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Chilean Nutrition Management Protocol for Patients With Phenylketonuria

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Abstract

Since neonatal screening and early nutritional treatment began, it has been possible to reverse the neurological damage that phenylketonuria (PKU) causes. Scientific evidence gathered over more than 50 years on the monitoring of individuals with PKU indicates that a phenylalanine level of about 6 mg/dL (360 μmol/L) is ideal and points to the necessity of starting a long-term phenylalanine-restricted diet in which blood phenylalanine level should stay between 2 and 6 mg/dL (120-360 μmol/L). This article aims to establish the general basis for proper monitoring of people with PKU and provide a useful tool for clinicians overseeing treatment. We hope to establish similar criteria throughout Latin America and create a uniform protocol in order to have comparative monitoring results for the region.

Keywords

phenylketonuria, blood phenylalanine level, PHE levels in follow-up.

Introduction

Phenylketonuria (PKU; OMIM 261600) is caused by a defect in the enzyme phenylalanine (PHE) hydroxylase, which is responsible for transforming PHE to tyrosine (TYR). Inheritance is autosomal recessive and recurrence is 25% in each pregnancy. Starting at neonatal diagnosis, PHE restriction is used as a treatment for PKU in order to prevent the neurological sequelae that this disease causes. The Medical Research Council has established that any child with a PHE level of 6 mg/dL (360 μmol/L), normal or decreased TYR, and receiving a normal diet should start a PHE-restricted diet in combination with protein-free PHE substitutes, minerals and essential fatty acids supplementation, and special foods low in protein. Optimal treatment requires diagnosis to be done as soon as possible, ideally in the second week of life (before 1 month of life), strict monitoring throughout life and maintaining a PHE-restricted diet. Additionally, dietary intake must be adjusted to the PHE value that is considered safe for maintaining normal growth and development. Good metabolic control means maintaining blood levels between 2 and 6 mg/dL (120-360 μmol/L) throughout life.[1-7]

The diet prohibits all foods of animal origin because of the high PHE content. Foods such as cereals and most fruits and vegetables should be carefully monitored, and the exact PHE content of each should be known. To provide energy, protein, and TYR, the diet must include PHE-free protein substitutes. Nutritional therapy should be monitored periodically for clinical, biochemical, and nutritional status methods, mainly by observing physiological and pathophysiological changes that lead to increases or decreases in PHE level.

This article aims to establish the general basis for proper monitoring of people with PKU and provide a useful tool for clinicians responsible for treatment. The article is meant to be used as educational material to facilitate clinical monitoring and encourage similar criteria be used across Latin America. In this way, a single protocol could facilitate treatment-monitoring comparisons in the region.

Objectives of Diet Therapy Treatment

The objective is to maintain optimal growth and development and plasma PHE levels within ranges that prevent mental retardation, normal plasma TYR level, and promote anabolism.[8]

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Table 1. Allowed Levels of Phenylalanine for Patients With Phenylketonuria (PKU) by Age.

Age Group	Phenylalanine Level (mg/dL)
Newborn to 2 years old	2-4
>2 years old	2-6
Pregnant patients with PKU	2-6

Metabolic Control Goals

Plasma PHE level keeps blood values between 2 and 6 mg/dL (120-360 μmol/L), which vary according to age (Table 1).[1,6] Plasma TYR level maintains levels between 1.0 and 1.8 mg/dL (55-100 μmol/L). If levels fall below 0.8 mg/dL (<44 μmol/L), TYR intake should be evaluated and, if necessary, PHE-free protein substitutes should be increased or free form supplementation (600-1200 mg/d) should be considered depending on availability and following up 1 month later with acylcarnitines to adjust dose.[9,10]

Plasma PHE Level, Intake Tolerance, and Mutation Type

Classic PKU has plasma PHE above 20 mg/dL (1200 μmol/L) at the time of diagnosis. The plasma PHE level for neonatal screening is greater than 7 mg/dL, with a ratio of PHE/TYR greater than 5. The PHE dietary tolerance until 1 year is between 25 and 45 mg/kg/d (130-330 mg/d). Between 2 and 5 years, the recommended level is below 20 mg/kg/d, maintaining a plasma PHE value less than 5 mg/dL (300 μmol/L). After 5 years of age, less than 12 mg/kg/d of PHE is tolerated, with the goal being to maintain plasma PHE level between 2 and 6 mg/dL (120-360 μmol/L).

