J Inherit Metab Dis (2010) 33:659–664
DOI 10.1007/s10545-010-9043-4

ADVANCES AND CHALLENGES IN PKU

Nutritional issues in treating phenylketonuria

François Feillet · Carlo Agostoni

Received: 9 September 2009 / Revised: 25 November 2009 / Accepted: 22 December 2009 / Published online: 12 February 2010

Abstract A phenylalanine (Phe)-restricted diet is the mainstay of phenylketonuria (PKU) treatment, and, in recent years, the nutritional management of PKU has become more complex in order to optimize patients' growth, development and diet compliance. Dietary restriction of Phe creates a diet similar to a vegan diet, and many of the nutritional concerns and questions applicable to vegans who wish to avoid animal products are also relevant to patients with PKU. Owing to their nutritional characteristics, breast milk and breastfeeding should be given greater consideration as a useful food in patients with PKU and in those with other inborn errors of metabolism. Further key issues for consideration include the quality of the available amino acid substitutes, the neurotrophic and neuroprotective effects of added long-chain polyunsaturated fatty acids (e.g. docosahexaenoic acid), micronutrient deficiencies, bone disease and antioxidant status. Long-term dietary guidance and monitoring of the nutritional status of patients with PKU should be part of a follow-up programme that continues for life.

Communicated by: Nenad Blau

Presented at the Serono Symposia International Foundation Meeting, "Advances and Challenges in PKU", 16–17 January 2009 in Barcelona, Spain.

Competing interest: None declared.

F. Feillet (✉)
Centre de référence des maladies héréditaires du métabolisme de Nancy, INSERM U 954, Hôpital d'Enfants, CHU Brabois, Allée du Morvan, Vandoeuvre les Nancy, 54500, France
e-mail: f.feillet@chu-nancy.fr

C. Agostoni
Department of Maternal and Pediatric Sciences, Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico, University of Milan,
Via della Commenda, 9, I-20122 Milano, Italy

Abbreviations

AA	arachidonic acid
DHA	docosahexaenoic acid
Ig	immunoglobulin
LCPUFA	long-chain polyunsaturated fatty acid
LDL	low-density lipoprotein
OMIM	Online Mendelian Inheritance in Man database
Phe	phenylalanine
PKU	phenylketonuria
PUFA	polyunsaturated fatty acid

Introduction

Treatment options for the management of phenylketonuria (PKU; OMIM 262600) are expanding, with the introduction of new possibilities, such as large neutral amino acids, tetrahydrobiopterin and, potentially, phenylalanine (Phe) ammonia lyase or gene therapy. However, these options do not always allow a complete relaxation of the patient's diet, and nutritional follow-up is, therefore, essential in the management of this condition. Most patients with PKU need to follow a natural-protein-restricted diet, which represents a nutritional challenge because it is necessary for the patient to restrict the amount of natural protein consumed in order to reduce Phe intake while avoiding the effects of a deprived diet. After diagnosis, affected individuals undergo dietary intervention, which involves special products that contain no Phe, variable amounts of low-Phe foods, and fruits and vegetables chosen on the basis of their Phe content. In essence, the PKU diet may be looked upon as a medically prescribed vegan-like diet.

In this paper we discuss some of the key nutritional issues relevant to PKU, such as breastfeeding, the vegan-

like diet, polyunsaturated fatty acids (PUFAs), bone disease, amino acid supplementation and antioxidant status—all of which emphasize the need for the nutritional status of patients with PKU to be closely monitored.

