# Oral Amino Acid Administration in Patients with Diabetes Mellitus: Supplementation or Metabolic Therapy?

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**Amino acids are essential for body protein synthesis. Moreover, they can be used to produce energy within the cells. For protein turnover, normal plasma amino acid concentration enhances proteolytic suppression by insulin; furthermore, hyperaminoacidemia can stimulate protein synthesis both in the presence of baseline insulin and in hyperinsulinemic subjects with type 1 diabetes. In humans, the availability of amino acids represents a factor more important than insulin in maintaining protein synthesis in skeletal muscle. Among amino acids, branched-chain amino acids exert an anabolic effect on heart protein metabolism, and their uptake by the myocardium is increased by increasing their circulating concentrations. An important aspect of branched-chain amino acid metabolism in the heart (mainly in the ischemic heart) is that branch-chain amino acid infusion can diminish myocardial lactate; in this way, the inhibition of anaerobic energy phosphate caused by accumulation of lactate can be overridden. Plasma amino acid availability plays an important role in promoting protein synthesis and in energy production, both in peripheral skeletal muscle and in the myocardium.** 

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Amino acids are required for normal metabolic function. They are responsible for protein synthesis; for providing energy by oxidation and formation of carbon dioxide, water, and ammonia; and for producing secondary messengers, such as neurotransmitters and hormones. Normal subjects have postabsorptive rates of whole-body protein synthesis of about 3 g/kg/day and a greater rate of whole-body protein degradation. Thus, in normal postabsorptive subjects, a net protein catabolism of 1.5 g/kg/day occurs.[1] Approximately 315 g of body proteins are degraded daily in a healthy 70-kg man. An estimated 80% of the resulting amino acids, namely from skeletal muscles, are reused for the synthesis of new proteins (endogenous protein turnover). The remaining 20% are metabolized to glucose, ketones, fats, and energy.

Insulin is the main anabolic hormone. The effects of insulin on protein regulation are to decrease proteolysis and enhance protein synthesis. Insulin has been shown to decrease net amino acid release across the human forearm.[2,3] As a consequence, insulin exerts its primary effect by suppressing proteolysis and its secondary effect by decreasing amino acid oxidation.[4,5] Data from volunteers fasting overnight indicate that the major influence of insulin in vivo is to inhibit proteolysis in a dose-dependent manner.[6]

The in vivo effect of insulin on protein kinetics is dependent on the prevailing plasma levels of amino acids.[6] Protein synthesis, protein degradation, and amino acid oxidation have been shown to have insulin-responsive and insulin-unresponsive components.[6] The insulin-unresponsive component of these processes is highly dependent on the presence of circulating plasma amino acids. In the presence of normal amino acid levels, proteolytic suppression by insulin is enhanced.[6] Low levels of circulating plasma amino acids is associated with a lower rate of protein degradation.

It has also been shown that insulin infusions do not stimulate skeletal muscle protein synthesis in postabsorptive patients with insulin-dependent diabetes mellitus but, rather, strongly inhibit proteolysis.[7] These findings suggest that the anabolic effect of insulin is related to the inhibition of protein degradation more than the stimulation of protein synthesis. Conversely, whole-body protein synthesis is augmented in the setting of hyperinsulinemia associated with elevated levels of amino acids both in healthy subjects[8–10] and in patients with type 1 diabetes,[11] whereas protein synthesis is reduced when insulin is infused only with glucose.[8,11] Thus, elevated plasma amino acid levels stimulate protein synthesis even in the presence of elevated baseline insulin levels, and a 10-fold increase in insulin concentration does not further stimulate protein formation.[12]

In humans, amino acid availability is a more important factor than insulin in maintaining skeletal muscle protein synthesis. The main role of insulin in vivo appears to be inhibition of protein degradation.

