# Hypercatabolic Syndrome: Molecular Basis and Effects of Nutritional Supplements with Amino Acids

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**Hypercatabolic syndrome (HS) is a biochemical state characterized by increased circulating catabolic hormones (eg, cortisol, catecholamines) and inflammatory cytokines (eg, tumor necrosis factors, interleukin–1β), and decreased anabolic insulin effects with consequent insulin resistance. The most important metabolic consequence of HS is the skeletal and cardiac muscle protein breakdown that releases amino acids (AAs), which in turn supports indispensable body energy requirements but also reduces skeletal and cardiac physiologic and metabolic functions. HS occurs in many diseases such as diabetes mellitus, chronic heart failure, chronic obstructive pulmonary disease, renal and liver failure, trauma, sepsis, and senescence. All of these conditions have predominant catabolic molecules with significant muscular wasting and metabolic impairment. Macronutrients such as AA supplements, taken together with conventional therapy, may maintain muscular protein metabolism and cell functions.** **© 2008 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2008;101[suppl]:11E–15E)**

As pointed out by Anker and associates and others,[1,2] hypercatabolic syndrome (HS) is a biochemical state characterized by increased circulating catabolic molecules such as hormones (eg, cortisol, glucagons, catecholamines) and inflammatory cytokines (e.g., tumor necrosis factor [TNF]–$\alpha$, interleukin [IL]–1$\beta$, IL-6), and decreased anabolic insulin effects with subsequent insulin resistance and muscular wasting.

## The Molecular Basis of Hypercatabolic Syndrome

In normal cardiac and skeletal muscles, the continual turnover of proteins is a basic process of cell life. Data show that in healthy humans, approximately 250–350 g of proteins are degraded in the muscles each day. Although some of the amino acids (AAs) produced are reused from cells to synthesize cytoplasmic and mitochondrial new proteins or to produce energetic intermediates, a large quantity of AAs are released into the blood to maintain the blood pool of AAs (Figure 1). Thus, the balance between protein synthesis and breakdown determines the overall cell protein content and metabolism. The balance of protein production or degradation is regulated by the balance of catabolic and anabolic stimuli (Figure 1). The increase of catabolic hormones and/or molecules (eg, catecholamines, cortisol, glucagon, TNF-$\alpha$) and the reduction of anabolic hormone (eg, insulin) create an HS that has various metabolic consequences, including reduced cytoplasmic and mitochondrial cell proteins synthesis and impaired cell functions and energetic metabolism. Indeed, AAs are used not only for cellular protein replacement and/or cellular energy production but also for the metabolism of the human body (Figure 2).[2–5] The AAs released from skeletal and cardiac muscle are used in the liver to produce glucose by gluconeogenesis, because glucose is essential for maintenance of the glucose-dependent metabolism of fundamental structures such as the brain and erythrocytes (Figures 1 and 2). Consequently, the muscle is not merely an organ restricted to movement or contraction; it also has an important role in maintaining the general metabolism of the human body. In addition, muscle mass is approximately 45% of the dry weight of a healthy person, and most receptors for insulin, cortisol, and glucagon are located in the muscle.[5–8]

## When Does Hypercatabolic Syndrome Occur?

Recent studies have identified HS with muscular wasting and cellular energy impairment in chronic diseases, including diabetes mellitus, chronic heart failure (CHF), chronic

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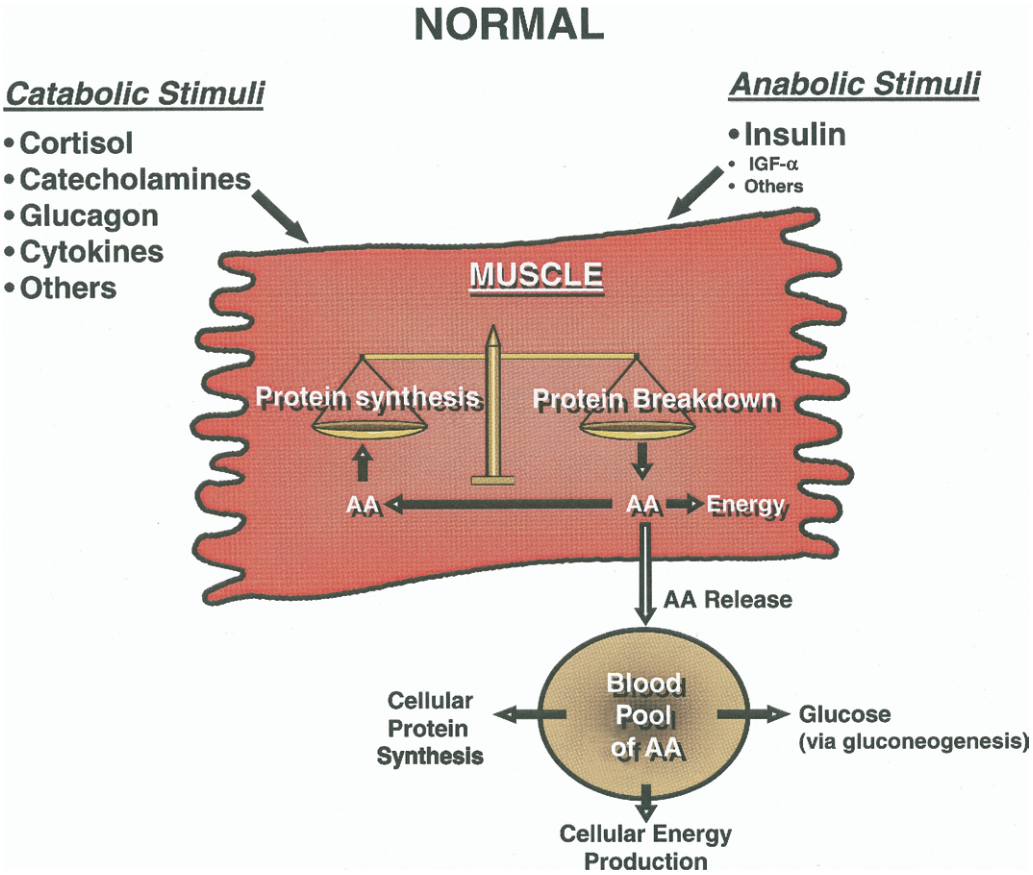


