Eur J Pediatr (2000) 159 [Suppl 2]: S129–S135

REVIEW

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Nutrition, physical growth, and bone density in treated phenylketonuria

Abstract Dietary treatment of phenylketonuria is well established to be safe and to prevent developmental and mental impairment in patients with low or absent phenylalanine hydroxylase activity. The use of semi-synthetic diets necessitates careful and longitudinal control not only of physical and intellectual development, which are both near normal in well treated patients, but also of potential diet inherent insufficiencies of essential nutrients. Concern has been raised by some reports on growth retardation in young patients on strict diets and on decreased bone density in older phenylketonuric children. The clinical significance of these findings is not known.

Conclusion Changes have been found, although inconsistently, in connection with selenium, zinc, iron, retinol and polyunsaturated fatty acid status in dietetically treated patients with phenylketonuria. Both the mechanism and significance of these changes is doubtful at present.

Key words Bone density · Dietary treatment · Growth · Phenylketonuria

Abbreviations *AA* arachidonic acid · *AAS* amino acid score · *DHA* docosahexaenoic acid · *EPA* eicosapentaenoic acid · *IAA* indispensable amino acids · *Phe* phenylalanine · *PKU* phenylketonuria

Introduction

Dietetic control of plasma phenylalanine (Phe) levels in patients with phenylalanine hydroxylase deficiency is an efficient strategy to prevent neurological impairment and mental retardation. The mainstay of dietary treatment is restriction of the Phe intake which in practice means restriction of nearly all protein-rich foods and supplementation of necessary nitrogen in the form of indispensable (IAA) and dispensable amino acids by Phe-free amino acid mixtures. These amino acid mixtures are to be enriched with mineral salts, trace elements and vitamins, because foods of animal origin rich in these nutrients are almost completely absent from the phenylketonuria (PKU) diet.

The nutritional goals for PKU patients are the same as for the normal population "satisfactory growth and the avoidance of deficiency states" because "good nutrition helps to prevent acute and chronic illness and to develop physical and mental potential" and is "also providing reserves for stress" [8].

The phenylketonuria diet and growth

The PKU diet, however, deviates from the normal diet in several aspects, which shall be discussed in connection with potential influences on growth.

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Energy

Energy intake should be the same as in the non-PKU population. However, energy intake in healthy children fluctuates widely from day to day [41] and can be expected to do so in PKU children. In diet prescriptions for PKU children, attention focuses primarily on the amount of Phe in natural protein and of the Phe-free protein substitute. Energy intake depends on fat and carbohydrate in protein-free or protein-poor foods and very much on the abilities of dieticians, parents and manufacturers to provide palatable and attractive meals. Energy intakes in diet studies are rarely recorded. When they have been evaluated they often appeared to be lower than recommended intakes [3, 4, 5] even in normal growing children, and especially in infancy. This apparent discrepancy is found also in nutritional studies in healthy children in recent years and seems to indicate that the estimates on energy requirements may have been too high [38]. Energy intake, on the other hand, has direct implications on nitrogen retention: energy insufficiency will make nitrogen balance negative even in the presence of normal or high protein intake. Loss of appetite and catabolism during infections will disturb the balance between protein synthesis and degradation in favour of the latter. It has to be compensated by increases in both energy and protein intake as soon as is feasible [1].

It is an unresolved question if the substitution of L-amino acids for intact protein increases energy requirement. In one study on amino acid requirements of infants, the use of a complete amino acid mixture raised the energy requirement by 25% compared to whole protein [36]. Prolonged experience over 30 years with amino acid mixtures in patients does not support this finding in hospitalised infants. In contrast to amino acid mixtures for PKU patients, the amino acid pattern of the mixture in the study on threonine requirement was marginal in contents of histidine, cystine and methionine. Mean energy intakes in 16 adolescent PKU patients (aged 11–15.6 years) still on a Phe restricted diet were lower than in 14 controls of the same age by 16% but this difference was not statistically significant [17]. Median energy intakes of 82 PKU patients between 12 and 29 years of age still on diet and 17 patients off Phe-free protein substitutes were all below the recommended energy intake by 13% to 20%, however, with a wide interindividual variation [39].

