Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2018 January ; 21(1): 42–48. doi:10.1097/MCO.0000000000000428.

Effects of Medical Food Leucine Content in the Management of Methylmalonic and Propionic Acidemias

Jennifer G. Myles, MS, RD¹, Irini Manoli, MD, PhD², and Charles P. Venditti, MD, PhD²

¹Nutrition Department, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

²Organic Acid Research Section, Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Purpose of review—This review highlights the varied effects of medical foods high in leucine and devoid of valine and isoleucine in the management of methylmalonic and propionic acidemias (MMA and PA) and cobalamin C (*cbIC*) deficiency, aiming to advance dietary practices.

Recent findings—Leucine is a key metabolic regulator with a multitude of effects on different organ systems. Recent observational studies have demonstrated that these effects can have unintended consequences in patients with MMA as a result of liberal use of medical foods. The combination of protein restriction and medical food use in MMA and PA results in an imbalanced branched-chain amino acid dietary content with a high leucine to valine and/or isoleucine ratio. This leads to decreased plasma levels of valine and isoleucine and predicts impaired brain uptake of multiple essential amino acids. Decreased transport of methionine across the blood-brain barrier due to high circulating leucine levels is of particular concern in *cbIC* deficiency where endogenous methionine synthesis is impaired.

Summary—Investigations into the optimal composition of medical foods for MMA and PA, and potential scenarios in which leucine supplementation may be beneficial are needed. Until then, MMA/PA medical foods should be used judiciously in the dietary management of these patients and avoided altogether in *cbIC* deficiency.

Keywords

Leucine; medical foods; methylmalonic acidemia; propionic acidemia; cobalamin C deficiency

INTRODUCTION

The inborn errors of metabolism (IEM) are a heterogeneous group of disorders caused by defective enzymes and/or cofactors that facilitate the metabolism of fats, carbohydrates, or proteins. Typically, a deficiency or block at an important step of a metabolic pathway results in the buildup of toxic precursors and/or a deficiency of downstream metabolites. Most

IEMs follow an autosomal recessive inheritance pattern, present in childhood and are accompanied by significant morbidity and mortality.

Propionic acidemia (PA) and methylmalonic acidemia (MMA) are rare, autosomal recessive organic acidemias characterized by enzymatic blocks in the degradation pathways of valine (Val), isoleucine (Ile), methionine (Met), and threonine (Thr), odd-chain fats, and cholesterol (1, 2). In PA, there is a deficiency of the propionyl-CoA carboxylase enzyme, which converts propionyl-CoA to methylmalonyl-CoA (2). Live-birth incidence of PA is 1:105,000 to 1:130,000 in the United States (2). Isolated MMA results from a defect in methylmalonyl-CoA mutase (*mut⁰*, *mut⁻*) (which converts methylmalonyl-CoA to succinyl-CoA), the synthesis of the coenzyme 5'-deoxyadenosylcobalamin (*cblA*, *cblB*, *cblD* variant 2), or a deficiency of methylmalonyl-CoA epimerase (1). Birth incidence ranges from 1:50,000 and 1:100,000 (1). Neonatal onset is characterized by potentially fatal progressive encephalopathy that may present as lethargy, seizures, or coma (1, 2). Long-term effects may include growth failure, intellectual disability, seizures, basal ganglia lesions, pancreatitis, cardiomyopathy, tubulointerstitial nephritis with progressive renal failure, immune dysfunction, and optic nerve atrophy (1, 2).

In contrast to isolated MMA, cobalamin C (*cblC*) deficiency causes combined methylmalonic acidemia and homocystinuria that results from a defect in 5'-deoxyadenosylcobalamin (the cofactor for methylmalonyl-CoA mutase), and methylcobalamin (the cofactor for methionine synthase, which catalyzes methylation of homocysteine to form methionine) (3).

Patients with cobalamin C deficiency typically present with failure to thrive, neurologic findings including seizures, global developmental delay, hemolytic uremic syndrome, cardiopulmonary manifestations, and vision loss due to a severe, progressive retinopathy and maculopathy (3).

