RESEARCH
Review

Food Products Made with Glycomacropeptide, a Low-Phenylalanine Whey Protein, Provide a New Alternative to Amino Acid–Based Medical Foods for Nutrition Management of Phenylketonuria

Sandra C. van Calcar, PhD, RD; Denise M. Ney, PhD, RD

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ABSTRACT

Phenylketonuria (PKU), an inborn error in phenylalanine metabolism, requires lifelong nutrition management with a low-phenylalanine diet, which includes a phenylalanine-free amino acid-based medical formula to provide the majority of an individual's protein needs. Compliance with this diet is often difficult for older children, adolescents, and adults with PKU. The whey protein glycomacropeptide (GMP) is ideally suited for the PKU diet because it is naturally low in phenylalanine. Nutritionally complete, acceptable medical foods and beverages can be made with GMP to increase the variety of protein sources for the PKU diet. As an intact protein, GMP improves protein use and increases satiety compared with amino acids. Thus, GMP provides a new, more physiologic source of low-phenylalanine dietary protein for people with PKU.

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PHENYLKETONURIA (PKU) IS AN INBORN ERROR OF phenylalanine metabolism caused by the deficiency of phenylalanine hydroxylase, which converts phenylalanine to tyrosine (Figure 1). Tyrosine is an amino acid that is indispensable in the diet for those with PKU given their inability to normally hydroxylate phenylalanine to tyrosine. PKU is an autosomal recessive disorder with an incidence in the United States of one in 10,000 to 15,000 births in those of European, Asian, and American Indian descent, although PKU can be diagnosed in other ethnic and racial groups and shows a lower incidence in those of African and Hispanic descent.[1,2] There are an estimated 15,000 individuals with treated PKU in the United States and 50,000 worldwide.[1,2]

First described in 1934, the untreated phenotype includes severe mental retardation, seizures, autistic-like behavior, and a musty odor caused by elevations in plasma phenylalanine concentrations and/or its major metabolites, including phenylpyruvate, phenyllactate, and phenylacetate (Figure 1).[1] The exact mechanism for the neurological damage remains unclear, although poor myelination of the developing central nervous system and disturbances in neurotransmitter production has been suggested.[3] PKU is detected presymptomatically by state-mandated population-wide newborn screening programs. Phenylalanine concentrations are measured on blood spots collected at 24 to 48 hours of age; infants with elevated phenylalanine levels are referred to specialized centers for initiation of diet treatment.[4]

Use of a phenylalanine-restricted diet for treatment of PKU was first described in 1953. Initially, the special diet was discontinued as early as 3 to 4 years of age; however, the National PKU Collaborative Study (1967 to 1983) clearly demonstrated that those remaining on diet showed greater cognitive functioning skills than those randomized to discontinue the diet.[5,6] This eventually led to the diet-for-life policy now accepted by all US and international clinics as best practice for treatment of PKU.[2,7-9]

This article briefly reviews the physiology of PKU and the current dietary management of this inborn error of metabolism; a comprehensive review of PKU is presented elsewhere.[1] The potential for glycomacropeptide (GMP), an intact whey protein, to provide a low-phenylalanine alternative to amino acids in medical foods designed to treat this disorder is discussed.

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PROCESS FOR FINDING SOURCES

The literature search for this review was conducted using PubMed MEDLINE and Web of Science using the key words *PKU* and *phenylketonuria*, *glycomacropeptide*, and *low-phenylalanine diet* for articles published from 2000 to February 1, 2012. Additional articles and peer-reviewed chapters in

