Changing dietary practices in phenylketonuria

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In recent years, there has been much focus on research on non-dietary treatments in phenylketonuria (PKU). However, diet is likely to remain the major treatment for many years to come, since it has continued to be developed and consistent improvements have occurred. For example, with protein substitute, studies have tried to define the optimal dose and timing of intake; changes in palatability and presentation appear to have led to the long-term maintenance of acceptable blood phenylalanine control in teenage patients, and the low phenylalanine protein source glycomacropeptide is being considered as an alternative source to non-phenylalanine amino acids. Some countries are now adopting a simpler approach to dietary management, allowing a wider range of lower low phenylalanine foods without measurement, in combination with controlled phenylalanine exchange systems. Patients with PKU who are partially responsive to sapropterin dihydrochloride still require some dietary treatment. Long-term studies are required for examining the combined use of sapropterin dihydrochloride and diet to determine its impact on nutritional adequacy, growth, and blood phenylalanine variability. Generally, whether diet is used alone or in combination with sapropterin dihydrochloride, its true impact on quality of life and lifestyle should be investigated. Overall, it is likely we will continue to see many changes in the dietary treatment in the next five years, and hopefully this will lead to a better outcome for patients.

Key words: phenylketonuria, dietary practices.

The world of phenylketonuria (PKU) is changing day by day. New non-diet therapies have created a huge interest in the treatment of PKU. However, diet is likely to be the major therapy for many years to come, so it is essential that there is a heightened momentum to improve dietary treatment for patients with PKU. The optimal diet in PKU should provide acceptable blood phenylalanine control, be nutritionally complete, and maintain normal growth. In addition, it should be palatable, flexible, easy to comply with, and compatible with a modern day lifestyle[1]. Health professionals should no longer accept that diet is difficult or unpalatable; with modern technology and dietetic and home economic expertise, it should be possible to ensure that a low phenylalanine diet is equally as acceptable as a normal diet. There is now a wider choice of protein substitutes and an expanding range of 'normal' lower protein foods in retail shops and supermarkets; the choice, palatability, packaging, and internet availability of specialist low protein foods has improved; and some countries are now starting to adopt a simpler approach to dietary management. However, there are still a number of practical considerations that place extra demands on caregivers and affect the lifestyle of patients. The aim of this paper was to review changing dietary practices in the management of PKU.

What do we know about dietary treatment?

Optimal dietary treatment requires early onset of treatment and continuous dietary treatment throughout childhood, adolescence and probably life. If dietary control is lost in the first two years of life due to social problems, it is difficult to re-establish blood phenylalanine control[2].

Phenylalanine allocation and free foods

Dietary phenylalanine is severely restricted in PKU. Phenylalanine, an aromatic amino acid, is the precursor of tyrosine. Both are needed mainly for protein synthesis, and a small amount for catecholamine and thyroid synthesis. The precise tolerance for phenylalanine (200-500 mg) varies among patients even with the same mutant PAH genotype. Phenylalanine tolerance is affected by many factors including severity of PKU, target blood phenylalanine, compliance with protein substitute, and energy intake[3].

Methods of allocating phenylalanine intake vary throughout the world, and there has been much controversy internationally about the minuté of allocating dietary phenylalanine, its impact on blood phenylalanine levels on a day-to-day basis and the overall quality of blood phenylalanine control. All appear to produce satisfactory control, but no randomized controlled trial has compared approaches, and the ability of families to comply with different dietary regimens is unreported. In the United Kingdom (UK), phenylalanine is given in the form of a simple 50 mg exchange system (each exchange equivalent to 1 g natural protein). This system has existed since the early 1980s in the UK and it is a much simpler system than those used in other European countries, Australia and the United States, which either calculate the phenylalanine content of most foods given in the diet or use at least a two-tier system of phenylalanine exchanges. Every system has its own limitations. The UK 50 mg phenylalanine system is the least rigorous. Most patients with classical PKU under strict control are allowed between four to eight exchanges daily. When phenylalanine analysis is not available, 1 g of protein is assumed to contain 50 mg phenylalanine. This system includes a very generous free food system. Most fruits and vegetables only yield 30-40 mg phenylalanine per gram of protein. With the exception of potatoes, all fruits and vegetables containing less than 75 mg phenylalanine/100 g are allowed freely. Other free foods include sugar, sweetened drinks, butter, jam, and special low protein foods that contain less than 20 mg/100 g of phenylalanine. It is possible with the UK system that children may inadvertently eat a significant quantity of extra phenylalanine from free foods in addition to allocated exchanges, and the amount may vary from day to day. MacDonald et al.[4] found that some children may effectively increase their protein intake by a mean of almost 50% and sometimes even 100% from free foods with this system. However, surprisingly, it did not adversely affect plasma phenylalanine concentrations in this group of well-controlled children with PKU. This exchange system is easily understood and allows some flexibility. It also allows dietary freedom and aids variety, and excellent blood phenylalanine control can be achieved and maintained in the long-term[1,3].