IEM's are managed uniquely, but in many cases, one of the core therapies includes some form of dietary restriction specific to the disorder, plus use of medical foods. A medical food, as defined by the Food and Drug Administration (FDA) in section 5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)), is "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 (4)." Medical foods for IEM's contain little to no precursors of the "toxic" dietary precursors and supply essential nutrients that may be inadequately provided by a therapeutic diet restriction.

Leucine (Leu), an additive to many MMA/PA medical foods, has multiple metabolic effects, including modulation of branched-chain amino acid (BCAA) oxidation and transport of large neutral amino acids across the blood brain barrier (BBB) (5, 6). Medical foods for MMA and PA contain normal to high amounts of Leu and contain trace to no amino acid precursors metabolized by the defective enzymatic pathway, including Val, Ile, Met, and Thr. The use of medical foods in these disorders results in chronic and unbalanced Leu

supplementation compared to the other BCAAs, and overuse can induce unintended effects on amino acid metabolism and transport (7).

IMBALANCE OF BCAA's IN MEDICAL FOODS USED FOR MMA AND PA

While Val and Ile degradation contributes to the accumulation of toxic metabolites in MMA and PA, Leu oxidation diverges from the early shared committed step of the pathway after the branched-chain alpha-ketoacid dehydrogenase enzyme complex (BCKDH) step and is unaffected in MMA and PA.

Similar to the approach used in the dietary management of other IEM's, medical foods developed for use in MMA and PA were formulated with minimal to no propiogenic precursors (Val, Ile, Met, and Thr) but with regular content of non-offensive amino acids, including Leu, to help meet overall protein needs. Medical foods currently on the market are composed of Leu : protein ratios approximately 1.1–1.9 times higher than the average ratio found in protein-rich foods such as cow's milk, chicken, beef, and eggs. Dietary protein restriction, combined with an equivalent or higher dose of supplemental amino acids from medical foods, results in an imbalance of Leu intake compared to the other BCAA's, Met, and Thr. The Leu content of MMA/PA medical foods, in the setting of absent/trace valine and isoleucine, renders these the only food products with an unbalanced BCAA composition.

METABOLIC EFFECTS OF A LEUCINE LOAD

Leu loads and Leu-enhanced diets have been extensively studied in humans and animals and found to have many regulatory functions (see Figure). The roles of Leu include stimulation of insulin secretion and protein synthesis, as well as inhibition of protein degradation (5, 8). Recent studies have contributed further evidence to support these functions. Leu supplementation or a Leu-supplemented diet may: mitigate the growth hormone resistance induced by severe protein-energy malnutrition in rats during protein repletion through enhanced synthesis of insulin-like growth factor (IGF)-1 (9); prevent low dietary protein-induced hepatic steatosis in mice (10); improve hepatic mitochondrial biogenesis and energy metabolism in weaning piglets (11); function as a nitrogen donor to glutamate, which serves as the major excitatory neurotransmitter in the brain (12); and stimulate mammalian target of rapamycin (mTOR), which has many important brain functions (12). Whether such Leu effects would be of benefit in MMA and PA has yet to be determined, and the dietary Val and Ile restriction experienced by most patients might limit beneficial Leu effects.

Despite the described benefits of Leu supplementation, excess Leu intake is linked to effects that could be potentially detrimental in MMA and PA. For one, Leu signals the hypothalamus to modulate appetite suppression and decreases energy intake (5, 8, 12–14), which is an undesirable effect in a disease where poor feeding and growth failure are common. Moreover, short-term, high doses of Leu, over 500 mg/kg/d in healthy adults, causes an increase in blood ammonia levels, an effect that could be consequential in MMA and PA patients who are at high risk for hyperammonemia (15).

