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Review Article

Phenylketonuria, Diagnosis and Medical Nutrition Treatment

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Abstract

Although consanguineous marriages to be widely seen in countries like Turkey prevalence more often, globally the overall prevalence of 100.000 newborns determined with the phenylketonuria as 6.002 (PKU), it is a rare, autosomal recessive genetic disease characterized by the disruption of the conversion of phenylalanine to tyrosine as a result of insufficient activity of the hepatic enzyme phenylalanine hydroxylase. As a result of the inability to metabolize phenylalanine, plasma phenylalanine levels increase 20-30 times the normal and reach the brain by crossing the blood brain barrier. Accordingly, progressive and irreversible cognitive disorders, mental retardation, microcephaly, neuromotor disorders, autism, seizures, psychiatric symptoms, eczematous rashes, mildew odor in urine, light hair and skin color can be seen in patients. Early diagnosis is of great importance in order to prevent all these complications. The blood sample taken from the heel in the first 24 - 48 hours of life takes us to a conclusion through the Guthrie test. Natural protein (hence phenylalanine) restriction in the diet and used protein substitutes form the basis of PKU management in the diagnosed patient. In addition, there is use of special manufactured low protein foods which provide energy to the diet and increase dietary compliance in patients. Although breast milk provides natural protein to the baby's diet and problems may develop in breastfeeding, breast milk intake should be encouraged by taking into account the beneficial components of breast milk and the mother-baby bond. In addition, it is important that the patient continues the treatment for life. Keeping blood phenylalanine within the specified range (120 to 360 µmol/L) during this treatment has been associated with optimal clinical outcomes. In order to increase the quality of life in PKU, it is inevitable to be diagnosed from the first days of life and to require lifelong medical nutrition therapy.

Keywords: *Phenylketonuria; Phenylalanine; Diagnosis; Nutrition Therapy*

Introduction

Phenylalanine hydroxylase is a gene on chromosome 12 (region q22-24.1), consisting of 13 exons and 12 introns, with a genetic data of 100 kb [1]. Phenylketonuria (PKU) is the result of inadequate activity of the hepatic enzyme L-phenylalanine-4-hydroxylase. It is a rare genetic disorder characterized by the disruption of its conversion to tyrosine [2,3]. In PKU, which is the most common congenital metabolism disease on a global scale, the plasma phenylalanine level increases 20 - 30 times the normal level as a result of phenylalanine not metabolized [4], furthermore, some of the accumulated phenylalanine is due to phenylketones (phenylacetic acid, phenylacetic acid, phenylpyruvic acid) are converted into urine (phenylketonuria) and cause a musty odor in the urine [5]. Excessive plasma phenylalanine results in phenylalanine crossing the blood-brain barrier in the central nervous system, where protein, myelin, serotonin, dopamine and norepinephrine. It prevents the production of neurotransmitters. The transport of valine, lysine, leucine, isoleucine, tyrosine, and tryptophan, which are required at the receptor level in the blood-brain barrier, which are known as L-amino acids, occurs in a racing manner and the high phenylalanine inhibits this. Phenylalanine, which becomes a toxic metabolite, is characterized by progressive and irreversible cognitive impairment [2,5,6]. In patients with PKU, a delay in starting treatment every four weeks results in a decrease in intelligence quo-

tient (IQ) of about four points [1]. In addition, these patients may exhibit mental retardation, microcephaly, neuromotor disorders, autism, seizures, psychiatric symptoms, eczematous eruptions, a musty odor in urine, fair hair, and skin color [5,7]. Since high blood phenylalanine concentrations are strongly associated with neuroscience outcome, Treatments are aimed at reducing blood Phe concentrations [7].