Branched-chain amino acids—such as leucine, isoleucine, and valine—have unique anabolic effects on muscle protein metabolism. In incubated and perfused skeletal muscle, protein synthesis was stimulated by leucine but not by valine or isoleucine.[13] In humans, increasing concentrations of circulating branched-chain amino acids promotes whole-body protein me-

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tabolism.[14] Important effects of branched-chain amino acids on myocardial protein turnover and amino acid oxidation, as well as on energy metabolism, are documented both in animal and in human studies. In perfused hearts, the same stimulation of protein synthesis attained with a complete mixture of amino acids was achieved with branched-chain amino acids alone.[15] Chua et al[16] demonstrated that high levels of the decarboxylated products of leucine, valine, and isoleucine decreased protein degradation in perfused rat hearts, but only the decarboxylated products of leucine and valine stimulated protein synthesis, indicating that the degradation of branched-chain amino acids and/or the accumulation of their catabolic products appeared to be necessary for suppression of proteolysis.

A negative myocardial protein balance has been demonstrated in postabsorptive patients with chronic coronary artery disease, and a short-term infusion of branched-chain amino acids had an anabolic effect on heart protein metabolism.[17] In addition, the myocardial uptake of branched-chain amino acids and their ketoacid derivatives was enhanced by increasing the circulating concentrations. Interestingly, during an infusion of a balanced mixture of amino acids, the uptake of branched-chain amino acids increased, but the myocardial balance of the other amino acids remained unchanged.[18] Branched-chain amino acids and their keto derivatives are likely oxidized because branched-chain amino acid transaminase and branched-chain ketoacid dehydrogenase enzymes responsible for the initial step toward oxidation of these substances are abundantly present in the heart.[19] During branched-chain amino acid infusion, myocardial lactate uptake diminishes secondarily to the use of branched-chain amino acids and their keto derivatives as oxidative fuels. Of importance, branched-chain amino acid infusion does not change insulin concentration.

Branched-chain amino acid degradation leads to an appreciable amount of adenosine triphosphate (ATP). The input of amino acids into the tricarboxylic acid cycle provides comparable or even greater amounts of ATP compared with the oxidation of pyruvate or lactate. This may be particularly important in acute ischemia, where the aerobic energy production from amino acids can reduce the conversion of pyruvate derived from glycolysis to lactate, favoring the formation of alanine.[20] As a consequence, the inhibition of glycolysis and anaerobic production of high-energy phosphate caused by accumulation of lactate can be overridden.[21,22]

## CONCLUSION

The myocardial availability of branched-chain amino acids (and their keto derivatives) has a specific direct anabolic action on heart protein metabolism, as well as an energetic function. Based on the effects of branched-chain amino acids on protein turnover and energy supply, both in skeletal and myocardial muscles, studies were conducted to determine the effects of supplementation with a balanced mixture of amino acids on metabolic control in patients with type 2 diabetes and on ventricular function of subjects with diabetes but no cardiac disease during isometric exercise (handgrip). A study on isolated ischemic rat heart was also conducted to ascertain the effect of amino acid supplementation on overall myocardial energy production. The results of these studies, which are reported in this supplement, together with published findings discussed above, lead to the conclusion that oral administration of amino acids in patients with diabetes may not only be a supplementation but also a metabolic therapy.


**1.** Shaw JHF, Wildlore M, Wolfe RR. Whole body protein kinetics in severely septic patients. *Ann Surg* 1987;205:288–296.

**2.** Barrett EJ, Revkin JH, Young LH, Zaret BL, Jacob R, Gelfand RA. An isotopic method for measurement of muscle protein synthesis and degradation in vivo. *Biochem J* 1987;245:223–228.

**3.** Gelfand RA, Barrett EJ. Effect of physiologic hyperinsulinemia on skeletal muscle protein synthesis and breakdown in man. *J Clin Invest* 1987;80:1–6.

**4.** Fukagawa NK, Minaker KL, Rowe JW, Goodman MN, Matthews DE, Bier DM, Young VR. Insulin-mediated reduction of whole body protein breakdown: dose-response effects of leucine metabolism in postabsorptive men. *J Clin Invest* 1985;76:2306–2311.

**5.** Flakoll PJ, Kulaylat M, Frexes-Steed M. Aminoacids augment insulin's suppression of whole body proteolysis. *Am J Physiol* 1989;2570:E839–E847.