In addition, the Leu load delivered from medical foods designed for patients with MMA and PA may alter Val, Ile, and Met plasma levels, transport, and metabolism. It has been well described that an oral or intravenous Leu load lowers plasma concentrations of the other two branched chain amino acids (5). As discussed by Manoli et al (7), decreased plasma levels of Val and Ile in response to an oral Leu load in fasting children was initially documented by Nyhan et al. in 1961 and the decreased plasma Val and Ile levels were not accounted for by increased urinary excretion. This same effect was observed after intravenous administration of Leu, which rules out a competitive inhibition effect of Leu on intestinal absorption of Val and Ile as the primary mechanism (5). A more recent study has demonstrated that an oral Leu dose as low as 10–20 mg/kg body weight significantly lowered plasma concentrations of Val, Ile, and Phe in five healthy men who fasted overnight and then ate rice one hour prior to Leu dosing (16). Leu doses up to 90 mg/kg body weight also induced non-significant decreases of Met and Tyr (16). Interestingly, an oral Leu load or Leu-enriched diet not only affects circulating Val and Ile levels, but was shown to decrease levels of Val and Ile in cardiac tissue in mice (17) and in skeletal muscle in rats (18).

The understanding of the mechanisms for these secondary effects of Leu on other amino acid plasma levels has been recently explored. A Leu load provided to fasted mice induced significant decreases in plasma levels of Val, Ile, Met, Phe, and Tyr (19) which were blunted when the system L amino acid transporter (LAT), a plasma membrane transporter, was blocked (19). This suggests the LAT may mediate plasma amino acid changes (19). Interestingly, a decrease in plasma levels of these amino acids lags after Leu levels peak, suggesting that intracellular concentration of Leu may have more important regulatory effects on LAT than do plasma levels (19).

Other intermediary effects on the oxidation of BCAA, mediated by the BCKDH reaction, are also possible. BCKDH catalyzes the oxidation of the BCAA ketoacids and is inactivated by phosphorylation by BCKDH kinase (5). The ketoacid of Leu, alpha-ketoisocaproate (KIC), protects BCKDH from inactivation through inhibition of BCKDH kinase (see Figure) (5). Wessels et al examined changes in BCKDH activity and levels of amino acids in plasma and tissue in piglets fed a diet 2.3 or 3.3 times higher in Leu than control diets (20). On the highest Leu diet, BCKDH activity significantly increased in kidney, liver, cardiac muscle and brain, leading to increased oxidation of all three BCAAs (20). Both high Leu diets decreased the concentrations of Val and Ile in plasma and in all tissues analyzed except for the duodenal mucosa (20). Furthermore, Val, Ile, Met, Alanine (Ala), and Tryptophan (Trp) levels were significantly lower in the brain in response to the highest Leu diet (20). The competition that takes place at the large neutral amino acid transporter (LAT1), which transports large neutral amino acids across the BBB (6) may explain the effects of Leu on cerebral levels of these amino acids (AAs). Leu has a low K_m for LAT1 and at higher concentrations, Leu inhibits the transport into the brain of other large neutral amino acids, including Val, Ile, Met, Thr, Phe, Tyr, Trp, histidine (His), and glutamine (Gln) (see Figure) (6).

EFFECTS OF A LEUCINE LOAD FROM MEDICAL FOODS IN MMA, PA, AND *cb/C* DEFICIENCY

Several of the Leu-induced effects described were evident in a cohort of fifty-one patients with isolated MMA (37 *mut* MMA) recently studied at NIH (7). These patients were drawn from diverse U.S. and international metabolic centers and were treated using a broad range of dietary protocols. Medical food was used in the management of 85% of the *mut* MMA patients (7). In the youngest cohort, total intakes of Leu were 222 $\pm$ 24.9 milligrams/kilogram/day (range: 60–510 mg/kg/day) or 4–5 times the recommended requirement and well above the single dose amount shown to decrease plasma Val and Ile levels in healthy men {Manoli, 2016 #32;Matsumoto, 2014 #27}. Leu intake at the high end of this range surpassed levels associated with hyperammonemia in healthy adults and the proposed tolerable upper limit for adults (15). It should be noted that 35% of the *mut* subset were consuming more medical food protein equivalent than complete protein (7). Medical food use was associated with significantly increased plasma ratios of Leu : Val and Leu : Ile and decreased plasma concentrations of Val, Ile (as well as Met and Thr), even in those consuming complete protein at a level above the RDA. Because of the abnormal amino acid concentrations, seven *mut* patients were prescribed supplemental Val and/or Ile (propiogenic and therefore toxic amino acids for MMA and PA patients) to correct chronically low plasma levels, a counterintuitive practice in the management of this disorder (7). A case study presented by the authors demonstrated that by reducing medical food intake in a patient with low blood concentrations of Val and Ile, BCAA homeostasis was restored, and supplemental AA intake could be eliminated.