Adolescent PKU patients who in Germany are allowed to relax their diet from age 10 years but who are advised to keep their Phe levels under control (<900 μmol/l <15 years of age; <1200 μmol/l >15 years of age) [10] need dietary advice and supervision because of a tendency to substitute an imbalanced diet poor in protein for their Phe-free protein substitute while adhering to customary dietary habits with avoidance of foods of animal origin and a high intake of carbohydrate rich foods. They are at risk of deficient intake of the micronutrients which used to be provided by the amino acid mixture.

Protein

In the strict diet of PKU patients protein is provided for 50% to 90% by a Phe-free protein substitute. Policy as to the nature of the protein substitute differs between countries: hydrolysate versus mixture of L-amino acids and complete formula providing besides "protein" also carbohydrates, fat, minerals, vitamins and trace elements versus incomplete products with negligible fat and carbohydrate content. The latter permit more variability in the diet of especially older patients because of being less bulky and suitable to be taken apart from natural foods. They are, however, more demanding as to the provision of essential nutrients via other foods.

Protein quality of protein substitutes now in use, assessed by amino acid scores (AAS) as proposed by Food and Agricultural Organisation of the United Nations [13], is good in contrast to earlier casein hydrolysates. Compared to the requirement patterns for infants, their AAS were 70 [3], which might explain the higher "protein" need for normal growth in participants of the United States Collaborative Study of Children Treated for Phenylketonuria.

AAS in modern Phe-free amino acid mixture are above 100 both compared to the reference patterns for infants and older children and adults. In fact the "protein" quality of PKU diets (both Phe-free product plus natural protein) as assessed by AAS is much above the proposed reference patterns for PKU patients above the age of 1 year [29]. It is not known if the reported imbalances in the amino acid patterns of PKU diets have clinical implications beyond the fact that nitrogen is predominantly supplied by IAA instead of by dispensable amino acids. A reduction in the content of IAA, which seems to be possible for products for toddlers and older patients according to this study, would, however, have to be compensated by increases in dispensable amino acids to assure an appropriate nitrogen intake because the nitrogen requirement of PKU patients is normal.

As a rule PKU patients take in less protein than non-PKU age matched controls, however, their protein intake must certainly not be lower than the recommended dietary protein intakes. Although the "protein" (Phe-free protein substitute plus natural protein) of PKU diets has been shown to have the same net protein utilisation as egg or milk protein in rats [27], there are open questions about the digestibility factor for this "protein" to correct the AAS. It has been shown in healthy humans that the "protein" of PKU diets made up with free amino acids leads to earlier appearance of amino acids in plasma after ingestion and to faster decreases than natural protein [16, 17]. This could mean that these fast absorbed amino acids are preferentially oxidised as was indeed shown by Mönch et al. [33] especially if Phe is unavailable in sufficient amounts for protein synthesis. The Phe-free protein substitute, therefore, has to be divided over at least three portions during the day and should be combined with intake of natural protein providing Phe.

It has been argued that the growth faltering observed in PKU patients, especially during the first 2 to 3 years of life, in several countries [12, 37, 43] is the result of too low an intake of protein [1]. For example, in the German Collaborative Study which aimed at therapeutic plasma Phe levels of 120 to 360 μmol/l, increasing deviations of the mean standard deviation scores (SDS) for height by age were seen in 82 patients up to the age of 2.5 years with some catch-up growth thereafter, however, not to zero at age 6 years [37]. Similar observations were reported retrospectively for 87 patients by Weglage et al. [44], however, with catch-up growth already during the 2nd year of life and a normal height in all at a mean age of 12.2 ± 4.8 years without intervention. There was no association between plasma tyrosine and Phe levels or the amount of protein taken and loss of height. In contrast, the patients of the United States Collaborative Study with a higher protein intake in the form of a Phe-poor casein hydrolysate (with a low AAS with reference to infants) did not differ in linear growth compared to that of normal North American infants and children [31]. Both males and females had lengths/heights at all ages until 10 years at or above the 50th percentile (exception males at 4 years of age). Comparison of the mean lengths/heights of the German infants/children shows that all females are on the 50th percentile of European reference values [35], whereas boys' heights decrease from the 50th percentile at age 1 to the 25th percentile at age 2 to 4 years and increase thereafter to the 40th percentile at age 5 years. Mean weights by age were lower in the children of the German study at all ages until 6 years than in their North American counterparts [1] with weights by length/height close to the 50th percentile in both sexes [37]. Mean protein intake (both Phe-free protein substitute plus natural protein) in the German patients was higher than the recommended intakes of the WHO/FAO [46] and of the German Nutritional Society [11] at all ages [45]. However, especially during the 1st year of life the reported standard deviation of the mean protein intake suggests that some infants at least had a protein intake below the recommended values. This is to be avoided as these recommendations are valid for protein of high biological value and good digestibility only.

