Clinical and Experimental Health Sciences

Disease Management in Individuals with Phenylketonuria

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Received: 18.09.2023 **Accepted:** 31.01.2024

ABSTRACT

Phenylketonuria (PKU), one of the most common metabolic diseases, is a recessive, congenital and hereditary disease that occurs with the absence or deficiency of the enzyme called phenylalanine hydroxylase, which converts phenylalanine to tyrosine. Therefore, the aim of this review was to discuss the disease management in individuals with phenylketonuria. As a result of the inability to metabolize phenylalanine amino acid in patients with PKU, the level of phenylalanine increases in the systemic circulation and brain, which may lead to neurocognitive activity and psychosocial dysfunctions and various disorders. If infants with PKU, who are indistinguishable from healthy babies at first birth, are fed like normal babies, phenylalanine accumulates in the body and symptoms occur and gradually worsen. To keep the blood sugar phenylalanine level at the desired range various medical treatment methods (pharmacological treatment and gene therapy), especially nutritional therapy, can be preferred. However, alternative treatment methods should be carried out in combination with diet therapy. Some dietary restrictions are maintained for life, while patients follow a strict diet in dietary protein intake to prevent high plasma phenylalanine levels and neurological damage. In this review, the definition, classification and phenylalanine-restricted diet treatments of phenylketonuria are discussed.

Keywords: Phenylketonuria, phenylalanine restriction, phenylalanine hycroxylase, enzyme deficiency, nutritional therapy

1. INTRODUCTION

Phenylketonuria (PKU) is an autosomal, recessive disorder associated with the deficiency or absence of hepatic phenylalanine hydroxylase (PAH) enzyme, which catalyzes the conversion of phenylalanine (Phe) to tyrosine as a result of a genetic defect in the PAH (1,2). The absence or deficiency of a functional PAH enzyme that catalyzes the hydroxylation of phenylalanine to tyrosine causes increased production of phenylketone bodies and thus increased Phe levels. These untreated Phe accumulations can lead to serious physiological, neurological and mental disabilities (3,4). While intellectual disability, hyperactive behaviors and autistic features can be seen, it can also lead to significant delays in developmental milestones. If treatment is started in the first 4 weeks of life, babies with PKU can be evaluated as normal babies and can lead their lives independently, provided that metabolic controls are made. Diagnosis and modern treatment of PKU were made by three key findings (5):

1. In the 1930s, Asbjorn Folling identified high phenylalanine levels (hyperphenylalaninemia) in the blood as the cause of neuropsychological disorders.
2. Horst Bickel recommended the treatment of a low phenylalanine diet to treat Phenylketonuria in the 1950s.
3. In the 1960s, Robert Guthrie introduced the Guthrie Test, which is suitable for mass screening for hyperphenylalaninemia, which is used in the diagnosis of PKU in many countries around the world today.

In metabolic diseases, metabolites that can cause toxic effects due to the absence or deficiency of enzymes in the synthesis or catabolic pathways of macromolecules such as carbohydrates, proteins and fats accumulate, or the final product cannot be produced (6). PAH is an enzyme produced in the liver that converts phenylalanine to tyrosine and its cofactor is tetrahydrobiopterin (BH4). Phe exists in nature as D and L enantiomers, and especially L-Phe is an essential amino acid for protein synthesis (7). This amino acid, which

DOI: 10.33808/clinexphealthsci.1360624

is indispensable for the continuity of protein production and homeostasis for human metabolism, is converted to tyrosine by being metabolized in the liver by PAH when it is not included in protein production. This essential amino acid, which is obtained not only by diet and protease activity, takes part in protein synthesis and is converted to tyrosine, but also is important for the synthesis of substances such as dopamine, norepinephrine and melanin. The main metabolic pathway of Phe refers to its hydroxylation to tyrosine by the enzyme PAH found in the liver and kidney (4,8).

Studies and data presented confuse clinical symptoms in untreated patients with blood Phe levels of 360 – 600 µmol/L, regardless of central nervous system damage (9). In addition to the normal results, low levels of neurocognitive disorders were also detected. Although it does not draw a definite limit, treatment is not recommended in infants with blood Phe concentration of 120 – 360 µmol/L, and it is recommended to be followed for at least the first 2 years of their lives. For this reason, trying to keep the blood phenylalanine level within these ranges is the first goal of all treatment methods. In Table 1, the classification of PKU based on blood Phe levels was demonstrated (10,11).

