IU (approximately 7500–15,000 μg).[87,88] However, the research to support vitamin A supplementation for wound healing is lacking.[89,90] Therefore, vitamin A supplementation appears to be indicated only for patients who are specifically vitamin A deficient. Vitamin A is stored in the liver, so true deficiency is rare. Clinical vitamin A deficiency is defined as a serum vitamin A level of <0.35 μmol/L. The Recommended Dietary Allowance is 900 μg/day for males and 700 μg/day for females.[47] The tolerable upper intake level (UL) is 3000 μg/day.[47] Since vitamin A is stored in the liver, high doses can be toxic.

Vitamin C

is a water-soluble vitamin that contributes to the synthesis of connective tissue, in particular, collagen.[91] Impaired wound healing resulting from decreased collagen synthesis is associated with vitamin C deficiency that can be reversed with adequate supplementation.[92] Although vitamin C supplementation has been proven to enhance wound healing in deficient patients, the benefit of supplementation in non-deficient patients remains unclear.[90] Some studies in non-deficient patients have found no significant improvement in wound healing with vitamin C supplementation.[92,93] Other research has shown that when vitamin C intake is inadequate, collagen synthesis is reduced,[94] and low concentrations of leukocyte vitamin C levels were associated with subsequent pressure ulcer development in older adults with femoral neck fractures.[95] Vitamin C supplementation levels reported in the literature range from 120 to 240 mg/day[96] and up to 4000 mg/day.[90] Vitamin C status can be measured by blood, serum, or plasma levels; however, these measurements are expensive. A deficiency is defined as a plasma level of <0.2 mg/dL.[97] The RDA for vitamin C is 75 mg/day for adult women and 90 mg/day for adult men. The UL is 2000 mg/day.[48] Toxic levels are unlikely to occur, but high doses of vitamin C can have adverse effects such as nausea, abdominal pain, and diarrhea. Overall, scientific evidence to support the use of vitamin C supplementation in patients without a deficiency or to accelerate wound healing is lacking and sometimes conflicting, and further research is needed.

Vitamin E

is a fat-soluble vitamin that acts as an antioxidant which reduces peroxidation of lipids to help stabilize cell membranes. It is also used for skin care to reduce scar formation because it inhibits collagen synthesis and decreases tensile strength of wounds.[88] Research on the role of vitamin E and wound healing is lacking, and the few studies that have been conducted show conflicting results.[90] Excess vitamin E has been found to impair wound healing and inhibit blood clot formation in animals.[88] The RDA is 15 mg for adult men and women.[39] The UL is 1000 mg/day.[48] Until more research is conducted on vitamin E and wound healing, supplementation should be used only for patients who are deficient.

Zinc

is an essential trace mineral required for cellular growth and replication. It is necessary for DNA synthesis, cell division, and protein synthesis, all processes vital for tissue growth and repair. Zinc deficiency affects wound healing by decreasing protein and collagen synthesis.[88] Chronic, severe zinc deficiency results in abnormal neutrophil and lymphocyte function, delayed wound healing, and an increased susceptibility to infection.[48] Zinc deficiency can occur through wound drainage, gastrointestinal losses (such as diarrhea), or a prolonged low dietary intake. Neither zinc status nor dietary intake of zinc has been shown to be a risk factor for developing pressure ulcers.[36,43,95,98,99] Studies of zinc supplementation for wound healing range from 15 to 60 mg/day.[87,88] Zinc supplementation remains controversial, and there is no significant evidence that routine zinc supplementation promotes pressure ulcer healing.[100] Zinc supplementation should be given only to patients who are deficient because it does not appear to improve wound healing in nondeficient patients. In addition, excess zinc supplementation can adversely affect wound healing.[88] The potential toxic effects of zinc include interference with copper metabolism and impaired immune function.[51] Zinc levels can be measured by plasma or serum levels, but they are not sensitive nor specific indicators of zinc status.[88] However, serum zinc levels of <100 μg/dL are associated with impaired wound healing.[88] The RDA for zinc is 8 mg/day for adult women and 11 mg/day for adult men.[47] The UL is 40 mg/day for adult men and women.[47]