Comparison of North American patients and German PKU infants fed amino acid mixtures as protein substitutes show in fact quite similar mean intakes: 2.3 g/kg per day between 3 and 6 months versus 2.26 g/kg per day between 4 and 6 months [1, 45]. Protein intake of North American infants fed a casein hydrolysate was higher (4.2–2.5 g/kg per day). The notion that low protein intake in the German study patients is responsible for faltering in height does not seem to be very likely. Unfortunately, energy intakes are not reported for the German study group. Phe insufficient diets were probably the reason for profound malnutrition during the 1st year of life manifest with deficient growth, anaemia, hypoproteinaemia, radiological bone changes described among others by Hanley et al. [18]. These infants had a high protein and energy intake. However, in view of the low therapeutic Phe levels of 40 to 240 μmol/l now recommended in Germany for the first 10 years of life [10], this danger has to be kept in mind and must be avoided by both frequent Phe level monitoring and diet evaluations.

Carbohydrates

Carbohydrate intake tends to be high in PKU patients with high percentages of easily digested carbohydrates. Intake of dietary fibre is often below recommended values.

Fat

Fat content of PKU diets shows a tendency to be lower than in normal diets. There is no need to restrict fat intake below recommendations for the normal population. This could mean that a sufficient energy intake becomes a problem. Because food of animal origin is almost absent from the diet, fat is predominantly supplied as plant oils with high contents of unsaturated fatty acids and no cholesterol. Depending on which type of oil is customary, e.g. olive oil in Italy [14] and corn or sunflower oil in other countries, the pattern of unsaturated fatty acids varies. Linoleic acid dominates regularly over linolenic acid and there are practically no preformed long-chain polyunsaturated fatty acids of the n-3 series, eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) and very low amounts of the n-6 fatty acid arachidonic acid (AA). Consequently EPA, DHA and AA levels were low in plasma lipids, whereas AA was high and DHA low in erythrocyte membrane lipids [15]. Polyunsaturated fatty acids are components of structural lipids in all cell membranes and play a critical role for the development and the function of the central nervous system and the retina. AA plays an important role as a precursor of eicosanoid mediators of biological functions. AA is considered by some to be semi-essential for somatic growth [28]. In PKU patients receiving strict diets with normal linoleic acid intakes (3.7% of energy intake), DHA was reduced in plasma cholesterol esters only and in erythrocyte phosphatidylethanolamine and phosphatidylcholine combined with a decrease in EPA and the sum of n-3 fatty acids, whereas AA and the sum of n-6 fatty acids was increased. The authors concluded that DHA deficiency is the result of a reduced intake of n-3 fatty acids [34] which should be increased to achieve a ratio linoleic/linolenic acid of 5 to 10:1. In young infants and probably also during pregnancy, DHA and AA supplements will be useful and have been shown to sustain normal DHA and AA status over 5 to 6 months in infants [20, 21]. Visual function in PKU children (mean age 10.5 years) was reported recently to be improved by a balanced supplement of AA, EPA and DHA compared to placebo [6].

Dhondt et al. [12] reported length/height growth reduction in French PKU patients under dietetic treatment until 8 years of age. In France, diet control is relaxed at that age and plasma Phe concentrations are allowed to rise to 910–1200 μmol/l. Height deficit was significantly greater in patients with a low lipid intake on diet. After relaxation of the diet, both SDS for height by age and weight by age increased to levels above normal.

Vitamins and trace elements

Phe-free protein substitutes are enriched with vitamins, minerals and trace elements to substitute for the amounts that are normally ingested with food rich in protein. In spite, however, of nutrient intakes at or above recommended dietary intakes with modern enriched protein substitutes [2, 5] there are reports on high incidences of iron depletion [4, 9] and on low plasma retinol and zinc concentrations [2, 4] in PKU infants and children.

