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Introduction

HMB (β -hydroxy- β -methylbutyrate) is an amino acid metabolite that occurs naturally in human muscle cells. HMB is also found in foods such as avocado, citrus fruit, cauliflower, alfalfa, and catfish,¹ and it is available commercially as a nutritional supplement, calcium HMB monohydrate (CaHMB). Studies in animals and in humans demonstrated that HMB increases protein synthesis and decreases protein degradation.² Traditionally, HMB has been used by athletes to enhance performance and build muscle mass.² Recent research has focused on the use of HMB to preserve or rebuild muscle mass in populations in whom loss of lean body mass (LBM) would increase risk for injury, disability, or mortality. This research has demonstrated the benefits of HMB supplementation along with other amino acids in rebuilding LBM in the elderly as well as in persons with chronic diseases such as AIDS and cancer.³⁻⁶

Rebuilding LBM loss has the potential to influence disease processes and improve quality of life related to mobility and self-sufficiency. In populations compromised by LBM loss, preserving or rebuilding LBM may reduce morbidity and mortality by⁷⁻¹¹:

- improving physical function
- maintaining immune function
- assisting wound healing

HMB alone and in combination with other amino acids has been shown to provide benefits such as these to elderly individuals, to people with LBM loss due to AIDS, to late-stage cancer patients, and to patients in critical care.^{3-6,12,13} This monograph presents the rationale for HMB supplementation to preserve and rebuild LBM in individuals who have risk for LBM loss or have already lost LBM. It reviews the role of LBM and LBM loss in general health and in illness and injury, describes HMB and its mechanism of action, and presents clinical efficacy and safety data from controlled trials to date. These studies have shown that HMB, alone or as part of an amino acid–nutrient mixture, has rebuilt LBM in the elderly as well as in patients with AIDS and stage IV cancer, and has improved protein synthesis in critical care patients.

HMB alone or in combination with amino acids has been shown to improve physical function (along with exercise), support immune function, and assist wound healing in the elderly, in people with AIDS- or cancer-related LBM loss, and in critical care patients.

The role of lean body mass in health

Lean body mass (LBM) includes all body tissue except fat and accounts for 75% of normal body weight.¹¹ Skeletal muscle comprises 50% to 60% of LBM by weight. In the absence of nutrient intake, muscle is the principal repository of protein and amino acids used in protein synthesis.^{11,14} As such, muscle plays a central role in protein metabolism. Maintaining muscle mass is essential to support whole-body protein metabolism, wound healing, physical strength, organ function, skin integrity, and immune function.^{14,15} All of the complications associated with involuntary weight loss arise from the loss of protein from LBM.¹¹

Progressive LBM loss (sarcopenia) occurs naturally with age. Sarcopenia affects as many as 30% of adults older than 60 years of age and 50% of those older than 80 years.^{16,17} The process underlying the loss of LBM begins around age 30 and normally continues unabated¹⁷⁻²¹:

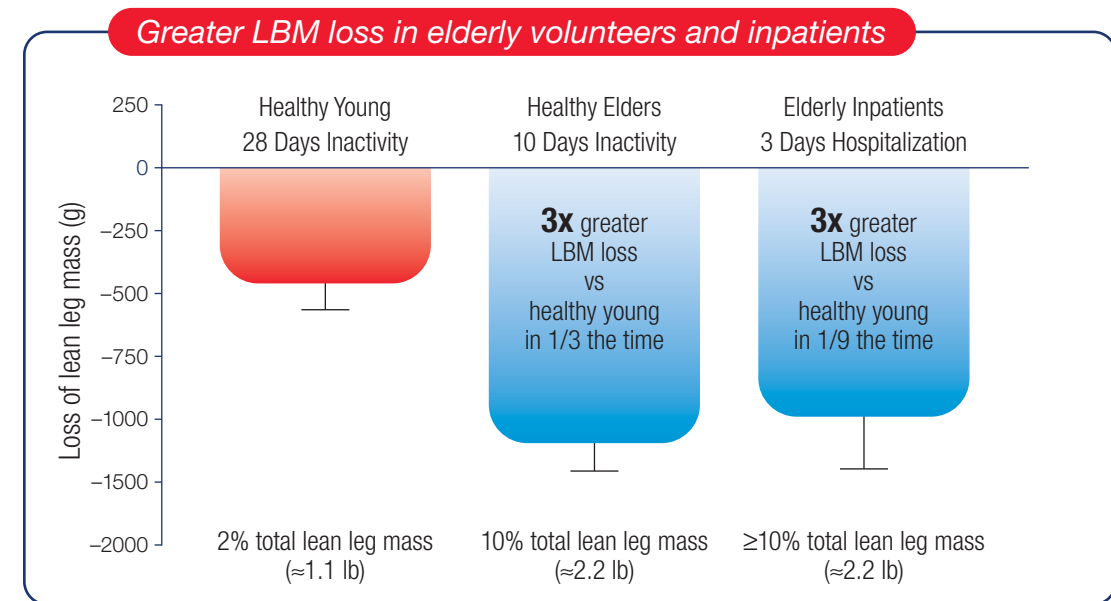
- At 30, weight gain begins to be preferentially accrued as fat instead of muscle
- By 40, LBM loss is occurring at 8% per decade
- After 70, the rate of LBM loss is up to 15% per decade

Chronic conditions, such as cancer, nonhealing wounds, HIV/AIDS, chronic obstructive pulmonary disease, and congestive heart failure are also associated with LBM loss.^{11,22}

Illness and injury can cause or accelerate LBM loss. In healthy young people, bed rest alone can lead to 2% to 3% loss in skeletal muscle in the leg.²³⁻²⁵ With illness or injury, the rate of LBM loss increases to as much as 10%, with even greater LBM loss in the elderly.^{25,26} This was shown in separate studies comparing LBM loss in elderly and younger individuals (Figure 1). In 3 separate studies, healthy younger adults were confined to bed for 28 days; healthy elderly adults, for 10 days; and elderly inpatients, for 3 days.²⁵ All healthy volunteers consumed the RDA for protein; the elderly inpatients did not.²⁵ LBM loss was measured in elderly inpatients after 3 days of hospitalization.²⁵

- Healthy young volunteers lost 2% (~500 g = 0.5 kg = 1.1 lb) LBM in the leg during 28 days of bed rest²⁵
- Healthy elderly subjects lost 10% (~1000 g = 1 kg = 2.2 lb) LBM in the leg during 10 days of bed rest—nearly 3 times greater LBM loss in one third of the time of the younger healthy volunteers²⁵
- Elderly inpatients lost at least 10% (~1000 g = 1 kg = 2.2 lb) LBM in the leg during 3 days of hospitalization—3 times greater LBM loss in less than one ninth of the time of the younger healthy volunteers²⁵

Figure 1. LBM loss associated with bed rest or hospitalization in healthy younger adults, healthy elderly, and hospitalized elderly patients²⁵



Adapted with permission from Paddon-Jones.²⁵

Loss of LBM can be debilitating, impacting immune function, wound healing, and overall body function.¹¹ In the elderly, loss of lean mass compromises physical strength and energy, increasing fatigue and risk for falls and fractures; weakens the immune system, increasing susceptibility to illness and infection; and compromises healing, reducing ability to recover from surgery, illness, or disease.^{11,22,27-30} Documented consequences of LBM loss in the elderly include^{11,27,30}:

- 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

Maintaining muscle mass is essential to support whole-body protein metabolism, wound healing, physical strength, organ function, skin integrity, and immune function.

In illness, surgery, or injury, as well as in the elderly, LBM loss increases morbidity and mortality; the complications increase with greater LBM loss (Table 1).¹¹

In cancer, LBM loss is associated with poor response to therapy, increased susceptibility to treatment-related toxicity, poor outcome, greater mortality, and diminished quality of life.³¹ Body composition is an important determinant of chemotherapy toxicity: women are more likely to have low LBM in relation to body surface area, which determines dosing for many therapies, and are more prone to toxicity.³² Diminished LBM reduces the volume of distribution of cytotoxic chemotherapies, leading to higher overall toxicity.^{32,33} Many patients may receive reduced chemotherapy dosage and treatment interruptions to avoid or overcome toxicity.³⁴

Table 1. Regardless of age or cause, LBM loss compromises immune function and affects all organs¹¹

<i>Complications increase with greater LBM loss</i>		
% Loss of total LBM	Complications*	% Mortality
10	Impaired immunity, increased infection	10
20	Decreased healing, weakness, infection, thinning of skin	30
30	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.¹¹

Loss of LBM increases risk for wounds and impedes wound healing. In addition, the process of wound healing may cause rapid LBM loss because the inflammatory response associated with wound healing places additional demands on body protein stores.³⁵⁻³⁷ Lean body mass, including critical tissues involved in immune defense mechanisms, accounts for approximately half of the weight loss associated with the inflammatory response.¹¹ Chronic wounds, such as pressure ulcers, remain in the inflammatory phase of healing and cannot heal until the inflammatory response has been addressed.³⁸

Wound healing requires protein, and the requisite amino acids are drawn from LBM: primarily muscle and vital organs.^{11,39,40} As functional proteins, amino acids are not “stored” like other nutrients. Healing wounds compete with muscles and organs for amino acids for use in the synthesis of new tissue. For chronic wounds to heal with minimal LBM loss, dietary protein intake must be adequate to supply the required amino acids.³⁷

Supplementation with protein and calories may not be enough to reverse LBM loss. Oral nutritional supplements have been shown to increase nutrient intake as well as weight and nutritional parameters, but not LBM.^{22,41-43} Protein requirements are higher for people with sarcopenia, chronic disease, acute illness, or critical injury. These patients generally need 1.5 g/kg of protein per day to meet the increased demand for protein synthesis and to avoid or overcome LBM loss (Table 2).¹¹

Table 2. Aging, illness, injury, and poor nutritional status increase protein requirements¹¹

<i>Protein requirements for patients at risk for LBM loss</i>	
Condition	Daily protein needs, g/kg/d
Normal	0.8
Elderly	1.2–1.5
Presence of wound	1.5
Trauma, infection, surgery	1.5–2.0
Critical illness	1.5–2.0
Chronic illness	1.5

Adapted from Demling.¹¹

Increasing protein and calorie intake alone may not overcome the metabolic stress or disease process causing the LBM loss, because stressed, depleted patients cannot metabolize more than 1.5 g/kg of protein per day.¹¹ HMB has been shown to enhance protein synthesis and attenuate the process of protein degradation to help increase lean body mass.