Table 1. *Blood phenylalanine values and daily tolerance classification for 5-year-old PKU patients (10,11).*

PKU Types	Blood Phenylalanine Levels	Daily Tolerable Phe Values
Classic Degree PKU	1200 µmol/L	20 mg/kg and below
Intermediate PKU	900 µmol/L – 1200 µmol/L	20 – 25 mg/kg
Mild PKU	900 µmol/L	More than 25 – 50 mg/kg
Mild Hyperphenylalaninemia	600 µmol/L	Nutritional therapy may not be needed.

PKU infants, who appear normal at newborns, will only show nonspecific symptoms such as feeding difficulties, hypotonia, and the characteristic musty odor due to phenylacetic acid ingestion if not treated in the first weeks of life (12). The retardation in psychomotor development, which is the most important and constant feature in phenylketonuria, progresses continuously and occurs in the 4th-6th phase of life. It starts to appear after a month. This period of neurocognitive damage, in which seizures can also begin, reaches its peak around the age of 3-4 years. They lag behind their peers in acquiring basic skills such as sitting, walking and speaking. Babies with PKU who are indifferent to their environment may also exhibit hyperkinetic and autistic behaviors (13).

1.1. Aim of the Review

In this review, it was aimed to discuss the disease management in individuals with phenylketonuria including the phenylalanine-restricted diet treatments of phenylketonuria.

2. PKU TREATMENT METHODS

For most individuals who begin treatment shortly after birth, individuals generally fall within the normal range of general cognitive ability (14). Treatment of phenylketonuria should be initiated as soon as possible (15). This shortest possible period is usually the first 2 weeks of life, and during these first 2 weeks blood Phe values should be suitable for initiation of therapy (16). It is aimed to reduce blood Phe levels to the desired range as soon as possible in babies who are diagnosed and treated. In the first place, a Phe-restricted diet is started depending on the blood Phe levels and Phe is removed from the diet until the Phe values fall into the desired range (17). Breastfeeding is usually possible with medical support (18). It is possible to start treatment early with diagnosis and follow-up tests. Communication between families and primary health care services and access to specialist physicians are very important in this process. Although many treatment centers in North America starting treatment at blood Phe levels of 360 µmol/L and above, the accepted opinion in Turkey and most other countries is that infants whose blood Phe levels exceed 600 µmol/L should be start the treatment. In addition, clinical outcomes for untreated infants with blood Phe values in the 360 – 600 µmol/L range are mixed. Clinical evaluations and consultations with families suggest that infants with Phe values >360 µmol/L are at risk from a neuropsychiatric point of view and should begin the treatment. Although no negative threshold is specified for blood phenylalanine levels, it is thought that infants with phenylalanine levels of 120-360 µmol/L do not need treatment but should be monitored for at least the first 2 years of life. At the same time, blood Phe monitoring should be performed annually or biennially in subsequent evaluations so that Phe levels do not shift to higher levels (15). In Table 1, blood Phe concentration control and clinical monitoring frequency in PKU are given.

2.1. Medical Nutrition Therapy

As with all congenital metabolic diseases, medical nutrition therapy has a great role in the management of PKU, and medical nutrition therapy is a long process that must be continued throughout life (19). The basic principle of diet therapy is to restrict and remove foods containing the amino acid phenylalanine, which cannot be converted to tyrosine due to the absence of PAH, and to support the body's need for tyrosine amino acid (20). The main aim of the treatment of PKU, especially nutritional therapy, is to keep blood Phe levels at desired, reliable levels (21). Principles of nutritional therapy have 3 goals to be followed:

1. Natural protein/phenylalanine intake should be strictly monitored and excessive Phe accumulation in the blood and brain should be prevented (22).
2. Instead of natural proteins eliminated from the diet, synthetic proteins, amino acid mix supplements or safe proteins called protein substitutes should be used (23).

3. It is important to ensure the continuity of the normal growth and development process along with nutrition. This is only possible with a balanced distribution of all nutrients and energy in the diet. At this stage, vitamin – mineral supplements that play a role in growth and development are added to protein substitutes or given separately (24).