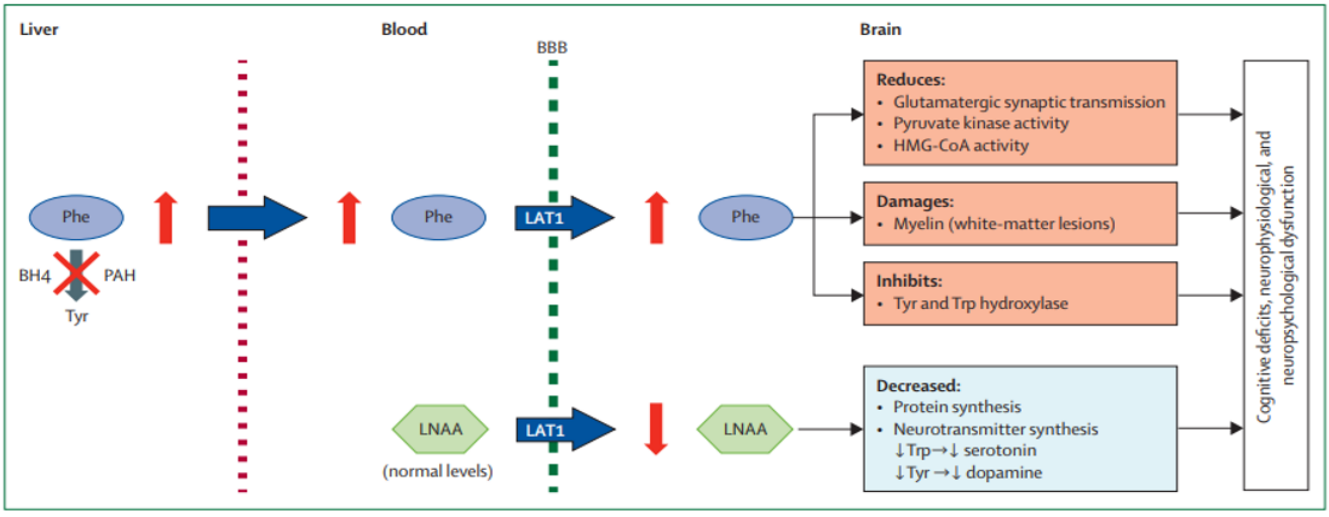

Figure 1: *Pathophysiology of PKU [1].*

Epidemiology

Phenylketonuria is an autosomal recessive phenylalanine metabolism disorder that causes severe cognitive impairment due to the accumulation of Phe in the brain [3,8-10]. The prevalence of PKU worldwide shows heterogeneity. It has been emphasized that this may be due to differences in factors affecting the disease such as consanguineous marriages, genetic reserves, study performance, diagnostic tests, border points and sample sizes [11]. In addition, the incidence of PKU also varies between ethnic groups and geographical regions. The prevalence is 1/10,000 in the United States (USA), 1/22,000 in Canada, 1/200,00 in Finland, 1/4,500 [10] in Ireland, and 1 in 34,000 - 40,000 live births in Taiwan is assumed [12].

Held with 119,152,905 participants between the years 1964 - 2017 and systematic review and meta-analysis of a total of 53 were included in the study, the highest prevalence in Turkey with 38.13 per 100,000 newborns have been reported in Thailand, with the lowest prevalence is still 100,000 newborn 0.3. In addition, according to 46 studies included for the aggregate prevalence estimate, the overall prevalence worldwide was 6,002 per 100,000 newborns [11].

Diagnosis

Until the 1960s, most children born with PKU spent their lives in a mentally handicapped state, usually under an institutional roof, in care. The foundations for early detection and modern management of PKU were laid in three key stages: In 1934, Asbjørn Følling detected ketone bodies in the urine of individuals and identified high levels of phenylalanine (hyperphenylalaninemia) in the blood as the underlying cause of neuropsychological defects; In 1953, Horst Bickel first introduced a low phenylalanine diet to treat a child with PKU and reported the effectiveness of this diet; Finally, in the 1960s, Robert Guthrie developed a simple diagnostic test suitable for mass screening of hyperphenylalaninemia in large populations (Guthrie test). This development has enabled PKU to take the first place in the diagnosis of disease by newborn screening [7,8].

PKU Screening Program began in 1987 and 1993 across the whole of Turkey has become PKU screening is done. The National Neonatal Screening Program was initiated on 25.12.2006 with the addition of Congenital Hypothyroidism screening to PKU screening. PKU Within the scope of the Screening Program, a Newborn Screening Test is applied to each newborn baby approximately 24 - 48 hours after the first feeding. Here, heel blood is taken from babies after their birth, and then heel blood samples are sent to the Newborn Screening Laboratories as soon as possible. Babies who seem suspicious for PKU should be directed to the relevant clinics in terms of diagnosis and results, and it is also important to follow up these patients [13].