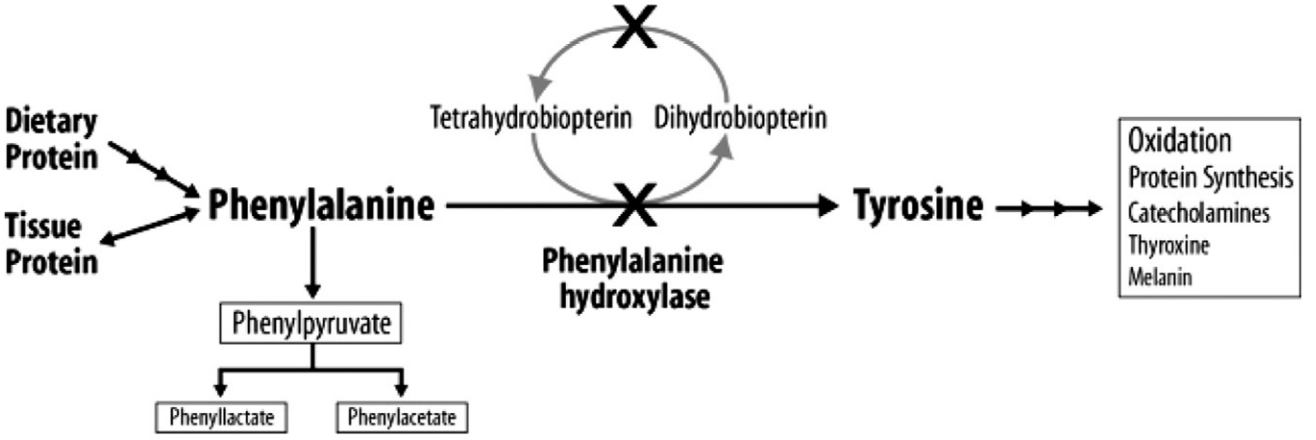

Figure 1. Phenylalanine metabolism in phenylketonuria (PKU). As indicated by the "×", PKU results from mutations (>600 have been identified) that typically affect the hepatic phenylalanine hydroxylase enzyme needed for the hydroxylation of the dietary indispensable amino acid phenylalanine to tyrosine. PKU may also result from mutations in the recycling of the essential cofactor tetrahydrobiopterin. Due to these mutations, which reduce the conversion of phenylalanine to tyrosine, phenylalanine accumulates in blood and is transaminated and decarboxylated into many compounds that appear in blood and urine; 3 compounds that are measured clinically are shown here. Tyrosine, a precursor for multiple biological products, becomes an indispensable amino acid and must be provided through the diet for those with PKU.

books were identified from reference lists cited in doctoral dissertations and personal communication.

DIETARY MANAGEMENT OF PKU

The primary goal of nutrition management of PKU is to restrict intake of phenylalanine to reduce blood, and thus, brain concentrations of phenylalanine, yet provide sufficient intake of this amino acid to allow for adequate growth and protein turnover. In infants with classic PKU, minimum phenylalanine needs to support protein synthesis range from 200 to 500 mg/day, which can be provided by limited breastfeeding or limited quantities of a standard infant formula.[10,11]

The dietary prescription for phenylalanine, expressed as total milligrams phenylalanine per day, changes little from infancy through age 10 years.[11,12] However, with the onset of the adolescent growth spurt, phenylalanine needs increase and reassessment of the dietary prescription for phenylalanine is important to provide for optimal growth and control of blood phenylalanine levels.[11,13]

Using stable isotope methodology, Courtney-Martin and colleagues[14] demonstrated a mean phenylalanine requirement for prepubertal children with classic PKU of 14 mg/kg with a safe population intake (upper 95% CI) of 20 mg phenylalanine per kilogram body weight, and Zello and colleagues[15] demonstrated a mean phenylalanine requirement for adults of 9.1 mg phenylalanine per kilogram body weight. Reassessment of the phenylalanine prescription in relation to ideal body weight throughout the life span is needed as clients age and body weight increases.[16]

Dietary phenylalanine adjustments are typically based on frequent monitoring of phenylalanine in blood or plasma to maintain phenylalanine levels in the treatment range.[11,17] Current recommendations for optimal metabolic control include maintenance of phenylalanine concentrations between 120 and 360 μmol/L (2 to 6 mg/dL) for neonates through age 12 years and 120 and 600 μmol/L (2 to 10 mg/dL) for those older than age 12 years.[2]

For children, adolescents, and adults with PKU, appropriate foods include weighed quantities of fruit and vegetables, although starchy vegetables are particularly high in phenylalanine.[18,19] Use of specialty breads and pasta products made from wheat starch is essential for success of the diet because regular grain products often have too much phenylalanine to include in the dietary management of classic PKU.[18,19] So-called free foods, which contain no phenylalanine, are freely allowed, but these tend to be sugar-based beverages, candy, or fat-based foods that are unrealistic to eat in large quantities. Typically, phenylalanine intake is counted as either milligrams of phenylalanine or phenylalanine exchanges (1 exchange=15 mg phenylalanine). Resources listing the phenylalanine content of various foods[18] and recipes for low-phenylalanine cookery are available.[20]

A diet restricting phenylalanine intake is very low in total protein. Thus, to prevent deficiency, a protein source containing synthetic amino acids must be provided by medical foods.[11] A medical food, as defined by the US Food and Drug Administration, 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 . . .".[21] For infants and young children with PKU, more than 80% of energy needs and more than 90% of protein needs are met by a phenylalanine-free amino acid formula.[17]

Invariably, poor consumption of a medical food leads to poor metabolic control in those with PKU because excessive intake of phenylalanine-containing foods is common without an adequate intake of energy provided by most medical foods. In addition, nutrient deficiencies can develop when dietary intake of protein is restricted without adequate daily consumption of a complete protein substitute. Specifically, vitamin B-6, vitamin B-12, calcium, folate, iron, and n-3 essential fatty acids may be inadequate.[22-24]

In those with early-treated PKU, intelligence and cognitive testing is typically normal, but reductions can be seen in those

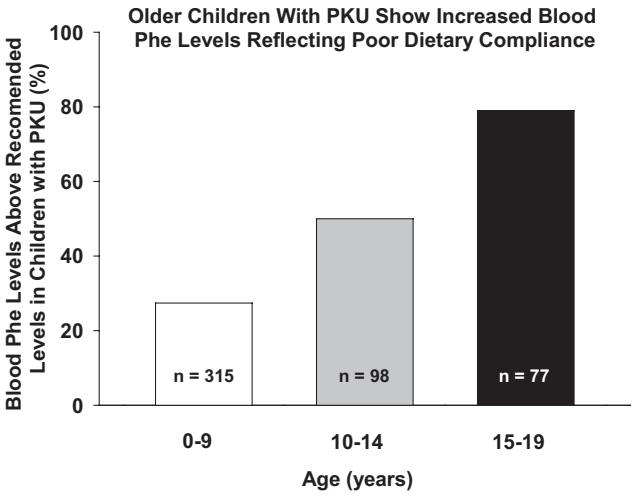

Figure 2. The proportion of children with phenylketonuria (PKU) in different age groups who show median blood phenylalanine (phe) levels above the maximum recommended limit. As children with PKU enter adolescence, noncompliance with the low-phe diet increases. Data shown are reprinted from *The Lancet*,[34] Copyright 2002, with permission.