Fluid

Fluid is an essential nutrient that is important for the normal functioning of cells. Dehydration can occur if a person does not consume enough fluid or if fluid loss exceeds fluid intake. Wound drainage can be a major source of fluid loss and can lead to dehydration and electrolyte imbalance. Dehydration frequently occurs with malnutrition and is a risk

factor for pressure ulcer development[97,101] because it can reduce blood volume, thereby interfering with peripheral circulation and decreasing nutrient and oxygen supply to tissues.

Optimal hydration is attained when fluid intake equals fluid output. Current recommendations are that total water intake from all beverages and foods should be 2.7 L (approx. 9 cups) for women more than 19 years old and 3.7 L (approx.13 cups) for men more than 19 years old.[46] Fluid is particularly important for older adults because they are at increased risk for dehydration as a result of the decreased thirst sensation that occurs with aging. A rule of thumb is to provide 30–35 mL of fluid per kg body weight per day, or 1 mL of fluid per calorie fed for persons receiving enteral tube feeding.[102] Patients on air-fluidized beds require an additional 10–15 mL fluid/kg body weight to prevent dehydration that can occur from the drying effects of these specialty beds.[52]

Nutrition Screening, Assessment and Intervention

Current State of Nutrition Screening, Assessment and Intervention.

It has already been established that malnutrition is common, under-recognized, and under-treated in various patient populations, which emphasizes the need for nutrition screening and assessment. In the absence of formal nutrition screening, more than half of patients at risk in various healthcare settings are not recognized and/or referred for treatment.[103] Further, failure to recognize hospital patients with malnutrition and refer them for assessment and treatment has been reported in 60-85% of hospitalized patients.[104-106] Moreover, in a study of four hospitals, only 24% (41 of 168) of malnourished patients were referred to a dietitian.[105] These data demonstrate that the majority of patients who are malnourished or at risk may not been receiving the nutritional care they need.

A study by Rasmussen et al. looked further into the issue of nutrition screening and assessment.[107] This study examined the prevalence of nutritional risk at 15 randomly selected departments in five hospitals. Of the 590 patients evaluated, 39.9% were determined to be at nutritional risk, but only 7.6% of the patient records contained any information about nutritional risk. In addition, only 14.2% of patients had a nutritional plan, and further only 55.2% of these patients' plans included a plan for monitoring nutritional status and only 28.1% had a dietitian consult.

