Role of medical food in MMA

To the Editor: As senior metabolic dietitians who have provided nutritional management for individuals with methylmalonic acidemia (MMA), we wish to comment on the recent article by Manoli et al., "A Critical Reappraisal of Dietary Practices in Methylmalonic Acidemia Raises Concerns About the Safety of Medical Foods. Part 1: Isolated Methymalonic Acidemias"[1], published online in this journal in August 2015. This title is misleading because it seems to imply that poor outcomes are due solely to the use of medical foods. We believe that their study does raise some concerns about some of the current management and monitoring practices[2] in the context of a complex disease that, in many cases, cannot be optimized by diet alone.

Medical food, a term created in 1988 by the Orphan Drug Amendments, is defined as "a food 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" (http://medpolicy.ibx.com/policies/mpi.nsf/f12d23cb982d59b485257bad00552d87/85256aa800623d7a85257bf2004f103f!OpenDocument). Although the authors refer to these products as incomplete proteins, they are technically not proteins but, rather, amino acid mixtures that are formulated to minimize the intake of those amino acids that are not catabolized in a specific metabolic disorder, e.g., the propiogenic amino acids in medical foods designed for MMA or propionic acidemia. Medical foods are never intended to be the sole source of nutrient intake for the individual. Limited intake of dietary intact protein (also referred to as natural protein, food protein, or complete protein) is titrated to provide the required essential amino acids, as well as carbohydrates and fat, to provide a nonprotein energy source.

The authors suggest that individuals with MMA may be able to meet their protein needs solely with dietary intact protein. However, this overlooks the fact that many individuals with MMA are poor eaters. This may be due in part to chronic acidosis causing anorexia, neurological sequelae that limit the ability to chew and swallow, or aversion to certain textures and tastes. The use of medical foods (in combination with other dietary components containing the propiogenic amino acids) can provide a consistent energy and nutrient source for these poor eaters or for others during intercurrent illness or metabolic crisis.

The authors also failed to address the issue of the biological value/quality[3] of intact or dietary proteins. Proteins derived from plant sources are less likely to be of high biological value and contain limiting amounts of certain essential amino acids. Moreover, these are the very foods—fruits, vegetables, and some grains—that are the major source of intact dietary protein for individuals with MMA. Reliance solely on these sources can compromise protein status. There are some individuals with milder forms of MMA who can tolerate an intake of intact protein that meets the Dietary Reference Intake for age, but even for these individuals, addition of medical food can provide a "buffer" to allow some leeway in intact protein sources as well as provide an important source of nonprotein energy and micronutrients to meet individual needs.

It is important to emphasize that nutritional intervention is not a panacea for the management of individuals with various forms of MMA; these are complex disorders with probable mitochondria dysfunction, chronic renal disease, and risk for decompensation during intercurrent illness. Therefore, it is difficult to equate growth parameters with nutrient intake. The subjects enrolled in this study had diverse nutritional, medical, and supportive interventions and illness histories. Some were identified only after significant decompensation. All of these factors can impact their growth and development, even if they had all followed similar dietary interventions.

The authors raise important concerns about practices of increasing total protein intake by giving very large quantities of medical food and the negative impact of elevated leucine intake on the concentration of other essential amino acids. Medical foods available for use by individuals with MMA vary widely in their leucine content, as shown in **Supplementary Table S2** online. The composition of some of these products deserves careful reevaluation. Attempts to establish normal plasma amino acid ratios have been shown to improve growth parameters in other inborn errors of metabolism, such as phenylketonuria,[4] and may be an important goal for individuals with MMA. Short-term use of intact dietary protein alone may help establish appropriate plasma amino acid ratios, but the data are not available to show the long-term nutritional, anthropometric, and developmental outcomes of omitting medical foods in the management of individuals with MMA.

We believe their data suggest that the use of close and frequent monitoring should guide the balance between the amount of medical food amino acids and intact protein in providing the total protein required for adequate growth and maintenance. Even when using amino acids (medical foods) as part of the nitrogen source, total protein intake more than 1.2–1.5 times the Dietary Reference Intake is probably unnecessary. The authors demonstrated this by comparing anthropometric data with total protein intake. If additional energy is needed to promote anabolism, then this should probably come from nonprotein sources, rather than from additional amino acid–based medical food. If plasma levels of valine and isoleucine are low, then additional intact protein sources can be used and an equivalent decrease in amino acids from medical food can be considered.

LETTER TO THE EDITOR

We feel that medical foods play an important role in providing adequate nutrient intake for individuals with MMA. This is especially important for the individuals with *mut*^{0} and those with intercurrent illness, anorexia, and neurological deficits. The authors have raised important concerns about total protein and leucine intake and establishing appropriate amino acid ratios. These should be examined further through cooperative collection of intake, monitoring, and outcome data among clinicians managing these interesting and challenging individuals.

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Response to Cunningham *et al*.

To the Editor: We appreciate the expert opinion offered by our colleagues, senior dietitians and metabolic formula specialists[1], and welcome a dialogue to critically examine the role of medical foods in the nutritional management of these challenging patients.

It is important for the practicing physicians and dietitians that we emphasize bilateral agreement on the main points raised by our study:[2] (i) growth and body composition outcomes in isolated methylmalonic acidemia (MMA) patients are very poor; (ii) dietary therapy is not highly effective for patients with this complex disorder; (iii) the design of MMA/propionic acidemia (PA) medical foods neglected the effects of leucine on plasma levels of valine and isoleucine, making leucine content an important confounding parameter that complicates patient management; and (iv) the provision of large amounts of medical foods, up to twice the recommended daily allowance (RDA) for total protein (natural protein + medical foods), is unjustified.

The title and text of our paper[2] do not imply that the poor outcomes in this disorder are due *solely* to the use of medical foods, or that medical foods should be completely omitted from the management of MMA patients, rather that there are unintended sequelae associated with their use. Our study began as an effort to explore factors behind the obesity and growth delay of MMA patients using systematically collected data in a large patient cohort over the course of a decade. The results were counterintuitive and concerning: we expected to discover an ameliorated phenotype in MMA patients consuming medical foods but noted the opposite.

Cunningham *et al*. argue in favor of medical foods because (i) the patients have anorexia and neurological disease and need enteral feeds to support their nutrition; (ii) essential amino acids from low-biological-value and low-quality proteins have low bioavailability; and (iii) medical foods provide a "buffer" to allow some leeway in intact protein sources. Although these points have merit, they lack direct relevance to the concept that medical foods have potential iatrogenic toxicity when overprescribed and do not specifically support the use of the currently available formulations for the following reasons. (i) The requirement for enteral feeding does not, by itself, warrant the need for medical foods because protein and nonprotein energy and micronutrients can, and are, routinely provided by a variety of essential amino acids or protein-free formulas. (ii) The limited bioavailability of essential amino acids from low-biological-value protein sources supports the increased administration of *complete* protein/essential amino acids rather than medical foods.