**6.** Brown LL, Williams PE, Becker TA, Ensley RJ, May ME, Abumrad NN. Rapid high-performance liquid chromatographic method to measure plasma leucine: importance in the study of leucine kinetics in vivo. *J Chromatogr* 1988;426:370–375.

**7.** Pacy PJ, Nair KS, Ford C, Halliday D. Failure of insulin infusion to stimulate fractional muscle protein synthesis in type 1 diabetic patients: anabolic effect of insulin and decreased proteolysis. *Diabetes* 1989;38:618–624.

**8.** Castellino P, Luzi L, Simonson DC, Haymond M, DeFronzo RA. Effect of insulin and plasma amino acid concentrations on leucine metabolism in man: role of substrate availability on estimates of whole body protein synthesis. *J Clin Invest* 1987;80:1784–1793.

**9.** Tessari P, Inchiostro S, Biolo G, Trevisan R, Fantin G, Marescotti MC, Iori E, Tiengo A, Crepaldi G. Differential effects of hyperinsulinemia and hyperaminoacidemia on leucine-carbon metabolism in vivo: evidence for distinct mechanisms in regulation of net amino acid deposition. *J Clin Invest* 1987;79:1062–1069.

**10.** Bennet WM, Connacher AA, Scrimgeour CM, Jung RT, Rennie MJ. Euglycemic hyperinsulinemia augments amino acid uptake by human leg tissues during hyperaminoacidemia. *Am J Physiol* 1990;259:E185–E194.

**11.** Bennett WM, Connacher AA, Smith K, Jung RT, Rennie MJ. Inability to stimulate skeletal muscle or whole body protein synthesis in type 1 (insulin-dependent) diabetic patients by insulin-plus-glucose during amino acid infusion: studies of incorporation and turnover of tracer L-[1-$^{13}$C] leucine. *Diabetologia* 1990;33:43–51.

**12.** Fukagawa NK, Minaker KL, Young VR, Matthews DE, Bier DM, Rowe JW. Leucine metabolism in aging humans: effect of insulin and substrate availability. *Am J Physiol* 1989;256:E288–E294.

**13.** Tischler ME, Desautels H, Goldberg AL. Does leucine, leucyl-cRNA or some metabolite of leucine regulate protein synthesis and degradation in skeletal and cardiac muscle? *J Biol Chem* 1982;257:1613–1621.

**14.** Schwenk WF, Haymond MW. Effects of leucine, isoleucine or threonine infusion on leucine metabolism in humans. *Am J Physiol* 1987;253:E428–E434.

**15.** Rannels DE, Hjalmarson AC, Morgan HE. Effects of noncarbohydrate substrates on protein synthesis in muscle. *Am J Physiol* 1974;226:528–539.

**16.** Chua BHL, Siehl DL, Morgan HE. A role for leucine in regulation of protein turnover in working rat hearts. *Am J Physiol* 1980;239:E510–E514.

**17.** Young LH, McNulty PH, Morgan C, Deckelbaum LI, Zaret BL, Barrett EJ. Myocardial protein turnover in patients with coronary artery disease: effect of branched chain amino acid infusion. *J Clin Invest* 1991;87:554–560.

**18.** Schwartz RG, Barrett EJ, Francis CK, Jacob R, Zanet BL. Regulation of myocardial aminoacid balance in the conscious dog. *J Clin Invest* 1985;75:1204–1211.

**19.** May RC, Mitch WE. The metabolism and metabolic effects of ketoacid. *Diabetes Metab Rev* 1989;5:71–82.

**20.** Mudge GH, Mills RM, Taegtmeyer H, Gorlin R, Lesch M. Alterations of myocardial aminoacid metabolism in chronic ischemic heart disease. *J Clin Invest* 1976;58:1185–1192.

**21.** Neely JR, Whitmer JT, Rovetto MJ. Effect of coronary blood flow on glycolytic flux and extracellular pH in isolated rat hearts. *Circ Res* 1975;37:733–741.

**22.** Rovetto MJ, Lamberton WF, Neely JR. Mechanisms of glycolytic inhibition in ischaemic rat hearts. *Circ Res* 1975;37:742–751.