with poorer lifelong phenylalanine control.[25,26] Executive function skills, linked to areas in the mid-dorsolateral prefrontal cortex, include memory, processing tasks, inhibitory control, attention, and vigilance skills. Those with PKU can show deficits in these areas and severity of these deficits often correlates with the degree of phenylalanine control, both lifelong and short-term.[26,27]

In addition, a concern for women with PKU of childbearing age is maternal PKU syndrome. As a teratogen, elevated phenylalanine can cause microcephaly, mental retardation, growth retardation, and/or congenital heart abnormalities in any offspring born to a woman with PKU.[28,29] The Maternal PKU Collaborative Study (1983 to 2000) clearly demonstrated that the primary determinants of infant outcome are the degree of plasma phenylalanine elevation and gestational age at which control of plasma phenylalanine is achieved. The best fetal outcomes are achieved by reducing phenylalanine concentrations before pregnancy and maintaining phenylalanine concentrations between 120 and 360 μmol/L (2 and 6 mg/dL) throughout pregnancy.[30,31] Nutrition plays a key role in the outcome of maternal PKU pregnancies. Significant factors associated with abnormalities found in infants include low prepregnancy weight, poor weight gain during pregnancy, and low intake of protein from medical food.[32,33]

Thus, continuation of a phenylalanine-restricted diet and consumption of an adequate amount of medical food are important for long-term health of those with PKU. However, as with many chronic diseases, compliance with dietary treatment for PKU can become a problem for school-aged children, adolescents, and adults.[34] For example, in a study conducted in the United Kingdom and Australia, approximately 25% of children from birth through age 9 years had median blood phenylalanine levels above the maximum recommended limit and this proportion increased to 50% in the 10- to 14-year age group; and to >75% in the 15- to 19-year age group[34] (Figure 2). Often, those discontinuing the diet as a teenager will attempt to reinstitute the diet as an adult. Despite strategies such as simplified methods to calculate phenylalanine intake[35,36] and various medical food modifications,[37,38] it is extremely difficult to reestablish the low-phenylalanine diet. One study found that only 55% of adults were able to achieve dietary compliance for 3 months after diet reintroduction and only 19% were able to follow the diet for 9 months. However, those who returned to diet showed improved scores in various measures of life skills.[39] Other studies have found similar benefits.[40,41]

New Strategies to Improve Metabolic Control of PKU

Other strategies for treatment of PKU have included dietary supplementation of large neutral amino acids (LNAAs), with or without the traditional diet. Phenylalanine competes with the other LNAA (eg, arginine, histidine, isoleucine, leucine, lysine, methionine, threonine, tryptophan, tyrosine, and valine) for specific carrier proteins that transport LNAA across the intestinal mucosa into the blood and across the blood–brain barrier into the brain.[42] The carrier protein responsible for LNAA transport into the brain has a high affinity for phenylalanine. This, in combination with high plasma concentrations of phenylalanine relative to other amino acids in poorly controlled PKU, allows for excessive transport of phenylalanine into brain. Individuals with PKU given daily supplements of LNAA have shown decreased plasma phenylalanine concentrations[43-45] and reduced brain phenylalanine concentrations measured by magnetic resonance spectroscopy.[46] Supplementation with LNAA is not a substitute for medical food and a low-phenylalanine diet, and is not recommended for individuals younger than age 12 years. However, for individuals who have difficulty in complying with diet and show elevated plasma phenylalanine concentrations, LNAA may offer a cost-effective option to improve metabolic control of PKU.

More recently, supplementation with the cofactor for the phenylalanine hydroxylase enzyme, tetrahydrobiopterin (BH4), has been shown to stabilize enzyme function and thus increase phenylalanine tolerance in approximately 40% to 60% of those with PKU.[47,48] BH4 supplementation has been especially effective for those with milder forms of PKU.[47,49] However, BH4 supplementation rarely allows an individual with PKU to completely discontinue diet treatment.[50] In addition, clinical trials are currently underway to determine safety and efficacy of injectable PEGylated phenylalanine ammonia lyase to improve metabolic control in those with PKU.[51] Even with pharmaceutical advances, diet continues to remain the mainstay of treatment for PKU.