Human breast milk and breastfeeding

After diagnosis, the first question in the case of classical PKU is how to deal with human breast milk and breastfeeding. Human breast milk is a whole 'animal' food and contains complete and structurally intact 'animal' proteins, with all the essential amino acids. Human milk is a low-protein food. Indeed, while showing an average content of 0.9–1.0 g protein/100 ml, 0.3–0.4 g protein/100 ml of human breast milk is made up of functional protein [0.2 g lactoferrin, 0.1 g immunoglobulin (Ig) A, some lysozyme and minor components], and just 0.6 g/100 ml fulfils the protein requirements of infants. Within this amount, approximately 50 mg/100 ml is represented by Phe and 50 mg/100 ml is represented by tyrosine; in contrast, a standard infant formula contains two to three times as much Phe per 100 ml. Hence, human breast milk can also be considered to be a relatively low-Phe food, and the advantages and disadvantages of allowing it in the diet of patients with PKU should be carefully evaluated. A practical approach would be to allow 300–400 ml of human breast milk per day, although individual tolerance should be strictly monitored. Similar schedules have been suggested for managing PKU by alternating an infant's feeds with human breast milk and Phe-free products (van Rijn et al. 2003). Being breast fed versus formula fed in the first weeks before diagnosis has been associated with better performance in visual evoked potential tests at 12 months of age (Agostoni et al. 2003a) and also with higher neurodevelopmental scores in primary-school-age children (Riva et al. 1996). This may be related to the reduced protein content and supply of long-chain polyunsaturated fatty acids (LCPUFAs) in human breast milk and the closer mother–infant bonding from breastfeeding. Despite this, breastfeeding is less common in individuals with PKU than in the general population (Agostoni et al. 2000a). In view of the major biological and developmental advantages, and when feasible or not contraindicated, human breast milk and breastfeeding should be given greater consideration in PKU and other inborn errors of metabolism than is currently granted (Huner et al. 2005; MacDonald et al. 2006a).

Vegan-like diet and PKU

The characteristics of the diet for patients with PKU, once solids have been introduced, resemble those of a vegan diet with respect to the composition of permitted natural foods. In dietary schedules the quantities of permitted natural, unmodified, foods are calculated from a method of Phe equivalence (dependent upon how much Phe a food contains for a given weight). Vegan diets have been recently considered within healthy populations for the presumed health benefits. Lacto-ovo vegetarian diets (no red meat, poultry, fish, shellfish or animal flesh of any kind, but dairy and egg products are eaten) and vegan diets (no animal products at all) offer a number of nutritional benefits, including lower levels of saturated fat, cholesterol and animal protein, as well as higher levels of carbohydrates, fibre, magnesium, potassium, folate, antioxidants (e.g. vitamins C and E) and phytochemicals. Vegetarians, in general, have been reported to have lower body mass indices than non-vegetarians, as well as lower rates of death from ischaemic heart disease, lower blood cholesterol levels and lower blood pressure, and lower rates of hypertension, type 2 diabetes and prostate and colon cancer. Historically, much of the scientific data collected on the deficiency of key nutrients in vegetarians has included evidence of a lack of protein, iron, zinc, calcium, vitamins A, B2 (riboflavin), B12 and D, omega-3 fatty acids and iodine, but more recent research shows that both vegetarian and vegan diets can meet current recommendations for all of these nutrients. Although, PKU patients do follow a vegan-like diet, some of the components of usual vegan diets (cereals, nuts...) are restricted in these patients because of their high protein contents. These foods are rich in micronutrients, and, therefore, a usual vegan diet might meet recommendations for these nutrients, while a PKU diet might not. In some cases the use of fortified foods or supplements can be helpful in meeting the recommended levels for individual nutrients (American Dietetic Association 2003). In spite of this, the Committee of Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has recently suggested that infants and young children receiving a vegetarian diet should be given a sufficient amount (approximately 500 ml) of milk (breast milk or formula) and dairy products (Agostoni et al. 2008), based mainly on the possible dietary deficiencies affecting growth in the first 2 years of life (Dagnelie and van Staveren 1994). In the planning of vegan diets, breast-fed vegan infants may need supplements of vitamin B12 if the maternal diet is inadequate; older infants may need zinc supplements and reliable sources of iron and vitamins B12 and D. According to some studies, such children may also have particularly low levels of calcium. In addition, the bioavailability of zinc and iron from plant foods can be low. Protein needs are slightly higher for vegan children but are easily met with a varied diet that provides adequate energy. Special attention should be given to dietary practices that enhance the absorption of zinc and iron from plant foods.

