Amino Acids, Blood Sugar Balance and Muscle Protein Maintenance

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Blood sugar dysregulation and hypoglycemia, along with insulin resistance are all conditions which health care practitioners routinely see. Estimates indicate that approximately 60% of the American population is overweight, ~20% are obese, and over 7% are self reported Type-2 diabetics.[1] An escalating proportion of these patients, along with an increasing incidence of childhood obesity and a generally unhealthy lifestyle make this an important topic of evaluation. Left untreated, there is a general progression from hypoglycemia, to dysinsulinism, or insulin resistance and eventually onto either Syndrome-X or overt Type-2 diabetes.

In addition to a quality source dietary protein, an increase in branched-chain amino acids plays an important role in blood sugar stabilization. Essential amino acids serve to stimulate protein anabolism by increasing muscle protein synthesis, particularly when ingested 1-3 hours following resistance exercise.[2] As a consequence of the oral ingestion of essential amino acids, an increased stimulation of protein synthesis occurs, evidenced by an increase in the level of plasma amino acid.[3] In regards to muscle maintenance the intake of amino acids may offer dual advantages; first as positive contributor to muscle protein synthesis, and secondly as an important intervention for prolonged periods of inactivity, specifically that resulting from illness or incapacity. A positive relationship has been established between extracellular essential amino acids and an increase in muscle protein synthesis.[4] Additionally, the ingestion of essential amino acids was shown to be superior in stimulating protein synthesis, as compared to a combination of nonessential amino acids.[5,6]

Poor Diet is a Primary Issue in Blood Sugar Control

A diet high in refined sugars results in a quick absorption of sugar into the bloodstream, producing a spike in blood sugar. In turn insulin from the β cells of the pancreas is released, which subsequently drives blood sugar down. A decrease in blood sugar causes symptoms of hypoglycemia, resulting in feelings of shakiness, heart palpitation, sweating or nausea, or a combination thereof. In response to the rapid fall in blood glucose, the adrenals are stimulated to secrete epinephrine (adrenaline), which results in a successive rapid elevation in blood glucose levels. More specifically, glucocorticorids are released and the liver normalizes blood glucose levels by the release of stored glycogen. Over time, this constant flux in blood sugar puts excessive stress on the adrenal glands, which in turn leads to adrenal exhaustion due to the constant demand of balancing blood sugar. Subsequently, adrenal fatigue and insulin resistance result, as a consequence of an increased cellular exposure to insulin. Due to a lack or diminished response of the adrenals, reactive hypoglycemia ensues. Eventually, as this process continues, the blood sugar control mechanisms become further stressed, and the body goes into insulin sensitivity. Prolonged periods of insulin sensitivity in turn cause insulin *in*sensitivity (insulin resistance), as a result of the constant stimulation of insulin. Ultimately, if left untreated, diabetes ensues as a result of this continual cycle. In addition to diabetes and insulin resistance, poor glycemic control has been implicated as a significant underlying factor in cardiovascular disease.

Balancing Fluctuations in Blood Sugar

Balancing blood sugar in an effort to prevent spikes and drops is an important component in the prevention of the above noted consequences. A steady balance, otherwise termed glycemic control plays an important role in preventing these overt symptomatologies. The diet is the primary foundation for regulation of blood sugar, thus avoiding foods that cause a destabilization in blood glucose is paramount. Incorporating foods that act as blood sugar stabilizers, or promote glycemic balance is a key factor. An increase in dietary protein, with a corresponding lowering in carbohydrates is known to be a beneficial factor in stabilizing blood glucose. Dietary proteins provide a source of the naturally occurring twenty amino acids, most importantly the nine essential amino acids. Due to the importance of dietary protein, amino acids offer a beneficial effect in the stabilization of blood sugar, as proteins are broken down into amino acid constituents.

Amino Acids and Blood Sugar Regulation

As indicated above, amino acids play a functional role in blood sugar stabilization. Of the twenty amino acids the glycogenic amino acids play a significant role in this function. A glycogenic amino acid (also referred to as glucogenic amino acid) is defined as one that can be converted into glucose via gluconeogenesis.[7,8] The glycogenic amino acids in humans include glycine, serine, threonine, valine, histidine, arginine, cysteine, proline, alanine, glutamate, glutamine, aspartate, asparagine and methionine.