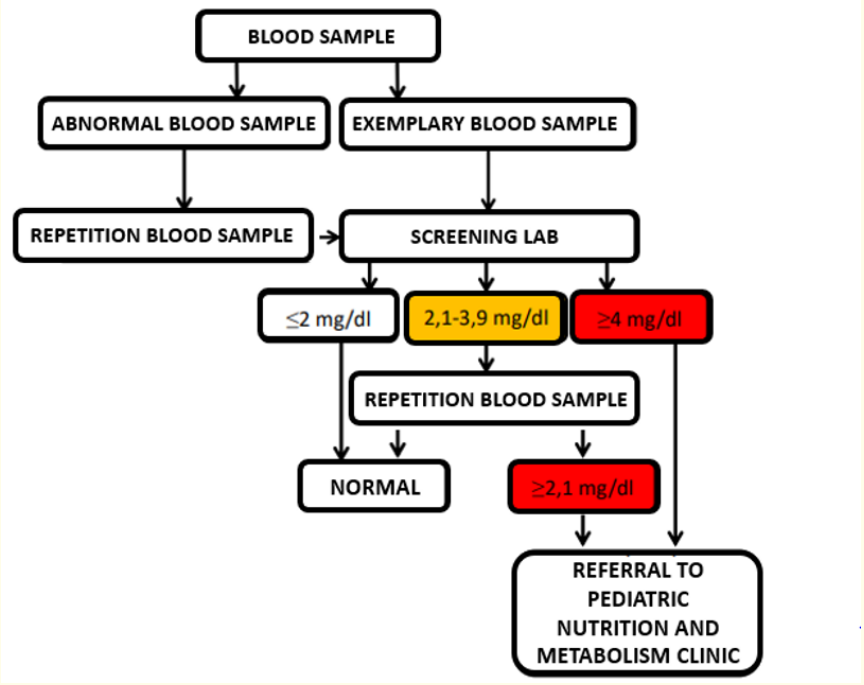

Figure 2: *The PK results in Turkey evaluation [13].*

Disease severity, classic or severe PKU (1,200 µmol/L; ≥ 20 mg/dL), mild to moderate PKU (600 - 1,200 µmol/L; 10 - 20 mg/dL), or mild hyperphenylalaninemia, depending on the blood phenylalanine level at the time of diagnosis (360 - 600 µmol/L; 6 - 10 mg/dL). Non-PKU hyperphenylalaninemia is a condition in which the plasma phenylalanine level is below 6 - 10 mg/dL. Finally, BH4-responsive hyperphenylalaninemia, hyperphenylalaninemia cases with plasma phenylalanine level above 360 µmol/L are responsive to the phenylalanine hydroxylase enzyme Tetrabiopterin (BH4). Treatment should ensure safe Phe blood concentrations (< 360 µmol/L for < 12 years of age, < 600 µmol/L for 12 years of age, < 240 µmol/L during pregnancy) [9,14]. Untreated PKU during pregnancy as maternal PKU is known and can cause malformations in offspring, including low birth weight, microcephaly, congenital heart defects and developmental retardation. The biggest challenge in maternal PKU, but also the key to achieving metabolic control, is the adequate consumption of Phe-free amino acid formula. Also, given the increased protein, vitamin and mineral requirement during pregnancy, the amino acid formula will provide support in meeting the requirements [15,19].

Treatment

There are more than one treatment approach in PKU. Independent of the mechanism of central nervous system damage, a meta-analysis of a large set of published data revealed that retention of blood Phe between 120 and 360 µmol/L is associated with optimal clinical outcome. Therefore, keeping blood Phe within this range should be the primary goal of all treatment modalities [17].

Medical nutrition treatment

Dietary management in medical nutrition therapy is basically based on three principles:

1) Preventing excessive accumulation of phenylalanine in the blood (and therefore in the brain) by strict control of natural protein/phenylalanine intake.
2) Replacing the natural protein removed from the diet with a safe or non-phenylalanine protein called synthetic protein, amino acid mixture/supplement, or protein substitute (Not all protein substitutes contain phenylalanine or are very low in phenylalanine).
3) Achieving normal growth and normal nutritional status (This is achieved by ensuring a balanced intake of all nutrients and energy in the diet. Vitamin and mineral supplements are either added to protein substitutes or given as a separate supplement.

Immediate initiation of a lifetime protein-restricted diet with an amino acid mixture substitution that does not contain phenylalanine in babies diagnosed as a result of neonatal screening will result in normal cognitive development [18].

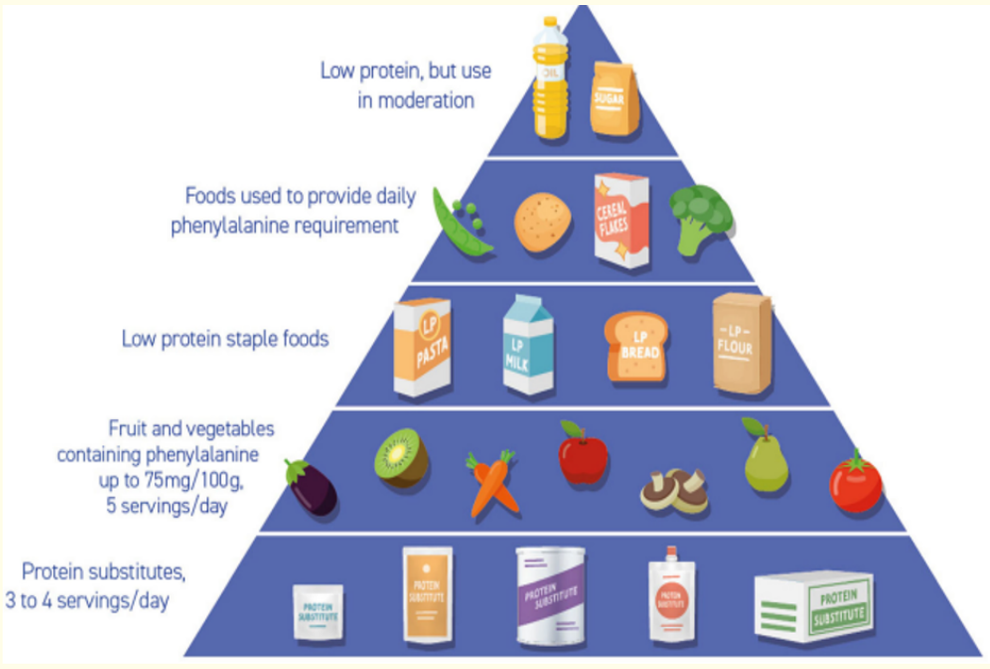

Figure 3: *Nutrition pyramid for PKU [3].*

Restricted diet of phenylalanine

Dietary phenylalanine restriction is the cornerstone of PKU management [8,19]. Usually, this restriction begins immediately after confirmation of neonatal hyperphenylalaninemia [8]. The goal with dietary restriction is to keep blood Phe concentrations within defined targets, within limits (120--360 μmol/L or 2 - 6 mg/dL) [19]. Accumulating evidence; It shows that adult individuals who are incompatible with treatment and have hyperphenylalaninemia may develop neuropsychological and psychosocial problems, these symptoms improve after restarting the restricted phenylalanine diet, and the need for a lifetime low phenylalanine diet [20].

Natural protein or phenylalanine in the diet limits regular intake to 25% or less to keep blood phenylalanine concentrations within target ranges under the European PKU Directives [3]. All high-protein foods should be avoided in this context: meat, chicken, fish, eggs, animal milk. cheese obtained (cow, goat, sheep); snack, seeds, quinoa, wheat, oats, rye, barley; foods made from Quorn, a meat substitute made from mushroom-derived protein; soy, tempeh, legumes, lentils; plant algae such as gelatin and spirulina; aspartame [3,8].