Figure 1. In healthy humans, proteins are degraded in the muscles every day. Although some of the amino acids (AAs ) produced are reused from the cells to synthesize cytoplasmic and mitochondrial new proteins or to produce energetic intermediates, a large quantity of AAs are released into the blood to maintain the blood pool of AAs. The balance of protein production or degradation is regulated by the balance of catabolic and anabolic stimuli. IGF-$\alpha$ = insulin-like growth factor–$\alpha$.

obstructive pulmonary disease (COPD), and renal and liver failure, as well as in infectious diseases and sepsis. Interestingly, HS is also present in healthy elderly individuals.[1,2,9,10]

## Oral Amino Acids: A Possible Therapeutic Approach to Counteracting Hypercatabolic Syndrome

The availability of AAs is a key factor in maintaining both cellular and general metabolism and muscle protein synthesis in mammals. Preliminary data suggest that exogenous oral AA supplements, administered with traditional therapy, counteract muscular wasting and cellular energy reduction, and may improve cardiac function and muscle performance, thereby enhancing the patient's quality of life.[11–18]

In healthy subjects, AAs in the diet are absorbed after protein digestion. However, the pancreas uses large amounts of AAs to produce digestive enzymes.[7] In HS, the efficiency of the pancreas and mesenteric circulation may be progressively reduced. These conditions lead to impaired AA digestion and absorption and, consequently, to reduced AA plasma patterns that may therefore be insufficient to maintain the protein synthesis and energetic needs of patients with HS.

In contrast, individual AAs in nutritional supplements are not digested. They are rapidly absorbed and therefore immediately available in the bloodstream and transported into the cells, where they stimulate cellular protein synthesis and mitochondrial biogenesis as shown by preliminary results.[2,4,19]

## Why Are Orally Administered Amino Acids Active in Hypercatabolic Syndrome?

High physiologic concentrations of AAs activate important processes of both cytosolic and mitochondrial protein synthesis.[4] Data have shown that AAs influence fundamental enzymes involved in cell protein synthesis such as p70 S6-kinase (S6K1) and eukaryotic initiation factor eIF4F regulation. Interestingly, AAs act through a mammalian target of rapamycin (mTOR)–mediated mechanism that is an insulin-independent pathway. mTOR is an ubiquitous protein kinase that integrates signals from hormones and