Supplementation with protein and calories may not be enough to reverse LBM loss.

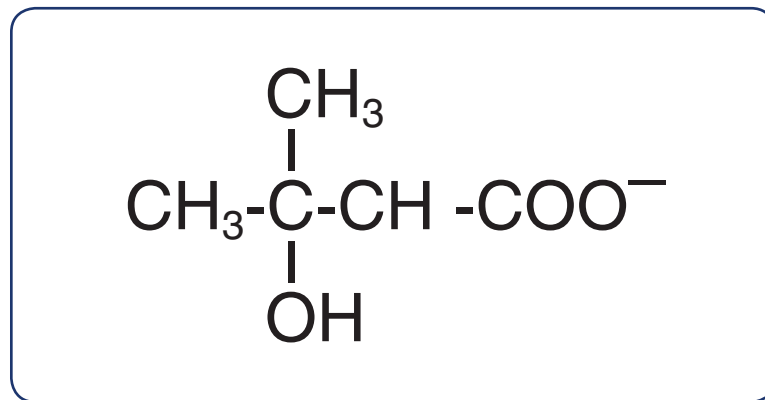
HMB chemical profile

HMB (β -hydroxy- β -methylbutyrate) is a metabolite of leucine, a branched-chain essential amino acid consumed from dietary sources.⁴⁴ Leucine regulates protein synthesis and helps maintain nitrogen balance, an indicator of the availability of protein for the body's use.^{45,46} HMB is the active metabolite of leucine that regulates protein synthesis in muscle cells.⁴⁷ HMB has been shown to inhibit muscle proteolysis and modulate protein turnover.⁴⁸⁻⁵¹

Chemistry

The chemical formula of HMB is $C_5H_{10}O_3$ (Figure 2); its molecular weight is 118.13. HMB is produced commercially by organic chemical synthesis and is supplied as a calcium salt: CaHMB monohydrate ($Ca(C_5H_9O_3)_2 \cdot H_2O$).

Figure 2. β -hydroxy- β -methylbutyrate chemical structure



HMB pharmacodynamics

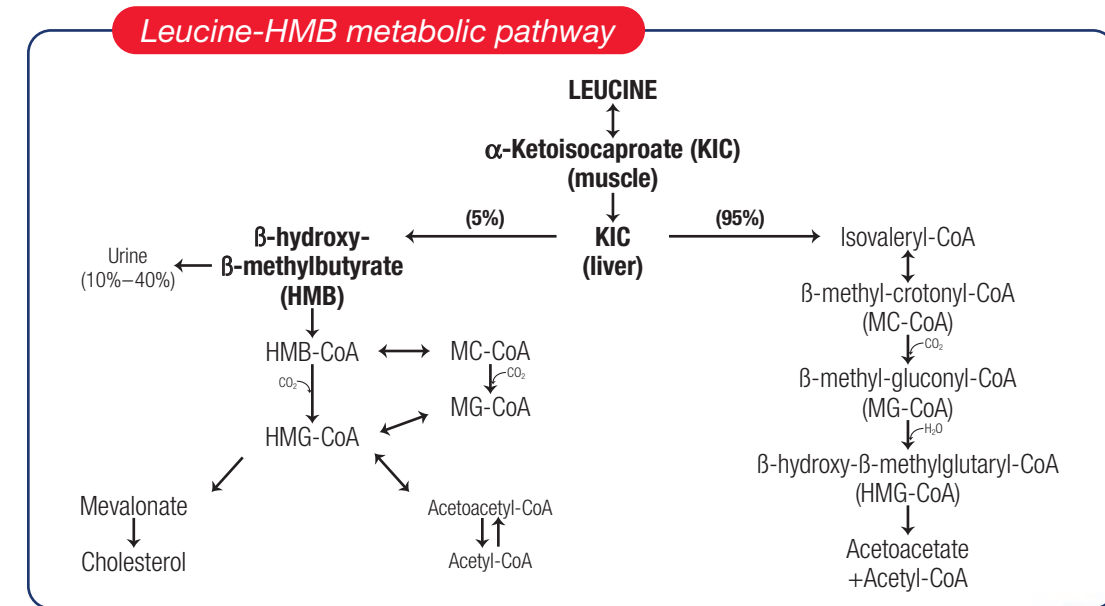
Metabolism

An overview of the leucine-HMB metabolic pathway in mammals is shown in Figure 3. The first step in leucine metabolism is transamination to α -ketoisocaproate (KIC) in muscle cells. KIC is excreted from muscle and transported to the liver. In the liver⁴⁴:

- The majority of KIC is oxidized to isovaleryl coenzyme A (isovaleryl-CoA) in the mitochondria and ultimately metabolized acetoacetate and acetyl-CoA
- Approximately 5% of KIC is metabolized to HMB by KIC-dioxygenase, a cytosolic enzyme
- HMB is released into circulation

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.^{44,49}

Figure 3. HMB is a leucine metabolite and a precursor of cholesterol synthesis in skeletal muscle⁴⁴



Reprinted with permission from Nissen and Abumrad.⁴⁴

HMB is a metabolite of leucine, an essential amino acid that regulates protein synthesis.

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.

In a multistep process, HMB is converted to β -hydroxy- β -methylglutaryl-coenzyme A (HMG-CoA) in the cytosol of muscle cells.⁴⁴ HMG-CoA is converted to cholesterol. Muscle produces its own cholesterol to maintain the integrity of the cell membrane, typically from HMG-CoA, because it cannot supply its cholesterol needs via absorption from the circulation.⁴⁴

Pharmacokinetics

The pharmacokinetic profile of exogenous HMB was examined in 2 randomized controlled studies involving 8 healthy male volunteers. The first study compared the pharmacokinetic disposition of 1 g CaHMB with placebo; the second compared 3 g CaHMB and 3 g CaHMB administered with glucose. HMB demonstrated dose-dependent kinetics that were altered by glucose coadministration (Table 3)⁵²:

- Peak plasma concentrations occurred more quickly after larger HMB doses, but the difference in plasma half-life was minimal
- Ingestion of HMB with glucose lowered the peak plasma concentration and time to peak plasma concentration, and increased HMB half-life

Intake of HMB increases plasma HMB levels and causes plasma HMB concentration to peak between 1 and 2 hours. The half-life was approximately 2.3 hours. Previous studies have shown that approximately 10% to 40% of HMB is excreted in urine⁴⁴; in this study, approximately 71% to 86% of an HMB dose remained in the body following the 3 g or 1 g dose, respectively.⁵²

Table 3. Exogenous HMB pharmacokinetics profile⁵²

<i>Dose-dependent pharmacokinetics</i>			
Pharmacokinetic parameter	1 g HMB dose	3 g HMB dose	3 g HMB + 75 g glucose
Peak plasma concentration	~120 nmol/L	~480 nmol/L	~350 nmol/L
Time to peak plasma concentration	2.0 hr	1.0 hr	1.9 hr
Plasma half-life	2.37 hr	2.38 hr	2.69 hr
% Accumulation in urine	~14%	~29%	~27%

Exogenous HMB also serves as a precursor for cellular cholesterol in muscle and contributes to cell membrane stabilization. This de novo synthesis in this case is restricted to local use, based on the lack of increase in circulating cholesterol with supplemental HMB.⁵³

Mechanism of action

HMB exerts its effects through protective, anticatabolic mechanisms and has been shown to directly influence protein synthesis.² HMB has been shown to:

- stabilize the muscle cell membrane⁴⁴
- modulate protein degradation⁵⁴⁻⁵⁶
- upregulate protein synthesis^{2,54,57}

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.⁴⁴

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.^{13,54,56} For example:

- Tumor necrosis factor-alpha (TNF- α) and interferon-gamma (IFN- γ) are increased in chronic obstructive pulmonary disease (COPD) and HIV/AIDS^{13,54}
- Angiotensin II (Ang II) is increased in congestive heart failure (CHF)⁵⁴
- Lipopolysaccharide (LPS) is the signaling factor in COPD and sepsis^{13,54}
- Proteolysis-inducing factor (PIF) is released by cancer tumors⁵⁶

HMB interrupts 2 pathways that promote protein degradation in skeletal muscle cells (Figure 4). Although initiated by these different signaling factors, both pathways result in the activation of a regulator that promotes protein degradation, nuclear factor kappa B (NF κ B). NF κ B accumulates in the nucleus and increases the production of enzymes that break proteins apart, called proteasomes. In this way, protein degradation is increased.⁵⁴⁻⁵⁶

HMB exerts its effects through protective, anticatabolic mechanisms and has been shown to directly influence protein synthesis.