Moderate PKU has a plasma PHE level between 15 and 20 mg/dL (900-1200 μmol/L) at diagnosis. The ratio of PHE/TYR is greater than 3. Dietary PHE tolerance until 1 year of life is between 45 and 50 mg/kg/d. Between 2 and 5 years, the recommended level is between 20 and 25 mg/kg/d (350-400 mg/d), maintaining a plasma PHE value less than 5 mg/dL (300 μmol/L). Over 5 years, patients have a PHE dietary tolerance between 12 and 18 mg/kg/d, maintaining plasma PHE level between 2 and 6 mg/dL (120-360 μmol/L).

Mild PKU has PHE plasma level 10 to 15 mg/dL (600-900 μmol/L), with a ratio of PHE/TYR greater than 3. The phenylalanine dietary tolerance up to 1 year is 55 mg/kg/d. Between 2 and 5 years, it is 25 to 50 mg/kg/d (400-600 mg/d), maintaining PHE plasma less than 5 mg/dL (300 μmol/L). Over 5 years, the PHE dietary tolerance is greater than 18 mg/kg/d, maintaining PHE plasma level between 2 and 6 mg/dL (120-360 μmol/L).

Moderate hyperphenylalaninemia or gray area has PHE plasma level between 6 and 10 mg/dL (360-600 μmol/L). The PHE/TYR ratio is greater than 3. Dietary tolerance of PHE in the first year is 70 mg/kg/d. Between 2 and 5 years, it is greater than 50 mg/kg/d, maintaining a plasma PHE value of less than 5 mg/dL (300 μmol/L).

Moderate hyperphenylalaninemia not requiring nutritional treatment has plasma PHE level between 2 and 6 mg/dL (120-360 μmol/L). The PHE level for neonatal screening between 2.5 and 6 mg/dL (151-360 μmol/L). An average PHE/TYR ratio is 3.3 (between 0.8 and 8.25). Normal dietary PHE intake and normal PHE value.

Tetrahydropterin deficiencies have normal or elevated plasma PHE levels. The PHE blood level of neonatal screening between 2 and 35 mg/dL (120-2120 μmol/L). Patients tolerate PHE intake and have variable PHE values. A specific genotype has not been determined. Many of protein deficiencies require BH4 supplementation and neurotransmitter precursors.[6]

Nutritional Therapy at Diagnosis by PHE Level

Nutritional therapy should be started as early as possible, preferably during the second week of life, considering that diagnostic confirmation will take place during the first week of life. Depending on the initial value, PHE intake should be excluded until PHE values attain ranges that do not cause neurological damage. It is important to note that beginning treatment in a timely manner requires coordination between the neonatal screening laboratory, a search of the suspect cases, and a short confirmation period to establish a correct case.[11] On this basis, we recommend:

- If, at diagnosis, the newborn has a PHE value less than 6 mg/dL (360 μmol/L), patient should maintain exclusive breast-feeding, with PHE blood levels checked weekly. If value is greater than 6 mg/dL, patient should begin nutritional treatment, controlling PHE intake.
- When PHE value is between 6 and 10 mg/dL (360-600 μmol/L), treatment should begin in the form of a PHE-restricted diet. As PHE value is not extremely high, 50% of the total volume should be PHE-free formula and 50% breast milk or infant formula. This requires estimating the total volume of liquids, considering the recommendation of 150 mL/kg/d *(recommended dietary intake [RDI])*. Blood PHE value should be measured weekly, and according to the results obtained, PHE intake should be adjusted. If values remain high, the contribution of breast-feeding should be reduced and the volume of PHE-free formula increased. The recommendation is always to provide PHE-free formula first and then place the baby to the breast.
- When initial value of PHE is over 10 mg/dL (600 μmol/L), breast-feeding and/or infant formula should be discontinued immediately. First, determine the total fluid volume (150 mL/kg/d); 100% of the daily volume should be PHE-free formula, which provides all the nutrient necessities for this age group. After 5 to 7 days, if PHE value has dropped below 10 mg/dL, PHE intake is reintroduced through combined breast milk with special formula, providing the lower amount of PHE recommendations (Table 2). It is important to note that

Table 2. Recommended Intake of Phenylalanine (PHE), Tyrosine (TYR), and Protein for Individuals With Phenylketonuria (PKU).

	PHE, mg/d	TYR, mg/d	Protein RDI + 30%, g/kg
Age, months			
0-3	130-430	1000-1300	2.1
3-6	135-400	1400-2100	1.7
6-9	145-370	2500-3000	1.7
9-12	135-330	2500-3000	1.7
Age, years			
1-4	200-320	2800-3500	1.1-1.2
4 to adult	200-1100	4000-6000	1.2-1.5

Abbreviation: RDI, recommended dietary intake.