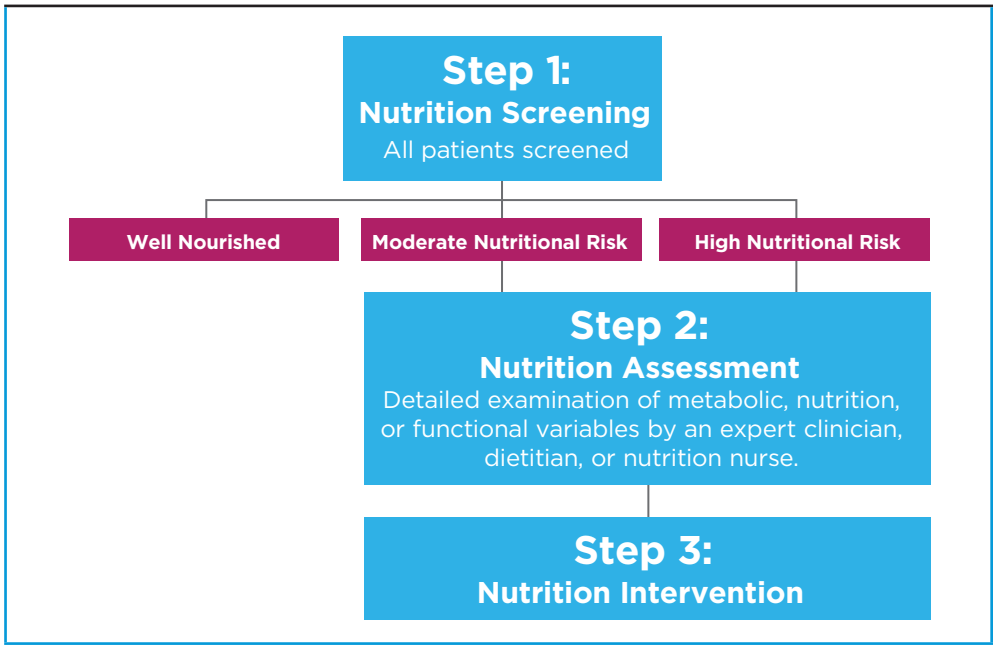
Another study explored this issue further.[108] This study analyzed the incidence of nutritional risk in 750 randomly selected patient admissions to three hospitals. The results showed that only 60% of cases were screened for nutrition problems and of the patients who were deemed at nutritional risk (22%), only 25% received adequate energy and protein intake, only 47% had a nutrition plan, and only 30% were monitored for dietary intake and body weight. The researchers also conducted a questionnaire with the nursing staff to determine their interest and knowledge of nutrition screening. Most of the staff agreed that nutritional support would prevent complications during hospital stay; however, only 20% performed nutritional screening and/or assessment including dietary intake and BMI. The reasons given for not initiating nutritional intervention included insufficient knowledge of nutrition, low priority given to nutritional care, unclear assignment of responsibility, lack of procedural guidelines to perform screening, and patients' short duration of stay.

There is a definite need in many health care settings for nutrition screening and assessment. Research has shown many benefits of nutrition screening, assessment and, in particular, nutrition intervention to both the patient and health care institution. These benefits include decreased morbidity,[109-111] decreased mortality,[112,113] increased quality of life and functioning,[114-116] decreased admissions/readmissions and length of stay,[109,117] and decreased health care costs.[118,119]

A Nutrition Screening, Assessment and Intervention Strategy

If not already doing so, health care facilities need to implement a nutrition screening, assessment and intervention strategy to help identify patients with or at risk of malnutrition and implement appropriate strategies to address the issue. An example of a nutrition care pathway is shown in Figure 10.

Figure 10: Example of a nutrition care pathway



Nutrition screening

Nutrition screening is defined as the process of identifying patients who are at risk for malnutrition or those suspected of becoming at risk because of disease or treatment. The goal of nutrition screening is early identification of patients at risk for malnutrition. The AHCPR/AHRQ guidelines define clinically significant malnutrition as albumin <3.5 g/dL, total lymphocyte count <1800/mm^3, and weight loss >15%.[49] In addition, according to the SCCM (Society of Critical Care Medicine) and A.S.P.E.N. (American Society for Parenteral and Enteral Nutrition) guidelines, initial nutrition screening is encouraged for all patients.[120]

As inexpensive nutrition screening may identify those at risk for malnutrition, confirming the presence of malnutrition through more thorough, comprehensive assessment and characterizing its severity may be a cost-effective procedure. For this and other reasons, nutrition screening is crucial a crucial first step for every patient. Malnourished or at risk patients will go on to a more thorough nutrition assessment in Step 2.

There are numerous nutrition screening tools. A good nutrition screening tool should be validated, simple and easy to use, and should provide reliable results. Selecting the appropriate tool depends upon the population and the available resources. Here are examples of nutrition screening tools:

- **Malnutrition Screening Tool (MST):** simple and quick screening tool with two questions related to weight loss and appetite, can be completed by nursing staff. http://www.ensurenutrition.com/static/cms_workspace/videos/MST.pdf

- **Malnutrition Universal Screening Tool (MUST):** screening tool developed by the British Association of Parenteral and Enteral Nutrition (BAPEN), based on BMI, weight loss, estimation of effect of illness on nutritional intake.