Furthermore, good sources of the omega-3 fatty acid, linolenic acid, should be emphasized to enhance synthesis of the long-chain fatty acid, docosahexaenoic acid (DHA). Accordingly, dietary professionals who counsel vegan families should help parents identify good sources of vitamins B2 and B12, zinc, calcium and, if sun exposure is not adequate, vitamin D (Mangels and Messina 2001; Messina and Mangels 2001).

In the case of patients with PKU who are on a prescribed diet, lower intakes have been observed for some micronutrients (vitamins A, C and E, selenium, coenzyme Q10), vitamins B2, B6 and B12, and folates (which can increase homocysteine levels in the blood), iron, zinc, carnitine and LCPUFAs (discussed below). Although no major clinical consequences have been reported, there is a general agreement that patients with PKU need long-term dietary guidance throughout adult life, and, in view of the potential benefits, costs and risks, daily vitamin supplementation is justified in these patients (Hvas et al. 2006). Low blood cholesterol levels have been repeatedly reported in patients with PKU, in association with some genetic polymorphisms concerning cholesterol metabolism (Verduci et al. 2004) and micronutrient status. For example, larger and fewer atherogenic low-density lipoprotein (LDL) particles have been observed with a high zinc-to-copper ratio (Schulpis et al. 2004), although supporting biological evidence is lacking. From a speculative standpoint, the generally low-atherogenic profile could be a counterbalance for the potential harm of a lower antioxidant status (although data are controversial) and higher homocysteine levels. Finally, it has been hypothesized that a vegan diet could reduce the risk of suffering from Parkinson's disease later in life, through several biomechanisms (McCarty 2001), and this could be particularly helpful in the case of adults with treated PKU. Therefore, while the less positive facets of a vegan-like diet (the 'cons') can be expected and counteracted with appropriate dietary supplementations, the advantages ('pros') should also be considered.

Long-chain polyunsaturated fatty acids

Pre-formed LCPUFAs, in particular arachidonic acid (AA; C20: 4 n-6) and DHA (C22: 6 n-3), have important roles in neurological development (Koletzko et al. 2008). Previous studies have shown that healthy breast-fed infants have better long-term neurological outcomes than formula-fed infants, and this has been attributed partly to the presence of pre-formed LCPUFAs in breast milk, which have only recently been introduced to infant formulas (Anderson et al. 1999). Patients with PKU represent a vulnerable group for whom LCPUFA supplementation during infancy may be especially beneficial. Infants are more exposed to neural damage owing to high blood Phe peaks, in the case of poor dietary compliance, and LCPUFAs may exert neuroprotective effects (Bazan 2007). The vegan-like diets usually prescribed tend to be very poor sources of pre-formed LCPUFAs. Both children and adults with PKU have been found to have poor LCPUFA (particularly DHA) status (Galli et al. 1991; Moseley et al. 2002); the addition of DHA, either in special LCPUFA preparations or in the form of fish oil, to the diets of older children with PKU raises plasma levels of these fatty acids, improving the visual responses of treated children (Agostoni et al. 2000b; Beblo et al. 2001). Improvements in fine motor skills have also been seen with the dietary supplementation of fish oil (Beblo et al. 2007). The extent to which such supplementation may affect LCPUFA status and visual function in the long term is unknown, because, in older children with PKU, biochemical and functional differences between supplemented and un-supplemented subgroups were not found 3 years after supplementation had ceased (Agostoni et al. 2003b). In infants with PKU a dietary supply of LCPUFAs prevents the decline in DHA concentrations associated with a diet supplying minimal sources of LCPUFA, and the early DHA status, irrespective of any specific supplementation, is associated with indices of visual maturation (Agostoni et al. 2006). The extent to which DHA supplementation taken by pregnant women with PKU could benefit the child (or children) they give birth to is still totally unknown, although the theoretical background is promising. Future research would also be beneficial into the status of fatty acids in adolescents with PKU (taking or not taking a Phe-restricted diet) in order to identify accurately disease-related changes and the possible role of dietary LCPUFAs.