Counting every milligram of phenylalanine or using phenylalanine exchange systems of less than 20 mg portions is more precise. This system involves counting many of the free vegetables. Although there is merit in these systems, there are also a greater number of drawbacks. Unfortunately, there is limited information on the phenylalanine content of many commercial foods, and even with the more accurate dietary exchange systems, there can only be an approximate estimation of phenylalanine intake. Generally, these diets are more complex and restrictive. Gökmen Özel et al.[5] found that the blood phenylalanine concentrations were higher in children whose mothers had limited knowledge about the exchange score compared to those who did not. The rigidity of this system could reduce low protein food intake and may affect quality of phenylalanine control.

Progress and challenges with protein substitutes

Protein substitute without phenylalanine is recommended for all dietary-treated patients with PKU. It supplies over 75% of protein requirements, usually in the form of L-amino acids, and it also provides all tyrosine requirements[1,2]. Its functions are many and include suppression of plasma phenylalanine concentrations, increased nitrogen retention, and increased phenylalanine tolerance[6]. Historically, patient compliance with protein substitutes is poor[1,7], but palatability and presentation have improved in recent years. MacDonald et al.[8] reported that only 38% of young children took their entire protein substitute each day. Prince et al.[9] found that patients consumed less protein substitute (57%-75%) than documented on diet record forms and much less than prescribed. Schulz et

al.[10] described in a group of older patients that 20% had stopped taking their protein substitute but were still following a low-protein diet.

Administration of protein substitutes

Protein substitutes are now available as amino acid powders, flavorless enteric-coated granules, capsules, tablets, and bars. Many are pre-measured in dose-related packaging. Some are targeted towards different age groups and circumstances (e.g. pregnancy). Many new, novel protein substitutes have also been introduced, and a popular development is the ready-to-drink pouch. These eliminate the need for mixing powders, any subsequent mess, and reduce wastage[11], and contemporary packaging similar to common 'high-street' drinks has helped ease patient embarrassment when taking protein substitutes outside the home. Short- term studies have demonstrated that liquid protein substitutes are efficacious and reduced self-consciousness, and blood phenylalanine control and nutritional biochemical and hematological markers are satisfactory. Importantly, they have improved compliance and the independence of teenagers and adults with PKU[11], but there is no data to demonstrate that their effectiveness is sustained over time. In fact, there are no studies describing the long-term adequacy of any type of protein substitute in PKU. We, therefore, in a retrospective study, evaluated the long-term efficacy of ready-to-drink protein substitute in a group of older children and adults with PKU. Thirty-four patients (17 females, 17 males; median age: 14.9 years, range: 7.2 to 53.8 years) with PKU on dietary management were recruited from Birmingham Children's Hospital. All patients who were taking a liquid protein substitute (*PKU Cooler 10, 15, or 20; Vitaflo International*) for a median of 2.4 years (range: 6 months to 4.1 years) and who had their plasma phenylalanine concentrations, anthropometric measurements and nutritional biochemical markers reviewed before and whilst taking the ready-to-drink protein substitute were included. It was found that there was a significant improvement in median plasma phenylalanine ($p<0.05$), vitamin B_{12} ($p<0.01$), calcium ($p<0.05$), and albumin ($p<0.05$) concentrations in subjects ($n=13$) over the age of 18 years whilst taking the liquid protein substitute. In the children aged between 7-18 years ($n=21$), median plasma phenylalanine concentrations were maintained on liquid protein substitutes. Their plasma selenium concentrations ($p<0.05$) deteriorated, but calcium ($p<0.05$), albumin ($p<0.01$), hemoglobin ($p<0.01$) and hematocrit ($p<0.01$) significantly improved. This retrospective review would suggest that in adult patients, the long-term use of ready-to-drink protein substitute is associated with better compliance by decreases in blood phenylalanine and increases in markers of nutritional biochemistry. It appeared to help older children and teenagers maintain blood phenylalanine concentrations within target ranges.