For patients w ith PKU, the Phe requirement refers to the Phe uptake required for protein synthesis and growth. Phe tolerance is affected by many factors such as *in vivo* Phe hydroxylation rate, net protein catabolism, non-protein energy ratio, age, gender, growth, pregnancy, target blood Phe concentration, BH4 treatment [21]. Dietary Phe tolerance in patients with classical PKU varies by age. For example, an infant (0 - 6 months old) with PKU can tolerate 20 - 70 mg Phe/kg/day (0.4 - 1.4 g/kg/

day of natural protein), while an older child (> 5 years of age) < 20 mg Phe/kg/day (0.4 g/kg/day natural protein) can be tolerated. A typical adult with PKU can tolerate 350 - 1200 mg of Phe, equivalent to 7 - 24g of natural protein per day [17]. In Phe deficiency, aciduria, anorexia, weakness, alopecia, perianal rash, insufficient growth and even death in preschool children can occur. It is possible that young children, in particular, are at risk of Phe deficiency if control of blood phenylalanine is excellent but most diets reject the source of phenylalanine due to feeding difficulties. There is a risk of Phe insufficiency in maternal PKU. Especially in the third trimester period, the fetal liver metabolizes maternal phenylalanine and fetal growth increases the Phe requirement [21].

Although Phe/protein intake varies according to individual tolerances, it can be calculated in grams of protein or milligrams of Phe per day. There are five methods for calculating Phe uptake. 1) Phe exchange system (e.g. 50, 25, 20 mg phenylalanine), 2) One g protein exchange, 3) 1g protein change (but using phenylalanine analysis of fruits and vegetables and calculating the weight that yields 50 mg of phenylalanine), 4) Paper lists/applications listing the Phe content, 5) Paper lists/applications listing the protein content of foods [3].

Food groups	Examples of low protein foods that can be eaten without calculation or restrictions on a low phenylalanine diet
Fruits and vegetables	≤ 75 mg/100g Fruits and vegetables containing Phe. The exception to this rule is potatoes that are calculated and measured within the Phe exchange system.
Fats	Butter, margarine, ghee, and vegetable oils. generally, ≤ 1g/100g protein any type of fat containing fat can be given in the diet without calculating the Phe/protein content
Starches	≤0,5 g/100g protein-containing cassava flour, arrowroot starch, sago, tapioca, and cornstarch (Phe its content ≤ 25 mg/100g).
Vegan cheese	Protein its content ≤ 0.5 g/100g (or ≤ 25 mg phenylalanine/100g) Any vegan cheese containing phenylalanine/protein can be given in the diet without calculating the protein content.; > 0.5g/100g (or > 25 mg phenylalanine/100g) if it contains phenylalanine/natural protein must be measured/calculated within the permit.
Candies	≤ 0.5g/100g protein containing sugar, glucose, jam, honey, marmalade, golden syrup, maple syrup, fruit purees, ice cream candies and desserts (phenylalanine its content ≤ 25 mg/100g)
Vegetarian jelly/ agar agar (non-gelatin)	Jelly/agar protein ≤ 0.5g/100g (or phenylalanine ≤ 25 mg/100g) can be given without dietary restrictions. Protein its content > 0,5g/100g (> 25 mg phenylalanine/100 g if it contains), Should be measured/calculated in the phenylalanine/natural protein allowance.
Special low protein products	Low protein breads, flour mixes, pizzas, pastas, biscuits and egg substitutes are available. Special low protein products, if all ingredients are free, e.g. food starch and fat can be given without restriction in the diet. If they contain protein-containing ingredients and > 25 mg phenylalanine/100 g phenylalanine must be calculated in the diet if they contain.
Herbs/spices	All herbs, spices and seasonings can be included in the diet without calculating phenylalanine, as the amount used in cooking is very small.
Beverages	Water, lemonade, cola drinks, fruit juice, black tea, fruit tea, green tea, coffee, tonic, soda and mineral water are allowed on the condition that they do not contain aspartame.
Special milk with low protein/low Phe	Within 24 hours at the consumed volume > 25 mg Any low protein specific milk substitutes that provide total phenylalanine intake should be taken into account when calculating phenylalanine. Total intake of low protein milk substitutes phenylalanine within 24 hours ≤ 25 mg If it provides phenylalanine/24 hours, it can be given without restriction.
Herbal milks	> 0.1g/100 ml protein Any plant milk containing (e.g. coconut, rice, almond) must be calculated/measured in the diet.
Others	Food essences and food coloring are used in small quantities and can be given without restrictions.

Table 1: *Examples of low protein foods that can be eaten on a low phenylalanine diet without calculation or restrictions [3].*

Although all fruits and vegetables containing Phe ≤ 75 mg/100g contribute small amounts of daily phenylalanine, this is generally not enough to alter blood phenylalanine control. These fruit and vegetable sources are not included in the daily calculation of phenylalanine and are given without restriction [3].