New Dietary Approaches Are Needed for PKU

Although successful in preventing mental impairment when implemented at birth, there is clearly difficulty in following the low-phenylalanine, amino acid-based diet throughout life and evidence of suboptimal growth and nutrition outcomes in patients with PKU treated with diet alone.[52] Thus, new approaches are needed for dietary management of PKU. The ideal low-phenylalanine diet would contain at least one source of a phenylalanine-free or low-phenylalanine intact protein providing a complete source of dietary indispensable amino acids, and that protein would have functional properties suitable for making a variety of foods, including baked

goods, that have acceptable sensory properties, including taste, texture, and odor. To our knowledge, a phenylalanine-free, complete protein that is suitable for making acceptable foods does not exist for individuals with PKU. An ideal phenylalanine-free protein could potentially be produced using genetic engineering of microbes or plants, as has been the focus of investigations in treatment of food allergies.[53] However, production of acceptable, palatable foods from such recombinant proteins would be challenging and the cost may prohibit commercialization.

What does exist and is supported by short term research in subjects with PKU is GMP, a protein that contains minimal phenylalanine and can be made into nutritionally complete, acceptable low-phenylalanine foods for those with PKU.[54-57] Compared with the ideal dietary protein for PKU, GMP is not phenylalanine-free and requires supplementation with five limiting amino acids to provide a complete source of protein. Moreover, GMP is not optimal for use in baked products such as bread.

GMP

GMP is a 64–amino acid glycosylated peptide that occurs naturally in bovine milk within the whey fraction and is released in the newborn and adult human gastrointestinal tract by pepsin mediated proteolysis after milk ingestion.[58] Commercial GMP is a byproduct of cheese production when bovine κ-casein is cleaved by the action of chymosin into para-κ-casein, which remains with the curd, and κ-caseino-GMP, which remains in the whey.[59] GMP is an abundant protein: it comprises 15% to 20% of the total protein in sweet cheese whey.[59] GMP is currently sold as a food ingredient and has an excellent safety record based on widespread supplementation of foods with whey protein and the use of whey-predominant infant formulas.[60] GMP demonstrates a number of interesting biological activities that have been the focus of recent research and commercial activity as summarized in current reviews.[61,62] In vitro studies have shown that GMP inactivates toxins of *Escherichia coli* and *Vibrio Cholerae*, inhibits adhesion of cariogenic bacteria with use in toothpastes,[63] promotes growth of bifidobacteria, modulates immune response,[64] attenuates colitis in rats,[65] increases zinc absorption in rhesus monkeys,[66] and may promote satiety in human beings.[57,67]

GMP is uniquely suited to the PKU diet as an alternative to amino acid formula because pure GMP contains no aromatic amino acids, including phenylalanine.[59] Isolation of GMP from cheese whey results in contamination from other whey proteins, such as β-lactoglobulin and α-lactalbumin, which contain phenylalanine. Thus, commercially available GMP contains 2.0 to 5.0 mg phenylalanine per gram protein.[54,56] GMP contains two to three times the amount of the LNAAs isoleucine, threonine, and valine compared with other dietary proteins and must be supplemented with indispensable amino acids to provide a complete source of protein for individuals with PKU.

Initial estimates for supplementation of GMP with dietary indispensable amino acids provided 130% to 150% of the 2002 Dietary Reference Intakes for tyrosine, histidine, leucine, methionine, and tryptophan.[68,69] To evaluate this supplement profile, an inpatient metabolic study was completed to compare amino acid and GMP diets in 11 subjects with PKU.[55] Results from this study suggest that supplementation of GMP-based medical foods needs to include arginine and levels of dietary indispensable amino acids to provide at least 150% of the most current recommended intake as summarized by the 2007 World Health Organization standards.[13] Moreover, studies in mice with PKU demonstrate that GMP, supplemented with dietary indispensable amino acids, provides an adequate source of protein to support normal growth and body composition.[70]

Acceptability of GMP Medical Foods

Various low-phenylalanine foods and beverages utilizing GMP as the primary protein source have been developed. Unlike synthetic amino acids, GMP has functional properties suitable for making foods, including good heat stability and solubility in acid.[59] To evaluate the acceptability of GMP products, blind sensory studies were performed with PKU subjects attending three PKU summer camps and two family conferences from 2004 to 2007 (n=18 to n=32 subjects/product, age range 7 to 37 years).[54] Products were rated using a 5-point hedonic scale (1=dislike very much, 2=dislike, 3=neither like nor dislike, 4=like, 5=like very much) to evaluate five sensory categories, including appearance, odor, taste, texture, and overall acceptability. Overall acceptability scores for six tested products were >3, indicating a positive response to products made with GMP (Figure 3). Further, at the conclusion of an 8-day inpatient metabolic study establishing short-term safety of GMP, 10 of 11 subjects believed the GMP foods were better tasting and added variety to the low-phenylalanine diet compared with their usual amino acid formula.[55]

Since the initial publication with sensory evaluation data of GMP food products,[54] additional foods and beverages have been developed and recipes have been modified using a GMP source with a reduced phenylalanine content of 2 mg phenylalanine per gram GMP protein (ARLA Foods). These medical foods include beverages, pudding, puffed cereal, crackers, salad dressings, and a snack bar. All are nutritionally complete with a nutrient profile similar to commercially available amino acid medical foods. Each of these GMP products provides 5 to 15 g protein equivalents and only 15 to 25 mg phenylalanine/serving.[56] Recently, two commercial GMP-based beverages have been released for diet treatment of individuals with PKU (BetterMilk and Restore, Cambrooke Foods) using Glytactin (Cambrooke Foods), a patent-pending blend of GMP and dietary indispensable amino acids.