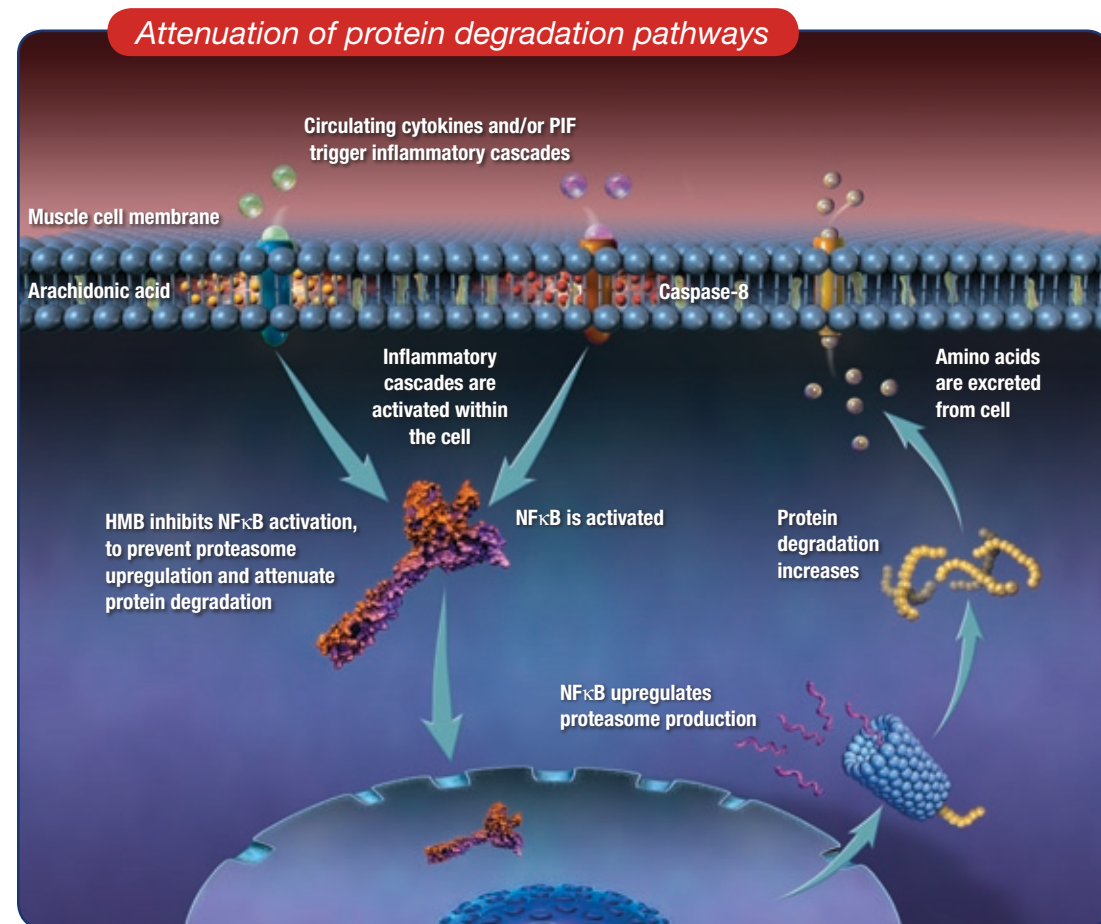
TNF- α , IFN- γ , Ang II, and LPS activate caspase-8, a protein in the cell membrane that activates another protein within the cell, caspase-3. Interaction between caspase-3 and an intracellular protein reduces protein synthesis in the nucleus. HMB inhibits the activation of caspase-8, thereby^{54,55,58}:

- preventing the downregulation of protein synthesis
- increasing inhibition of protein degradation initiated by NF κ B

Thus, by inhibiting caspase-8 activation on the cell membrane, HMB maintains protein synthesis and prevents additional protein degradation.

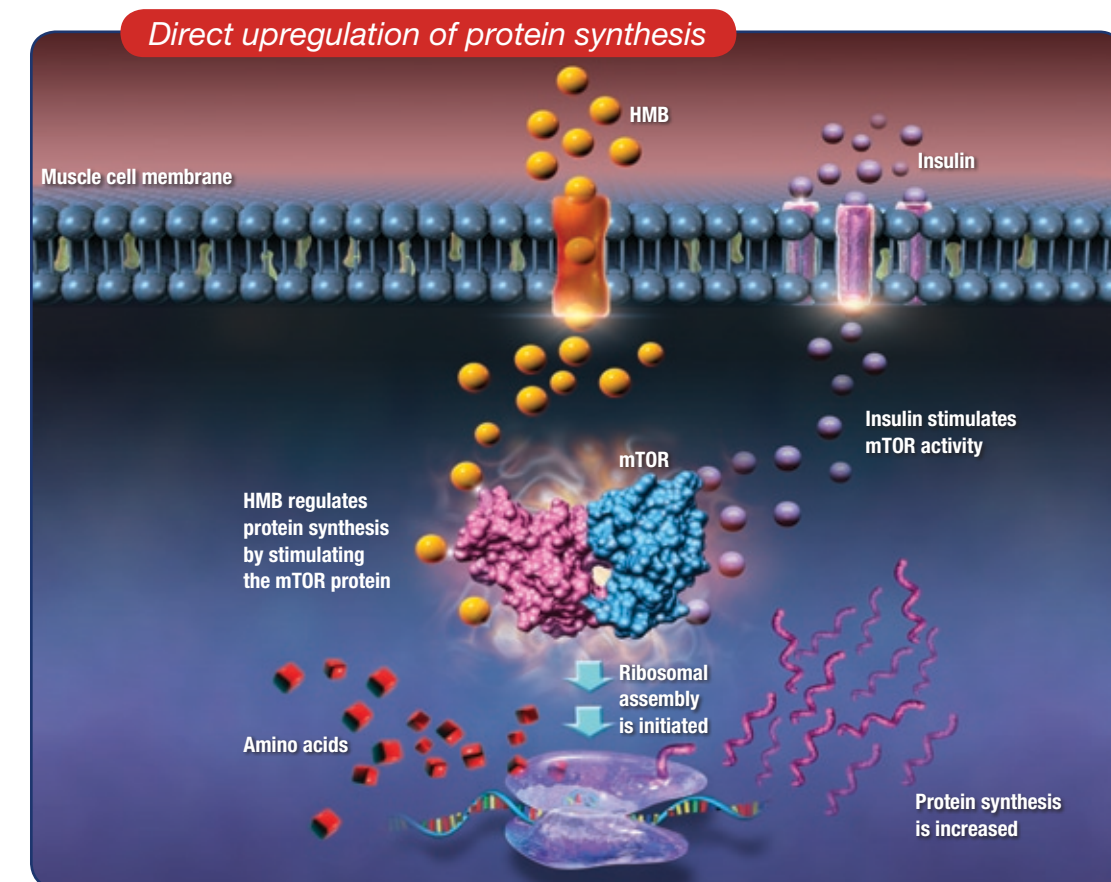
In cancer, PIF activates arachidonic acid in the muscle cell membrane, leading to the subsequent production of inflammatory mediators within the cell cytoplasm. An interaction between these inflammatory mediators and intracellular proteins activates NF κ B. HMB interrupts the interaction between an arachidonic acid product and intracellular protein to prevent the NF κ B activation, thereby attenuating the upregulation of protein degradation.^{54,55,58}

Figure 4. HMB selectively inhibits intracellular inflammation to attenuate protein degradation^{44,50,51,58}



Direct upregulation of protein synthesis. HMB increases protein synthesis directly by activating mTOR (the mammalian target of rapamycin), the intracellular protein that controls protein synthesis. HMB is the active leucine metabolite that consistently activates the mTOR signaling pathway⁴⁷ (Figure 5). The mTOR pathway is regulated by growth factors, hormones, amino acids, glucose, cellular energy levels, and stress conditions. mTOR is activated when adequate levels of nutrients (glucose, amino acids, lipoproteins, minerals) are available. mTOR turns on the cell's mechanisms for protein synthesis, including enzymes that assemble proteins, called ribosomes.⁵⁹ Insulin-like growth factor-1 (IGF-1) is one of the growth factors that activates mTOR in muscle cells. HMB also activates mTOR, and its effects are boosted by IGF-1.^{47,57} In this way, HMB may help overcome the age-related reduction in tissue response to endogenous growth hormones such as IGF-1 that contributes to sarcopenia.^{42,60}

Figure 5. HMB increases protein synthesis in the muscle cell^{47,57}



HMB selectively inhibits intracellular inflammation to attenuate protein degradation pathways. In addition, HMB increases protein synthesis through direct upregulation of the mTOR protein.