Fruits		
Fresh, frozen or canned syrup/molasses (≤ 75 mg phenylalanine /100g)		
Apple	Kiwi	Pomegranate
Apricot	Lime	Prickly fig
Banana	Lemon	Dried plum
Blueberries	Pineapple	Quince
Blackberries	Ginger	Raisins
Currant	Banana (type of plantain)	Raspberry
Blueberries	Mandarin	Red currant
Tangerine (Clementina)	Mango	Polished candied cherries
Cherry	Melon	Satsuma (small orange)
Cranberry	Medlar	Trabzon Persimmon
Dried currant	Mulberry	Star fruit
Damson plum	Nectarine	Strawberry
gooseberry	Peach	Watermelon
Grapefruit	Pear	Mixed fruit peels
Grape	Golden strawberry	Dragon fruit
Orange	Olive	Raisins
Plum	Mandarin	Green plum
Vegetables		
Fresh, frozen, or canned vegetables (≤75 mg phenylalanine /100g)		
Avocado	Chicory	Parsnips
Artichoke	Fennel	Pepper
Eggplant	Pickled Gherkins	Radish
Beans	Gourd	Sapphire
Beet root	Mighty pomegranate	Fresh onion
Cabbage	Chinese cabbage	Pumpkin: acorns
Carrot	Okra	Turnip
Capers	Leek	Sweet potato
Celery	Lettuce	Tomato
Celery root	Zucchini	Tomato Puree
Chayote squash	Mooli (Japanese radish)	Radish-turnip
Chicory-sunflower	Mustard and cress	Watercress
Pumpkin	Onion	Chestnut
Cucumber	Parsley and all herbs	Garlic

Table 2: *≤ 75 mg phenylalanine/100 g3 containing Fruits and vegetables.*

Vegetables and fruits with a Phe content of 75 - 99 mg/100g	Fig, asparagus, bamboo shoots, bean sprouts, broccoli, brussel sprouts, cauliflower, sweet peas, palm tree sap For 1 Phe change, a standard portion size of 60 g is used.
Vegetables and fruits with Phe content > 100 mg/100g	Passion fruit, broad beans, chestnuts, corncob, kale, peas, pyramid cauliflower (romanesco), arugula, spinach, corn kernels, vine leaves, sweet potatoes, sweet potato fries The Phe content is used to determine the amount of 1 Phe change.
Potato	All potato and potato products
Vegetable chips	All vegetable chips (except cassava)

Table 3: *> 75 mg phenylalanine/100g containing fruits and vegetables [22].*

It was investigated whether consumption of free fruits and vegetables containing less than 75 mg Phe per 100 g affects metabolic control in children with PKU. A two-week crossover study was conducted on conventional therapy (taking into account protein from fruits and vegetables) and free fruit and vegetable consumption. Protein-free amino acid mixtures were administered 3 doses/day and morning fasting blood Phe values were measured. Although total Phe intake increased by an average of 58 mg per day during 2 weeks of free fruit and vegetable consumption, blood Phe concentrations were unchanged. In other words, free fruit and vegetable consumption for two weeks does not impair metabolic control in PKU patients. While it is common practice to restrict fruits and vegetables on the PKU diet in many European countries, this may not be necessary. In addition, fruits and vegetables contain less protein and provide additional advantages in terms of providing vitamins and dietary fiber [18].

Aspartame

Aspartame (E951) is an artificial sweetener and 56% is converted into free phenylalanine. For this reason, Phe should not be included in a restricted diet. Aspartame, it can be added to soft drinks, chewing gum, sweets, jelly and table sweeteners. The European Commission 1129/2011 publishes maximum safe levels of aspartame that can be added to individual food and beverage categories. Aspartame can be added to some drugs. Care should be taken to read the label and package insert. Neotame contains aspartame, but the production of phenylalanine is limited by its inability to break the peptide bond between aspartic acid and phenylalanine, thus reducing the production of phenylalanine. This sweetener is safe in PKU, but it is more expensive and therefore less used by the industry. Acesulfame K, saccharin, steviol glycosides, sucralose, fructose, sucrose, maltodextrin, mannitol, sorbitol and xylitol are safe sweeteners for PKU [3].

Kefir

Kefir is an unnatural fermentative beverage produced from milk and it is known that it was the first in history to be found in the Caucasus Mountains in Russia. The benefits of kefir come from combinations of lactic acid, carbon dioxide, alcohol ethyl and aromatic during the fermentation process. PKU patients cannot consume kefir because it contains high amounts of protein. In a study aiming to develop a highly nutritious and acceptable analogue kefir drink for these patients, kefir was produced in 17 different formulations. One of them is enriched with 3% glycomacropeptide. Said beverage; Milk permeate contains cream powder and glycomacropeptide as a protein source, starter trans glutaminase enzyme as a fermentation source, dough stabilizer and modified corn starch as a texture builder, salt and water. This sample had a higher percentage of protein, Phe, salt, dry matter and a lower calculated pH and alcohol compared to the other 16 samples without glycomacropeptides. This study showed that the analogue kefir has low levels of phenylalanine (30.40 mg/100g) and may be beneficial for patients with PKU in this regard [24] (Full-fat kefir 150 mg Phe/100) and dairy products containing small amounts of Phe can be produced commercially [24].

Spices

Determination of Phe content in foods is important for individuals with PKU who receive limited Phe for medical nutrition treatments. It is common to use spices to increase the taste of the food/food and to make it more palatable. Although the amount of spices added to meals seems negligible, these amounts can become important for individuals with PKU who experience fluctuations in blood Phe concentrations. Turkey's spice samples collected from different regions, in a study carried out to determine the total Phe amount of 12 different spices sample (rosemary, basil, black pepper, clove, thyme, caraway, mint, paprika, sumac, cinnamon, ginger, turmeric) Turkey. It was obtained from herbalists located in 7 different provinces (Adana, Ankara, Bursa, Gaziantep, Konya, Sakarya and Trabzon) in 5 different

regions. The amount of phenylalanine in the spices has been determined in a wide range of measures such as 42.42 - 3174.35 mg/100g. In addition, Phe amounts in spice samples in Trabzon were found to be higher than other provinces. It was emphasized that the differences in the content of phenylalanine in the spice types may have been caused by the spreading of the species in Iran and Georgia to the spices produced in Trabzon by spreading to the environment. As a result of the study, it has been reported that there are visible regional differences in the Phe contents of some spices and conscious consumption of spices can be beneficial in the regulation of blood Phe concentrations of individuals with PKU [25].