GMP and Protein Use

An amino acid-based low-phenylalanine diet provides approximately 80% of protein needs from synthetic amino acids and 20% from the intact protein found primarily in fruits and vegetables. In contrast, a GMP-based low-phenylalanine diet provides approximately 70% of protein needs from intact protein found in GMP, fruits, and vegetables and approximately 30% of protein needs from synthetic amino acids needed to supplement GMP with dietary indispensable amino acids.

Studies have found slower absorption and improved protein use with an intact protein source compared with a mixture of single amino acids mimicking the intact protein.[71,72] Similar benefits in phenylalanine and amino acid use were found based on significantly higher postprandial (PP) plasma concentrations of total amino acids and significantly lower

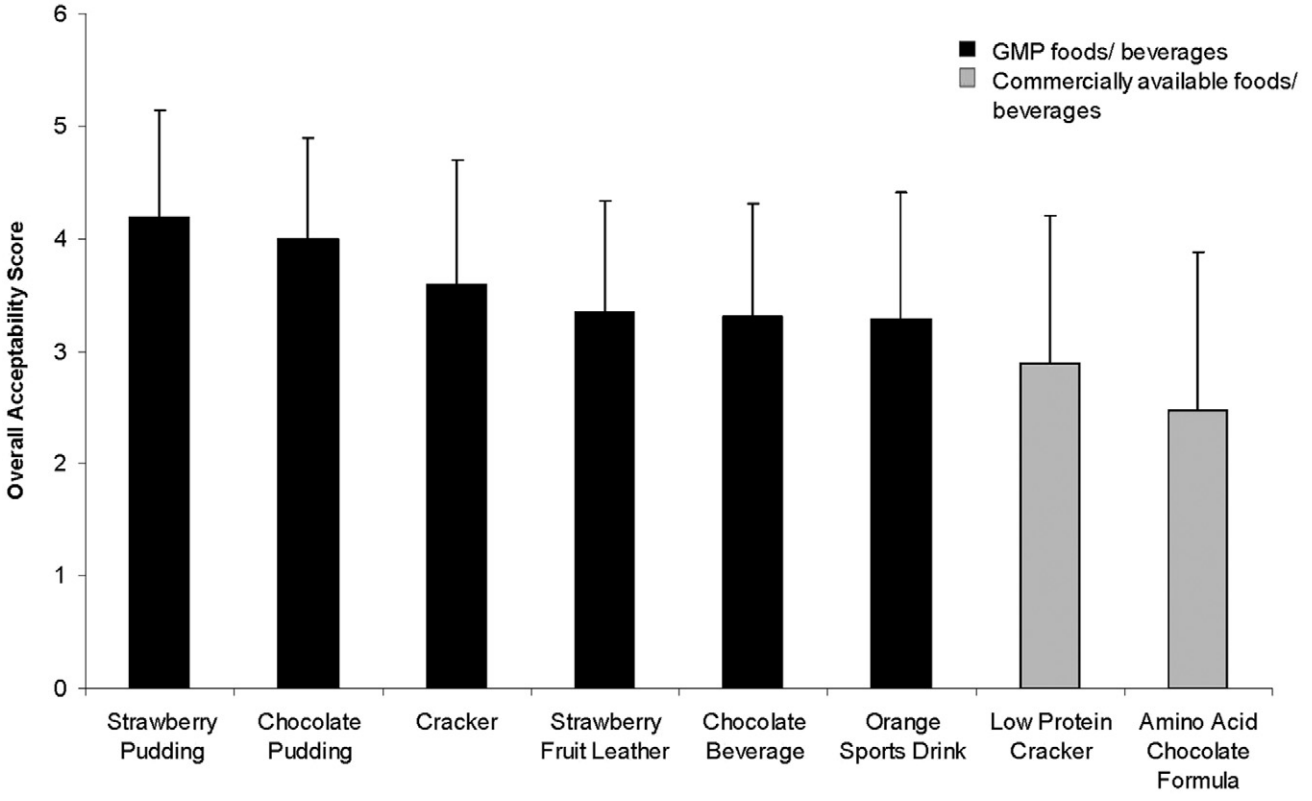

Figure 3. Overall acceptability of foods and beverages made with glycomacropeptide (GMP) and amino acid medical foods as tested by subjects with phenylketonuria, ages 7 to 37 years. Acceptability scores are mean±standard deviation with 1=dislike very much, 2=dislike, 3=neither like nor dislike, 4=like, and 5=like very much. Tested products (n=18 to n=32 subjects per product) included 6 products containing GMP: strawberry pudding (4.19±0.95), chocolate pudding (4.00±0.90), snack crackers (3.59±1.11), strawberry fruit leather (3.35±0.98), chocolate beverage (3.31±1.00), and an orange-flavored sport drink (3.28±1.13). Two commercial products, a chocolate-flavored amino acid based formula (Chocolate PhenylAde, Applied Nutrition Corp) and a low-protein cracker (Loprofin, Scientific Hospital Supplies), were also included in the sensory evaluations.