Iron depletion was apparent by low serum ferritin concentrations, whereas haemoglobin concentration and mean erythrocyte volume were normal. The children were growing normally. Low bioavailability of iron from PKU diets is unexplained. Vitamin C intake which promotes absorption of iron salt is generally high in PKU patients. Possible reasons for insufficient absorption of iron are interactions with calcium and phosphorus salts and a high amount of polyunsaturated fatty acids in the diet. Serum ferritin should be monitored in patients on strict PKU diets.

Vitamin A deficiency, on the other hand, may lead to iron-resistant anaemia. In vitamin A depleted animals iron was shown to accumulate in liver. Low plasma retinol levels, compared to normal children, were found in infants and young children with vitamin A intakes up to three times the recommended intake [2, 4]. Prealbumin levels were found to be low in many infants and young children. Retinol bound to retinol binding protein is transported in the blood coupled to prealbumin [2]. However, it is unexplained why functional proteins like transferrin (for iron) and prealbumin (for retinol transport) should be deficient in individuals growing well and obtaining sufficient protein and energy.

Low serum zinc concentrations have been seen in a number of infants and children despite numerically adequate zinc intakes, more often in patients receiving Phe-poor casein hydrolysates than in those on amino acid mixtures. Zinc status is not well assessed by zinc levels in serum. Zinc absorption is negatively influenced by casein hydrolysate, by high amounts of polyunsaturated fatty acids, by high iron, phosphorus and fibre intakes; it should be enhanced by free amino acids [2]. Consequences of mild zinc deficiency in children are a reduced growth rate, impaired resistance to infection and, in animals, a reduction in the utilisation of dietary vitamin A.

Selenium used to be absent from most protein-substitutes for PKU patients. Consequently a low selenium status as assessed by serum, whole blood, urine and hair selenium concentrations and low activities of glutathione peroxidase, more pronounced in plasma than in erythrocytes, have been reported in PKU patients on strict diets low in selenium, both in children and pregnant women [30, 40]. These parameters increase with relaxation of or lack of compliance with diet. A total of 87 participants of the German collaborative study for children with PKU (age 5 to 15 years) showed in addition increases (within the normal range) of thyroxine in plasma and a negative correlation of ALAT activity in serum with whole blood selenium. There were no clinical symptoms of selenium deficiency [24]. As reported earlier, SDS of height were negative for boys and girls in comparison to three sets of European reference values (exception: girls in comparison to reference [35]). Type 1 5′iodothyronine deiodinase is a selenoprotein that converts thyroxine into tri-iodothyronine (T_3). T_3 and thyroid stimulating hormone levels were normal in PKU patients [24]. Selenium supplements with a high dose of 4 μg/kg per day (as selenite) over 3 months in 17 patients normalised selenium status parameters and increased free thyroxine and decreased total thyroxine and reverse T_3 levels. In addition, there was a reduction in (normal) total cholesterol and LDL-cholesterol concentrations in serum. There was no interaction with serum copper, zinc, magnesium, calcium and phosphorus, however, there was an unexpected significant rise in malondialdehyde concentration in plasma after selenium supplementation (from 1.95 ± 0.5 to 2.49 ± 0.41 μmol/l; normal 1.64 ± 0.43 μmol/l). Immunological status parameters did not change. Male patients displayed an increase in muscular strength. All probands showed an increase in the (normal) left ventricular cardiac index [25]. It is doubtful whether selenium insufficiency is responsible for the growth faltering observed in the study population of the German collaborative study via effects on the thyroid hormone status considering the normal bone age development in these children [37].

Vitamin B_{12} deficiency with neurological impairment has been reported in adolescent and adult patients only who did not take any or enough of their protein substitute enriched with this vitamin and who excluded all foods of animal origin from their diet [19]. In adolescent and adult PKU patients off Phe-free substitutes and on self-selected, mostly vegetarian, diets calcium, folate and iron intakes were less than 60%, thiamine, riboflavin, niacin, vitamin B_6 and vitamin B_{12} intakes were 30% to 50% lower than recommended amounts [39].