Protein substitutions

Lifetime dietary management of PKU includes supplementation with protein substitutes, which are usually amino acids without phenylalanine, in addition to severely restricting phenylalanine [26,27]. Phenylalanine-free protein substitution is the primary source of protein in PKU patients treated with a low Phe diet only. These are predominantly based on L-amino acids without phenylalanine [28].

Protein substitutes; available as non-phenylalanine amino acid mixtures, glycomacropeptide-based protein substitutes and major neutral amino acids. The number of substituents present in each country protein 30 (Turkey) 105 (Germany) ranged. Turkey substitutions in proteins, amino acid mixtures and LNAA Pressure Liquid counts were 30, 29, 0 and 1. The nutritional composition of protein substitutes is regulated by European legislation 'Foods for Special Medical Purposes' (Commission Directive 1999/21/EC of 25 March 1999; as amended by Directive 2006/141/EC). In addition, nutrients that can be used in food production for specific medical purposes are summarized in the legislation: Commission Regulation (EC) No. 953/2009. In addition, all 'Food for Special Medical Purposes' must comply with the European Food Information Consumers Regulation 1169/2011 and Regulation 609/2013 [27].

Providing adequate dose of protein substitution based on amino acid supplements that do not contain phenylalanine; It is useful in promoting normal growth and development, preventing protein deficiency, providing a source of tyrosine, eliminating micronutrient deficiencies, optimizing blood Phe levels [3,27,28]. Protein substitutes are estimated to provide 52% to 80% of total protein intake [28].

Protein substitutes, instead of once or twice a day, it is recommended to be given in small and frequent doses, evenly 3 - 4 times a day, and to be consumed with a natural protein and carbohydrate source. Protein substitutes, it is in the form of amino acid powders, capsules, tablets, bars and liquids and may contain additional carbohydrates, fat, vitamins and minerals. General types and properties of protein substitutes are summarized in table 4. Patients may have problems adjusting to protein substitutes. It is important to select age and nutritionally appropriate products [3].

Baby protein powder (dust)	The powdered infant formula, which does not contain phenylalanine, has a similar nutritional composition to the normal formula used in babies without PKU.
Baby protein shakes	The liquid infant formula, which does not contain phenylalanine, has a similar nutritional composition to the normal formula used in babies without PKU.
Dust protein powder in milk cuts	Powdered amino acids (thickened) that do not contain phenylalanine, used in weaning. The semi-solid consistency can be adjusted to suit the developmental age of the older baby/toddler.
Half solid protein chunks in milk cut	Ready-to-use semi-solid protein substitutes for older babies/toddlers containing amino acids mixed with juice puree
Salt protein supplements	Powdered amino acid supplements (with or without vitamins, minerals, long-chain fatty acids, carbohydrates and fats) are mixed with water to make a semi-solid (spoonable consistency) or beverage. They are suitable for varying age groups and come in different flavors.
Liquid protein supplements	Ready-to-use liquid protein substitutes (usually with the addition of vitamins, minerals, long-chain fatty acids, carbohydrates and fats) are suitable for variable age groups and come in different flavors.
Tablet protein derivatives	Phenylalanine ± vitamin and mineral-free tablets containing amino acids. Often a high number of tablets are required to meet the complete protein substitution requirement, but they can be used in combination with other protein substitutes to meet requirements and aid diversity.
Bar protein supplements	Snack bars that do not contain phenylalanine and contain amino acids. They are often supplied with other protein substitutes to meet requirements and aid variety. Some may not contain added vitamins and minerals.

Table 4: *Protein substitutes [3].*

The irregular application of L-amino acid protein substitutes is a factor that causes changes in plasma Phe concentrations over a 24-hour period in treated PKU patients. In a study investigating the effect of the change in the timing of protein substitution on the change in plasma Phe level; Well-controlled 16 children with PKU, ages 1 to 11, were included in a randomized crossover study comparing four different protocols of the same daily protein replacement dose. The application of the protocols is as follows:

- Protocol A: Protein substitution administered in three equally divided doses over a 10 hour period, given for 7 days at 07:00 to 08:00, 12:00 to 13:00 and 17:00 to 18:00.
- Protocol B: Protein substitution administered in three equally divided doses over a period of 14 hours, given at 07:00 to 08:00, 15:00 to 16:00 and 21:00 to 22:00 for 7 days.
- Protocol C: Protein substitution administered in four equally divided doses over a period of 14 hours, 07:00 to 08:00, 12:00 to 13:00 and 17:00 to 18 for 7 days. It is given at 00 and 21.00 - 22.00.
- Protocol D: Protein substitution, in six equally divided doses over a 24-hour period, with doses administered for three consecutive days at 08:00, 12:00, 16:00, 20:00, 00:00 and 04:00, and this protocol.

There are 3 subjects taken for blood samples were collected every 4 hours for 48 hours in each study protocol. Except for protocol D, a significant variation in 24-hour plasma Phe levels was observed in all others. Thus, the differences between the highest and lowest concentrations were recorded as (μmol/L): For Protocol A, 140; for protocol B, 100; for protocol C, 120; and for protocol D, 40.