blood urea nitrogen concentration suggesting decreased ureagenesis[73-75] when PKU subjects replaced their entire protein prescription from amino acid formula with GMP products for 4 days (Figure 4).[55] When comparing fasting with PP, fasting phenylalanine concentrations were significantly greater than PP concentrations with the amino acids but not with the GMP diet, suggesting a more constant phenylalanine concentration over 24 hours with the GMP compared with the amino acid diet. Reduced fluctuation in phenylalanine levels may be of importance because a recent study suggests that long-term variation in plasma phenylalanine concentrations may have significant influence on cognitive outcome.[25]

GMP and Satiety

Several studies have suggested that GMP may decrease food intake and promote satiety.[57,67] In a recent study, subjects without PKU ate approximately 10% less at lunch following a breakfast with whey that included GMP compared with a breakfast with whey that did not include GMP.[76] Satiety associated with whey protein has been attributed to its rapid digestion and absorption, resulting in rapid increases in plasma amino acids, insulin, glucagon-like peptide-1, and cholesystokinin levels compared with more slowly digested proteins such as casein.[76-78]

Protein is the most satiating nutrient. Individuals with PKU often experience hunger in association with inadequate distribution of protein equivalents throughout the day and the rapid absorption of amino acids from amino acid medical foods. Higher PP plasma amino acid and insulin levels as noted in subjects fed a GMP-based breakfast compared with an amino acid-based breakfast are consistent with satiety (Figure 4).[55,57] In addition, the hormone ghrelin increases during fasting to stimulate hunger and decreases following a meal in proportion to energy intake.[79,80] In an inpatient study of subjects with PKU, plasma ghrelin concentrations were measured in a fasting state and after consumption of isocaloric breakfasts containing amino acids and GMP.[57] PP plasma ghrelin concentration measured 2.5 hours after the start of the amino acid-based breakfast was not different from fasting ghrelin measured before eating breakfast (Figure 4). In contrast, the GMP breakfast induced significantly lower PP plasma ghrelin concentrations compared with ghrelin concentrations measured in a fasting state. This suggests that the amino acid-based breakfast did not allow for normal meal-induced, sustained suppression of ghrelin and thus, satiety was reduced compared with the meal containing GMP.[57] In other words, subjects with PKU "felt fuller longer" after ingestion of a GMP breakfast compared with an amino acid-based breakfast.