Clinical experience with HMB

HMB (β -hydroxy- β -methylbutyrate) has been extensively studied in healthy adults, alone and in combination with other amino acids, as an adjunct to exercise to help improve body composition and performance. Twenty human-research publications support the effectiveness of HMB in²:

- 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 3 g per day.²

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 body composition and functionality in healthy elderly men and women^{3,4}
- increased LBM in patients with stage IV cancer and AIDS-associated wasting^{5,6}
- improved protein synthesis in patients in the ICU and critical care unit^{12,13}

Building LBM in elderly volunteers

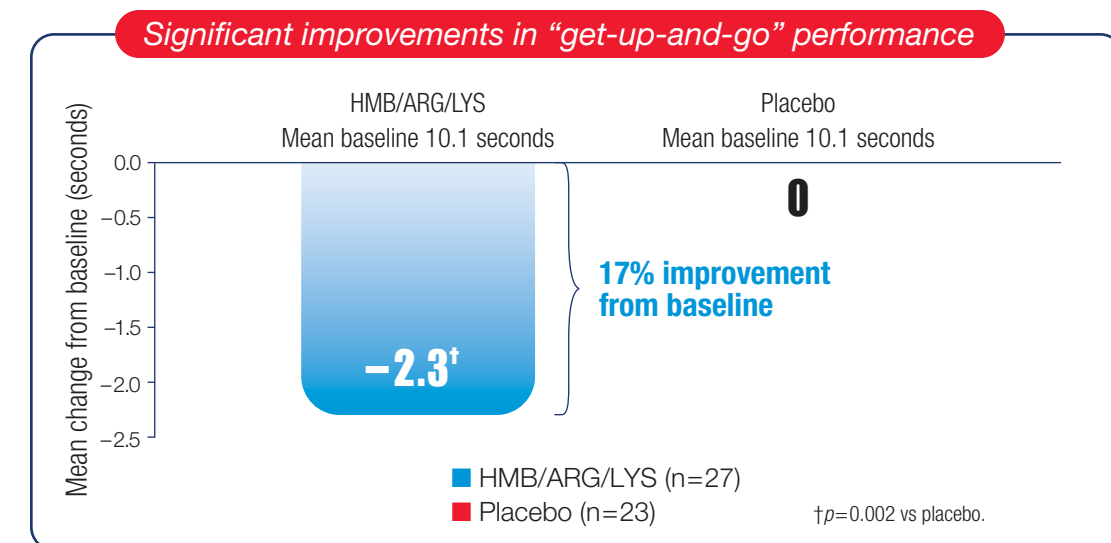
In elderly women, HMB in combination with arginine and lysine significantly increased protein synthesis and improved body composition, strength, and functionality. A 12-week randomized, double-blind, placebo-controlled study compared the effects of once-daily administration of a nutrient mixture containing 2 g calcium HMB, 5 g arginine, and 1.5 g 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 LBM⁴:

- 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 (Figure 6): “get-up-and-go” performance* improved 17% (a decrease of 2.3 seconds from baseline) vs no change with placebo ($p=0.002$).⁴

Figure 6. Elderly women who received HMB/ARG/LYS showed significant improvement in functionality (“get-up-and-go” performance) at 3 months⁴



*The “get-up-and-go” performance test involves the subject starting from a seated position, standing, walking 3 meters, turning around, walking back to the chair, and returning to a seated position.⁴

20 primary research publications support the effectiveness of HMB in decreasing markers of muscle damage, reducing body fat, and increasing LBM and strength.

In one well-controlled study, protein synthesis increased 20% vs placebo in elderly women taking HMB/ARG/LYS for 12 weeks.

Muscle strength was measured in 14 HMB/ARG/LYS subjects and in the 14 women who received the isocaloric isonitrogenous mixture. Women who received HMB/ARG/LYS demonstrated significant gains in muscle strength compared with placebo (Figures 7 and 8)⁴:

- Mean change in knee flexor force from baseline: +0.8 kg with HMB/ARG/LYS, -1.3 kg with placebo ($p=0.05$)
- Mean change in knee extensor force from baseline: +3.0 kg with HMB/ARG/LYS, -0.5 kg with placebo ($p=0.10$; data not shown)
- Mean change in handgrip strength from baseline: +0.6 kg with HMB/ARG/LYS, -1.1 kg with placebo ($p=0.04$)

Figure 7. Elderly women who received HMB/ARG/LYS showed significant improvements in knee flexor force compared with placebo at 3 months⁴

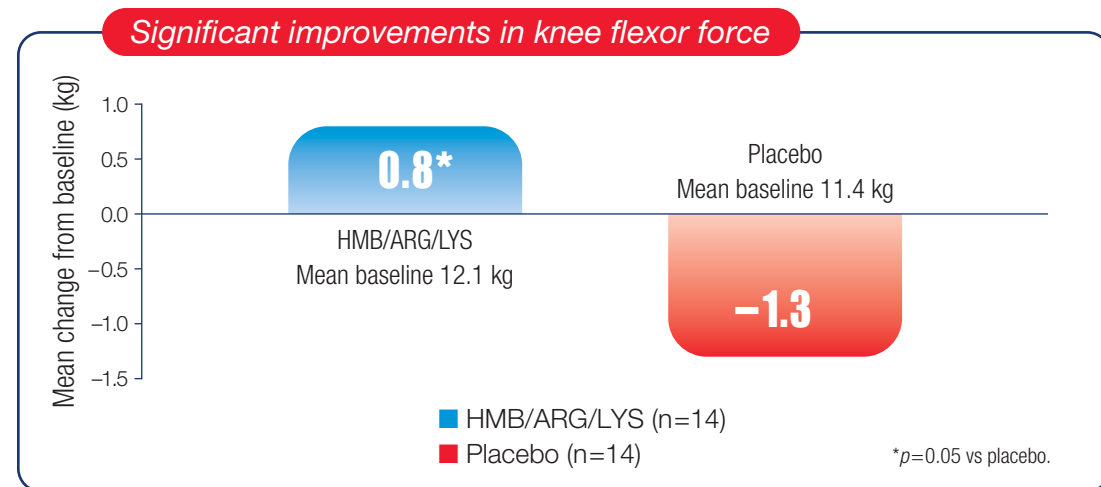
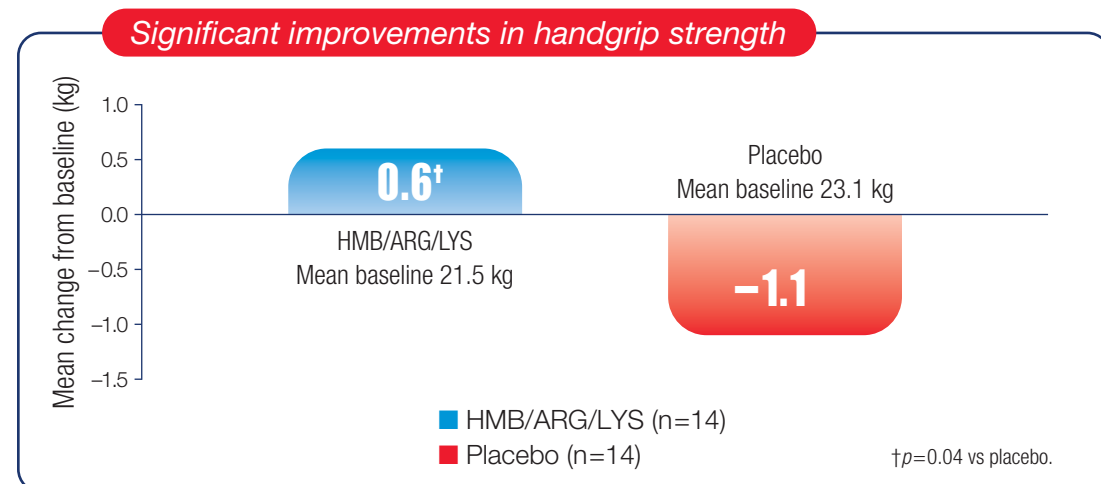


Figure 8. Elderly women who received HMB/ARG/LYS showed significant improvements in handgrip strength compared with placebo at 3 months⁴