2.1.1. Foods to Avoid on a Low Phe Diet

In most individuals with phenylketonuria, natural protein intake and phenylalanine are limited to 25% or less of normal to keep blood Phe concentrations within the target Phe ranges of the European PKU Guidelines (25). The amount of Phe allowed in PKU, which is a congenital metabolic disease, is quite low compared to healthy individuals. For this reason, all protein-containing foods are given in a limited way (11). It is necessary to avoid high-protein foods such as those listed below or to limit high-protein foods (1,6):

- animal foods such as meat, chicken, fish
- egg
- cheeses made from animal milk such as cow, goat or sheep
- nuts, seeds, quinoa, wheat, oats, rye, barley
- meat substitutes made from fungal protein
- soy, tempeh, pulses/lentils
- plant algae such as gelatin and spirulina
- sweeteners (aspartame)

2.1.2. Aspartame Content of Food and Beverages

Aspartame is an artificial sweetener with the food additive code E951 and 50% is converted to the free phenylalanine molecule (26). For this reason, it should not be included in low Phe diets. Aspartame is often added to soft drinks, chewing gums, desserts, jellies, and candies. Although it mentions that it contains aspartame on food labels, the amount is often not specified (1).

2.1.3. Foods Containing Phenylalanine

Phenylalanine is an essential amino acid found in natural proteins (14). Different foods contain different amounts of phenylalanine. Meat, chicken, fish, eggs and milk from animal proteins as well as wheat flour and breakfast cereals, which are among the cereal protein sources, 1 g protein amount generally enters our body as 50 mg phenylalanine. Animal and cereal proteins contain about 5% of the amino acid phenylalanine. This situation leads to the conclusion that food protein labeling can be done without knowing the phenylalanine content of foods. In addition to animal and cereal proteins, fruits and vegetables have a variable phenylalanine content of 20–40 mg per 1 g of protein (27). Just like animal and cereal proteins, the phenylalanine content of fruits and vegetables cannot be accurately calculated in this way from a nutrient analysis label on a package/container that declares protein content alone. Looking at the protein content alone, it can be assumed that these foods have a high phenylalanine content. There are vegetables that are exceptionally high in phenylalanine/protein. These are: spinach, peas, seaweed, cabbage and corn (25).

Phe intolerance is the amount of phenylalanine that can be consumed by an individual with PKU while keeping blood Phe values within the target treatment range (14). The American College of Medical Genetics and Genomics guidelines on PKU recommend maintaining blood phenylalanine levels between 120–360 µmol/L in all patients (17). The amount of dietary phenylalanine tolerated, based on the severity of PKU for each individual patient, as well as depending on the dose, compliance, and daily distribution of protein substitutes (20). Medication, Pegvaliase (used for patients ≥18 years of age) and sapropterin are also part of the treatment (17, 28). In addition, conditions such as pregnancy, growth and development during the disease are affected in the catabolic state. Most nutritional therapy patients tolerate less than 500 mg/day Phe. Patients sensitive to sapropterin are expected to at least double their tolerance to phenylalanine or be able to tolerate the safe protein intake defined by the WHO/FAO/UNU (20).

Control of blood Phe value by nutritional therapy requires a low-protein diet that provides limited but necessary Phe intake, together with natural and specially produced low-protein food sources (29). Diets low in protein lead to insufficient intake of not only Phe but also other amino acids. This leads to the conclusion that the diet should be supplemented with protein substitutes (amino acids). Foods made with low Phe are universally available and provide an important dietary source of Phe (30). For this reason, it is very difficult to control blood Phe values without specially produced foods that are poor in Phe amino acids (29).

2.1.4. Intake of Dietary Free Nutrients

Foods that are free in the diet can be defined as foods with a Phe value that is allowable without being measured (30). They are both naturally occurring and have very low Phe values. Although free foods show some variation in different treatment centers in different countries, some free foods that basically all treatment centers agree can be itemized as follows oils, some candies, honey, jam, spices, and apple juice (31).

2.2. Medical Nutrition Therapy of Babies

Infants with blood Phe >360 µmol/L are treated with a diet low in phenylalanine (32). Protein intake is tried to be controlled by giving a small amount of breast milk and a standard infant formula along with infant formula that does not contain Phe (25).

Some studies have shown that acceptable blood Phe values, growth and weight gain can be achieved when a Phe-free infant formula and breastfeeding are combined (33). Breastfeeding is advantageous in many ways compared to standard formula. These advantages are as follows:a)

a) It has a low Phe value of 46 mg in 100 mL and contains long chain polyunsaturated fatty acids.

b) Breastfeeding helps to establish a strong mother-baby bond.

c) Breastfeeding includes the mother in the feeding process and gives her control.

d) Breastfeeding is a process that takes place in line with the baby's demand and reduces the number of bottle feedings.