PHE-free formula is always given before breast milk. The PHE values are tested weekly until PHE is able to stabilize between 2 and 4 mg/dL (120-240 μmol/L).

Calorie intake provides recommendations based on age and sex, keeping a ratio of 150 kcal/g of nonprotein nitrogen. Maltodextrin and vegetable oil, preferably with oils containing essential fatty acids precursors (eg, α-linolenic acid and docosahexaenoic acid [DHA]), can be used to complete 120 to 150 kcal/kg/d and promote anabolism.

Long-Term Nutritional and Metabolic Monitoring

Phenylalanine prescription according to blood PHE levels.

- The PHE levels measured every 7 days, making sure that there is adequate physical growth.
- If plasma PHE level is less than 2 mg/dL (120 μmol/L), the supply of PHE should be increased to 50 mg/d. If PHE is more than 6 mg/dL (360 μmol/L), PHE intake should decrease 30 to 100 mg/d depending on the detected plasma level.
- Each change in diet is followed by an assessment of PHE value every 7 days after a change, and necessary adjustments should be made to the diet in order to maintain PHE values between 2 and 4 mg/dL (120-240 μmol/L) in infants and between 2 and 6 (120-360 μmol/L) in older children.
- For actual PHE intake measurement, a 24-hour dietary recall close to PHE measurement date should be completed by parents or caregivers in order to evaluate PHE requirements according to the metabolic status of the child.
- Between the third and fifth month of life, there is a slowdown in growth, thus PHE contribution should be discreetly decreased and adjusted in each case if PHE value increased without apparent cause. If the child spontaneously stops taking formula during the night, total volume must be distributing during the day.
- At 5 months, pureed fruit (50-150 mL/d) is introduced. It should be noted that delivery time is midmorning and this contribution of PHE not be quantified due to its low PHE level. Fruits low in PHE, such as pears or apples, are suggested.
- At 6 months, solid meals of vegetables begin with PHE contributions between 100 and 120 mg. This amount of PHE should be considered within the total PHE estimated for each child. It is important to teach parents or caregiver how to calculate the daily PHE. Written explanation and examples should be provided if possible, together with a table of the PHE contents of different foods.[12]
- At 8 months, the second solid food meal begins, increasing the contribution of PHE from natural foods such as vegetables, grains, and fruits to about 200 mg/d. The volume of each meal will vary according to gastric tolerance of the child (200-250 mL in average). At least 3 doses of phenylalanine-free protein substitutes should be kept, if possible, these should be divided in more takes in order to promote anabolism. Increasing intake of solid foods involves a reduction in breast milk and/or infant formula. At this age, in addition to the formula indicated, the child must consume 2 meals and 1 snack (preferably midmorning and consisting of natural fruit).
- At 1 year, PHE intake recommendations are set according to plasma level of previously maintained PHE. First, pureed or semipureed foods are introduced. At 15 months, children have molars, thus chopped foods can be provided, and by 18 months, whole foods are offered. The use of low-protein foods, specially formulated for aminoacidopathies, is an excellent tool to increase volume, providing satiety, and promoting diet adherence.

Recommended PHE level during times of physiological stress.

- Vaccines should be applied when PHE value is low or equal to 2 mg/dL (<120 μmol/L), as these induce increased plasma level for protein catabolism. If the value of PHE is above 2 mg/dL, PHE intake should be reduced between 10% and 25% (depending on plasma value) and reevaluated after 1 week. If, after 1 week, PHE values have dropped below 2 mg/dL, vaccination should proceed. Regular intake of PHE must be reset 72 hours postvaccination, as long as the child is without fever, if not wait until the fever is gone.
- In the presence of infectious conditions or surgeries, a reduction in the intake of PHE by 15% to 25% is suggested since PHE level tends to increase regardless of diet. Energy intake should increase by 10% over normal intake (from maltose dextrin, vegetable oil, etc.) to prevent catabolism. An adequate level of hydration and electrolyte balance should be maintained. Oral rehydration salts can be used where appropriate.
- Keep recommended intake of PHE-free formula at all times; if there is less tolerance, reduce volumes no greater than 50 to 100 mL/h.