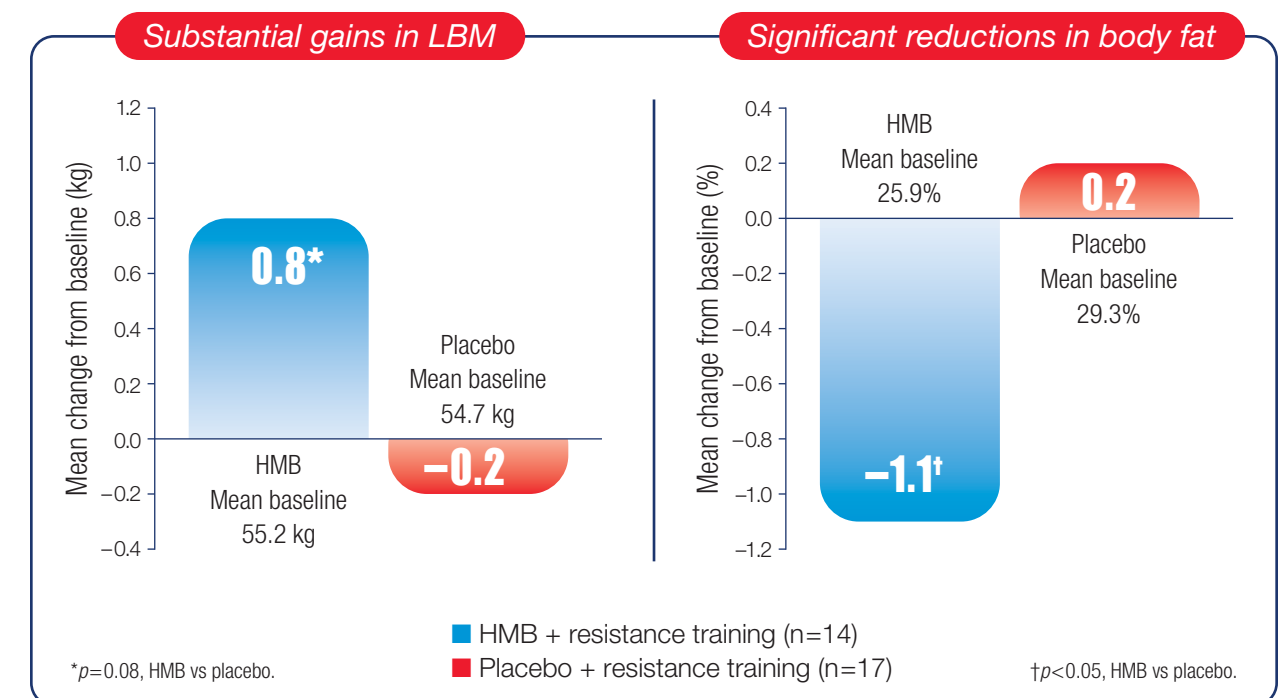


HMB plus exercise significantly increased LBM in healthy elderly volunteers. An 8-week randomized, double-blind, placebo-controlled study evaluated the effects of adding 3 g calcium HMB per day ($n=14$) or placebo ($n=17$) to a 5-days/week program of weight training (overhead press, bench press, latissimus pull-down, elbow extension and flexion, double leg flexion, double leg extension, and leg press resistance exercises) in healthy men and women (mean age 70 years). Participants had no contraindications to exercise, were taking no medications, and had no history of uncontrolled hypertension, cardiovascular disease, diabetes, or kidney problems.³

After 8 weeks, elderly adults taking HMB alone showed significant improvement from baseline in body composition compared with those who were taking placebo (Figure 9)³:

- Change in LBM: +0.8 kg with HMB, -0.2 kg with placebo ($p=0.08$)
- Change in body fat: -1.1% with HMB, +0.2% with placebo ($p<0.05$)

Figure 9. Elderly men and women receiving HMB showed substantial improvement in LBM and body fat vs placebo³



After 8 weeks, elderly adults taking HMB showed significant improvement vs placebo in body composition.

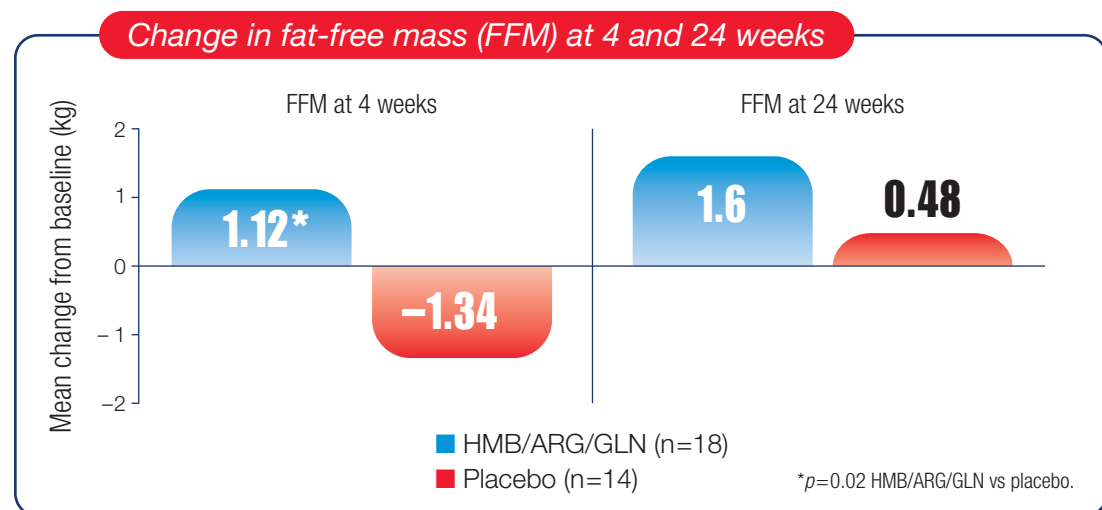
Reversing LBM loss due to cancer or AIDS

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 3 g/day of calcium HMB in combination with 14 g/day of L-arginine and 14 g/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 $\geq 5\%$ overall weight.⁶

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 10). With HMB/ARG/GLN, the majority of weight gain was LBM, whereas with placebo, patients who gained weight gained only fat⁶:

- 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 10. Patients with stage IV tumors gained significantly more fat-free mass after 4 weeks of HMB compared with those who received placebo⁶



Baseline LBM was not reported.

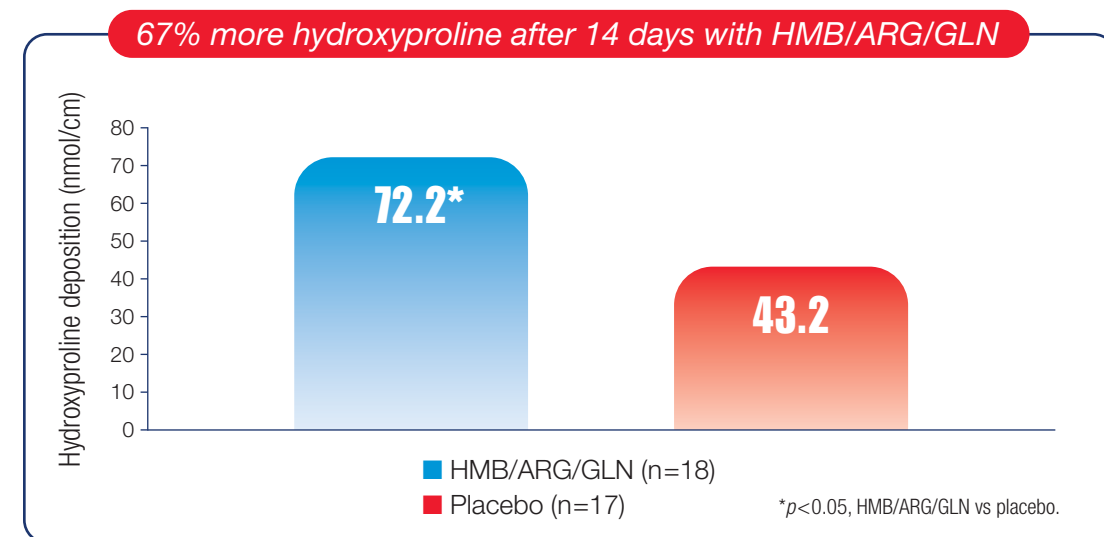
The HMB mixture was well tolerated by these advanced-stage cancer patients, in spite of gastrointestinal disturbances from ongoing cancer treatment regimens; no treatment-related adverse events were reported.⁶

Enhanced wound healing in elderly volunteers

A combination of HMB, arginine, and glutamine significantly increased collagen deposition in response to an experimental wound model. In a 14-day randomized, controlled, double-blind study, 2 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 3 g HMB, 14 g arginine, and 14 g 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).⁶¹

After 14 days, hydroxyproline content was 67% greater ($p<0.05$) with HMB/ARG/GLN compared to placebo, indicating significantly greater collagen deposition (Figure 11). 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.⁶¹

Figure 11. HMB/ARG/GLN produced significantly greater collagen deposition vs placebo after 14 days in elderly volunteers⁶¹



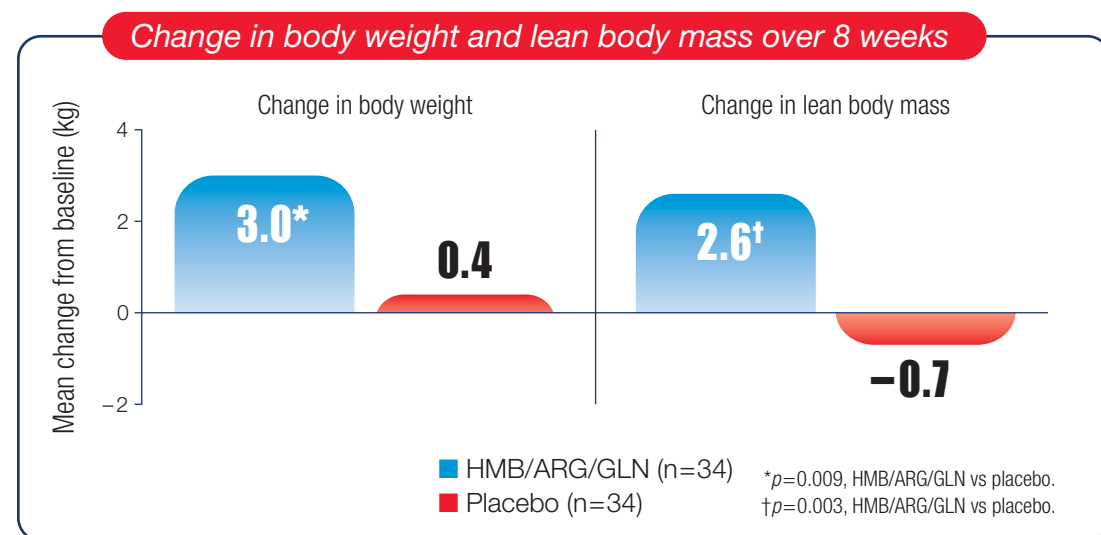
In patients with stage IV cancer, the majority of weight gain with HMB/ARG/GLN was LBM, whereas with placebo, patients gained only fat.

