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Phenylketonuria Patients and Recent Approaches

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Abstract

Background and objective: Infant formula is a food that mimics human milk and is intended for use by infants under 1 year old. Phenylketonuria (PKU) is a congenital defect in the synthesis of phenylalanine (Phe) and is caused by the failure of phenylalanine hydroxylase converting Phe to tyrosine. In this review the current treatments for PKU are discussed.

Results and conclusion: Patients with PKU should still be treated with dietary therapy, but in the long term the introduction of a wide array of new treatment approaches such as more palatable foods. Treatment, which includes a low Phe diet supplemented with amino acid formulas, commences soon after diagnosis within the first weeks of life. Other potential issues associated with dietary therapy by micronutrients. Advances in dietary therapy such as the use of neutral amino acids and glycomacropeptides (GMP) have yielded more promising data in the recent years. In conclusion, GMP medical foods and micro/macronutrient supplementation will be useful in providing the evidence allowing for standardization of management and will alternatively provide in a cost-effective way an individualized management plan for PKU patients.

Keywords: Essential amino acids; Glycomacropeptide; Infant Formula, Phenylketonuria

1. Introduction

Infant formula is currently a food that imitates human milk and is intended for use by infants under the age of one either as powdered formula or liquid formula [1]. In addition to the ingredients, it is continuously improved based on the new nutritional information and technology. Focusing on nutritional interventions in the early life stages may improve health status [2].

A new formula is required for a particular treatment due to the deficiency of phenylalanine hydroxylase in infants. This enzymatic deficiency results in an inborn error of phe metabolism called PKU which converts phe to tyrosine. Tyrosine is an essential amino acid in the diet of patients with PKU which makes it difficult to hydrolyse Phe to tyrosine under normal circumstances. Phe is an essential amino acid to ensure normal anabolism [3]. PKU diet management is to limit the combination of natural protein in the diet to reduce the intake of Phe, and to supplement special medical formulas to provide enough essential amino acids, energy, vitamins and

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minerals [4]. The main purpose of PKU treatment is to strictly control the blood Phe level, mainly during the early stages of life and new treatment methods are needed to improve the quality of life of PKU patients [5].

During new-born screening, the majority of patients with PKU who need lifelong care are identified [6]. The control of phe levels is crucial throughout childhood, especially for behavioral and mental functions [7]. Growth is one of the main results that need to be considered and its optimization plays a key role in PKU [3]. The views of patients should be taken into account when developing and approving new therapies and treatments for PKU [8].

2. PKU diet management

PKU diet management should be appropriate and lifelong to achieve the desired results. PKU is often found in worldwide population which is more observed in the Middle East comparing to the Western world. Previous studies have been carried out mainly on skimmed milk product powder and also milk to remove phe from these products based on activated carbon usage together with enzymatic hydrolysis by hydrolysates originated from different microorganism. Lopes et al. used activated carbon to remove phe from skim milk powder with enzymatic hydrolysates [9]. Silvestre et al. prepared low phe milk hydrolysates using activated Carbon as the adsorbent support [10]. Silva et al. run a research with the aim of Phe removal from skim milk powder by activated carbon and enzymatic hydrolysates using a protease from Aspergillus oryzae, isolated or in association with papain [11]. Ahmed et al. produced a dairy-based drink by emulsifying corn germ oil with casein GMP solution in milk permeates leading to 30% - 80% reduction of serum Phe levels in all PKU patients consumed this product [12].

2.1. Glycomacropeptide (GMP)

GMP is a plentiful 64-amino-acid glycophosphopeptide produced in the cheese production process. Bovine kappa (κ)-casein is cleaved by chymosin into para-κ-casein remaining with the curd while GMP remains with the whey. Compared to typical dietary proteins, GMP has a large profile of indispensable or essential amino acids [13]. Pure GMP has a unique amino acid profile that includes higher concentration of threonine and isoleucine and no aromatic amino acids, including Phe, tyrosine and tryptophan [3]. GMP is currently being marketed as an ingredient that demonstrates a strong food safety record according to the global supplementation of foods with whey protein and the use of whey-predominant infant formulas [13]. While synthetic amino acids are not suitable for food production, GMP has good functional properties for foods manufacturing, including good thermal stability and solubility in acids. GMP has different theoretical advantages such as enhancing protein retention and nitrogen utilization, strengthening bones, enhancing immunological activities; and improving taste and acceptance [14].

Comparing medical foods containing GMP with traditional amino acid medical foods, the results show that GMP medical foods are an acceptable and safe source for the nutritional management of PKU and can improve people's lifetime compliance with the essential low-Phe diet [3]. Compared with the free synthetic amino acids that have been used as test meals in PKU patients, GMP does not significantly affect any biomarkers. GMP can be used to make palatable, low-Phe foods and beverages to provide an alternative low-Phe protein source in the PKU diet [15].