Breastfeeding of infants with phenylketonuria is known to be relatively beneficial (30). Breast milk is low in Phe and is also a good source of BH4. In the long term, some studies have shown that breastfed babies are healthier than formula fed babies. The recommended and widely used method of breastfeeding is based on the principle of giving Phe-free infant formula before each feed. This situation indirectly reduces the baby's appetite and the desire to suck. Thus, the amount of breast milk taken decreases and Phe intake decreases (1).

2.3. Eating Behavior in Young Children with PKU

Nutritional problems are common in young children with PKU. The problems at the root of these problems are limited variety of food consumption and loss of appetite (20). Other causes of nutritional problems are:

- Energy content of the protein substitutes used: Some of the frequently used protein substitutes help to obtain additional energy from carbohydrates and fat (20). They provide up to 25% of the energy needs of children aged 1-3 years. Therefore, parents have unrealistic expectations about how much food their children should eat and may force their children to eat even though they are not hungry (34).
- Refusal of the nutrients provided by the Phe allowance: Parents may particularly insist on feeding their children all the foods provided by the Phe allowance (20). This leads children to repeated food refusal behavior.
- Preparing special meals for children at mealtimes: Families preparing two kinds of meals at mealtimes or giving meals to children at different times can have adverse effects on the nutrition of children with PKU and cause children to acquire isolated eating behavior (35).
- Difficulty in consuming protein substitutes: After a while, negative attitudes such as retching, vomiting and deliberately spilling products can be seen when consuming protein substitutes in young children (35).
- Food neophobia: It is a common behavior in childhood in general. It is also seen at high rates in children with PKU (36). Children prefer familiar foods than experiencing new ones. This is due to reasons such as not being exposed to various nutrients during the weaning period, and poor associations with protein replacement (35).

3. PKU AND CHANGES IN BODY METABOLISM

Although the pathophysiological mechanisms of the destruction of brain function found in patients with PKU are not yet clearly understood, there is ample evidence of metabolic changes in studies in both patients and animal models (37). Such changes include energy metabolism disorder, oxidative stress, damage to lipid and protein metabolism, and disruption of calcium homeostasis and neurotransmitter synthesis in the brain (20).

3.1. Neurotransmitter Metabolism

Neurochemical and behavioral studies have shown that animals fed diets rich in Phe have reduced brain serotonin levels and impaired certain problem-solving abilities (38). Recently, it has also been noticed that these patients are more susceptible to neurological manifestations caused by cerebral dopamine deficiency, such as Parkinsonism (39). Various studies have also shown that high Phe levels are associated with decreased dopamine, serotonin and norepinephrine levels in human and mouse PKU. The decrease in the levels of these neurotransmitters was thought to be related to the effect of high Phe concentration on amino acids transported through the blood-brain barrier (BBB) or on enzymes involved in neurotransmitter synthesis (40). It is important to emphasize that the large neutral amino acid (LNAA) transporter has a high affinity for Phe, competing with other amino acids to cross the BBB, ultimately reducing the amount of Trp and Tyr available for neurotransmitter synthesis (37).

3.2. Oxidative Stress

Oxidative stress is defined as the imbalance between the production of reactive oxygen/nitrogen molecules and the antioxidant system (41). This imbalance can cause oxidative damage to proteins, lipids or DNA. Including oxidative stress, it has been also associated with the pathophysiology of many neurodegenerative diseases such as Parkinson's and Alzheimer's diseases, epilepsy, and demyelination. In recent years, oxidative damage to macromolecules has been the subject of research in animal models of HPA and biological samples from PKU patients (39). It has been found that high Phe concentrations in patients with PKU are associated with DNA, protein and lipid damage as well as decreased antioxidant defense.

3.3. Protein Metabolism

Blocking and inhibiting the neutral amino acid transporter by Phe negatively affects protein synthesis (37). Because amino

acids, which are essential for the production of neutral amino acids, are not found in sufficient quantities. These patients have low levels of IgG and IgA, and a decrease in the production of antioxidant enzymes was also seen. This was associated with more cellular oxidative stress and therefore less protein production (20).