Bone disease and PKU

Progressive reduction in bone density is a well-known complication of PKU (Al-Qadreh et al. 1998; Porta et al. 2008; Schwahn et al. 1998). The pathogenesis of this common feature, however, remains unclear. Different and contradictory causative mechanisms have been suggested, such as poor dietary compliance, with a consequent rise in plasma Phe, and a restrictive diet (Barat et al. 2002; Porta et al. 2008). A decrease in bone mineral density found in total body, femoral neck or spine (L1–L4) was reported by Modan-Moses et al. (2007) in 31 adult PKU patients (18 female), mean age 25±5.3 years (range 19–41 years). In their study, mean [± standard deviation (SD)] bone mineral density was lower in the diet-adherent group (L1–L4 Z-score −0.806±1.21) than in those that did not adhere to the diet (L1–L4 Z-score −0.367±1.21), although this was not significant and was seen despite significantly higher

calcium intake and serum vitamin D levels in the diet-adherent patients than in the non-adherent patients (2,594.0± 1,125.0 mg/day versus 541.8±471.7 mg/day and 32.7± 7.3 ng/ml versus 24.8±7.8 ng/ml, respectively). Recently, the increased excretion of bone resorption markers has been demonstrated in patients with PKU (Millet et al. 2005), consistent with a high osteoclast activity (Ambroszkiewicz et al. 2008; Porta et al. 2008). This increase in bone resorption could not be explained by a nutritional deficiency. Bone de-mineralization with increased bone resorption has also been seen in other metabolic disorders, such as glycogen storage diseases (Rake et al. 2003). Bone strength in patients with glycogen storage disease has been related to muscle capacity (Schönau et al. 2002; Schwahn et al. 2002), and it is well known that a decrease in physical activity is associated with an increase in bone resorption (Karlsson et al. 2003). As the mechanisms of bone de-mineralization in PKU remain unclear, patients' osteodensitometry must be checked regularly, particularly during adolescence. In cases of low bone mineral density, the micronutrient intake must be controlled, together with physical activity, which plays a crucial role in bone mineralization.

Amino acid supplements

Nutritional treatment for patients with PKU is based on a low-Phe diet: natural foods containing some Phe in combination with a protein substitute (a mixture of amino acids that are free from or low in Phe) and special low-protein foods, to meet the patient's energy requirements. It is interesting to notice that there are no clear scientific data showing the efficacy of amino acid supplements in PKU (Rutherford and Poustie 2005). Nevertheless, as a randomized controlled trial would not be ethical, the conclusion of this review is that the use of protein substitutes should continue to be observed and monitored with care. The number of protein substitutes available for patients is increasing constantly with time (Cleary et al. 2006; MacDonald et al. 2003, 2004, 2006b; Rohr et al. 2001). At present, more than 20 different mixtures are available, with a notable range of differences in micronutrient and macronutrient compositions. The absence of Phe is the one constant in these mixtures; there is a variability in the presence or absence of lipids, vitamins and minerals, and the content of these micronutrients can differ markedly from one substitute to another. It is not possible in this paper for us to review the status of each micronutrient in these amino acid supplements specifically for patients with PKU; we will, however, stress some points concerning the lipid content and fat-soluble vitamins in these supplements.

(1) Supplements for infants aged between 0 and 12 months

There are four different protein substitutes available for newborn babies; three of these contain PUFAs (one of these contains DHA but not AA) and one does not, although it does contain 20% saccharose, which was not recommended in the last European Union recommendations for infant formulas. Apart from these considerations, the composition of each of the four products meets newborn babies' requirements.

(2) Supplements for infants, adolescents and adults

There are many products available, with broad differences in composition and presentation. This represents a great advantage for patients, as they can choose the product most likely to meet their needs. Whilst the multiplicity of product availability provides a chance for patient compliance, it does, however, make the diet more complicated to equilibrate. Lipid content can vary from 0–2% (PKU Express™, Vitaflo) to 53% (Add Ins, SHS Ltd.) of the total calorie content of the substitute, which may have an impact on fat-soluble vitamin absorption. The vitamin A intake, for example, can be calculated from the quantity of amino acid supplements taken by the patient, but the amount absorbed will depend on the proportion of lipids in the supplement. The most recent supplements tend to be more concentrated, with a very high proportion of amino acids as part of the macronutrient composition (nearly 80% in PKU Express™ with less than 2% of fat). As amino acid supplements are rarely planned to be eaten concomitantly with lipids, we may speculate that patients taking fat-free supplements may have a deficiency of vitamin A , although this remains to be proven in long-term studies.

