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Minireview

Micronutrient status in phenylketonuria

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ABSTRACT

Patients with phenylketonuria (PKU) encompass an 'at risk' group for micronutrient imbalances. Optimal nutrient status is challenging particularly when a substantial proportion of nutrient intake is from non-natural sources. In PKU patients following dietary treatment, supplementation with micronutrients is a necessity and vitamins and minerals should either be added to supplement phenylalanine-free L-amino acids or given separately. In this literature review of papers published since 1990, the prevalence of vitamin and mineral deficiency is described, with reference to age of treatment commencement, type of treatment, dietary compliance, and dietary practices. Biological micronutrient inadequacies have been mainly reported for zinc, selenium, iron, vitamin B_{12} and folate. The aetiology of these results and possible clinical and biological implications are discussed. In PKU there is not a simple relationship between the dietary intake and nutritional status, and there are many independent and interrelated complex factors that should be considered other than quantitative nutritional intake.

Contents

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1. Introduction

Patients with phenylketonuria (PKU) encompass an 'at risk' group for micronutrient imbalances. Foods are natural sources of all nutrients. In PKU, with conventional dietary treatment, protein rich-foods are mildly to severely restricted. In classical PKU, natural protein tolerance is usually equivalent to less than 10 g natural protein daily. Milk, dairy products, meat and fish are replaced by phenylalanine-free (phe-free) L-amino acid supplements. Therefore, a low phenylalanine diet mainly consists of fruit, vegetables, and low protein special foods (e.g. flour, bread and pasta prepared from cereal starches, sugar and vegetable oils) with a small amount of natural protein containing food sources. This strategy has an important impact on nutrient intake and status, and so supplementation with micronutrients is a necessity. Vitamins and minerals should either be added to supplement phenylalanine-free L-amino acids (*Vitamins and Minerals (VM) phe-free L-amino acids*) or given separately to all patients with PKU.

In classical PKU, VM phe-free L-amino acids provide up to 85% of protein intake and usually the majority of the vitamin and mineral requirements. Any tolerated natural protein, with exception of patients with mild PKU or treated with diet and Sapropterin, is likely to make only a small contribution to overall micronutrient intake. It is well established that animal protein foods provide valuable sources of bioavailable micronutrients and so offer nutritional advantages. For example, haem iron, high in meat protein, shields the iron from interaction with other food components, maintains its solubility in the intestine, and is absorbed intact through a specific transport system on the gut cells surface [1]. Calcium in milk products has a relatively high bioavailability, with mean absorption ranging in healthy adults from 20 to 45% [2]. Lactose and caseinophosphopeptides (CPP) (formed during digestion of caseins) may enhance calcium absorption although CPP may inhibit availability of iron [3]. Meat, but not fish, contains highly bioavailable selenium in the form of selenomethionine [2]. Animal protein may also form soluble ligands with zinc, iron and copper thus enhancing their absorption [4].

In PKU, biochemical micronutrient deficiencies have been reported for zinc, selenium, iron and vitamin B_{12} [5–8] but the cause is sometimes difficult to identify, particularly when the calculated intake is high from added supplements in the diet. However, clinical symptoms are rarely reported, and mostly described for vitamin B_{12} deficiency in patients who have stopped their micronutrient supplement or VM phe-free L-amino acids whilst following a vegan style diet [5].

In contrast many VM phe-free L-amino acid supplements contain micronutrients in excess of the 'highest' reference nutrient intake when they are prescribed to achieve protein requirements in PKU. The practice with micronutrient supplementation of phe-free L-amino acids has gradually changed over the last 20 years. In the early days of dietary treatment [9], most commercially available phe-free L-amino acids did not contain micronutrients. However, low adherence and lack of availability of disorder specific vitamin and mineral supplements have led to the addition of micronutrients to most of the available phe-free L-amino acid sources. Commercial companies do not explain clearly the criteria they use when defining the amount of micronutrients included in their L-amino acid supplements. In PKU, long term adherence and impact on micronutrient status are reported only for one VM phe-free L-amino acid supplement [10] and one separate micronutrient supplement [11].

The purpose of this report is to review the literature published since 1990, observing the prevalence of vitamin and mineral deficiency, with reference to age of treatment commencement, type of treatment, dietary adherence, and dietary practices.

2. The evidence base for micronutrient status in PKU

2.1. Methodology

Publications were identified from a PubMed search using the terms 'vitamins', 'minerals', 'micronutrients' and 'individual micronutrients' and 'phenylketonuria'. Other publications came from the reference list of other papers, hand searches, and from the personal reference data bases of the authors. Most of the data originated in only a small number of countries, particularly the USA, South America, Australia, and European countries. The majority of reports are case series, or single case reports, and there are only a limited number of controlled trials. There was a very wide age range of patients studied, under variable types of dietary conditions.

3. Individual nutrient at risk of inadequacy or excess in PKU

3.1. Vitamin B_{12} (Table 1)

As plants do not synthesize vitamin B_{12}, an absence of meat or fish in the diet without supplementation increases the risk of deficiency. Therefore, vitamin B_{12} deficiency is mainly reported in adolescents or adult patients who have stopped or relaxed their diets [5,6,12–14] and who are less adherent with VM phe-free L-amino acid supplements. In one study, where the majority of patients were on relaxed diets, taking large neutral amino acids without added vitamins and minerals, almost 40% had low vitamin B_{12} intakes [15]. There is only one report describing vitamin B_{12} deficiency in both children and adults adhering to a low phenylalanine diet [16]. Another at risk group are patients taking Sapropterin who have stopped formal dietary treatment, but may still restrict some animal foods through either fear or dislike [13], without vitamin or mineral supplements.

Symptoms such as spastic paraparesis, tremor, and slurred speech are associated with deficiency but patients may be unaware of the early manifestations of vitamin B_{12} deficiency as they appear insidiously [5,12].

Plasma or serum vitamin B_{12} is routinely used to determine status, but may be unreliable in some cases [17]. Other measures including serum/urine methylmalonic acid or plasma total homocysteine (tHCY) are advised to diagnose functional vitamin B_{12} deficiency [14,16]. Vitamin B_{12} acts as co-factor for the conversion of methylmalonyl-Coa (MMA-C0A) to succinyl-CoA (Suc-CoA) and the conversion of homocysteine to methionine [18] (Fig. 1).

3.2. Folic acid

In PKU, high red cell and serum folate concentrations have been reported for many years [19]. MacDonald et al. [11] reported high serum folate and red cell folate concentrations in up to 40% of adult patients ($n = 15$) on diet and taking a new vitamin and mineral supplement. In a cohort of 74 French patients with PKU aged 3 months to 45 years, Feillet reported that 35% of erythrocyte folate concentrations were above the upper laboratory reference range [20]. This was associated with a high folic acid content of the VM phe-free L-amino acid and intakes may reach approximately 400 μg/day when taking 60 g/d protein equivalent from VM phe-free L-amino acids. Recently, the folic acid content has been reduced in at least one VM phe-free L-amino acid supplement. In 20 European phe-free L-amino acids supplements suitable for children over the age of 1 year to adulthood, the dietary folate varies from 26 to 128 (median 64) μg/10 g protein equivalent [21].

One issue associated with high intakes of folic acid is masking the diagnosis of vitamin B_{12} pernicious anaemia because it has corrected the anaemia [22]. Also dietary folate is essential for the replication, repair and methylation of DNA. Cancer cells, like all cells, synthesize DNA during mitosis and require a supply of folate. The relationship of