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 3 g calcium HMB, 14 g L-glutamine, and 14 g L-arginine (HMB/ARG/GLN; n=34) or a maltodextrin placebo (n=34) in AIDS patients with documented weight loss of $\geq 5\%$ within the previous 3 months.⁵

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 (Figure 12)⁵:

- 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

Figure 12. Changes in body weight and fat-free mass in patients with AIDS: HMB/ARG/GLN vs placebo⁵



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) subsets⁵:

- Change in total circulating lymphocyte count: $+0.29 \times 10^3$ cells/mm³ with HMB/ARG/GLN, -0.31×10^3 cells/mm³ with placebo
- Significant increases in CD3 and CD8 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: $-0.7 \log_{10}$ 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.⁵

AIDS patients gained significantly more weight with HMB/ARG/GLN vs placebo, and gained primarily LBM.

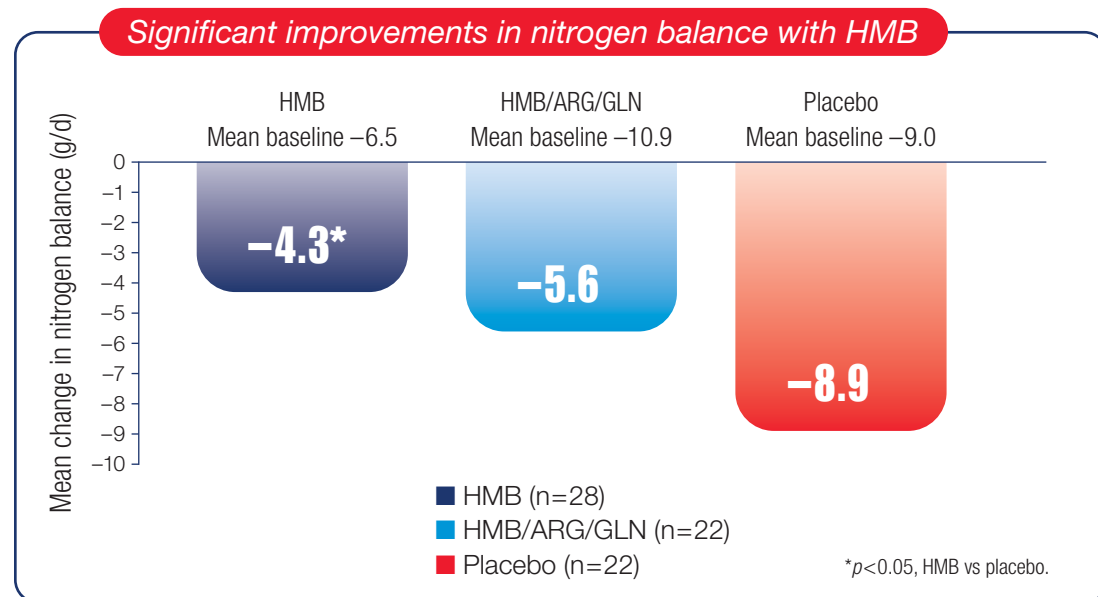
Improved protein metabolism in critical care patients

HMB plus arginine and glutamine improved nitrogen balance, indicating increased protein synthesis.

An HMB nutrient mixture improved nitrogen balance in severely ill trauma patients. Severely ill trauma patients are typically in negative nitrogen balance despite adequate nutritional supplementation, an indication that protein or muscle catabolism has not been reversed. A 28-day randomized, controlled, blinded study evaluated the effects of supplementing standard tube feedings twice daily with 3 g calcium HMB (n=28), 3 g calcium HMB + 14 g arginine + 14 g glutamine (HMB/ARG/GLN; n=22), or placebo (n=22) in adult trauma patients with Injury Severity Score >18.¹²

- Average nitrogen balance at baseline was -10.9 for HMB/ARG/GLN, -6.5 for HMB, and -9.0 for placebo (Figure 13)¹²
- HMB showed the greatest improvement in nitrogen balance from the first 7 days of feeding to the last 7 days: -4.3 g/d vs -5.6 g/d for HMB/ARG/GLN and -8.9 g/d for placebo (p<0.05 HMB vs placebo)¹²
- Muscle proteolysis (measured using urinary 3-methylhistidine, 3-MH, as a proxy) was not affected by dietary treatment¹²
- The investigators hypothesize that the improvement in nitrogen balance for the HMB group may reflect increased protein synthesis¹²

Figure 13. Nitrogen balance improved from the first 7 days to the last 7 days of HMB-containing therapy¹²



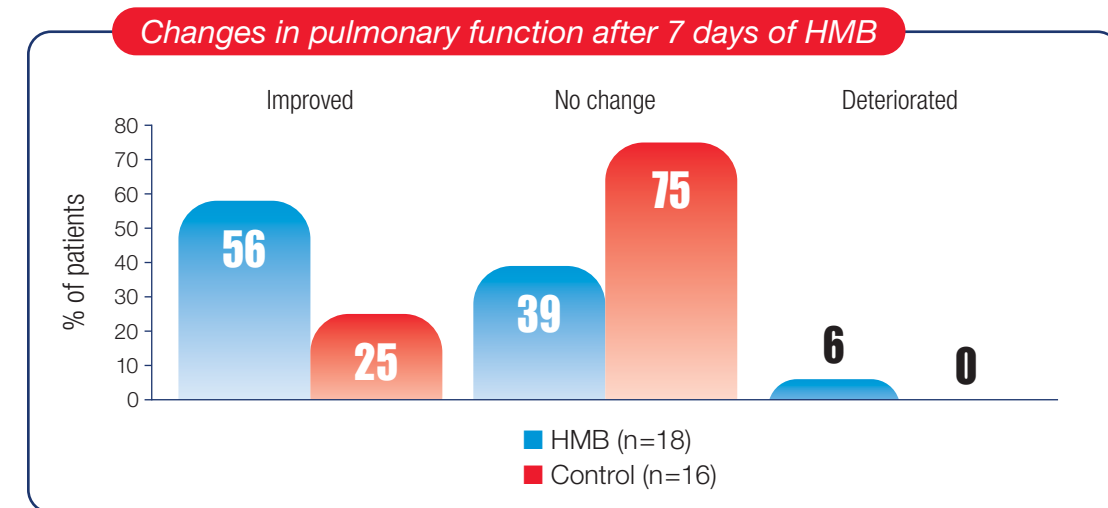
Improved protein metabolism and pulmonary function in intensive care (ICU) patients.

A 7-day randomized trial examined the effects of HMB supplementation (3 g calcium HMB/day) on inflammation, protein metabolism, and pulmonary function in 18 ICU patients requiring mechanical ventilation for chronic obstructive pulmonary disease; an additional 16 patients who did not receive HMB served as controls. After 7 days, patients who received HMB had significant reductions in C-reactive protein (CRP) and in white blood cell (WBC) counts from baseline¹³:

- Mean change in CRP after 7 days: -65.37 mg/L with HMB (p<0.05 vs baseline), -37.94 mg/L in control group (p=NS vs baseline)
- Mean change in WBC count after 7 days: -4.36 x 10³/mm³ with HMB (p<0.01 vs baseline), -1.11 x 10³/mm³ in control group (p=NS vs baseline)

HMB patients also demonstrated a 21% decrease in serum creatinine (p<0.05 vs baseline), accompanied by a moderate decrease (16%, p=0.079) in blood urea nitrogen, suggesting modulation of protein metabolism. In addition, 56% of subjects (10 patients) in the HMB group had improved pulmonary function compared with only 25% (4 patients) of the subjects in the control group (Figure 14).¹³

Figure 14. Pulmonary function was improved in the majority of patients who received HMB¹³



ICU patients who received HMB had significant reductions in CRP, WBC counts, and serum creatinine, accompanied by a moderate decrease in blood urea nitrogen.