Protein substitute dose

There continues to be ongoing debate regarding the dose of protein substitute in people of all ages with PKU. MacDonald et al.[12] documented that higher doses of protein substitute (children 2-10 years take 2 g/kg body weight/day of phenylalanine free amino acids) are associated with better blood phenylalanine control, although there was considerable variability between subjects, which was partly influenced by energy. In addition, it has been demonstrated that when total protein intake from the protein substitute increases, phenylalanine tolerance improves[13,14] and may also be important in optimizing growth. Others have shown that the protein quality may be more important than the total protein intake in improving growth and head circumference[15,16] in PKU. Inversely Prince et al.[7] demonstrated normal growth on relatively low doses of protein substitute intake. However, data suggest that the synthetic nature of the protein substitute may lead to its poor utilization.

Protein substitute timing

There is evidence that some patients take all their protein substitutes in one or two doses daily despite recommendations to the contrary. This is associated with rapid plasma phenylalanine changes, increase in nitrogen excretion, oxidative utilization of amino acids, and urinary losses. It is currently recommended to give protein substitute in three or four doses throughout daytime hours. In a study that manipulated the timing of protein substitute in order to reduce plasma phenylalanine variability, it was found that administering

protein substitute in either three or four equal doses over 14 hours resulted in little difference in overall 24-hour variability[17].

Large neutral amino acids

Large neutral amino acid (LNAA) supplementation was first shown to decrease the influx of phenylalanine into the brain in 1996[18], although they have been used by the John F. Kennedy Institute in Denmark in older patients with PKU since 1985[19]. In rats, single amino acid or a combination of LNAA was reported to lower brain phenylalanine concentrations as early as 1976[20]. It has been suggested that phenylalanine transport from the plasma into the brain is via the neutral amino acid transporter and is driven by a concentration gradient. This neutral amino acid transporter is competitively inhibited by the presence of other LNAA (e.g. tyrosine, tryptophan, leucine, valine, lysine isoleucine, histidine, methionine, threonine and arginine) in the plasma, which should decrease the influx of phenylalanine into the brain. LNAA have also been shown to reduce blood phenylalanine[21] by up to 55%, depending on the dosage used[22]. It has been proposed that there may also be competitive inhibition of phenylalanine with LNAAs in the intestinal mucosa. LNAAs have been shown to have a positive effect on executive function, specifically verbal generativity and cognitive flexibility[21]. For patients already complying with diet and protein substitute, additional LNAA supplementation will have limited benefit[21]. Although a few PKU centers are routinely administering LNAA to adult patients who fail to comply with conventional dietary treatment, long-term studies are needed to examine their efficacy and safety[23].

Glycomacropeptide

New potential protein sources are being explored for protein substitutes. Glycomacropeptide (GMP) is a whey protein (a peptide released by rennet in cheese manufacture) produced during cheese-making. GMP constitutes 15-20% of whey. GMP has elevated amounts of threonine and isoleucine and minimal aromatic amino acids, including phenylalanine, tyrosine and tryptophan. When used as the primary source of protein in PKU, it must be supplemented with leucine, histidine, tryptophan and tyrosine. It contains approximately 2.5-5 mg phenylalanine per g of protein. There is some evidence that GMP, when given to PKU mice, competitively inhibits phenylalanine transport into the brain, and PKU mice show comparable growth and reduced concentrations of plasma and brain phenylalanine concentrations when compared to a conventional amino acid source[24]. Its use is also being considered in low phenylalanine foods[25]. In a further study with 11 subjects with PKU, fasting phenylalanine concentrations were significantly lower with a protein substitute based on GMP compared with amino acid based substitute[26]. A case report in an adult with classical PKU who was given the GMP as a protein substitute replacement for 10 weeks indicated both the safety and acceptability of GMP, and a 13-14% reduction in blood phenylalanine concentrations ($p<0.05$)[27]. Research is needed to evaluate the long-term safety and efficacy of GMP in the nutritional management of PKU.