Antioxidant status

Oxidative stress, which is defined as an imbalance between the total antioxidant defences and the reactive species formed in the tissues (Gutteridge and Halliwell 2000), is an important event that has been related to the pathogenesis of neurodegenerative disorders. It is also commonly observed in some inborn errors of intermediary metabolism (Colomé et al. 2000; Wajner et al. 2004) and PKU (Colomé et al. 2002; Schulpis et al. 2003, 2005). Restricted diets in patients with PKU may alter their antioxidant status as a result of deficiencies in selenium (van Bakel et al. 2000) or coenzyme Q10 (Artuch et al. 2004). As a consequence, it has been shown that lipid peroxidation, total antioxidant reactivity and glutathione peroxidase activity were significantly altered in patients with untreated PKU, at diagnosis (Sirtori et al. 2005; Sitta et al. 2006). As there is a link

between antioxidant status and ageing (Fusco et al. 2007), it seems very important that we follow the antioxidant status of patients with PKU and correct their nutritional deficiencies in selenium and vitamin E, even if a supplementation trial of antioxidant vitamin cocktails has failed to show clear efficacy against Alzheimer's disease or cognitive impairment in the elderly (Praticò 2008).

Conclusion

Despite the appearance of new treatments, a Phe-restricted diet remains the mainstay of PKU treatment. The nutritional management of PKU has become more complex with the multitude of amino acid substitutes available, and with the different nutritional issues, such as PUFAs, micronutrient deficiencies, bone disease and antioxidant status, that have arisen. Long-term dietary guidance and monitoring of the nutritional status of patients with PKU should be part of a follow-up programme that continues for life.

Acknowledgements The authors take full responsibility for the content of this meeting report but thank Caudex Medical (supported by Serono Symposia International Foundation) for their assistance in editing this report and collating the comments of the authors and any other named contributors.

References

Agostoni C, Verduci E, Fiori L, Riva E, Giovannini M (2000a) Breastfeeding rates among hyperphenylalaninemic infants. Acta Paediatr 89:366–367

Agostoni C, Massetto N, Biasucci G et al (2000b) Effects of long-chain polyunsaturated fatty acid supplementation on fatty acid status and visual function in treated children with hyperphenylalaninemia. J Pediatr 137:504–509

Agostoni C, Verduci E, Massetto N, Radaelli G, Riva E, Giovannini M (2003a) Plasma long-chain polyunsaturated fatty acids and neurodevelopment through the first 12 months of life in phenylketonuria. Dev Med Child Neurol 45:257–261

Agostoni C, Verduci E, Massetto N et al (2003b) Long term effects of long chain polyunsaturated fats in hyperphenylalaninemic children. Arch Dis Child 88:582–583

Agostoni C, Harvie A, McCulloch DL et al (2006) A randomized trial of long-chain polyunsaturated fatty acid supplementation in infants with phenylketonuria. Dev Med Child Neurol 48:207–212

Agostoni C, Decsi T, Fewtrell M et al (2008) Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 46:99–110

Al-Qadreh A, Schulpis KH, Athanasopoulou H, Mengreli C, Skarpalezou A, Voskaki I (1998) Bone mineral status in children with phenylketonuria under treatment. Acta Paediatr 87:1162–1166

Ambroszkiewicz J, Gajewska J, Chelchowska M et al (2008) Concentration of osteoprotegerin, bone formation and resorption markers in patients with phenylketonuria (in Polish). Pol Merkuriusz Lek 25:57–60

American Dietetic Association, Dietitians of Canada (2003) Position of the American Dietetic Association and Dietitians of Canada: vegetarian diets. Can J Diet Pract Res 64:62–81

Anderson JW, Johnstone BM, Remley DT (1999) Breast-feeding and cognitive development: a meta-analysis. Am J Clin Nutr 70:525–535

Artuch R, Colomé C, Sierra C et al (2004) A longitudinal study of antioxidant status in phenylketonuric patients. Clin Biochem 37:198–203