Clinical safety of HMB

HMB (β -hydroxy- β -methylbutyrate) has been the subject of numerous safety trials. Animal toxicity studies showed no adverse effects with exposure to HMB⁶²:

- In vitro genotoxicity tests were negative
- In utero exposure trials in rats showed no significant adverse effects to the fetus

The clinical safety and tolerability of HMB is well documented in healthy adults, including the elderly, as well as in patients with LBM loss associated with AIDS or cancer in controlled clinical trials lasting up to 24 weeks.^{53,63} At the proposed dose of 3 g per day, HMB (alone or in combination with arginine and glutamine) appears to be safe and well tolerated with no untoward effects on indicators of health status. Rather, supplementation with HMB was shown to improve certain hematologic parameters.^{53,63}

Demonstrated tolerability and safety in healthy volunteers. Safety data were collected from 9 double-blind, placebo-controlled studies in which humans were fed 3 g HMB per day (Table 4). The studies were 3 to 8 weeks in duration and included young and elderly males and females. All but one study included a form of exercise. Participants completed a questionnaire every week examining whether they had experienced any of the common complaints related to major organ systems within the previous 3 days.⁵³

Table 4. Study descriptions of HMB use in healthy adult volunteers⁵³

	9 double-blind, placebo-controlled studies								
	Study number								
	1	2	3	4	5	6	7	8	9
Gender	Male	Male	Female	Male	Male/ Female	Female	Male/ Female	Male/ Female	Male
Exercise	Weight lifting	Weight lifting	None	Weight lifting	Running	Weight lifting	Weight lifting	Weight lifting	Weight lifting
Age, y	19–30	18–22	20–41	18–38	21–47	19–47	63–81	62–79	18–29
Placebo, n	13	15	19	18	6	18	18	16	11
HMB, n	15	10	18	21	8	18	18	13	7
Duration, wk	3	7	4	4	5	4	8	8	8

Adapted from Nissen.⁵³

Responses to the adverse-event questionnaires did not indicate any adverse events due to HMB. Changes in blood lipids suggested a beneficial treatment effect with HMB, particularly in high-risk patients (total cholesterol >200 mg/dL). Compared with placebo, HMB supplementation resulted in⁵³:

- 5.8% net decrease in total cholesterol ($p < 0.03$)
- 7.3% net decrease in LDL cholesterol ($p < 0.01$)
- no significant change in HDL cholesterol

Resting blood pressure, measured in 7 studies, also revealed a beneficial effect with HMB. Changes in systolic blood pressure were: -4.4 mm Hg with HMB and -0.8 mm Hg with placebo ($p < 0.05$).⁵³

Blood indicators of liver function did not reveal a significant difference between the effects of HMB and placebo for bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), γ -glutamyl transpeptidase (GGT), or iron. No significant differences between placebo and HMB occurred in creatine phosphokinase, glucose, uric acid, blood urea nitrogen (BUN), creatinine, BUN/creatinine, sodium, chloride, phosphorus, protein, albumin, or globulin. Small, but significant, changes with HMB vs placebo were seen in potassium (-1.9% , $p < 0.003$) and albumin/globulin ratio ($+5\%$, $p < 0.03$). No significant treatment-related effects were seen for the hematology variables measured, including white blood cells, red blood cells, hemoglobin, hematocrit, or platelets.⁵³

The clinical safety and tolerability of HMB is well documented.

The safety of HMB in combination with arginine and glutamine has been demonstrated in patients with LBM loss due to AIDS or late-stage cancer.

A meta-analysis of 3 randomized, double-blind, placebo-controlled studies of an HMB mixture with healthy elderly volunteers, cancer patients, and individuals with AIDS concluded that it is safe for enhancing protein synthesis in these populations (Table 5). The studies were 4 to 24 weeks in duration, and participants received twice-daily 3 g HMB in combination with 14 g arginine and 14 g glutamine (HMB/ARG/GLN) or an isocaloric placebo. Adverse events were measured weekly via a questionnaire that examined the presence of common complaints or symptoms related to major organ systems within the previous 3 days.⁶³

Table 5. Descriptions of HMB/ARG/GLN studies in healthy adults and patients with cancer or AIDS⁶³

<i>Studies in healthy, AIDS, and cancer populations</i>			
	Study 1	Study 2	Study 3
Population	Healthy male volunteers	AIDS patients with >5% unintentional weight loss in previous 3 months	Patients with stage IV solid tumors with >5% weight loss, ≥3 months' expected survival
HMB/ARG/GLN, n*	19	22	18
Placebo, n	Maltodextrin, 19	Maltodextrin, 21	Nonessential amino acids,† 14
Duration of study, wk	4	8	24
Blood sampling	Baseline, wk 4	Baseline, wk 8	Baseline, wk 12, wk 24

*Number included in analysis.

†Nonessential amino acid mixture was 11 g alanine, 1.75 g glutamic acid, 6.10 g glycine, and 4.22 g serine.

Across studies, supplementation with the HMB nutrient mixture was not associated with any adverse indicators of health. Improvements were noted as decreased feeling of weakness ($p=0.03$ vs placebo) and increased red blood cells, hemoglobin, hematocrit, lymphocytes, and eosinophils ($p<0.05$ vs placebo). Blood chemistries revealed an increase in blood urea nitrogen (BUN; $p=0.0001$, HMB/ARG/GLN vs placebo) despite unchanged blood creatinine levels. Increased BUN is to be expected in persons consuming excess nitrogen or protein; in this analysis, the average BUN was slightly outside the upper limit of normal. Significant, albeit inconsistent, treatment effects were demonstrated for HMB/ARG/GLN for sodium levels ($p=0.05$, HMB/ARG/GLN +0.06% vs placebo -0.3%) and for uric acid ($p=0.0001$, HMB/ARG/GLN +0.01 mg/dL vs placebo -0.27 mg/dL).⁶³

HMB has been available commercially for 12 years in the United States and internationally as a therapeutic nutritional supplement containing HMB, arginine, and glutamine.

The safety of HMB/ARG/GLN in clinical use has been tested in clinical trials lasting up to 24 weeks in populations of healthy adult and elderly volunteers, trauma patients, cancer patients, and people with HIV/AIDS. None of these studies showed any significant adverse effects.

Summary

HMB (β -hydroxy- β -methylbutyrate) is a naturally occurring leucine metabolite that rebuilds lean body mass (LBM) as well as muscle strength. Maintaining LBM, and muscle mass in particular, is essential to support whole-body protein metabolism, physical strength, immune function, skin integrity, wound healing, and organ function. LBM loss increases risk for physical disability, compromises immune function, impairs wound healing, and increases mortality in the elderly, in people with chronic illness, and in critically ill patients. HMB addresses underlying factors that alter protein metabolism and helps maintain and rebuild LBM by stabilizing the muscle membrane and by improving the balance of protein degradation and protein synthesis within the muscle cell.

The clinical benefits of HMB, alone and as part of a nutrient mixture containing arginine and glutamine or lysine, have been demonstrated in controlled studies involving elderly volunteers, patients with LBM loss due to AIDS or cancer, and critically ill patients. Patients in these studies who received HMB or an HMB–amino acid mixture showed shifts in body composition with gains in LBM and losses in body fat.

- Elderly women taking HMB plus arginine and lysine had substantial LBM gains accompanied by significant improvements in muscle strength and functionality
- In elderly volunteers adding HMB to a 5-day weight-resistance exercise program, substantial increases in LBM were accompanied by significant reductions in body fat
- Patients with LBM loss due to stage IV solid tumors saw significant improvements in LBM with HMB/ARG/GLN
- In patients with LBM loss due to AIDS, HMB/ARG/GLN provided significant LBM and body weight gains and significant immune benefits
- HMB improved protein metabolism in critical care patients hospitalized due to trauma or chronic obstructive pulmonary disease

HMB, at the recommended dose of 3 g daily, has an established profile of safety and tolerability in the elderly as well as in people with serious illness.

References

1. Zhang Z, Rathmacher J, Coates C, Nissen S. Occurrence of β -hydroxy- β -methylbutyrate in foods and feeds. *FASEB J*. 1994;8:A464 [Abstract 2685].
2. Wilson GJ, Wilson JM, Manninen AH. Effects of beta-hydroxy-beta-methylbutyrate (HMB) on exercise performance and body composition across varying levels of age, sex, and training experience: a review. *Nutr Metab*. 2008;5:1.
3. Vukovich MD, Stubbs NB, Bohlken RM. Body composition in 70-year old adults responds to dietary β -hydroxy- β -methylbutyrate similarly to that of young adults. *J Nutr*. 2001;131:2049-2052.
4. Flakoll P, Sharp R, Baier S, Levenhagen D, Carr C, Nissen S. Effect of β -hydroxy- β -methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. *Nutrition*. 2004;20:445-451.
5. Clark RH, Feleke G, Din M, et al. Nutritional treatment for acquired immunodeficiency virus-associated wasting using β -hydroxy β -methylbutyrate, glutamine, and arginine: a randomised, double-blind, placebo controlled study. *JPEN J Parenter Enteral Nutr*. 2000;24:133-139.
6. May PE, Barber A, D'Olimpio JT, Hourihane A, Abumrad NN. Reversal of cancer-related wasting using oral supplementation with a combination of β -hydroxy- β -methylbutyrate, arginine, and glutamine. *Am J Surg*. 2002;183:471-479.
7. Pirlich M, Schütz T, Kemps M, et al. Social risk factors for hospital malnutrition. *Nutrition*. 2005;21:295-300.
8. Forster S, Gariballa S. Age as a determinant of nutritional status: a cross sectional study. *Nutr J*. 2005;4:28.
9. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition: the Mini Nutritional Assessment. *Clin Geriatr Med*. 2002;18:737-757.
10. Roubenoff R. Sarcopenia: effects on body composition and function. *J Gerontol*. 2003;58A:1012-1017.
11. Demling RH. Nutrition, anabolism, and the wound healing process: an overview. *Eplasty*. 2009;9:65-94.
12. Kuhls DA, Rathmacher JA, Musngi D, et al. β -hydroxy- β -methylbutyrate supplementation in critically ill trauma patients. *J Trauma*. 2007;62:125-132.
13. Hsieh LC, Chien SL, Huang MS, Tseng HF, Chang CK. Anti-inflammatory and anticatabolic effects of short-term β -hydroxy- β -methylbutyrate supplementation on chronic obstructive pulmonary disease patients in intensive care unit. *Asia Pac J Clin Nutr*. 2006;15:544-550.
14. Wolfe RR. The underappreciated role of muscle in health and disease. *Am J Clin Nutr*. 2006;84:475-482.
15. Bourdel-Marchasson I, Joseph PA, Dehail P, et al. Functional and metabolic early changes in calf muscle occurring during nutritional repletion in malnourished elderly patients. *Am J Clin Nutr*. 2001;73:832-838.
16. Doherty TJ. Invited review: aging and sarcopenia. *J Appl Physiol*. 2003;95:1717-1727.