Research on docosahexaenoic acid (DHA) in PKU

The low phenylalanine diet is devoid of natural dietary sources of n-3 long chain polyunsaturated fatty acids (LC-PUFA), such as eggs, meat, milk or fish. Evidence suggests that children with PKU have reduced concentration of arachidonic acid (AA) and docosahexaenoic acid (DHA) in plasma and membrane phospholipids when compared to controls[28]. A strict low phenylalanine diet is also low in fat, α-linolenic acid and AA, and is devoid of any sources of eicosapentaenoic acid (EPA) and DHA[29]. Studies have shown that neural function in PKU children is improved by high-dose supplementation with n-3 LC-PUFA, as shown by significantly improved visual evoked potential latencies and fine motor skills and coordination, respectively. However, no dose response n-3 LC-PUFA relationship has been established thus far. In a multi-center EU double-blind randomized trial (in at least 5 centers across Europe), the study aims to determine the quantitative DHA requirements for optimal neural function in PKU children. Five different doses of DHA (0-15 mg) will be given to over 100 children (aged 5-13 years) over a six-month period. Biochemical (fatty acid composition of plasma phospholipids, marker of immune function and lipoprotein metabolism) and functional testing (visual evoked potentials, fine motor skills, cognitive

function) will be performed at baseline and after six months. Intake per kg body weight will be related to outcome parameters and thus a possible dose response relationship will be defined. It is hoped this study will define the daily dose of DHA that should be given to children with PKU.

Diet and BH_4

Kuvan ® (Merck Serona), sapropterin dihydrochloride, is the synthetic form of 6R-BH_4, a naturally occurring enzyme cofactor that works in conjunction with the enzyme phenylalanine hydroxylase to metabolize phenylalanine. Since 1999, an increasing number of patients with mild or moderate PKU are reported to be able to decrease their plasma phenylalanine concentrations after BH_4 challenge. In a short-term study of 10 weeks, 45 children were either randomized to treatment with BH_4 or placebo, together with a phenylalanine supplement to measure phenylalanine tolerance in the diet. After the initiation of the phenylalanine powder, in the BH_4 group, the mean increase in phenylalanine tolerance was 21 mg/kg/day[30]. However, so far, there is only limited data about any change in phenylalanine tolerance in patients with PKU on BH_4 long-term. Burlina and Blau[31] reported in a group of 12 BH_4 responsive patients on treatment for 2-7 years that BH_4 allowed a substantial relaxation of the dietary restriction. Daily phenylalanine tolerance increased by 2-3 fold from a mean of 498 mg/daily to 1475 mg/daily. Protein substitute was stopped although some degree of protein restriction was necessary in some patients.

The ideal scenario is that BH_4 is able to maintain excellent blood phenylalanine control without any dietary treatment. However, if BH_4 is used in combination with diet there are many unanswered questions that require addressing. Long-term studies are required to determine nutritional adequacy, growth, blood phenylalanine control during illness, diurnal blood phenylalanine variability, and changes in the quality and variety of foods eaten. Guidance is needed about the amount and type of natural protein that should be consumed before protein substitute is stopped and how best to introduce dietary phenylalanine with BH_4. In addition, little is known about longer-term compliance with BH_4. Managing patient and family expectations when the drug is ineffective or unaffordable is challenging.

Duration of diet therapy

Over the years, the duration of the diet has been the subject of much discussion and policy change. In the 1960s and 1970s, many PKU centers stopped diet as early as four or eight years, when it was argued brain development would be substantially complete. A series of studies showing deterioration in IQ in children under 12 years of age and neurological signs and neuropsychological deficits in problem-solving in young adults has led to the recommendation of diet for life in the UK. There are still limited data on adult neurological functioning in PKU and controversy remains over the ideal blood phenylalanine concentration for individuals older than 12 years of age. Some countries' recommendations are more liberal than others. Some small studies suggest that relaxation of the strict diet in adolescence does not affect non-executive functions if blood phenylalanine concentrations remain <1200 μmol/L whereas others demonstrate deterioration[3].