Protein recommendations. Natural protein intake is inadequate to maintain PHE values between 2 and 6 mg/dL, and foods of animal origin are prohibited, thus it is not possible to maintain adequate growth through natural foods only. Thus, it is mandatory to provide a PHE-free formula, which provides the necessary amounts of amino acids to maintain normal growth, and supplies the appropriate intake of vitamins and minerals. We recommend:

- The special PHE-free formula is the only source of protein of high biological value for children with classic PKU. To determine the amount of PHE-free formula to be delivered each the day, calculate the amount of protein according to the 2007 World Health Organization recommendations by age, sex, and weight and by adding 30% extra for a synthetic diet (Table 2).[13,14]
- At the beginning of treatment, less than 50% of total protein can come from PHE-free formula. The nutritional needs of this period, which is characterized by rapid growth, require that patients also receive breast milk or infant formula. Subsequently, protein intake from PHE-free formulas increases to 70% or 80%, becoming the only source of protein of high biological value. There is a wide variety of PHE-free products that differ in protein levels and can be consumed in amounts according to the age and PKU physiological stage. Products have different forms—powders, "ready-to-drink" liquids, and bars in order to improve intake adherence throughout life.[2]
- Currently, various products have been developed such as glycomacropeptide, a product that delivers intact natural proteins from whey, has excellent biological value and contains small amounts of PHE. Its use is recommended to improve both diet adherence and protein quality[15]; nevertheless, more evidence related to its effectiveness is needed.
- The PHE-free formula should be distributed evenly throughout the day and in similar quantities to ensure better absorption and stability of PHE plasma level. At the start of treatment, frequency will be every 3 hours (8 servings/day) and, subsequently, decreasing in the preschool stage 3 to 4 times a day and 3 servings/day in the adolescent stage. The recommendation is to keep as many servings as possible.
- Protein requirements increase during periods of rapid growth and physiological stress, needs that are satisfied by increasing the volume of PHE-free special formula.[1,2,6]

Calorie recommendations. Energy needs are set according to RDI, by sex and nutritional status, in order to maintain growth and development within normal ranges. Due to natural food restrictions and the contribution of PHE-free formula, we recommend the following:

- In children less than 12 months of age, 100 to 120 kcal/kg/d should be provided. If complete energy supply is not achieved with PHE-free formula, a caloric supplement (maltose dextrin) and/or vegetable oils (canola = α-linolenic acid or fish oil = eicosapentaenoic acid [EPA]/DHA) are recommended. Starting at 1 year, energy recommendations should be based on RDI, adjusted for nutritional status. At least 150 nonprotein kcal/g of nitrogen is recommended.
- Inadequate intake of energy can produce stunted growth and weight loss, among other complications. Weight loss is a catabolic process thus may induce an endogenous increase in plasma levels of PHE.

Low-protein food or low-protein–modified food products have been created, which are an excellent source of energy and provide satiety, but care must be taken in the quantities consumed daily, as they may increase risk of overweight or obesity if intake is not controlled. These products that include bread and pasta are prepared with wheat starch and other grains, are very low in PHE, and have allowed the diet of PKU children to resemble that of a child without PKU.

Liquid recommendations.

- In the first months of life, 150 mL/kg/d is recommended, corresponding to 1.5 mL by ingested calorie. In children and adults, 1 mL per calorie ingested is calculated.
- When there is an increase in body temperature, vomiting, or diarrhea, fluid requirements are increased according to the degree of temperature change.

Vitamin and mineral supplementation. Starting at the first month, in countries or regions at latitudes below 35° (southern Chile and Argentina), should include mandatory supplementation with 400 IU/d of vitamin D. If a daily dose is not consumed, give 2 to 3 doses of 100 000 IU during the first year of life.[16]

- Premature and/or low-birth-weight children should be supplemented with iron (2 mg/kg/d).[17]
- In the fourth month of life for breast-fed children, iron supplementation should start providing 1 mg/kg/d to prevent iron deficiency anemia.
- Supplementing with 5 mg/d of zinc between the fourth month and the first year and up to 3 years with 10 mg/d and then 15 to 20 mg/d.
- At 12 months, if calcium intake is low, 400 mg/d of calcium is recommended. At 10 years, between 800 and 1000 mg/d is suggested, as at this stage one-third of adult bone mass is deposited. Individuals with PKU have been observed to have lower bone densitometry compared to controls. Measurement of bone mineral density can be used as a complement to suggested supplementation.[18]
- From treatment start, supplementation with omega 3 fatty acids is recommended, as it is important in retina and central nervous system structure formation, which favors the development of visual, motor, and cognitive skills.

Table 3. Phenylalanine (PHE) Monitoring Frequency for Patients With Phenylketonuria (PKU).