17. Baumgartner RN. Body composition in healthy aging. *Ann N Y Acad Sci.* 2000;904:437-448.
18. Janssen I, Heymsfield SB, Wang Z, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *J Appl Physiol.* 2000;89:81-88.
19. Grimby G, Danneskiold-Samsoe B, Hvid K, Saltin B. Morphology and enzymatic capacity in arm and leg muscles in 78-81 year old men and women. *Acta Physiol Scand.* 1982;115:125-134.
20. Grimby G, Saltin B. The ageing muscle. *Clin Physiol.* 1983;3:209-218.
21. Larsson L, Grimby G, Karlsson J. Muscle strength and speed of movement in relation to age and muscle morphology. *J Appl Physiol.* 1979;46:451-456.
22. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. *Clin Nutr.* 2008;27:793-799.
23. Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA.* 2007;297:1772-1774.
24. Paddon-Jones D, Sheffield-Moore M, Urban RJ, et al. Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. *J Clin Endocrinol Metab.* 2004;89:4351-4358.
25. Paddon-Jones D. Lean body mass loss with age. In: Gussler J, ed. *The Role of Nutrition in Accretion, Retention, and Recovery of Lean Body Mass.* Report of the 110th Abbott Nutrition Research Conference: Selected Summaries. Columbus, Ohio: Abbott Nutrition; 2009:9-14.
26. Paddon-Jones D, Sheffield-Moore M, Cree MG, et al. Atrophy and impaired muscle protein synthesis during prolonged inactivity and stress. *J Clin Endocrinol Metab.* 2006;91:4836-4841.
27. Vetta F, Ronzoni S, Taglieri G, Bollea MR. The impact of malnutrition on the quality of life in the elderly. *Clin Nutr.* 1999;18:259-267.
28. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J.* 1994;7:1793-1797.
29. Nixon DW, Heymsfield SB, Cohen AE, et al. Protein-calorie undernutrition in hospitalized cancer patients. *Am J Med.* 1980;68:683-690.
30. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol.* 1998;147:755-763.
31. Argilés JM. Cancer-associated malnutrition. *Eur J Oncol Nurs.* 2005;9:S39-S50.
32. Prado CM, Baracos VE, McCargar LJ, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res.* 2007;13:3264-3268.
33. Prado CMM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol.* 2008;9:629-635.
34. Andreyev HJN, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer.* 1998;34:503-509.
35. Gilmore SA, Robinson G, Posthauer ME, Raymond J. Clinical indicators associated with unintentional weight loss and pressure ulcers in elderly residents of nursing facilities. *J Am Diet Assoc.* 1995;95:984-992.
36. Reed RL, Hepburn K, Adelson R, Center B, McKnight P. Low serum albumin levels, confusion, and fecal incontinence: are these risk factors for pressure ulcers in mobility-impaired hospitalized adults? *Gerontology.* 2003;49:255-259.
37. DeSanti L. Involuntary weight loss and the nonhealing wound. *Adv Skin Wound Care.* 2000;13(suppl 1):11-20.
38. Stechmiller JK, Childress B, Cowan L. Arginine supplementation and wound healing. *Nutr Clin Pract.* 2005;20:52-61.
39. Bergstrom N, Bennett MA, Carlson CE, et al. *Treatment of Pressure Ulcers.* Clinical Practice Guideline, No. 15. Rockville, Md: US Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 95-0652. December 1994.
40. Breslow RA, Hallfrisch J, Guy DG, Crawley B, Goldberg AP. The importance of dietary protein in healing pressure ulcers. *J Am Geriatr Soc.* 1993;41:357-362.
41. Ferrando AA, Paddon-Jones D, Hays NP, et al. EAA supplementation to increase nitrogen intake improves muscle function during bed rest in elderly [published online ahead of print May 4, 2009]. *Clin Nutr.* doi:10.1016/j.clnu.2009.03.009.
42. Bales CW, Ritchie CS. Sarcopenia, weight loss, and nutritional frailty in the elderly. *Annu Rev Nutr.* 2002;22:309-323.
43. Paddon-Jones D. Interplay of stress and physical inactivity on muscle loss: nutritional countermeasures. *J Nutr.* 2006;136:2123-2126.
44. Nissen SL, Abumrad NN. Nutritional role of the leucine metabolite β -hydroxy β -methylbutyrate (HMB). *J Nutr Biochem.* 1997;8:300-311.

45. Williams JZ, Barbul A. Nutrition and wound healing. *Surg Clin North Am*. 2003;83:571-596.
46. May ME, Buse MG. Effects of branched-chain amino acids on protein turnover. *Diabetes Metab Rev*. 1989;5:227-245.
47. Manzano M, Giron MD, Salto R, Sevillano N, Rueda R, Lopez-Pedrosa JM. Is β -hydroxy- β -methylbutyrate (HMB) the bioactive metabolite of L-leucine (LEU) in muscle? Molecular evidence and potential implications. Abstract presented at: European Society for Clinical Nutrition and Metabolism 31st Congress; Vienna, Austria; August 29-September 1, 2009. Abstract P267.
48. Alon T, Bagchi D, Preuss HG. Supplementing with beta-hydroxy-beta-methylbutyrate (HMB) to build and maintain muscle mass: a review. *Res Commun Mol Pathol Pharmacol*. 2002;111:139-152.
49. Nissen S, Sharp R, Ray M, et al. Effect of leucine metabolite β -hydroxy- β -methylbutyrate on muscle metabolism during resistance-exercise training. *J Appl Physiol*. 1996;81:2095-2104.
50. Smith HJ, Mukerji P, Tisdale MJ. Attenuation of proteasome-induced proteolysis in skeletal muscle by β -hydroxy- β -methylbutyrate in cancer-induced muscle loss. *Cancer Res*. 2005;65:277-283.
51. Smith HJ, Wyke SM, Tisdale MJ. Mechanism of the attenuation of proteolysis-inducing factor stimulated protein degradation in muscle by β -hydroxy- β -methylbutyrate. *Cancer Res*. 2004;64:8731-8735.
52. Vukovich MD, Slater G, Macchi MB, et al. β -hydroxy- β -methylbutyrate (HMB) kinetics and the influence of glucose ingestion in humans. *J Nutr Biochem*. 2001;12:631-639.
53. Nissen S, Sharp RL, Panton L, Vukovich M, Trappe S, Fuller JC Jr. β -hydroxy- β -methylbutyrate (HMB) supplementation in humans is safe and may decrease cardiovascular risk factors. *J Nutr*. 2000; 130:1937-1945.
54. Eley HL, Russell ST, Tisdale MJ. Attenuation of depression of muscle protein synthesis induced by lipopolysaccharide, tumor necrosis factor, and angiotensin II by β -hydroxy- β -methylbutyrate. *Am J Physiol Endocrinol Metab*. 2008;295:E1409-E1416.
55. Eley HL, Russell ST, Tisdale MJ. Mechanism of attenuation of muscle protein degradation induced by tumor necrosis factor- α and angiotensin II by β -hydroxy- β -methylbutyrate. *Am J Physiol Endocrinol Metab*. 2008;295:E1417-E1426.
56. Yeh SS, Blackwood K, Schuster MW. The cytokine basis of cachexia and its treatment: are they ready for prime time? *J Am Med Dir Assoc*. 2008;9:219-236.
57. Kornasio R, Riederer I, Butler-Browne G, Mouly V, Uni Z, Halevy O. β -hydroxy- β -methylbutyrate (HMB) stimulates myogenic cell proliferation, differentiation and survival via the MAPK/ERK and PI3K/Akt pathways. *Biochim Biophys Acta*. 2009;1793:755-763.
58. Eley HL, Russell ST, Baxter JH, Mukerji P, Tisdale MJ. Signaling pathways initiated by β -hydroxy- β -methylbutyrate to attenuate the depression of protein synthesis in skeletal muscle in response to cachectic stimuli. *Am J Physiol Endocrinol Metab*. 2007;293:E923-E931.
59. Bjornsti MA, Houghton PJ. The TOR pathway: a target for cancer therapy. *Nat Rev Cancer*. 2004; 4:335-348.
60. Paddon-Jones D, Short KR, Campbell WW, Volpi E, Wolfe RR. Role of dietary protein in the sarcopenia of aging. *Am J Clin Nutr*. 2008;87(suppl):1562S-1566S.
61. Williams JZ, Abumrad N, Barbul A. Effect of a specialized amino acid mixture on human collagen deposition. *Ann Surg*. 2002;236:369-375.
62. Data on file, Abbott Nutrition.
63. Rathmacher JA, Nissen S, Panton L, et al. Supplementation with a combination of β -hydroxy- β -methylbutyrate (HMB), arginine, and glutamine is safe and could improve hematological parameters. *JPEN J Parenter Enteral Nutr*. 2004;28:65-75.