Will home monitoring of blood phenylalanine improve metabolic control and dietary adherence?

Blood phenylalanine is the main biomarker used for dietary adjustment. It gives an indication of how well patients are doing and can help give 'parents and patients' a peace of mind. Many families take their own blood samples at home and return these to the hospital laboratory for analysis. It usually takes a minimum of two days before a blood phenylalanine level is available and this delay does not help facilitate meaningful interpretation of the relationship between dietary intake and blood phenylalanine concentration. Waiting for the blood results to be reported can also create unnecessary anxiety. In addition, there is evidence from one clinic that a significant number of families (47%) improved their diet just before blood testing[32]. This gives health professionals, caregivers and patients a false picture of overall blood phenylalanine control. Many patients/caregivers consider that home blood phenylalanine monitoring would facilitate better management of PKU through more regular and timely feedback[33], enable patients

and caregivers to understand their blood results in relationship to recent food intake and help overall self-management. The facilitation of more regular blood phenylalanine monitoring is likely to help improve overall adherence and blood phenylalanine control.

Frequency of blood phenylalanine testing: Does it make a difference to overall blood phenylalanine control?

Many countries issue recommendations on the frequency of blood phenylalanine monitoring in PKU. In many clinics, it is advocated that the frequency of blood phenylalanine monitoring decreases with increasing age; this is at a time when dietary adherence is reported to deteriorate. However, there have been no randomized controlled trials to determine the optimal frequency of blood phenylalanine testing and its impact on dietary adherence. The blood test frequency advocated by the UK MRC (1993) working group[33], and adopted by other countries, was based on opinion rather than any formal analysis. In an observational study, it has been shown that more frequent blood phenylalanine monitoring is associated with a greater probability that phenylalanine concentrations decrease. The relationship between test frequency and phenylalanine levels was more pronounced in older children[34]. Lack of information about blood phenylalanine levels will do little to encourage patients to adhere more carefully to their dietary treatment.

Variations in dietary treatment for PKU across Europe and beyond

A global consensus on dietary management is important now that there is an expansion of internationally available dietary products, increased migration of patients from country to country, and universal sharing of information through the internet. Before such a consensus can be achieved, it is important to have an understanding of the differences in dietary treatment across European PKU centers. Representatives from 10 European centers and beyond (Belgium, Denmark, Germany, Italy, Norway, Poland, Spain, the Netherlands, Turkey, and the UK) all provided information about their dietary practices. Dietary phenylalanine was either allocated in total daily amounts where all phenylalanine-containing foods were counted in the diet (n=7 centers), or by phenylalanine exchange systems (n=3), where portion sizes of phenylalanine-containing foods were pre-calculated for a defined amount of phenylalanine. Definitions of 'free foods' (i.e. foods that are so low in phenylalanine that they can be permitted without measurement) varied from minimal content to <25 mg/100 g. In all 10 centers, protein substitute dosage decreased with age from approximately 2-3 g/kg/day in infancy to 1.2-2 g/kg/day by the age of 10 years, and all except one center (Germany) gave 1-1.5 g/kg/day of protein equivalent to patients >10 years of age. Only three centers (Denmark, Italy and Norway) were prescribing large neutral amino acid supplements to their older patients. All 10 centers advocated a normal energy intake[35].

Despite these differences in dietary approach, a further one-year study in the same 10 centers retrospectively examining blood phenylalanine control found that blood phenylalanine concentrations were mainly similar. Therefore, it would appear that there is more than one dietary system capable of achieving acceptable blood phenylalanine control. Thus, it is important to do further work to identify the dietary system to which patients can most easily adhere.

Conclusions

Although it is often quoted that diet is difficult, impacts social eating and severely affects lifestyle, it has rarely been shown in studies that dietary treatment affects normal life or development. There is still much research to be done focusing on improving practical dietary application, adherence, teaching, and support. Generally, diet has developed and improved but any recognition of this is hampered by a lack of intervention trials examining the impact of dietary changes on quality of life and long-term nutritional status. It is likely we will continue to see many changes in the next five years, hopefully all leading to a better outcome for patients.

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