Age	PHE Monitoring Frequency
<12 months or breast-feeding	Every 7 days
1 to 2 years	Every 15 days
> 2 years	Monthly, depending on adherence

Between 1% and 3% of total calories, soybean oil, canola (α-linolenic acid, the precursor of DHA fatty acids), or fish oil containing EPA and DHA is recommended.[19]

Monitoring PHE and TYR Values

Dietary manipulation requires frequent monitoring of blood PHE, with the aim of keeping levels in safe ranges and preventing neurological damage but also enough to achieve growth with PHE in normal ranges. Together, PHE intake and PHE blood value must be adapted based on growth, physiological state, disease, and comorbidity. It is also important to monitor TYR value. We recommend:

- The Weekly PHE blood level checking in the first year of life is highly recommended with values between 2 and 4 mg/dL (120-240 μmol/L). In this period, many factors interfere with PHE level, such as physiological (growth, teething, breast-feeding, etc) and pathophysiological (infections and frequent vaccinations). A value less than 0.5 mg/dL (30 μmol/L) is considered as levels risky for affecting growth. If a child has values between 1 and 2 mg/dL (60-120 μmol/L) and has high PHE intake, they are considered low risk.[6,20] Between 1 and 2 years, testing PHE level every 15 days is recommended. After 2 years, frequency depends on adherence to the monthly diet (Table 3).
- The TYR value during the first year should be measured every 3 months in conjunction with PHE level, then semiannually or once a year, depending on child development. If there is growth arrest, TYR should be evaluated independent of age. Values between 1.0 and 1.8 mg/dL (55-100 μmol/L) are recommended.
- A profile of amino acids, transferrin, complete blood count, albumin, ferritin, 25-OH vitamin D, essential fatty acids, trace minerals (zinc, copper, and selenium), vitamin A, and folic acid. Between 6 and 8 years, a dual energy X-ray absorptiometry is recommended to evaluate bone health.

Education. Diet for PKU children is based on vegetables and fruits and small portions of cereals. Thus, nutrition education focuses on establishing good habits early in life and providing a varied diet, with different flavors and textures. We recommend creating written material to support education and improve adherence to nutritional therapy. Families should be taught to select foods with a low PHE contribution and avoid bad eating habits that, in the future, could affect adherence to nutritional therapy. It is important to note that starting at 10 years of age, education should include the concept of self-control, that is, learning to prepare the special formula, knowing how to calculate the PHE content of foods, to choose foods low in PHE, and maintain healthy habits as physical exercises.

Discussion

This work represents an effort to share the experience developed by a Chilean group with more than 25 years of experience in the treatment of more than 300 patients with PKU. There are similar criteria published by Singh and colleagues[21] regarding nutrition management guidelines for PKU, specifically in relation to metabolic control goals, critical nutrients intake, and parameters to start treatment.

The management guidelines for PKU recommend maintaining PHE levels between 2 and 6 mg/dL throughout life.[21] In Chile, we maintain the same level, except in the first 2 years of life, where we recommend a maximum level of 4 mg/dL. A lower level allows greater control over catabolism increases in PHE associated with vaccinations and intercurrent infections, both frequent occurrences during this period.

In our country, special formula intake represents 80% of the protein intake in children over 1 year of age. Through various efforts of our working group, PHE-free formula is now distributed by the ministry of health, up to 25 years of age. Certain special formulas generate high rejection in patients, due to low palatability. This has the consequence that patients do not consume 100% of the nutritional indication given as a special formula. Therefore, unlike the guidelines published by Singh and colleagues, we supplement children with calcium, iron, and zinc, to comply with micronutrient recommendations.[21]

In recent years, it has been shown that PKU treatment should be for life, and new nutrition management guidelines, emphasize this, exposing the neurological changes that occur in older children and adults without treatment.[21] Therefore in Chile, we have developed various strategies to promote self-care and educate patients and families to achieve compliance with lifelong treatment; this includes the creation of educational workshops for adolescents and adults, developing applications for patients and parents to access PHE levels and for calculating daily PHE. In addition, with the extension of the national program of special formulas provided by the ministry of health, it was possible to reengage the majority of patients older than 18 years who had left treatment.

Conclusion

A PHE-restricted diet, plus the use of special PHE-free formula and micronutrient supplementation, is effective in preventing the nerve damage caused by high levels of PHE in persons living with PKU. To achieve good metabolic control and prevent neurological disorders, PHE levels should be kept between 2 and 6 mg/dL throughout life.

Our goal was to present nutritional management guidelines based on our 25 years of experience in Chile and the current

literature. Our guidelines can be used as educational materials to facilitate clinical monitoring. We encourage similar criteria to be used across Latin America.

Declaration of Conflicting Interests

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