Although individual subclinical deficiencies of one or several nutrients cannot be excluded to impair length/height development in some cohorts of PKU children, conclusive proof is lacking. Reports on singular deficiency states should make us aware of the possibility and remind us that it is difficult or even impossible to formulate guidelines that guarantee optimal nutrition in an

individual patient. Protein substitutes and the pattern of nutrients they provide are a compromise which by all experience works well. The responsibility for appropriate assessment of clinical and biochemical parameters remains with the medical personnel. Impaired growth in PKU patients does not correlate with the strictness of dietary treatment [42]. It cannot be excluded that the present nutritional guidelines do not provide for dietary substances with specific functions in certain organs. The carotenoids lutein and zeaxanthine, which are found in the retina of the eye, may be essential for visual function.

Bone mineral density

Both bone mineral content and bone mineral density were found to be decreased in PKU children on diet and off diet. McMurry et al. [32] showed a normal increase in bone mineral content of the radius until the age of 8 years. Female patients (mean age 18.2 years) had a 21% decrease in bone mineral content compared to age-matched control. After the age of 8 years progression of mineral content with age decreased. Calcium in serum was no different from controls, however, alkaline phosphatase and magnesium were lower at all ages, 25-hydroxy-vitamin D and phosphorus were reduced in pre-school and school children, respectively. Plasma copper and red blood cell copper concentrations were decreased in many patients, plasma zinc was marginal whereas red blood cell zinc was in the normal range. Zinc values were not correlated with alkaline phosphatase activity. Parathyroid hormone was significantly lower in PKU patients than in controls and was not correlated to bone mineral content or serum calcium, phosphate or magnesium concentrations. Lack of dietary compliance and Phe levels >1200 μmol/l were associated with a decrease in bone mineral content. Intake of calcium and phosphorus was lower in PKU patients than in controls, magnesium intake was above recommended values. Bone mineral content was neither correlated to serum concentrations nor to mineral intake.

Decreased total body (97.1% of normal) and spine (92% of normal) mineral density was lower in 32 prepubertal PKU children than in controls, despite higher dietary intakes of calcium, phosphorus and magnesium than controls and than recommended intakes [7]. A more detailed analysis of 11 PKU children, 10.9 ± 4.2 years of age for parameters of mineral homeostasis and bone mineralisation showed that PKU children had lower serum calcium and magnesium concentrations than controls but normal values for phosphorus, zinc, copper and albumin and similar values for 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D and parathyroid hormone. Lean body mass assessed by dual energy X-ray absorption was normal, whereas bone mineral density of the lumbar spine and the legs was decreased. Markers of bone formation (bone alkaline phosphatase, osteocalcin and procollagen type 1 carboxyterminal propeptide) were unrelated to Phe levels in plasma, protein or mineral intake (protein intake 1.5 ± 0.6 g; calcium intake 948 ± 312 mg; phosphorus 948 ± 312 mg/kg per day). There was no indication that higher Phe concentrations in plasma were correlated with increased urinary mineral losses [22]. Variations in dietary protein intake in the presence of constant calcium and phosphorus intake influence bone turnover with increased bone resorption at high levels of protein intake (1.5 g/kg per day) and secondary hyperparathyroidism at low intake (0.7 g/kg per day) in young women [26]. However, the data reported on PKU children and adults on and off diet do not follow such a systematic pattern.

Dietary reference intakes for an adequate calcium intake for children and adults up to the age of 30 years to achieve a maximal calcium retention early in life have recently been revised and increased for ages from 9 years to 18 years to 1300 mg/day [23]. It remains to be seen if compliance with such a calcium intake in PKU children can normalise bone mineral accretion.

Conclusions

Dietary treatment, at present the only available option for PKU due to phenylalanine hydroxylase deficiency, is highly successful in preventing mental and neurological impairment and permits patients to achieve normal school and professional careers. More than 40 years of experience have optimised treatment strategies. Growth, although not always following normal standards, is almost normal. Decreased bone mineral content, as yet unexplained, will have to be investigated as to its pathogenesis and possible prevention to decrease the risk of osteopenia and its consequences in older patients.

Open questions as to sound advice for and guidance of older patients who choose to stop dietary treatment and the Phe-free protein substitute remain. This advice will have to be formulated in cooperation with the individual patient to find a compromise between nutritional needs which must be covered for reasons of health and personal life circumstances. If indeed supplementation of neutral amino acids can make PKU patients with elevated Phe levels due to diet relaxation function better, they should be enriched at least with the nutrients most likely to be deficient in their diets.

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