Barat P, Barthe N, Redonnet-Vernhet I, Parrot F (2002) The impact of the control of serum phenylalanine levels on osteopenia in patients with phenylketonuria. Eur J Pediatr 161:687–688

Bazan NG (2007) Omega-3 fatty acids, pro-inflammatory signaling and neuroprotection. Curr Opin Clin Nutr Metab Care 10:136–141

Beblo S, Reinhardt H, Muntau AC, Mueller-Felber W, Roscher AA, Koletzko B (2001) Fish oil supplementation improves visual evoked potentials in children with phenylketonuria. Neurology 57:1488–1491

Beblo S, Reinhardt H, Demmelmair H, Muntau AC, Koletzko B (2007) Effect of fish oil supplementation on fatty acid status, coordination, and fine motor skills in children with phenylketonuria. J Pediatr 150:479–484

Cleary MA, Feillet F, White FJ et al (2006) Randomised controlled trial of essential fatty acid supplementation in phenylketonuria. Eur J Clin Nutr 60:915–920

Colomé C, Sierra C, Vilaseca MA (2000) Congenital errors of metabolism: cause of oxidative stress? Med Clin (Barc) 115:111–117

Colomé C, Artuch R, Vilaseca MA et al (2002) Ubiquinone-10 content in lymphocytes of phenylketonuric patients. Clin Biochem 35:81–84

Dagnelie PC, van Staveren WA (1994) Macrobiotic nutrition and child health: results of a population-based, mixed-longitudinal cohort study in The Netherlands. Am J Clin Nutr 59(5 Suppl):1187S–1196S

Fusco D, Colloca G, Lo Monaco MR, Cesari M (2007) Effects of antioxidant supplementation on the aging process. Clin Interv Aging 2:377–387

Galli C, Agostoni C, Mosconi C, Riva E, Salari PC, Giovannini M (1991) Reduced plasma C-20 and C-22 polyunsaturated fatty acids in children with phenylketonuria during dietary intervention. J Pediatr 119:562–567

Gutteridge JM, Halliwell B (2000) Free radicals and antioxidants in the year 2000. A historical look to the future. Ann N Y Acad Sci 899:136–147

Huner G, Baykal T, Demir F, Demirkol M (2005) Breastfeeding experience in inborn errors of metabolism other than phenylketonuria. J Inherit Metab Dis 28:457–465

Hvas AM, Nexo E, Nielsen JB (2006) Vitamin B12 and vitamin B6 supplementation is needed among adults with phenylketonuria (PKU). J Inherit Metab Dis 29:47–53

Karlsson KM, Karlsson C, Ahlborg HG, Valdimarsson O, Ljunghall S, Obrant KJ (2003) Bone turnover responses to changed physical activity. Calcif Tissue Int 72:675–680

Koletzko B, Lien E, Agostoni C et al (2008) The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. J Perinat Med 36:5–14

MacDonald A, Ferguson C, Rylance G et al (2003) Are tablets a practical source of protein substitute in phenylketonuria? Arch Dis Child 88:327–329

MacDonald A, Lilburn M, Cochrane B et al (2004) A new, low-volume protein substitute for teenagers and adults with phenylketonuria. J Inherit Metab Dis 27:127–135

MacDonald A, Depondt E, Evans S et al (2006a) Breastfeeding in IMD. J Inherit Metab Dis 29:299–303

MacDonald A, Lilburn M, Davies P et al (2006b) 'Ready to drink' protein substitute is easier is for people with phenylketonuria. J Inherit Metab Dis 29:526–531

Mangels AR, Messina V (2001) Considerations in planning vegan diets: infants. J Am Diet Assoc 101:670–677

McCarty MF (2001) Does a vegan diet reduce risk for Parkinson's disease? Med Hypotheses 57:318–323

Messina V, Mangels AR (2001) Considerations in planning vegan diets: children. J Am Diet Assoc 101:661–669

Millet P, Vilaseca MA, Valls C et al (2005) Is deoxypyridinoline a good resorption marker to detect osteopenia in phenylketonuria? Clin Biochem 38:1127–1132