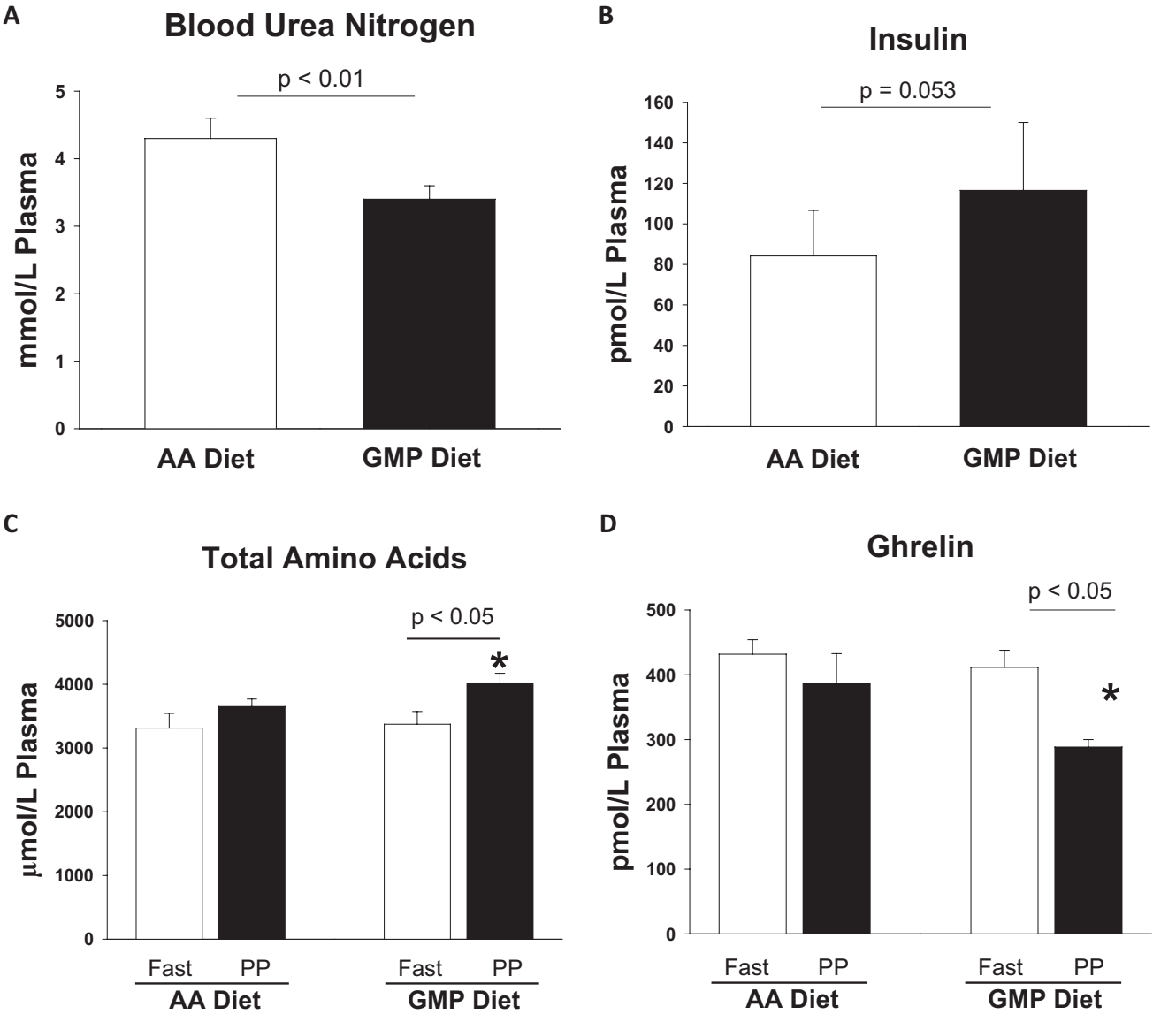

Figure 4. Plasma concentrations of blood urea nitrogen (A), insulin (B), total amino acids (C), and ghrelin (D) in subjects with phenylketonuria consuming a low-phenylalanine diet made with glycomacropeptide (GMP) compared with amino acids (AA) for 4 days in an inpatient study. Consuming a GMP-based diet resulted in significantly lower postprandial (PP) (2.5 h after breakfast) blood urea nitrogen concentration and significantly higher PP total AA concentration with moderately higher insulin concentration compared with the AA-based diet. This response is consistent with improved protein retention and decreased ureagenesis due to ingestion of GMP. With the AA-based diet, there was no significant difference in concentration of the appetite-stimulating hormone ghrelin after an overnight fast compared with 2.5 h after breakfast. In contrast, following the GMP-based diet, PP ghrelin concentration was significantly reduced compared with an overnight fast consistent with the expected response of meal-induced satiety. Values are means±standard error. Data shown were previously reported as original research findings in references 55 and 57. *Significantly different from PP concentrations with the AA-based diet.

Use of GMP in an Outpatient Setting

In a recent outpatient trial, a 29-year-old man with classic PKU replaced his usual prescribed amino acid formula with GMP products for 10 weeks at home.[56] This subject's average phenylalanine concentration measured in blood spots was 14% lower with the GMP diet compared with phenylalanine concentrations measured on the amino acid diet when expressed relative to phenylalanine intake.[56] One explanation for this response is that, because the subject enjoyed the GMP foods, he was able to space them throughout the day, unlike his amino acid formula, which he drank all at once in the morning. Adolescents and adults with PKU often consume their entire daily formula volume divided into only one or two servings.[56] Previous studies have shown improved protein use with lower plasma phenylalanine concentrations when protein equivalents are distributed in smaller, more frequent doses throughout the day.[81] Because GMP products improve the taste, convenience, and variety of choices in the PKU diet,

Table. Sample menus comparing a daily diet for phenylketonuria (PKU) containing amino acid (AA)-based formula or glycomacropeptide (GMP) products[ab]

	AA Diet				GMP Diet		
Meal items	Amount	Phenylalanine (mg)	Protein (g)	Items[c]	Amount	Phenylalanine (mg)	Protein (g)
Breakfast							
Phenex 2[d]	100 g powder	0	30	GMP Bettermilk[e]	50 g powder	23	15
Cheerios[f] cereal	1 c (28 g)	165	3.2	GMP crisp cereal	1 1/2 c (66 g)	30	10
Subtotal		165	33.2	Subtotal		53	25
Lunch							
Low-protein white bread[g]	2 slices (100 g)	9	0.2	GMP Restore beverage[e]	12 oz	11	8
Low-protein cheese	2 slices (40 g)	42	0.8	Low-protein white bread[g]	2 slices (100 g)	9	0.2
Mayonnaise	1 Tbsp (13 g)	8	0.2	Low-protein cheese	2 slices (40 g)	42	0.8
Grapes, green	20	19	0.7	Mayonnaise	1 Tbsp (13 g)	8	0.2
Apple juice	8 oz (240 mL)	2	0	Grapes, green	20	19	0.7
Subtotal		80	1.9	Subtotal		89	9.9
Snack							
Soda, regular	12 oz (360 mL)	0	0	GMP snack bar	1 bar (84 g)	28	15
Doritos[h] chips	30 g	97	2.0	Soda, regular	12 oz (360 mL)	0	0
Subtotal		97	2.0	Subtotal		28	15
Dinner							
Low-protein spaghetti[g]	1.5 c cooked (56 g dry)	7	0.3	GMP Restore beverage[e]	8 oz (240 mL)	8	5
Spaghetti sauce, no meat	1 c (230 g)	92	3.7	Low-protein spaghetti[g]	1.5 c cooked (56 g dry)	7	0.3
Carrot sticks	60 g	37	0.6	Spaghetti sauce, no meat	1 c (230 g)	92	3.7
Italian salad dressing	1 oz (30 mL)	0	0	Carrot sticks	60 g	37	0.6
Apple juice	12 oz (360 mL)	3	0.2	GMP salad dressing	1 oz (30 mL)	15	5
Subtotal		139	4.8	Subtotal		159	14.6
Snack							
Phenex 2[d]	67 g, powder	0	20	GMP strawberry pudding	1 c (255 g)	37	15
Amino Acid Blend[i]	20 g	0	15	Doritos[h] chips	30 g	97	2.0
Subtotal		0	35	Subtotal		134	17
Total		481	76.9	Total		463	81.5