Additionally, in the *mut* cohort, there was a significant cross-sectional correlation between the Leu : Val intake ratio and poorer growth outcome in terms of height, weight, and bone mineral density (7). These observations suggest that in the setting of a protein restriction, medical foods, via Leu effects, could increase the Val and Ile requirements by increasing BCAA oxidation and thereby negatively impact growth (5). Evans et al recently reported longitudinal growth data in an Australian cohort of 14 MMA/PA patients (21). Interestingly, better growth outcomes were seen in the Australian cohort for which medical foods were rarely used as compared to the largely U.S. cohort in which medical food use was common (7, 21). Of course, an exact comparison cannot be made between the two studies without detailed phenotypic and metabolic characterization to define the disease severity of the respective patients. Furthermore, renal function, the growth hormone axis, and periods of metabolic acidosis are additional variables likely to have strong effects on growth outcomes in MMA (7, 21).

In the setting of a balanced diet, a high Leu intake is a marker of increased levels of all BCAA's and thus the stimulation of BCAA degradation may be appropriate to aid in metabolizing the dietary BCAA load. However, the stimulation of BCKDH by high Leu levels in MMA and PA medical foods when Val and Ile intakes are restricted, exacerbates their deficiency, potentially adversely impacting growth.

Given that a Leu load at levels provided in routine use of medical foods could induce such effects, there may be additional perturbations that were not measured in the current studies.

For example, as demonstrated by Wessels et al, brain levels of Val, Ile, Met, Ala, and Trp potentially could be reduced on a high Leu diet, resulting in cerebral essential amino acid deficiencies (20). Such effects could have disparate consequences depending on the stage of body and brain growth. While essential amino acid deficiency in brain is detrimental during early development, inhibited brain uptake of Val and Ile could be protective of acute elevations of BCAA and toxic precursors in MMA and PA once brain growth is complete as a means to neuroprotect the CNS. The effects of amino acid imbalances on other transporters and in other tissues, such as kidney, gastrointestinal system, and pancreas have yet to be explored. Furthermore, in addition to amino acid effects, future studies should explore the role of high nitrogen load from medical food supplementation on the risk for hyperammonemia and the progression of kidney disease of MMA, and possibly PA. Additional studies are required to optimize the current evidence-based guidelines for age-appropriate prescription of medical foods for these patients.

In *cbfC* deficiency, the propionate-derived metabolic disturbances are less marked than in isolated MMA and parenteral hydroxocobalamin treatment can greatly reduce methylmalonic acid levels. However, in practice, protein restriction and/or medical foods are sometimes prescribed as a means to control the methylmalonic acid levels. Manoli et al reported that in a cohort of 28 patients with *cbfC* deficiency, 21% received complete protein intake <85% of the RDA and approximately 32% were taking medical foods designed for MMA and PA (22). Reported elsewhere, medical food was used in 67% of patients in a small cohort of *cbfC* deficiency (23). Methionine synthesis is inhibited in *cbfC* deficiency. Therefore, knowing that Leu may decrease plasma Met levels and the predicted brain uptake of Met through competitive inhibition at the LAT1 transporter (6, 20) the use of dietary protein restriction and medical foods devoid of Met would be expected to result in failure to restore the Met plasma and tissue levels. Indeed, those *cbfC* patients prescribed medical foods had significantly lower plasma levels of Met, Val, and Ile and significantly higher plasma ratios of Leu : Met and Leu : Val (22). The use of the cerebral influx model showed that the plasma Leu : Met ratio was negatively correlated to predicted cerebral methionine influx and the influxes of Met, Val, Ile, and Thr were significantly lower in patients receiving medical foods (22). Furthermore, the plasma Leu : Met ratio was negatively correlated with head circumference z-scores (22). Ahrens-Nicklas et al also found a correlation between long-term medical food consumption and poor head circumference, though causation could not be assigned in either study (23). Because cerebral synthesis of Met is impaired in *cbfC* deficiency, there is an increased reliance on brain uptake of Met. Met has many important functions in the brain and inadequate cerebral Met levels may be responsible, in part, for brain white matter hypomyelination occasionally observed in *cbfC* deficiency (22). Therefore, given that adequate brain uptake of Met is vital in this population, it is critical that future research investigates whether cerebral Met deficiency occurs with high Leu supplementation, even in the context of normal plasma levels of Met.