3.4. Lipid Metabolism

A study of lipid metabolism in PKU demonstrated impaired lipid metabolism in PKU, which has the potential to cooperate with hypomyelination found in patients (42). It showed that phenylketonuria patients have altered serum lipoprotein levels, including low total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and apolipoprotein AI/A-II levels (39).

3.5. Lipid Metabolism

Brain and energy metabolism changes play an important role in the pathophysiology of many congenital metabolic diseases (39). Related to this condition, impaired energy metabolism has been reported in HPA animal models and patients (42).

3.6. Calcium Metabolism

Calcium balance is very important for brain functions and has been the subject of studies (39). One of the types of metabolism that is impaired with PKU is calcium metabolism. In this context, parathyroid hormone, osteocalcin, and dehydrocholecalciferol, which are responsible for regulating calcium metabolism, were found to be increased, while calcitonin was found to be decreased in serum samples of infants with PKU. Studies have found that Phe can change the intracellular calcium concentration and affect the activity of the calcium ATPase enzyme in neurons (37). For this reason, it has been shown that Phe affects both the intracellular calcium concentration and the activity of the calcium ATPase enzyme in neurons, as the reason for the elevation of dihydroxycholecalciferol, parathormone (PTH) and osteocalcin levels in PKU patients. As a result, it was found that calcitonin hormone decreased in blood concentration controls due to these negative effects. As predicted, an increase at the levels of these hormones causes a decrease in bone density whereas the serum calcium value increases. Therefore, it was concluded that it may be related to neuropathological conditions together with PKU (39).

4. PKU COMORBIDITIES

There are not many studies on PKU comorbidities in PKU patients, for whom diet therapy is considered the gold standard, except for diseases caused by the diet brought on by a restrictive diet (14). Risk factors that may occur due to nutritional deficiencies can be listed as follows (32):

- Brain development
- Mental health disorders
- Diabetes and cardiovascular risks
- Kidney ailments
- Bone health
- Sarcopenia and fragility
- Gastrointestinal problems
- Inflammation and immune system

4.1. Brain Development

Although it is not known exactly how PKU affects brain functions, several different causes are discussed (43). High Phe levels in the blood can have a direct toxic effect on the myelin sheath, which is responsible for increasing the conduction velocity by wrapping the axons in the brain cells. In addition to all these, absence or limited PAH activity may reduce the amount of important neurotransmitter substances such as serotonin and dopamine (44). Because dopamine is synthesized from tyrosine and competes for tyrosine in the body (45). Phe competes with essential amino acids such as tryptophan, which is responsible for the synthesis of the hormone serotonin. Finally, high blood Phe levels are thought to inhibit the activities of tyrosine hydroxylase and tryptophan hydroxylase enzymes that function in the synthesis of dopamine and serotonin, respectively. Individuals with PKU may experience cognitive deficits due to minor neurological disorders even when treatment is initiated (46). These may result from demyelination due to damage to the myelin sheath in the central system and disruption in the synthesis of neurotransmitter substances. These disruptions in neuropathophysiology have been associated with impairments that should be seen in the natural aging process but seen at younger ages.

4.2. Mental Health Disorders

With phenylketonuria newborn screening, babies with PKU can be identified and treatment can be started immediately after birth (47). This treatment is a Phe-restricted diet therapy, which is widely used and has good results. Studies have shown that patients with PKU have lower IQ and lower cognitive functions than healthy individuals, despite early initiation of diet therapy (48). Although the most severe symptoms of the disease are tried to be eliminated by treating with diet, it is seen that individuals with PKU who start Phe-restricted diet therapy in the early period and are treated continuously have psychiatric problems such as attention deficits, behavioral and emotional problems (47). These psychiatric problems are thought to be due to fluctuations in blood Phe levels during the treatment process. High blood Phe levels can lead to both acute and chronic neuropsychiatric problems (49). While impairment in psychiatric, behavioral and neurocognitive functions may be due to the emotional burden of having a chronic disorder, the main consideration is the time, duration and intensity of Phe

exposure. In a meta-analysis study investigating the effect of high blood Phe levels on neuropsychiatric symptoms, it was stated that inattention, hyperactivity, depression, and anxiety symptoms were higher than the general population estimates. In addition to all these symptoms, which may be caused by disorders in neurotransmitter synthesis, discomfort from socializing, low self-perception and decreased positive emotions were included in the studies (48). Table 2 shows that untreated individuals and individuals who started treatment at different times may show similar symptoms of neuropsychological disorders (14).

