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Opinion

Balancing Branched Chain Amino Acids in Medical Foods for Inherited Disorders of Amino Acid Metabolism

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Inherited disorders of amino acid metabolism are caused by deficiencies of specific enzymes resulting in excessive amounts of intermediary metabolites due to mutations that are generally inherited as autosomal recessives. The treatment of individuals diagnosed with these disorders often involves nutritional management with medical foods comprised of synthetic mixtures of amino acids (AAs). A medical food is defined by the United States Food and Drug Administration as a "food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation" (United States Food and Drug Administration; URL:http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/). Despite their critical importance in improving disease outcomes, few studies have addressed the composition and efficacy of medical foods that provide the cornerstone of therapy for inherited disorders of amino acid metabolism detected through newborn screening. The appropriate balance of the indispensable branched chain amino acids (BCAA; Val, Leu and Ile) in medical foods is an important question.

The composition of BCAA in medical foods used for the management of methylmalonic academia (MMA, OMIM 251000) [1] and phenylketonuria (PKU; OMIM 261600) is a topic of recent interest [2]. With respect to MMA, Irini Manoli has demonstrated depletion of Val, Ile and Met when medical foods for MMA provided increased Leu with minimal Val, Ile, Met and Thr [3,4]. Our research to develop medical foods for PKU made from glycomacropeptide (GMP), a low-Phe protein isolated from cheese whey, illustrates the need for experimental evidence to develop safe medical foods [5,6]. The story of our research to find the optimal balance of BCAA in GMP medical foods follows.

Leu is a limiting AA in GMP and must be supplemented. We arrived at the current level of Leu supplementation available in medical foods for PKU containing Glytactin™ based on an earlier inpatient study where we analyzed the plasma AA profiles of individuals with PKU fed AA and GMP medical foods of known AA composition [7]. Surprisingly, we found that supplementing GMP to provide 130% of the Leu requirement was not enough Leu as this did not result in a normal postprandial profile of BCAA, as shown in Figure 1. The normal plasma concentrations of Val:Leu:Ile reflects a ratio of 3:2:1, as observed with AA medical formula, whereas the experimental GMP formulation used in our inpatient study showed a 2-fold increase in plasma Ile and a 25% decrease in plasma Leu with no significant change in plasma Val [7].

A significant factor is that the requirement for Leu is double the requirement for Ile - 60 mg Leu/g pro and 30 mg Ile/g pro [8]. The challenge to establish an optimal Leu supplementation for GMP is the high endogenous content of Ile within the GMP peptide, 2-fold higher compared with other natural proteins. In our early study the experimental GMP medical food provided 130% of the Leu requirement which was not sufficient relative to the high concentration of Ile within the GMP peptide resulting in a ratio of Leu:Ile of 0.70 and an abnormal postprandial profile of BCAA [7], Figure 1. The BCAA share a common catabolic pathway with branched-chain ketodehydrogenase controlling the irreversible catabolic step that commits the carbon skeletal of BCAA to the TCA cycle [9]. Thus, an imbalance in BCAA intake can stimulate catabolism of BCAA and limit their availability for protein synthesis. In the case of PKU, if an imbalance were to occur in BCAA intake, muscle catabolism might exceed muscle protein synthesis leading to increased plasma Phe concentrations.

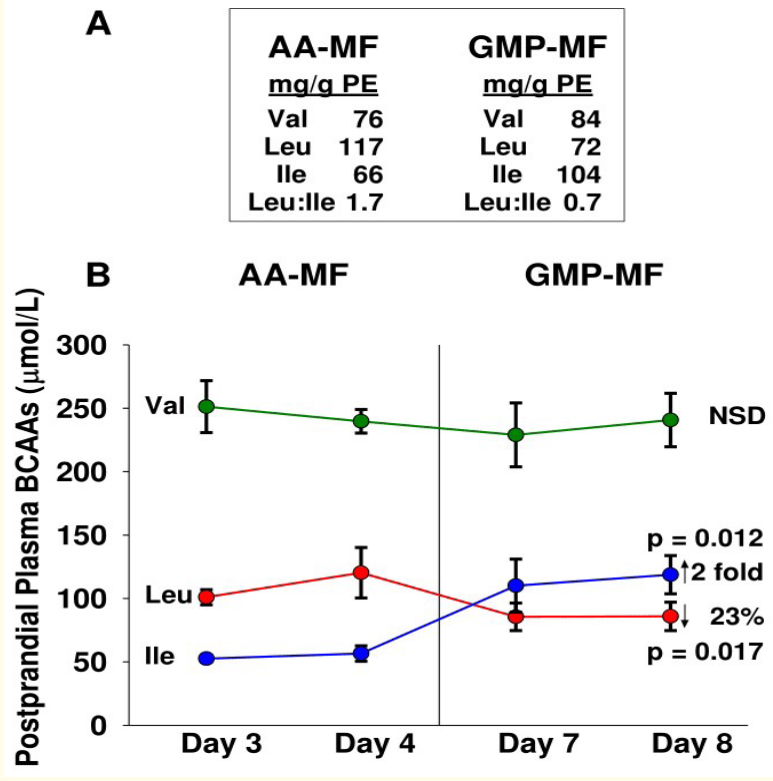

Figure 1: *Comparison of BCAA composition of commercial AA-MF and experimental GMP-MF (A) and subsequent postprandial concentrations of BCAAs in plasma 2.5 hours after breakfast (B). Six subjects with PKU consumed AA-MF and GMP-MF in an inpatient study; values are means ± SE (van Calcar SC et al, Am J Clin Nutr, 2009; 89:1068-77).*

AA-MF: Amino Acid Medical Food; GMP-MF: Glycomacropeptide Medical Food; BCAA: Branched Chain Amino Acids (Leucine, Isoleucine and Valine); PE: Protein Equivalent.

Leu plays a key role in protein synthesis. Compared to the other indispensable AAs, Leu has the highest concentration in human muscle (~10%) and thus, the highest dietary requirement. Leu is a precursor for newly synthesized protein and also a signaling molecule shown to induce muscle protein synthesis [10]. In fact, rapid postprandial increases in systemic Leu concentration have been demonstrated to be a primary driver of muscle protein synthesis in clinical studies [10,11].

The amount of Leu in currently available Glytactin™ containing GMP medical foods (150 - 200 mg Leu/g protein equivalent; PE) was used in our recent outpatient clinical trial. It provided 150 mg Leu/kg/day [2], a level well below the tolerable upper limit for Leu of 500 mg Leu/kg/day [9]. Importantly, a normal plasma AA profile was observed when 30 subjects consumed the GMP medical foods for 3 weeks. Insufficient supplementation of Leu in GMP medical foods (less than 100 - 150 mg Leu/g PE based on our research) may limit protein synthesis and contribute to increased Phe concentrations in blood. This could translate into impaired growth for children and maternal PKU, especially if natural protein intake is limited.

Take home message: Before new medical foods become available for patient care, we need clinical studies in patients fed medical foods with defined AA composition to assess the impact on plasma amino acid concentrations. Experimental evidence is needed to support the development of medical foods for the management of inherited metabolic disorders.

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