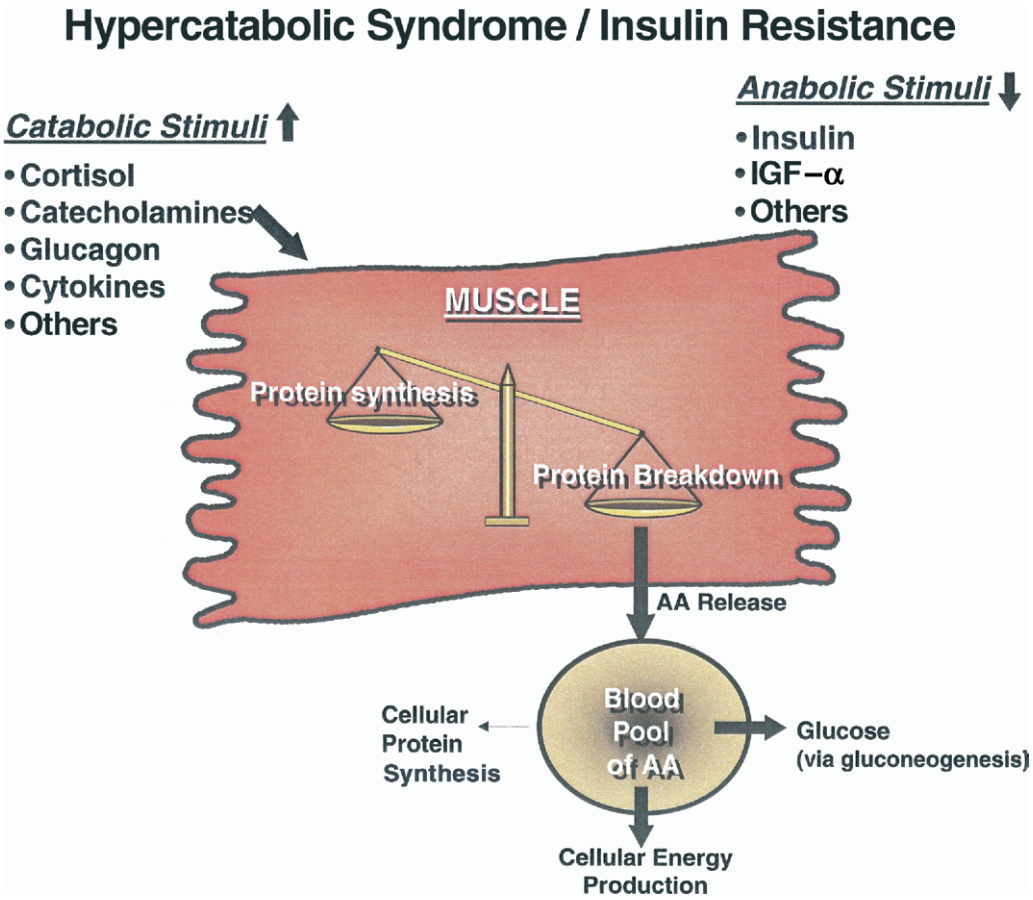


Figure 2. The increase of catabolic hormones and/or molecules (eg, catecholamines, cortisol, glucagon, tumor necrosis factor–α) and the reduction of anabolic hormone (eg, insulin) create a hypercatabolic syndrome that reduces cytoplasmic and mitochondrial cell proteins synthesis and impairs cell functions and energetic metabolism. Amino acids (AAs) are used not only for cellular protein replacement and/or cellular energy production but they also are released from skeletal and cardiac muscle and used to produce glucose or other metabolic intermediates that are essential to maintain the metabolism of fundamental body structures. IGF = insulin-like growth factor.

nutrients; it stimulates both protein and DNA synthesis and regulates cell growth, proliferation, and survival.[20]

Preliminary data also suggest that oral supplements of a specific mixture of AAs increase muscular number and volume of mitochondria. This point is particularly important for patients with chronic diseases such as diabetes, senescence, and CHF, where impaired mitochondrial activities and disarrangement of energy metabolism are present in the muscles.[21,22]

Furthermore, recent results suggest that prolonged oral supplementation with a specific AA mixture upregulates muscular glucose transporter-4 expression in diabetic rats without interfering with intracellular insulin signaling. On the other hand, clinical data show that oral AA supplementation reduces blood glucose and improves both insulin resistance and cardiac mechanical functions in patients with diabetes.[14–17,23,24] It is important to note that AAs can reactivate glucose cell metabolism in an insulin-independent manner.[25,26] These results suggest the existence in the muscles of archaic metabolic pathways that are (1) insulin independent and (2) stimulated by nutrients such as AAs. These pathways are silent under normal conditions, but they are stimulated by oral AA supplements when the insulin-dependent pathway is impaired.[20] Therefore, these insulin-independent pathways are important for overcoming cellular damage induced by HS that compromises cell metabolism.

## Conclusion

Chronic diseases, such as diabetes, heart failure, and senescence, share the common denominator of HS with insulin resistance. HS is characterized by increased hormonal catabolic stimuli that cause muscle protein breakdown and consequent cell release of AAs, muscular wasting, and altered energy production. Basic laboratory and clinical evidence shows that oral administration of AAs stimulates cytosolic muscle protein synthesis, mitochondrial biogenesis, and glucose intracellular transport and use. These mechanisms may help to maintain skeletal and cardiac muscle structures and energy content; importantly, these AA activities use an insulin-independent pathway. Increased protein intake with meals does not increase protein synthesis, be-

cause the meal must be digested and absorbed and, often, as in the case of chronic diseases, the exocrine pancreas and mesenteric circulation are impaired. Individual AAs introduced by nutritional supplementation are not digested, but are rapidly absorbed with massive blood increases and easily transported into cells, where AAs maintain myocyte structure and metabolism. As a result, nutritional supplementation with AAs counteracts catabolic stimuli present in chronic diseases by stimulating muscle metabolic and structural changes that prevent skeletal and cardiac muscular wasting and impaired energetic metabolism with consequent functional damage.

Supplementation with oral AA mixtures, taken together with conventional therapies, potentially may be used in chronic diseases such as diabetes and CHF or in physiologic conditions such as senescence that are characterized by catabolic stimuli with impaired protein metabolism and, consequently, muscular wasting and energy impairment.

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