2.2. Micronutrient supplemetation

In PKU, biochemical micronutrient deficiencies are common even though micronutrient intake is higher than the reference nutrient intake In the past few years, adding free L-amino acids, vitamins and minerals as supplements to the PKU diet has become a common practice [16]. It is not easy to set a good nutritional status because there are different contributors to the definition. PKU patients have lower intakes of certain micronutrients, such as vitamins A, C and E, selenium,

coenzyme Q10, vitamins B2, B6 and B12, folates, iron, zinc, calcium, carnitine, long-chain polyunsaturated fatty acid and vitamin D [16]. That is why supplementation with micronutrients is essential and vitamins and minerals should either be added to supplement phenylalanine-free L-amino acids or given alone.

2.3. Protein supplementation

At the clinical level, safe protein energy ratio should be used to promote optimal body composition and reduce long-term health risks. The concept of protein energy ratio considers the interdependence between protein and energy intake and describes the ratio of dietary energy obtained from protein [17].

The European PKU guidelines recommend that the total protein intake should be 40% more than the FAO/WHO/UNU safe protein intake. However, the amount is arbitrary and has not been confirmed by research. Since most of the available protein substitutes are entirely derived from amino acids that do not contain phe, it is recommended to give higher doses than FAO/WHO/UNU. This extra amount compensates for the ineffective absorption of natural/whole protein (mainly based on plants), poor L-amino acid utilization and insufficient energy absorption. When determining the dosage of protein substitutes, weight, age, growth and the prescribed amount of phe/natural protein should be considered. If a person with PKU is obese, protein replacement needs should be based on ideal body weight [18]. The prescribed amount of medical food is designed to meet protein requirement of each age group in the life cycle shown in Table 1 [4].

Table 1. Recommended daily nutrient intakes (ranges) for infants, children, and adults with PKU [4].

Age	Nutrients				
	Phe(mg/kg)	**Tyrosine(mg/kg)**	**Protein (g/kg)**	**Energy (kcal/kg)**	**Fluid (ml/kg)**
Infants					
0 to < 3 months	25 - 70	300 - 350	3.50 - 3.00	120 (145 - 95)	160 - 135
3 to < 6 months	20 - 45	300 - 350	3.50 - 3.00	120 (145 - 95)	160 - 130
9 to < 12 months	15 - 35	250 - 300	3.00 - 2.50	110 (135 - 80)	145 - 125
7 to < 9 months	10 - 35	250 - 300	3.00 - 2.50	105 (135 - 80)	135 - 120
Girls and boys	**(mg/kg)**	**(g/day)**	**(g/day)**	**(kcal/day)**	**(ml/day)**
1 to < 4 years	200 - 400	1.72 - 3.00	≥ 30	1300 (900 - 1800)	900 - 1800
4 to < 7 years	210 - 450	2.25 - 3.50	≥ 35	1700 (1300 - 2300)	1300 - 2300
7 to < 11 years	220 - 500	2.55 - 4.00	≥ 40	2400 (1650 - 3300)	1650 - 3300
Women					
11 to < 15 years	140 - 750	3.45 - 5.00	≥ 50	2200 (1500 - 3000)	1500 - 3000
15 to < 19 years	230 - 700	3.45 - 5.00	≥ 55	2100 (1200 - 3000)	1200 - 3000
≥ 19 years	220 - 700	3.75 - 5.00	≥ 60	2100 (1400 - 2500)	2100 - 2500
Men					
11 to < 15 years	225 - 900	3.38 - 5.50	≥ 55	2700 (2000 - 3700)	2000 - 3700
15 to < 19 years	295 - 1100	4.42 - 6.50	≥ 65	2800 (2100 - 3900)	2100 - 3900
≥ 19 years	290 - 1200	4.35 - 6.50	≥ 70	2900 (2000 - 3300)	2000 - 3300

Conclusion

The goal of this research is to introduce and review a few available approaches for PKU infant formula products. The incorporation of GMP into low-Phe diet has improved palatability, variety and convenience of the diet and has resulted in a better control of blood Phe levels providing a more physiological form of amino acid to be consumed by PKU patients. Although studies using GMP as an alternative to the amino acid supplement has been promising, long-term studies are needed to evaluate the safety and efficacy. All these data highlight the need to find alternative therapies for PKU that could be used safely and efficiently in all PKU patients regardless of genotype, phenotype or gender.

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Conflict of interest
The authors declare that there is no conflict of interest.