Table 2. *Psychological disorders in children, adolescents and adults with PKU (14,49).*

Untreated PKU	Children and adolescents who start treatment early	Adults treated early
Psychological symptoms	Attention problems	State of depression
Autistic behaviors	School problems	Social isolation/isolating oneself from society
Hyperactivity	Low achievement motivation	Generalized anxiety
Aggression	Low self-esteem	Lack of social maturity behavior
Anxiety	Decrease in social skills	Decrease in positive emotions
State of depression	Difficulty with autonomy	Low self-esteem
Social relationships impaired by intellectual disability	No data	Lack of autonomy

4.3. Diabetes and Cardiovascular Risks

The use of a Phe-restricted diet for the treatment of phenylketonuria leads patients to prefer foods containing more carbohydrates and less fat (50). It is stated that individuals who comply with the diet are vulnerable to the risk of developing diabetes, cardiovascular diseases and metabolic syndrome (32).

4.4. Kidney Ailments

As with diabetes and cardiovascular diseases, kidney disorders can also be diet-related. Since there is high Phe exposure when trying to take protein naturally, these patients are helped by synthetic amino acids that do not contain Phe (51). Since this situation can bring about high protein intake, kidney function disorders can also be encountered (32).

4.5. Bone Health

High Phe concentration in the blood disrupts the balance between bone formation and resorption (52). Although the relationship between bone mineral density and high Phe levels is not clear, dietary deficiencies and genetic factors are also effective on bone health, as well as restriction of protein intake (14).

4.6. Sarcopenia and Fragility

Sarcopenia is a progressive and common skeletal disorder (50). Although sarcopenia, also called muscle insufficiency, may occur in advanced ages, it can also occur in the early stages. It increases the risk of falls and fractures for human health and may interfere with life activities. Preservation of muscle mass and prevention of loss of strength through adequate dietary protein intake are important for sarcopenia. However, decreased natural protein intake, oxidative stress, and vitamin D deficiency are risk factors for sarcopenia in individuals with PKU (53,54).

4.7. Gastrointestinal Problems

Although there are no studies showing a direct link between gastrointestinal pathology and PKU, it is thought that a Phe-restricted diet may cause some digestive system problems (50). Conditions such as a low-fiber diet, the use of protein substitutes with high osmolality and acidity can cause constipation and indigestion (32).

4.8. Inflammation and the Immune System

Most studies on phenylketonuria and the immune system have reported increased concentrations of pro-inflammatory factors and decreased antibody (IgG and IgA) concentrations in the blood plasma of children and adults (≤ 22 years) with PKU (50,55).

5. MATERNAL PKU

When women with PKU who become pregnant without their blood Phe values are kept under control, there are undesirable risks of this situation when they stop their diet (56). It is known that more than 90% of babies born after conception in this way have mental retardation. Congenital heart diseases and microcephaly can also be seen in these babies, who usually have low birth weight (57). The reason for all these bad situations that may occur is due to the teratogenic effect of the mother's high blood Phe level (56). Maternal PKU risks can be prevented to a large extent if diet is controlled before pregnancy and if control is not left during pregnancy (57). However, the fetal morbidity is associated with HPA in individuals with PKU, blood Phe concentrations should be checked more frequently in mothers with PKU (7). Affected mothers require a pre-pregnancy diet with a Phe value of 100-360 µmol/L. At the same time, it is important to monitor blood Phe values weekly and keep them at reliable levels (56).

6. PKU AND SPORTS

Since there is little information on how a diet low in phenylalanine affects sports performance, the nutrients are essential for general sports nutrition and therefore adapted to PKU as follows (58):

- A diet rich in carbohydrates should be maintained. Carbohydrate-rich foods should be recommended before and after exercise, and low-fat, low-protein foods, such as low-protein pastas, should be preferred.
- Since sports drinks (without aspartame) will contribute to carbohydrate loading, the target carbohydrate intake should be 30–60 g/h for 1–2.5 hours of endurance exercise.
- Great attention should be paid to the hydration status.
- A dose of protein substitute should be taken during the recovery phase immediately after exercise. Approximately 20 g protein equivalent of protein replacement should be taken after exercise.

