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Minireview

Main issues in micronutrient supplementation in phenylketonuria

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ABSTRACT

For almost all patients with PKU, a low phenylalanine diet is the basis of the treatment despite a widely varying natural protein tolerance. A vitamin and mineral supplement is essential and it is commonly added to a phenylalanine-free (phe-free) source of L-amino acids. In PKU, many phe-free L-amino acid supplements have age-specific vitamin and mineral profiles to meet individual requirements. The main micronutrient sources are chemically derived and their delivery dosage is usually advised in three or more doses throughout the day. Within the EU, the composition of VM (vitamin and mineral) phe-free L-amino acid supplements is governed by the *Foods for Special Medical Purposes* (FSMP) directive (European Commission Directive number 1999/21/EC and amended by Directive 2006/141/EC). However the micronutrient composition of the majority fails to remain within FSMP micronutrient maximum limits per 100 kcal due to their low energy content and so compositional exceptions to the FSMP directive have to be granted for each supplement. All patients with PKU require an annual nutritional follow-up, until it has been proven that they are not at risk of any vitamin and mineral imbalances. When non-dietary treatments are used to either replace or act as an adjunct to diet therapy, the quality of micronutrient intake should still be considered important and monitored systematically. European guidelines are required about which micronutrients should be measured and the conditions (fasting status) for monitoring.

Contents

1. Introduction

Within nutrition science, the role of micronutrients is increasingly important in health and the prevention or treatment of disease [1]. Beyond protein, there are many more challenges in ensuring optimal

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nutritional status when adhering to a low phenylalanine diet in phenylketonuria (PKU). Diet is the basis of the treatment for the majority of patients with PKU. It consists of a limited and controlled amount of natural protein derived from food sources to provide essential phenylalanine requirements; some foods contain minimal amounts of phenylalanine so they can be eaten without restriction, with the majority of nutrient requirements being met by a phenylalanine-free source of L-amino acids with added micronutrients (vitamin and mineral (VM) phe-free L-amino acids). Their micronutrient composition is calculated to meet theoretical nutritional requirements. The main micronutrient sources are chemically derived and their delivery dosage is usually advised in three or more doses throughout the day. They are rarely validated by rigorous investigation. The bioavailability of all essential minerals is not well studied, and there is little longitudinal micronutrient status data in patients with PKU following both strict and relaxed dietary regimens. The aim of this paper is to discuss some of the practical and controversial issues that affect micronutrient intake and status in PKU.

2. Sources of micronutrients in the PKU diet

In PKU, the contribution of natural food sources to micronutrient intake has been unreported in recent years. Patients have widely varying phenylalanine tolerance depending on their residual enzyme activity, and it may vary from as little as 200 mg/day to over 2000 mg/day. The majority of patients with severe PKU will tolerate less than 500 mg/day of phenylalanine. This is mainly sourced from low biological value protein such as vegetables and cereals. Some countries permit some animal containing products [2], but the amount is small and unlikely to contribute significantly to micronutrient intake although it may aid bioavailability.

In a low phenylalanine diet, fruits and vegetables may be permitted in controlled or unrestricted amounts (dependent on local policy and phenylalanine tolerance) as they contain lower amounts of natural protein, and thereby, phenylalanine [3–5]. They are also high in vitamin C and beta-carotene. The diet also contains limited amounts of cereals and legumes, but there are few other foods that can be eaten without severe restriction with the exception of very low protein foods which generally contribute little to micronutrient intake. This may lead to nutrient imbalances and constricts the optimal utilization of some nutrients. Natural sources of iron, zinc, calcium and selenium are limited or of reduced bioavailability, unless small amounts of foods containing protein with a higher biological value are permitted.

The contribution of special low protein foods (e.g. low protein bread, pasta, flour and milk replacement) as micronutrient sources has not been evaluated and their use may vary between countries associated with availability and national reimbursement policies [2]. Low protein special foods are rarely supplemented with vitamins and minerals and accompanying full nutrient analysis is seldom declared. These foods mainly consist of food starches, such as wheat, maize, corn and potato starch, and vegetable oil. They may provide over 30% of energy intake and even displace the intake of natural food sources.