References

1. Mayer O, Cagil Y, Kerner J. Infant Nutrition. Pediatric nutrition for dietitians: CRC Press. 2022. 65-78.
2. Landry MJ, Ruiz LD, Gibbs K, Radtke MD, Lerman J, Vargas AJ. Perspective: Early life nutrition research supported by the US national institutes of health from 2018-2020. Advances in Nutrition. 2022; 14 (6): 682. doi: 10.1093/cdn/nzac061.066
3. Daly A, Pinto A, Evans S, MacDonald A. Glycomacropeptide in PKU—Does it live up to its potential? nutrients. 2022; 14(4):807. doi: 10.3390/nu14040807
4. Van Calcar S. Nutrition management of Phenylketonuria. nutrition management of inherited metabolic diseases: Springer; 2022. 127-51.
5. De Oliveira Filho JG, Alves JdS, Egea MB. Next-generation probiotics as a therapeutic strategy for the treatment of phenylketonuria: a review. Nutrition Reviews. 2022; 5; 80(10):2100-2112. doi: 10.1093/nutrit/nuac024.
6. Al-Bari AA. Current scenario and future direction of newborn screening and management program for Phenylketonuria in Bangladesh. Journal of Inborn Errors of Metabolism and Screening. 2022;10. doi: 10.1590/2326-4594-JIEMS-2021-0024
7. Liemburg GB, Huijbregts SC, Rutsch F, Feldmann R, Jahja R, Weglage J, et al. Metabolic control during the neonatal period in phenylketonuria: associations with childhood IQ. Pediatric Research. 2022;91(4):874-878. doi: 10.1038/s41390-021-01728-8
8. Turner A, Glinton KE, Sutton VR. Advancements in therapeutics for inborn errors of metabolism. Current Opinion in Pediatrics. 34(6): 559-564. doi: 10.1097/MOP.0000000000001168
9. Lopes DCF DF, Silvestre MPC. Use of activated carbon for removing phenylalanine from reconstituted skim milk powder hydrolysates. LWT. 2004:447-453. 10.1016/j.lwt.2004.07.021
10. Silvestre MPC DsM, Lopes Junior CO, Silva. M VD, Aguiar BJM, Afonso WO, Silva MR. . Effect of enzyme type, enzyme substrate ratio and temperature on phenylalanine removal from milk¨. American Journal of food technology. 2012:123-132.
11. M.Silva VD DML, Afonso WO, F.Lopse DC, Januario JN, B.Aguiar MJ, P.Starling AN, P.C. Silvestre M. Preparation of low phenylalanine whey hydrolysate, using papain and pancreatin immobilized on active carbon and alumina. American Journal of Food Technology. 2007: 327-341.
12. Abdel-Salam AM EL. Preparation and evaluation of a novel therapeutic dairy-based drink for phenylketonuria. . N Am J Med Sci 2. 2010:66–70. doi: 10.4297/najms.2010.266
13. Guo M. Ingredients selection for infant formula. Human milk biochemistry and infant formula manufacturing technology; 2014, 172-210. doi: 10.1533/9780857099150.2.172
14. Foisy Sauvé M, Spahis S, Delvin E, Levy E. Glycomacropeptide: A bioactive milk derivative to alleviate metabolic syndrome outcomes. Antioxidants & Redox Signaling. 2021;34(3):201-222. doi:10.1089/ars.2019.7994
15. Pena MJ, Pinto A, de Almeida MF, de Sousa Barbosa C, Ramos PC, Rocha S, et al. Continuous use of glycomacropeptide in the nutritional management of patients with phenylketonuria: a clinical perspective. Orphanet journal of rare diseases. 2021;16(1):1-10. doi:10.1186/s13023-021-01721-8

16. Coşkun T, Çoker M, Mungan NÖ, Özel HG, Sivri HS. Recommendations on phenylketonuria in Turkey. Turkish Journal of Pediatrics. 2022; 64(3):413-434. doi: 10.24953/turkjped.2021.4098.
17. Veronika AP, Puspitawati T, Fitriani A. Associations between nutrition knowledge, protein-energy intake and nutritional status of adolescents. J Public Health Res. 2021;10(2):239. doi: 10.4081/jphr.2021.2239
18. Robertson L, Adam S, Ellerton C, Ford S, Hill M, Randles G, et al. Dietetic management of adults with Phenylketonuria (PKU) in the UK: A Care consensus document. Nutrients. 2022;14(3):576. doi: 10.3390/nu14030576Di Stefano V, Grazia Melilli M. Effect of storage on quality parameters and phenolic content of Italian extra-virgin olive oils. Natural Product Research. 2019: 78-86. https://doi.org/10.1080/14786419.2019.1587434.