The application of protein substitution throughout the day and night benefits stable and lower plasma phenylalanine concentrations and allows improved dietary phenylalanine tolerance. Three different daytime protocols for protein substitution management failed in reducing 24-hour plasma phenylalanine variability, in contrast, in three subjects, administered every 4 hours during the day and night, almost completely reduced Phe variability [29].

Although Phe-free L-amino acid supplements are one of the cornerstones of medical nutrition therapy in PKU, the substitutes used contain bitter-tasting amino acids (L-isoleucine, leucine, tryptophan and histidine) [30]. Available protein substitutes are unpleasant and difficult to use. It causes difficulties for patients and low adherence to diet. It is also known that protein substitutes have high osmolarity and therefore can cause gastrointestinal disturbances such as abdominal pain, gas, bloating, diarrhea and constipation. Prospective, observational acceptability study of 13 children with PKU; bitter taste masks odor and osmolarity of free amino acids evaluated the use of an extended release protein substitute designed with an ethyl cellulose and alginate coating that reduces the study product, PKU GOLIKE PLUS 3–16 (APR Applied Pharma Research, Switzerland), is an off-white/pale yellow granular protein substitute for oral use, consisting of an extended release amino acid mixture enriched with vitamins. Containing vitamins, minerals, carnitine, taurine, choline and inositol, this product has been developed with a coating that can overcome the problems associated with free amino acids such as bitter aftertaste, bad taste, high osmolarity. The work product can be mixed with food or juice or taken as granules. It does not contain gluten, lactose or fat. Its nutritional profile is suitable for patients aged 3 - 16 years. As a result of the study, blood Phe control was satisfactory in the subjects (there was a decrease in blood Phe levels), and improvements were observed in Phe/tyrosine ratios. Subjects reported fewer gastrointestinal symptoms. In addition, the study product was well tolerated by the participants [26].

Special products with low protein

Containing low Phe and providing significant energy in the diet; specially produced starch-based low protein foods such as bread, flour, pasta and biscuits help in maintaining blood Phe control. However, due to reimbursement policies in different countries, not being financed by the government/insurance, and high price, patients have limited access to such special products [3,19].

Amino acid metabolism disorders in Turkey, urea cycle disorders, involving organic acidemia in protein metabolism disorders, specially formulated and pasta with special formula, noodles, cookies, specialty products such as chocolate is vital for patients. The monthly state support for these products, which can be obtained within the scope of the specialist doctor report, is as follows:

- 46.50 (forty-six point fifty) TL for 0-12 months,
- 90 (ninety) TL for 1-5 years old,
- 116.25 (one hundred and sixty point twenty five) TL for 5 - 15 years old,
- 120 (one hundred and twenty) TL [31] for over 15 years old.

Mother's milk

Dietary management in babies with PKU relies on the combined use of breast milk or a standard infant formula and a Phe-free infant formula to keep blood Phe levels within the target range [32]. How much in infants newly diagnosed with PKU in the past is due to variability in the content of Phe in breast milk and the volume of breast milk consumed. It was not known that it took Phe and therefore babies were not allowed to breastfeed [6,33]. However, today, breast milk contains immunoglobulins, growth factors, hormones, immunological factors and long-chain polyunsaturated fatty acids, higher iron absorption and breast milk has more with its low Phe content (4,419 µmol/L), it is believed that breastfeeding is advantageous due to the development of the mother-infant bond during breastfeeding [5,6,14]. In addition, breast milk is superior to cow's milk in terms of Phe content [14]. In addition, breastfeeding is higher in the general population, associated with less overweight and higher IQ Downloaded [32].

Breast milk/Cow's milk	Phe level (mg/100 mL)
Colostrum (first five days)	70
Transition milk (6 - 10 days)	60 - 70
Mature milk	48
Cow milk	180

Table 5: *Phe contents of breast milk and cow's milk [14].*

Phe restriction for babies with PKU requires limited breast milk and determination of the intake dose according to weekly blood Phe monitoring. Breastfeeding should be adapted to maintain desired Phe levels (120 - 360 µmol/L) according to the infant's Phe tolerance [6].

There is no universal approach to suckling and Phe-free infants with PKU. As a result, mothers provide breast milk and Phe-free medical formula to their babies using one of three different methods in line with metabolic clinical recommendations: 1) A fixed amount of medical formulation before breastfeeding, then breast milk until fullness. 2) A fixed amount of breast milk or a fixed amount of breastfeeding followed by Phe-free medical formulation until satiety. 3) Breastfeeding or switching between breastfeeding or breastfeeding with a Phe-free medical formula [6].

In a cross-sectional survey of 95 centers from 21 European countries; In breastfed infants, 53% of the centers (n = 50/95 centers) gave breast milk to fullness (no time-limited breastfeeding) followed by a certain amount of Phe-free infant formulation before each breastfeeding; 11% (n = 10/95) stated that they gave a certain amount of Phe-free infant formulation before time-limited breastfeeding and 6% (n = 6/95) gave a measured amount of Phe-free infant formulation in a bottle after breastfeeding. Twenty-three percent (n = 22/95 centers) stated that they gave alternative breastfeeding with the Phe-free infant formulation, and 7% (n = 7/95 centers) used different practices. When the standard infant formula is given as the source of Phe, 8% of the centers (n = 8/95 centers) first gave a certain amount of Phe-free infant formulation and then again a certain amount of standard infant formula, while 37% (n = 35/95) gave a certain amount of standard infants. She stated that she gave the formula and then gave the Phe-free infant formula until they were full. Forty-four percent of the centers (n = 42/95) used the combination of Phe-free formula and standard infant formula (mixed), 8% (n = 8/95 centers) and consecutively standard infant formula with Phe-free infant formula and 2% 'si (n = 2/95 centers) stated that they used different practices.