Modan-Moses D, Vered I, Schwartz G et al (2007) Peak bone mass in patients with phenylketonuria. J Inherit Metab Dis 30:202–208

Moseley K, Koch R, Moser AB (2002) Lipid status and long-chain polyunsaturated fatty acid concentrations in adults and adolescents with phenylketonuria on phenylalanine-restricted diet. J Inherit Metab Dis 25:56–64

Praticò D (2008) Evidence of oxidative stress in Alzheimer's disease brain and antioxidant therapy: lights and shadows. Ann N Y Acad Sci 1147:70–78

Porta F, Roato I, Mussa A et al (2008) Increased spontaneous osteoclastogenesis from peripheral blood mononuclear cells in phenylketonuria. J Inherit Metab Dis, epub ahead of print

Rake JP, Visser G, Huismans D et al (2003) Bone mineral density in children, adolescents and adults with glycogen storage disease type Ia: a cross-sectional and longitudinal study. J Inherit Metab Dis 26:371–384

Riva E, Agostoni C, Biasucci G et al (1996) Early breastfeeding is linked to higher intelligence quotient scores in dietary treated phenylketonuric children. Acta Paediatr 85:56–58

Rohr FJ, Munier AW, Levy HL (2001) Acceptability of a new modular protein substitute for the dietary treatment of phenylketonuria. J Inherit Metab Dis 24:623–630

Rutherford P, Poustie VJ (2005) Protein substitute for children and adults with phenylketonuria. Cochrane Database Syst Rev 4: CD004731

Schönau E, Schwahn B, Rauch F (2002) The muscle-bone relationship: methods and management—perspectives in glycogen storage disease. Eur J Pediatr 161:S50–S52

Schulpis KH, Tsakiris S, Karikas GA, Moukas M, Behrakis P (2003) Effect of diet on plasma total antioxidant status in phenylketonuric patients. Eur J Clin Nutr 57:383–387

Schulpis KH, Karakonstantakis T, Bartzeliotou A, Karikas GA, Papassotiriou I (2004) The association of serum lipids, lipoproteins and apolipoproteins with selected trace elements and minerals in phenylketonuric patients on diet. Clin Nutr 23:401–407

Schulpis KH, Tsakiris S, Traeger-Synodinos J, Papassotiriou I (2005) Low total antioxidant status is implicated with high 8-hydroxy-2-deoxyguanosine serum concentrations in phenylketonuria. Clin Biochem 38:239–242

Schwahn B, Mokov E, Scheidhauer K, Lettgen B, Schönau E (1998) Decreased trabecular bone mineral density in patients with phenylketonuria measured by peripheral quantitative computed tomography. Acta Paediatr 87:61–63

Schwahn B, Rauch F, Wendel U, Schönau E (2002) Low bone mass in glycogen storage disease type 1 is associated with reduced muscle force and poor metabolic control. J Pediatr 141:350–356

Sirtori LR, Dutra-Filho CS, Fitarelli D et al (2005) Oxidative stress in patients with phenylketonuria. Biochim Biophys Acta 1740:68–73

Sitta A, Barschak AG, Deon M et al (2006) Investigation of oxidative stress parameters in treated phenylketonuric patients. Metab Brain Dis 21:287–296

van Bakel MM, Printzen G, Wermuth B, Wiesmann UN (2000) Antioxidant and thyroid hormone status in selenium-deficient phenylketonuric and hyperphenylalaninemic patients. Am J Clin Nutr 72:976–981

van Rijn M, Bekhof J, Dijkstra T, Smit PG, Moddermam P, van Spronsen FJ (2003) A different approach to breast-feeding of the infant with phenylketonuria. Eur J Pediatr 162:323–326

Verduci E, Agostoni C, Biondi ML, Radaelli G, Giovannini M, Riva E (2004) Apolipoprotein B gene polymorphism and plasma lipid levels in phenylketonuric children. Prostaglandins Leukot Essent Fatty Acids 71:117–120

Wajner M, Latini A, Wyse AT, Dutra-Filho CS (2004) The role of oxidative damage in the neuropathology of organic acidurias: insights from animal studies. J Inherit Metab Dis 27:427–448