CONCLUSION

In summary, MMA, PA and *cbfC* deficiency present disorders where some of the normal regulatory functions of Leu may result in unintended consequences in the setting of an imbalanced BCAA diet induced by excessive medical food intake. Decreased plasma levels

and a predicted reduction in brain uptake of Val, Ile, and Met could result from Val, Ile, and Met restriction when a patient ingests relative high doses of Leu via MMA/PA medical foods. Further research is warranted to determine the optimal relative ratios of supplemental amino acids in these disorders and whether supplemental Leu may serve a beneficial role by limiting uptake of propiogenic amino acids into the brain and peripheral organs and delaying or attenuating long-term complications of the disease.

Recent dietary guidelines are supporting a lower reliance on medical foods in MMA and PA. The 2014 European guidelines for management of MMA and PA recommend that in situations where natural protein intolerance precludes protein intake at the Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO)/United Nations University (UNU) safe levels of intake, then medical foods should be provided to help meet protein requirements, but the guidelines do not recommend routine medical food use otherwise (24). In 2017, the Genetic Metabolic Dietitian International released revised dietary guidelines for PA (25) recommending that in patients who tolerate less than 100% of the daily protein requirement from complete protein, PA medical food should be added to meet 100–120% of the total protein requirement (25). This represents a significant reduction in medical food use from previous guidelines. Finally, 2017 European guidelines for *cbfC* deficiency clearly state that Met-free formulas are contraindicated in *cbfC* deficiency (26).

Medical foods are critical for the dietary therapy of many IEM's, but many questions about their optimal composition and effectiveness in patients with disorders of propionate oxidation, such as MMA and PA, remain unanswered. Until future research elucidates optimal medical food formulations for patients with MMA and PA, the prescription of large amounts of medical foods relative to complete protein should be avoided. Furthermore, the current MMA/PA medical foods are contraindicated in patients with *cbfC* deficiency.

Acknowledgments

We thank all patients and their families for their participation in our natural history protocol; referring physicians, nurses and dietitians for their help with patient's evaluations. This work was supported by the Intramural Research Program of the National Human Genome Research Institute and the Nutrition Department, Clinical Research Center of the National Institutes of Health, Bethesda, MD. USA.

Financial support and sponsorship: None

References

1. Manoli, I., Sloan, J., Venditti, C. Isolated Methylmalonic Acidemia. In: Pagon, RA. Adam, MP. Ardinger, HH., et al., editors. GeneReviews. University of Washington; Seattle, WA: 2005. Updated Dec 1, 2016. Available: <https://www.ncbi.nlm.nih.gov/books/NBK1231/> [Accessed July 11, 2017]
2. Shchelochkov, O., Carrillo, N., Venditti, C. Propionic Acidemia. In: Pagon, RA. Adam, MP. Ardinger, HH., et al., editors. GeneReviews. University of Washington; Seattle, WA: 2012. Updated Oct 6, 2016 Available: <https://www.ncbi.nlm.nih.gov/books/NBK92946/> [Accessed July 11, 2017]
3. Carrillo, N., Adams, D., Venditti, C. Disorders of Intracellular Cobalamin Metabolism. In: Pagon, RA. Adam, MP. Ardinger, HH., et al., editors. GeneReviews. University of Washington; Seattle, WA: 2008. Updated Nov 21, 2013. Available: <https://www.ncbi.nlm.nih.gov/books/NBK1328/> [Accessed July 11, 2017]

