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.

DISCLOSURE

All authors are past or present members of the Board of Directors of Genetic Metabolic Dietitians International. A.C. has received speaker/travel funds from Nutricia NA and Abbott Nutrition. D.F. has received speaker/travel funds from Abbott Nutrition, an honorarium from the Nutricia Advisory Board and an educational grant from Genetic Metabolic Dietitians International. B.M. is an employee of Abbott Nutrition and owns stock in that company. B.O. is a consultant for Sobi, Inc. F.R. has received speaker/travel funds from Abbott Nutrition, Vitaflo, and Nutricia NA and an honorarium for being a member of the Nutricia Advisory Board. S.V.C. has received speaker/travel funds and/or educational grants from Abbott Nutrition, Cambrooke Foods, Nutricia NA, Genetic Metabolic Dietitians International, the MSUD Family Support Group, the Glactosemia Foundation, and the National PKU Alliance. S.Y. is an employee of Nutricia NA. S.M. and K.U. declare no conflict of interest.

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Advance online publication 10 March 2016. doi:10.1038/gim.2016.11

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.

(iii) Finally, there is no evidence that medical foods play a role in dietary buffering in MMA.

Growth and protein status are dependent on the amount of the least available essential amino acid and hence cannot be supported by increasing essential amino acid–depleted medical foods. Indeed, we have not observed a need for supplementation with any other amino acids except for valine and isoleucine in our cohort, and we have identified a clear association between low plasma concentrations and the amount of deficient protein/medical food intake, even in patients exceeding the RDA intake for complete protein. This latter observation confirms well-documented effects of leucine administration on branched-chain amino acid metabolism[3] in an MMA cohort and, importantly, sheds new light on the biological effects of medical foods.

Although we agree that medical foods are incomplete/deficient amino acid mixtures rather than "protein," we referred to them as "incomplete protein equivalents" throughout our article. In the interest of space and readability, we occasionally used the terms "incomplete" versus "complete" protein. Importantly, although medical foods are not intended to be a source of complete protein, they represent a nitrogen-based nutritional supplement different from other nonprotein (carbohydrate and fat) energy sources, with concerning implications in a patient population with chronic renal failure and a propensity to develop hyperammonemia.

Our concerns about the efficacy of medical foods in the dietary management of MMA patients are consistent with the experience of our European and Australian colleagues in expert centers taking care of patients with *mut*^{0} MMA, where these products are used less often, if at all.[4] The metabolic community recognizes that, in contrast to phenylketonuria and maple urine disease, medical foods play only a minor role in the management of MMA/PA patients[5] and that dietary practice recommendations are based solely on uncontrolled studies[6] and expert opinion.[7]

As our understanding of metabolic disorders evolves, it will be imperative for physicians, dietitians, and scientists to pursue, as a joint transdisciplinary endeavor, the systematic evaluation of new dietary interventions to supersede opinion-based guidelines in the management of patients with inborn errors of metabolism such as MMA. At the present time, the imminent challenge for the larger biochemical genetics and dietitian community will be to determine the optimal composition of MMA/PA medical foods and when such formulas could offer a meaningful benefit to patients.

ACKNOWLEDGMENT

The views presented in this article are those of the authors and do not reflect the official position of the National Institutes of Health or the US Government.

DISCLOSURE

The authors declare no conflict of interest.

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Advance online publication 10 March 2016. doi:10.1038/gim.2016.12