  http://bapen.org.uk/pdfs/must/must_full.pdf

- **DETERMINE checklist:** self-administered screening checklist of eating and social habits for elderly patients; has professional healthcare forms for follow-up assessment of anthropometric measures, BMI, weight loss, and functional abilities.

  http://www.ensurenutrition.com/treatment-and-prevention/screening.html

- **Nutrition Risk Index (NRI):** technical screening tool that requires measurement of serum albumin levels and weight loss; precise but not practical in community setting
- **Nutritional Risk Screening (NRS-2002):** easy screening tool endorsed by ESPEN for use in the hospital.
- **Mini-Nutritional Assessment (MNA):** a validated nutrition screening and assessment tool endorsed by ESPEN for use in the elderly that can identify geriatric patients age 65 and above who are malnourished or at risk of malnutrition.

  http://www.mna-elderly.com/mna_forms.html

Regardless of the tool chosen for screening, it is important that all patients receive an evaluation of nutritional status. When deficiency or risk is identified, the level or severity of malnutrition or nutritional risk should be determined through a more thorough examination of a patient's nutritional status through a nutrition assessment.

Nutrition Assessment

Nutrition assessment is the process of collecting and assessing data about clinical conditions, diet, body composition, and biochemical data to identify patients with poor nutritional status and develop an appropriate nutrition therapy plan. Nutrition assessment should be performed by a qualified, trained healthcare professional.

There are numerous tools that may be used for the nutrition assessment; selecting the appropriate tool depends upon the population and the available resources. Here are a few examples of assessment tools:

- **Subjective Global Assessment (SGA):** validated assessment tool that employs medical history and physical examination
- **Patient-Generated Subjective Global Assessment (PG-SGA):** same as SGA but includes patient input on weight loss, intake, and functional capacity
- **Mini-Nutritional Assessment (MNA):** a validated nutrition screening and assessment tool developed by Nestle Nutrition and endorsed by ESPEN for use in the elderly, that can identify geriatric patients age 65 and above who are malnourished or at risk of malnutrition.

In addition to traditional nutritional assessments, it may also be helpful to assess lean body mass and/ or functionality in patients with wounds. Assessment parameters can include muscle mass, strength and physical performance, and there are many measurements that can be used. In clinical practice, muscle mass can be measured by bioimpedance analysis (BIA), dual energy X-ray absorptiometry (DXA) and anthropometry, and muscle strength can be measured by handgrip strength.[20] Tests of physical performance include usual gait speed, get-up-and-go test, and the short performance physical battery (SPPB).[20] The SPPB is an objective assessment tool for evaluating lower extremity functioning in older adult.[121] It was developed by the National Institute on Aging