4. Department of Health and Human Services, US Food and Drug Administration, Center for Food Safety and Applied Nutrition. [Accessed July 10, 2017] Frequently Asked Questions About Medical Foods. Guidance for Industry. 22016. [Available from: <https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM500094.pdf>]
5. Harper A, Miller R, Block K. Branched-chain amino acid metabolism. *Annual Review of Nutrition*. 1984; 4:409–54.
6. Manoli, I., Venditti, C. Branched chain amino acid disorders. In: Lee, B., Scaglia, F., editors. *Inborn Errors of Metabolism: From Neonatal Screening to Metabolic Pathways*. New York: Oxford University Press; 2015. p. 92-118.
7. Manoli I, Myles JG, Sloan JL, Shchelochkov OA, Venditti CP. A critical reappraisal of dietary practices in methylmalonic acidemia raises concerns about the safety of medical foods. Part 1: isolated methylmalonic acidemias. *Genet Med*. 2016; 18(4):386–95. This research article shows that the high leucine to valine and isoleucine intake ratios related to use of medical foods in MMA and PA can cause iatrogenic valine and isoleucine deficiencies and impair growth. [PubMed: 26270765]
8. Bifari F, Nisoli E. Branched-chain amino acids differently modulate catabolic and anabolic states in mammals: a pharmacological point of view. *Br J Pharmacol*. 2017; 174(11):1366–77. [PubMed: 27638647]
9. Gao X, Tian F, Wang X, Zhao J, Wan X, Zhang L, et al. Leucine supplementation improves acquired growth hormone resistance in rats with protein-energy malnutrition. *PLoS One*. 2015; 10(4):e0125023. [PubMed: 25909895]
10. Yokota S, Ando M, Aoyama S, Nakamura K, Shibata S. Leucine restores murine hepatic triglyceride accumulation induced by a low-protein diet by suppressing autophagy and excessive endoplasmic reticulum stress. *Amino Acids*. 2016; 48(4):1013–21. [PubMed: 26707165]
11. Su W, Xu W, Zhang H, Ying Z, Zhou L, Zhang L, et al. Effects of dietary leucine supplementation on the hepatic mitochondrial biogenesis and energy metabolism in normal birth weight and intrauterine growth-retarded weanling piglets. *Nutr Res Pract*. 2017; 11(2):121–9. [PubMed: 28386385]
12. Sperringer JE, Addington A, Hutson SM. Branched-Chain Amino Acids and Brain Metabolism. *Neurochem Res*. 2017; 42(6):1697–709. [PubMed: 28417264]
13. Steinert RE, Landrock MF, Ullrich SS, Standfield S, Otto B, Horowitz M, et al. Effects of intraduodenal infusion of the branched-chain amino acid leucine on ad libitum eating, gut motor and hormone functions, and glycemia in healthy men. *Am J Clin Nutr*. 2015; 102(4):820–7. [PubMed: 26289436]
14. Heeley N, Blouet C. Central Amino Acid Sensing in the Control of Feeding Behavior. *Front Endocrinol (Lausanne)*. 2016; 7:148. [PubMed: 27933033]
15. Elango R, Rasmussen B, Madden K. Safety and Tolerability of Leucine Supplementation in Elderly Men. *J Nutr*. 2016; 146(12):2630S–4. S. This article summarizes current evidence for Tolerable Upper Limit for leucine in adult men, a level reached by some MMA patient on medical foods. [PubMed: 27934655]
16. Matsumoto T, Nakamura K, Matsumoto H, Sakai R, Kuwahara T, Kadota Y, et al. Bolus ingestion of individual branched-chain amino acids alters plasma amino acid profiles in young healthy men. *Springerplus*. 2014; 3:35. [PubMed: 25674427]
17. Zhen H, Kitauro Y, Kadota Y, Ishikawa T, Kondo Y, Xu M, et al. mTORC1 is involved in the regulation of branched-chain amino acid catabolism in mouse heart. *FEBS Open Bio*. 2016; 6(1): 43–9.
18. Holecsek M, Siman P, Vodenicarova M, Kandar R. Alterations in protein and amino acid metabolism in rats fed a branched-chain amino acid- or leucine-enriched diet during postprandial and postabsorptive states. *Nutr Metab (Lond)*. 2016; 13:12. [PubMed: 26877757]
19. Zhen H, Nakamura K, Kitauro Y, Kadota Y, Ishikawa T, Kondo Y, et al. Regulation of the plasma amino acid profile by leucine via the system L amino acid transporter. *Biosci Biotechnol Biochem*. 2015; 79(12):2057–62. [PubMed: 26125295]
20. Wessels AG, Kluge H, Hirche F, Kiowski A, Schutkowski A, Corrent E, et al. High Leucine Diets Stimulate Cerebral Branched-Chain Amino Acid Degradation and Modify Serotonin and Ketone Body Concentrations in a Pig Model. *PLoS One*. 2016; 11(3):e0150376. [PubMed: 26930301]