Amino Acids and Muscle Integrity

Amino acids serve as both building blocks for muscle protein, as well as a source of energy for skeletal muscle. Dietary amino acid supplementation is known to have beneficial effects on muscle function, fatigue, and recovery in exercising athletes.[9] The combination of carbohydrates and essential amino acids has demonstrated a beneficial effect on muscle protein synthesis, which was shown to be greater than the summation of their individual effects.[10,11] Amino acids have also shown to benefit muscular fatigue as a result of exercise, resulting in favorable changes, including an increased oxygen-carrying capacity of blood.[9]

Specific Amino Acids and their Function

Glycine. Glycine is a nonessential amino acid synthesized *in vivo* from the amino acid serine. In addition to protein synthesis, glycine is also involved in many anabolic reactions, including the synthesis of purine nucleotides, heme, glutathione, creatine, and serine. Diabetes in general is known to significantly modify the humoral immune response capacity. In studies with diabetic-induced (streptozotocin) animals, glycine was shown to successfully reduce hemoglobin glycation,[12] as well as to inhibit enlargement of the glomerular basal membrane.[13] The accumulation of basement membrane is considered to be a characteristic of diabetic microangiopathy, as excess glucose has shown to result in the stimulation of the basement membrane accumulation.[14] Glycine could be an important therapeutic resource among diabetics to avoid the characteristic immunodeficiencies of this disease.[15]

L-Alanine. In an aqueous form glycogenic amino acids serve to normalize blood sugar fluctuations and support a homeostatic blood glucose range. As the primary amino acid released from muscle during starvation, alanine serves as an important substrate for hepatic gluconeogenesis. Furthermore, the transamination of alanine is a required step for the proper maintenance of fasting blood glucose concentrations. This step provides the amino nitrogen need to for the production of alanine from pyruvate. Following transamination alanine is transported from the muscle to the liver to support hepatic gluconeogenesis.[16] The glucose-alanine cycle is an important component of endogenous glucose production, reported to account for >40% of glucose production during exercise.[17] It has also been reported that splanchnic uptake of alanine along with other glycogenic amino acids was 1½-2 times greater in diabetics, while lactate and pyruvate uptake was increased by 65-115%.[18]

L-Arginine. As a required precursor of nitric oxide, via its essentiality for the enzyme endothelial nitric oxide (NO) synthase (eNOS), arginine plays an important role in vasodilation. Functionally, the L-arginine/NO pathway effectively contributes to the maintenance of important physiological functions, including vascular tone, platelet function and neurotransmission.[19] In addition to nitric oxide, L-Arginine is also a substrate for four other enzymes in the mammalian system, making it essential for the synthesis of creatine, urea, polyamines, and agmatine (the decarboxylation product of the arginine).[20] Irrespective of its *in vivo* production, various disease states may predispose one to an insufficient conversion of arginine, as required to accomplish specific metabolic tasks. Conditions that predispose one to vasoconstriction, including angina, atherosclerosis, coronary artery disease, erectile dysfunction, vascular disease and vascular headaches, may benefit from L-arginine supplementation. Supplemental arginine has been shown to result in the stimulation of protein synthesis. Arginine was also demonstrated to significantly increased exercise tolerance and duration ($P<0.03$).[21] Additionally, in an animal study the stimulation of thymic lymphocyte has been reported with arginine supplementation ($p<0.05$), [22] making it an important component in immunity.

L-Lysine. Lysine is a metabolically indispensable amino acid. It is important for proper growth, plays an important role in both collagen formation and in the production of carnitine, a nutrient responsible for converting fatty acids into energy. Supplemental lysine has also been correlated with the absorption and conservation of calcium.[23] In mammals lysine is metabolized to form acetyl-CoA, via α-ketoglutarate.[24]

L-Proline. Proline is made *in vivo* via the conversion of glutamate. As a critical component of cartilage, proline plays a role in the health of joints, tendons and ligaments. It is also involved in keeping heart muscle strong. Proline is also known to play a significant role in stabilization of alpha helices,[25] which are important in the structural integrity of proteins, DNA and RNA.

L-Histidine. As one of the ten essential amino acids histidine is recognized as an important nutrient, particularly in children. Structurally, histidine contains an imidazole functional group, making it a common participant in enzyme catalyzed reactions. In the vertebrate muscle histidine supports the intracellular non-bicarbonate buffering capacity by virtue its imidazole groups.[26] Histidine also performs a stabilizing role in the folded structure of proteins.[27] In athletes, as a result of conditioning, an enhanced buffering capacity exists primarily due to enhanced anaerobic power. This superior intracellular buffering capacity has been correlated to among others, protein-bound histidine residues.[28] Histidine has also been correlated with cardioprotection. In a study assessing myocardial preservation of the dilated heart during open heart surgery, a histidine-tryptophan-potassium solution was demonstrated to offer superior myocardial protection, as compared to a glucose-insulin-potassium solution.[29] A similar conclusion was observed in a mitral valve replacement study, noting that a solution of histidine-triptophanketoglutarate (HTK) was superior to that the standard cold blood cardioplegic solution. The authors concluded indicating that the HTK solution was cardioprotective in this aspect.[30]