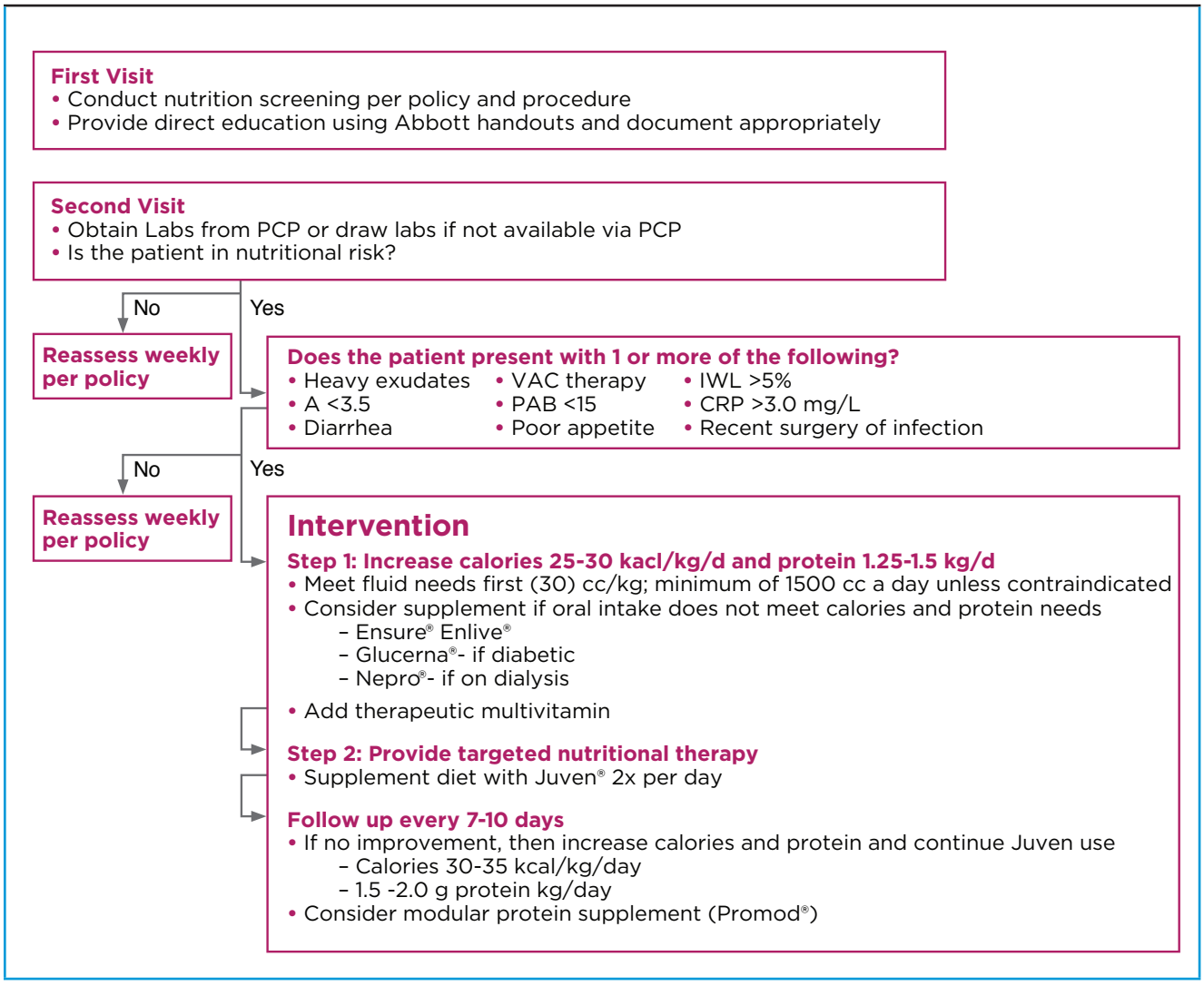
and consists of a hierarchical test of standing balance, a 4-meter walk, and five repetitive chair rises.[121] The SPPB helps assess physical functioning and disability in patients, and research has shown a relationship between SPPB scores and lean body mass.[122]

Nutrition Intervention

For patients with wounds, nutrition interventions are recommended for all appropriate patients who would benefit from future nutritional care. Protocols and standing orders can facilitate initiation of nutrition supplementation for patients at nutrition risk. Nutrition interventions can also be tailored by the dietitian based on the patient's needs and conditions and implemented by the health care staff. To optimize wound healing, nutrition interventions include the use of oral nutrition supplements (ONS) and targeted nutrition therapy. Figure 11 summarizes a strategy for administration of ONS to patients with wounds.

Protocol development guidelines for wound healing

Figure 11: Decision tree for administration of ONS for wound healing



Conclusion

Targeted nutrition therapy plays an important role in wound healing by providing nutrients that are critical for the healing process and through the preservation of lean body mass. Research has shown a clear correlation between nutritional status and healing. An overall well balanced diet, including adequate provision of calories, protein, fluid, vitamins, and minerals, is of fundamental importance in the healing process. Specific nutrients, namely, arginine, glutamine, and HMB may also be beneficial for wound healing. Nutrition screening, assessment, and intervention are key components of the health care team's approach to wound prevention and treatment. The work of the entire health care team can optimize nutritional management to help prevent wounds from developing and to help heal existing wounds.

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