3. Phenylalanine-free L-amino acid composition

Over the last 20 years, it has been common practice to add vitamins and minerals to phe-free L-amino acid supplements. Most available VM phe-free L-amino acid supplements are age specific with an individualized vitamin and mineral profile that meets the requirements of infants, children, or adults (including pregnancy). The aim is to ensure that the dietary needs for all vitamins and minerals are met when dosages are prescribed to meet at least the safe levels of protein intake [6]. However, higher or lower doses of phe-free L-amino acid supplements may affect vitamin and mineral intake accordingly. Few VM phe-free L-amino acid supplements have been submitted to rigorous, long term investigation. Commonly the micronutrient composition of VM phe-free L-amino acid supplements is determined by national or international legislation, and local dietary recommendations. There are some micronutrients added to phe-free L-amino acids whose fortification is high or close to upper safe levels of intake [7] and the rationale for this is unclear. For example, zinc intake from VM phe-free L-amino acids may exceed European Food Safety Authority [7] tolerable upper intake levels for vitamins and minerals (Table 1). Equally the provision of 60 g protein equivalent from some VM phe-free L-amino acids will supply >400 μg/day of folic acid daily, even though there is some suggestion that excess folic acid intake interferes with zinc homeostasis [8]. Generally, there has been little investigation on the long term impact of high supplementation of single elements on the bioavailability of other nutrients.

Table 1
Vitamin and mineral intake from VM phe-free L-amino acids[a] compared with tolerable upper intake level for vitamins and minerals (EFSA 2006).

Vitamins and minerals	Daily vitamin and mineral intake from examples of VM L-amino acids					Daily tolerable upper intake level for vitamins and minerals (EFSA 2006)				
	Protein equivalent					Age y				
	30 g/d	40 g/d	50 g/d	60 g/d	80 g/d	4–6 y	7–10 y	11–14 y	15–17 y	Adults
Vitamin A μg	417	556	695	834	1112	1100	1500	2000	2600	3000
Vitamin D μg	6.6	8.8	11	13.2	17.6	25	25	50	50	50
Vitamin E mg	7.8	10.4	13	15.6	20.8	120	160	220	260	300
Vitamin C mg	54	72	90	108	144	No upper level set				
Vitamin K mg	51	68	85	102	136	No upper level set				
Thiamin mg	1.1	1.4	1.8	2.1	2.8	No upper level set				
Riboflavin mg	1.1	1.5	1.9	2.3	3.0	No upper level set				
Nicotinamide mg	23.7	31.6	39.5	47.4	63.2	220	350	500	700	900
Vitamin B_6 mg	1.2	1.6	2	2.4	3.2	7	10	15	20	25
Folic acid μg	201	268	335	402	536	300	400	600	800	1000
Vitamin B_{12} μg	2.4	3.2	4	4.8	6.4	No upper level set				
Biotin μg	93	124	155	186	248	No upper level set				
Pantothenic acid mg	3.9	5.2	6.5	7.8	10.4	No upper level set				
Choline mg	300	400	500	600	800	No upper level set				
Calcium mg	600	800	1000	1200	1600	No upper level set				
Iron mg	11.1	14.8	18.5	22.2	29.6	No upper level set				
Copper mg	1.1	1.5	1.85	2.2	3	2	3	4	4	5
Zinc mg	11.1	14.8	18.5	22.2	29.6	10	13	18	22	25
Selenium μg	42	56	70	84	112	90	130	200	250	300
Manganese mg	1.5	2	2.5	3	4	No upper level set				
Iodine μg	126	168	210	252	336	250	300	450	500	600
Chromium μg	42	56	70	84	11	No upper level set				
Molybdenum μg	0.07	0.1	0.12	0.14	0.19	0.2	0.25	0.4	0.5	0.6

[a] All analyses taken from common VM phe-free L-amino acids available in the UK.