L-Serine. Serine is a required component in the biosynthesis of purines and pyrimidines, as well as an indispensable precursor for the synthesis of the amino acids glycine, cysteine and D-serine. It is also a precursor in the production of folate, and membrane lipids including phospholipids and sphingolipids. Consequently, it is an indispensable precursor to the synthesis of proteins, lipids, nucleotides.[31] Independent tissue culture studies have established that exogenously supplied serine "promotes neuronal survival and differentiation of sensory ganglia, hippocampal neurons, and cerebellar Purkinje cells."[32,33,34,35] In regards to neurological function, L-serine was shown to significantly improve neuronal survival and neurite growth, with the authors establishing that essentiality of L-serine in both the "survival and phenotypic growth of hippocampal neurons."[36] A separate study demonstrated the significance of L-serine as a key mediator in neuron-glial metabolic interactions, functioning in a key capacity for a range of central neurons.[32] In an additional study L-Serine supplementation was shown to result in the stimulation of the production of nitric oxide (NO), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF alpha),[37] implicating a role in immunopotentiating activities.

L-Threonine. L-Threonine is one of the ten essential amino acids, thus its dietary inclusion is a necessity. The mean daily requirement in healthy adults is 15mg/kg/day, raised in 2002 from the initially recommended value of 7mg/kg/day.[38] Like serine and tyrosine, threonine is recognized as a proteinogenic (protein building) amino acid,[39] and is recognized for its role in the formation of collagen and elastin. It has established benefits in the maintenance of proper protein balance, and in immune support via the production of antibodies and the promotion of thymic activity.[40] As a vital component of gene expression, essential amino acids in limited supply lend cellular populations susceptible to "both specific induction and repression of gene expression".[41] Animals on a threonine-free diet administered essential amino acids, also referred to as "growth-limiting amino acids," demonstrated an increased neuronal response, evidenced by an "increase in the firing rate in neurons from the lateral hypothalamus."[42]

L-Valine. Like L-Threonine, L-Valine is also an essential amino acid. It is a hydrophobic (water revulsion) amino acid, thus is typically located in the interior of proteins. Dietary sources of valine include meats, fish, vegetables, cottage cheese and soy flour.[43] As one of the branched chain amino acids, it is a necessary component of protein synthesis. The supplementation of branched chain amino acids, including valine, both before and after exercise has shown benefits in both decreasing exercise-induced muscle damage as well as encouraging the synthesis of muscle protein.[44]

By virtue of its integral association with proteins, amino acid supplementation represents an important component in supporting a healthy blood sugar balance, aside from its significance in the maintenance of muscular protein and muscle tone. In athletes, endurance training has shown to result in an increase in amino acid oxidation and urea excretion, along with a decrease in protein synthesis in the liver, heart and stromal fraction of the muscle,[45] implicating a probable benefit to amino acid supplementation. In the gastrointestinal tract protein is broken down into amino acids via the action of pepsins, which cleave peptide linkages. The ingestion of free form amino acids results in a rapid, multiple fold increase in the plasma amino acid level, which has been correlated to an increased production of red blood cells.[46] Free forms of amino acids, specifically the essential amino acids are absorbed quicker than that of the nonessential amino acids.[47] Along with exercise the intake of oral amino acids facilitates a decrease in muscle protein loss. The administration of amino acids in both a balanced combination as well as in an easily absorbed form, such as an aqueous solution or easily dissolvable capsules, offers distinct advantages over formulations contained in compacted tablets. One of the primary disadvantages of the latter form is their diminished absorption capacity. Additionally, inappropriately balanced combinations are typically of no benefit for those individuals with malabsorption issues or blood sugar imbalances, and characteristically offer little or no therapeutical value. With regard to therapeutically balancing blood sugar fluctuations, and stabilizing blood sugar, the use of less absorbable forms is typically less than desirable. Finally, persons with digestive disorders, including hypochlorhydria, celiac disease, irritable bowel disease, and colitis have an added need for amino acids, since absorption is limited or diminished. For these individuals and as for athletes wanting to offset amino acid oxidation, an oral, easily assimilated form of amino acid supplementation may be advantageous.

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