[a]Diets were designed for a girl with classic PKU age 12 years with weight 42 kg and height 152 cm. Her phenylalanine tolerance is 460-480 mg/d, minimum protein needs (1.0 g/kg) are 42 g/d, and daily energy needs are 2,300-2,400 kcal.
[b]Total energy content of AA diet=2,365 kcal (9,895 kJ) and GMP diet=2,325 kcal (9,728 kJ).
[c]Composition of nonbrand-name GMP products based on estimates provided by Cambrooke Foods in April 2011.
[d]Abbott Nutrition.
[e]Cambrooke Foods.
[f]General Mills.
[g]Made from wheat starch.
[h]Frito-Lay.
[i]Applied Nutrition.

individuals with this disorder may be more willing to consume these sources throughout the day and, thus, improve the daily distribution of protein.

Application of GMP in PKU Diets

The Table demonstrates how GMP products can be incorporated into a typical menu of an adolescent girl with classic PKU. Unlike amino acid-based formulas, food and beverages made with GMP contain some phenylalanine from both the GMP itself and the ingredients used to produce these products. This minimal amount of phenylalanine needs to be accounted for in each individual's daily phenylalanine prescription. This can be accomplished by either counting the mg phenylalanine in each GMP product as part of the daily phe-

nylalanine allowance or by determining an average phenylalanine intake from GMP products and subtracting this from the amount of phenylalanine allowed each day. This latter approach, although less accurate, would be adequate for adolescents and nonpregnant adults for whom a daily variance of <25 mg/day would likely have little effect on overall average plasma phenylalanine concentrations.

Use of GMP-based medical foods as a sole source of protein for young children with PKU needs to be evaluated carefully. Given the phenylalanine content of these products, they may be more difficult to incorporate into the diet for those with a daily allowance of <300 mg phenylalanine/day. In addition, the energy content of currently available GMP medical foods containing Glytactin is lower per gram of protein equivalents than amino acid-based medical foods designed for children. Thus, total energy intake needs to be considered when solely prescribing these products as a protein source to those younger than age 4 years.

Future Research Need for GMP Medical Foods

Consistent with the 2012 National Institutes of Health PKU Scientific Review Conference,[82] further research is needed to extend current understanding of the long-term safety, efficacy, and effects on nutritional status of GMP medical foods.[55,56] An ongoing clinical trial in individuals with PKU living at home funded by the US Food and Drug Administration Office of Orphan Products Development will address important questions regarding the efficacy of commercially available GMP medical foods (www.clinicaltrials.gov identifier no. NCT 01428258). Endpoints for the trial include influence on plasma phenylalanine concentrations and the overall amino acid profile, nutritional status, neuropsychological function, dietary compliance, and acceptability in subjects with PKU fed GMP medical foods containing Glytactin compared with amino acid-based medical foods for 3 weeks in a randomized crossover design. Additional research is needed to assess the ability of GMP to support long-term growth in young children and its effects during maternal PKU when provided as the predominant source of dietary protein.

CONCLUSIONS

New dietary options are needed to improve compliance with a low-phenylalanine diet and subsequent metabolic control for individuals with PKU. A variety of acceptable, nutritionally complete products can be made from GMP with the potential to replace, or partially replace, the traditional amino acid-based medical foods currently used in PKU diets. GMP-based medical foods represent a new paradigm to move current PKU diets from synthetic amino acids as the primary source of protein equivalents to a more physiologically normalized diet based on intact protein, which our research demonstrates improves protein use and promotes satiety.

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AUTHOR INFORMATION

S. C. van Calcar is an assistant professor, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, and a senior metabolic dietitian, Biochemical Genetics Program, Waisman Center, and D. M. Ney is Billings Bascom Professor, Department of Nutritional Sciences and Waisman Center, University of Wisconsin-Madison.

Address correspondence to: Denise M. Ney, PhD, RD, Department of Nutritional Sciences, University of Wisconsin-Madison, 1415 Linden Dr, Madison, WI 53703. E-mail: ney@nutrisci.wisc.edu

STATEMENT OF POTENTIAL CONFLICT OF INTEREST

D. Ney is a coinventor on US Patent Application no. US-2010-0317597, entitled "Glycomacropeptide (GMP) medical foods for nutritional management of phenylketonuria (PKU) and other metabolic disorders," which is held by the Wisconsin Alumni Research Foundation and licensed to Cambrooke Foods, LLC. A percentage of all royalty payments is awarded to the inventors. D. Ney and S. van Calcar have served as consultants for Cambrooke Foods, LLC.

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