As a result, it has been determined that different applications are used according to geographical regions [32].

Mothers may encounter many problems while breastfeeding their babies with PKU. Looking at common breastfeeding problems, basically four items are listed: 1) Breast pumping (45%). 2) Breastfeeding problems (35%). 3) Nipple confusion (28%) and 4) Common breastfeeding problems. The most common difficulty is pumping the breast. So much so that one mother stated that she spent hours pumping in order to breastfeed twice a day. Another frequently reported problem is nipple confusion, which occurs because the baby must take the breast and bottle together. The way you suck from the bottle and breast is different, and this can be confusing for babies. In the second part, mothers listed three basic items in the category of difficulty. These are management difficulties in breastfeeding their babies, what amount to suck or express, and the time to suck [6].

In a study in which the prevalence, duration and factors affecting breastfeeding of the babies of the mothers of children with PKU before and after the diagnosis were investigated, 48 males and 55 females in total 103 mothers of children with PKU participated; While 89 mothers (86%) were breastfeeding their babies immediately after birth, 72 mothers continued to breastfeed their babies after the diagnosis and while 14 mothers were feeding with a bottle before the diagnosis, 17 more mothers switched to bottle after the diagnosis. The addition of a standard commercial infant formula to the infant's diet by replacing some or all breast milk obtained from breastfeeding or expressed breast milk, i.e. the use of commercial infant formulas to support breastfeeding or expressed breast milk, has been associated with shorter breastfeeding times [33].

Considering all the beneficial effects of breast milk, supporting newly diagnosed babies with PKU or mothers planning to breastfeeding and encouraging them to continue breastfeeding, as well as a health service undertaking metabolic and nutritional care providers should instill in mothers that breast milk continues to be the most appropriate nutrition for babies with PKU [33].

The primary purpose of weaning is to gradually replace natural protein derived from breast milk or standard infant formula with solids containing equivalent Phe. Additionally, the second stage is a Phe-free L-amino acid supplement to replace Phe-free infant formula and is generally recommended from around 6 months. In a study in which 95 centers participated in total, 85% of weaning centers were between 17 - 26. It started between weeks, 12% after 26 weeks and 3% before 17 weeks. Infant's interest in solid foods and age have been identified as important determinants of weaning initiation. 51% of the centers are 17 - 26. It started to give foods containing Phe in weeks and 48% after 26 weeks. The first solids are mostly low Phe vegetables (59%, n = 56/95) and fruits (34%, n = 32/95). Phe-free L-amino acid supplementation with a higher protein equivalent was found in 41% of centers when infants were 26 - 36 weeks of age (mainly from Germany, Austria, Northern and Eastern Europe) and 37% after 1 year of age (mostly from Germany, Austria, Northern and Eastern Europe). Southern Europe). 53% of the centers recommended Phe-free L-amino acid supplements in spoon or semi-solid form [34].

Discussion

Phenylketonuria is a rare autosomal recessive genetic disorder characterized by impaired conversion of phenylalanine to tyrosine due to insufficient activity of the hepatic enzyme L-phenylalanine-4-hydroxylase. If left untreated, the resulting high blood Phe concentrations of crossing the blood brain barrier phenylalanine cause detrimental effects on brain development and function olmaktadır [2,3] worldwide overall prevalence in 100,000 newborns, while 6,002, consanguineous marriages are often observed in countries like Turkey prevalence 100,000 births in 38.13 to 11. The diagnosis is made by analyzing the blood samples taken from the baby's heel in the first 24 - 48 hours of life in the laboratory [13]. The basis of the treatment. Although there are different strategies such as lifelong phenylalanine-restricted medical nutritional therapy, protein substitutes and low-protein special products, keeping blood Phe within the established range remains the primary goal of all strategies [3,8,17].

Conclusion and Suggestions

PKU, one of the most common and inherited amino acid metabolism diseases in the world, should be diagnosed from the first days of life and the possible disruptions and deficiencies that may occur in the application of newborn screening tests should be eliminated in order to avoid interruption of treatment. It is likely that growth and development retardation will occur with late diagnosis, difficulty in

managing medical nutrition therapy, incorrect intake of amino acid mixtures. Therefore, strategies to increase the quality of life in patients with PKU are required.

Patients are told that it is important to take Phe-free amino acid mixtures, which are one of the cornerstones of the treatment, at appropriate doses and at recommended intervals, but these mixtures, which can make it difficult to adapt and subsequently cause bad metabolic results, can be improved in terms of taste, odor, appearance, consumption and tolerance and are commercially new. formulations should be improved. It should be ensured that special low-protein products are developed that help patients to close the remaining energy deficit due to the restricted diet, improve patients' compliance with diet, provide relaxation in their social life, create diversity in diet, and facilitate the access of patients to these products. Finally, although mothers abstain from breastfeeding their babies, mothers should be encouraged to breastfeed because the mother-baby bond strengthens, breast milk contains many beneficial ingredients and breast milk content has a good composition.

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Volume 17 Issue 1 January 2022