In addition, there is research suggesting that brief acute exercise does not affect blood Phe concentrations, but the effect of endurance exercise has not been studied (59).

7. WEIGHT MANAGEMENT IN PKU INDIVIDUALS

Being overweight is not uncommon in individuals with PKU. However, trying to lose weight quickly can lead to catabolism and loss of control of blood Phe values. Healthy weight loss behavior can be gained by making the following dietary changes (1):

- Sugary foods should be replaced by foods without sweetener/aspartame.
- Drink plenty of water.
- The carbohydrate/energy content of the protein substitute must be constantly checked. It should be ensured that ready-made medicines available as powders are prepared with only water.
- Special milks with low protein containing ≥ 60 kcal/100 mL should be replaced with plant milks with lower energy.
- Food should be eaten in smaller portions at mealtimes, but still be encouraged to eat 3 meals a day using low-protein pasta, rice and low-protein bread with a lower fat content.
- Candies, sweets, chips, vegetable chips, jams, honey, low protein chocolates or biscuits should be limited.
- A minimum amount of oil (preferably olive oil) or 'light' oil cooking sprays should be preferred while cooking.
- If possible, try to do physical activity such as light-paced walking for 30 to 45 minutes every day.

Table 3 lists foods and beverages that patients with PKU can consume safely and should not consume (14,27).

Table 3. *Foods and beverages that patients with PKU can consume safely and should not consume (14,27).*

Things not to be eaten	Freely consumable foods	Foods that should be consumed in limited amounts	Medical foods
Milk and dairy products (milk, yoghurt, buttermilk, tzatziki, cheese and its varieties, all foods made with them)	Corn starch	Vegetables	Low protein drink
Egg	Plain Turkish delight, plain hard candy	Fruits	Low protein pudding
Meat and meat products (red meat, chicken, fish, turkey, salami, sausage, sausage, pastrami, roasted meat, shellfish, mussels, etc.)	tea, linden, sage	floury foods	Low protein cereal
Internal organs of the animal (brain, liver, kidney, etc.)	Oil	Olives	Low protein pasta
Regular bread (wheat, rye, oat, corn breads)	Tea sugar	Margarine	Low protein bread
Dried nuts (hazelnuts, peanuts, roasted chickpeas, seed varieties, almonds, walnuts)	Apple juice, compote water	Butter	Low protein cookies
Dried legumes (dry beans, chickpeas, lentils, broad beans, soybeans, dried kidney beans)	Soda, cola drinks	Honey, molasses	Special gel for yoghurt making, milk sugar for yoghurt making
Ready-made food (crackers, biscuits, cakes, cookies, pastries and all prohibited foods)	No data	No data	Low phenylalanine cheese
All drinks, gums and foods containing aspartame and phenylalanine.	No data	No data	Low protein semolina

8. CONCLUSION

Some nutritional deficiencies in PKU individuals can cause different comorbidity. Breastfeeding has advantageous in many ways compared to standard formula. On the other hand, the results of the studies show that basic recommendations for a balanced and healthy life are possible for individuals with PKU. The protein substitute and phenylalanine dose to be taken should be divided into certain times of the day and included in the diet. Fruits and vegetables containing 75 mg or less Phe per 100 grams should be preferred. Care should be taken to consume 5 servings in total, with at least 1 serving at

each meal. Foods such as low protein bread and pasta can be preferred in most meals in order to close the calorie deficit, provide satiety and create variety. It should not be neglected to have blood Phe levels checked regularly, at the same times and on an empty stomach.

Acknowledgement: *This the study is produced from of licence's thesis.*

Funding: *This research recieved no grant from any funding agency/ sector.*

Conflicts of interest: *The authors declared that there is no conflict of interest.*

Ethics Committee Approval: *No needed.*

Peer-review: *Externally peer-reviewed.*

Author Contributions:

Research idea: EG

Design of the study: EG, AGB

Acquisition of data for the study: EG, AGB

Analysis of data for the study: EG, AGB

Interpretation of data for the study: EG, AGB

Drafting the manuscript: EG, AGB

Revising it critically for important intellectual content: EG, AGB

Final approval of the version to be published: EG, AGB

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How to cite this article: Gül E, Güneş Bayır, A. Disease Management in Individuals with Phenylketonuria. Clin Exp Health Sci 2024; 14: 572-581. DOI: 10.33808/clinexphealthsci.1360624