21. Evans M, Truby H, Boneh A. The Relationship between Dietary Intake, Growth, and Body Composition in Inborn Errors of Intermediary Protein Metabolism. *J Pediatr*. 2017 This research article reported protein and energy intake and growth patterns in a cohort of patients with MMA and PA largely not treated with medical foods. Although impaired growth was observed, outcomes were better than in the cohort reported by Manoli et al.
22. Manoli I, Myles JG, Sloan JL, Carrillo-Carrasco N, Morava E, Strauss KA, et al. A critical reappraisal of dietary practices in methylmalonic acidemia raises concerns about the safety of medical foods. Part 2: cobalamin C deficiency. *Genet Med*. 2016; 18(4):396–404. This research article shows that medical foods designed for methylmalonic acidemia and propionic acidemia were associated with lower plasma concentrations and predicted cerebral influx of methionine in patients with cobalamin C deficiency, potentially affecting brain growth and development. [PubMed: 26270766]
23. Ahrens-Nicklas RC, Whitaker AM, Kaplan P, Cuddapah S, Burfield J, Blair J, et al. Efficacy of early treatment in patients with cobalamin C disease identified by newborn screening: a 16-year experience. *Genet Med*. 2017 This research article reports on longitudinal treatment and outcomes in a cohort of patients with cobalamin C receiving medical food. Medical food was associated with better methylmalonic acid levels, but had no relation to cognitive outcome and was associated with lower head circumference *z*-scores.
24. Baumgartner MR, Horster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis*. 2014; 9:130. [PubMed: 25205257]
25. Southeast Regional Newborn Screening and Genetics Collaborative (SERC) and Genetic Metabolic Dietitians International (GMDI). [Accessed July 10, 2017] PROP Nutrition Management Guidelines. Mar. 2017 v1.1 Available from: [https://southeastgenetics.org/ngp/guidelines.php/100/PROP Nutrition Guidelines/Version 1.1](https://southeastgenetics.org/ngp/guidelines.php/100/PROP%20Nutrition%20Guidelines/Version%201.1)
26. Huemer M, Diodato D, Schwahn B, Schiff M, Bandeira A, Benoist JF, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. *J Inher Metab Dis*. 2017; 40(1):21–48. [PubMed: 27905001]

KEY POINTS

- Leu has multiple metabolic effects, including modulation of BCAA oxidation and transport of large neutral amino acids across the blood brain barrier.
- Liberal use of medical foods in MMA and PA results in decreased plasma Val and Ile levels and predicted decreased brain uptake of essential amino acids.
- Medical foods that contain an imbalanced ratio of BCAA and that are Met-free should be used judiciously in MMA and PA and should be avoided in *cb1C* deficiency.
- Additional research is needed to establish the optimal relative dosing of amino acids in these disorders.

Figure 1.

Leucine metabolic effects in multiple organ systems.

Leucine (Leu) displays a multitude of effects in various organs: plays a role in central nervous system (CNS) appetite regulatory circuits and feeding behavior; stimulates insulin secretion; and enhances protein synthesis and inhibits muscle protein breakdown. Leu-derived α -ketoisocaproate (KIC) is a potent inhibitor of the branched-chain ketoacid dehydrogenase (BCKDH) kinase, resulting in activation of BCKDH and increased branched-chain amino acid (BCAA) oxidation. Finally, Leu is transported via the large neutral amino acid transporter LAT1 at the blood–brain barrier (BBB), among other transporters, and can compete with other large neutral amino acids for uptake/transport affecting neurotransmitter biosynthesis. Abbreviations: Val (valine), Ile (isoleucine), Met (methionine), Thr (threonine), Phe (phenylalanine), Trp (tryptophan), Tyr (tyrosine), His (histidine), Gln (glutamine).