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Evaluation of the Effect of Diet Adherence on Nutritional Status and Metabolic Control in Children with Phenylketonuria Consuming a Phenylalanine-Restricted Diet: A Single-Center Study

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ABSTRACT

Objective: The aim of this study was to determine the dietary habits of patients with phenylketonuria (PKU) in different age groups, to assess energy, protein and phenylalanine intakes, and to evaluate dietary compliance and its effect on metabolic control.

Material and Methods: The study, conducted between 1 March 2022 and 30 September 2022, the study involved 20 children aged 2-18 diagnosed with PKU at the Department of Pediatric Metabolism Outpatient Clinic of Ankara Bilkent City Hospital. Participants were evaluated for diet compliance and had their blood phenylalanine and tyrosine levels were measured.

Results: Among the 20 patients, 42.9% (n=9) were female and 57.1% (n=11) were male, with a mean age of 4.7±3.22 years. Age distribution was 70% (n=14) aged 2-6, 20% (n=4) aged 6-10, and 10% (n=2) aged 10-13. Patients attended four follow-ups over six months. A moderate negative correlation was found between daily dietary phenylalanine and blood phenylalanine levels in the first and last controls, and a high negative correlation in the 2nd and 3rd controls ($p=0.006$, $p<0.001$, $p<0.001$, $p=0.013$). A positive moderate correlation was found between the frequency of daily amino acid mixture consumption and diet compliance ($p=0.025$). Increased meal frequency improved diet compliance. No significant relationship was found between blood phenylalanine levels and amino acid mixture consumption, diet compliance, or daily amino acid mixture consumption frequency.

Conclusion: In PKU, nutritional habits, daily phenylalanine intake and amino acid mixture consumption frequency impact dietary compliance and metabolic control. Lifelong medical nutrition therapy requires multidisciplinary team support, frequent follow-ups and adherence to the recommended diet.

Keywords: Metabolic control, Phenylalanine, Phenylketonuria

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INTRODUCTION

Phenylketonuria (PKU) is an inherited metabolic disease that develops as a result of deficiency or insufficiency of the phenylalanine hydroxylase (PAH) enzyme with an autosomal recessive inheritance (1). Due to PAH enzyme deficiency or insufficiency, phenylalanine cannot be converted to tyrosine and phenylalanine and can not be metabolized (2). As a result, toxic metabolites such as phenylalanine, phenylpyruvic acid, phenylacetic acid, phenylactic acid accumulate in the blood, brain and tissues, resulting in serious neurological complications and mental disability (3). In Türkiye, which is one of the countries where the disease is most common, it is aimed to prevent mental disability with early diagnosis and appropriate diet therapy with newborn screening (4).

In the treatment of phenylketonuria, restricting the amount of phenylalanine in the diet is the main effective method of controlling blood phenylalanine levels (5,6). With phenylalanine-restricted nutrition therapy, it is aimed to reduce the consumption of natural protein sources, to meet all other nutritional needs, especially the daily protein needs of patients, with special nutrition products and phenylalanine-free amino acid mixtures instead of natural protein sources (3).

Compliance with the diet of children with PKU who are on a phenylalanine-restricted diet constitutes the success of nutritional therapy. The fact that families play an active role in the implementation of the diet affects compliance with the diet (2,7). In patients about compliance with diet therapy, factors such as the education level of the family, insufficient knowledge about the disease and diet therapy, family culture, difficulties in consuming amino acid mixtures, dislike of the taste of special products or cooking problems, lack of access to special products due to insufficient social support are encountered (8).

It is known that metabolic control is positively affected by the increase in adherence to diet therapy; therefore, blood phenylalanine and blood tyrosine levels of patients should be closely monitored (3).

The aim of the study was to determine the nutritional habits, energy, protein and phenylalanine consumed by phenylketonuria patients in various age groups and to evaluate their compliance levels and its effect on metabolic control.

MATERIALS and METHODS

The study was conducted between 1 March 2022 and 30 September 2022 on 20 children between the ages of 2-18 who were followed up with the diagnosis of PKU in the department of Pediatric Metabolism Outpatient Clinic of Ankara Bilkent City Hospital Children's Hospital and consumed a phenylalanine-restricted diet in the Pediatric Metabolism Diet Outpatient Clinic who agreed to participate in the study.

This study was approved by the Clinical Research Ethics Committee No. 2 of Ankara Bilkent City Hospital with the decision number E2-22-1349 dated 02.02.2022. Before the application, the purpose of the research and the necessary information were explained to the participants by the researchers and the consent of the participants was obtained.

Patients in the 0-2 age group were not included in the study, while a total of 20 patients over the age of 2, who were being followed up with dietary treatment during the study period, were included. The number of patients who gave their consent and agreed to participate in the study was 20; since they were between the ages of 2-13, they were divided into 3 age groups as 2-6 years, 6-10 years and 10-13 years. The age groups in our study were determined as 2-6 years old preschool period, 6-10 years old primary school period and 10-13 years old adolescence period depending on the differences in the nutritional habits and needs of the patients. These patients were already being followed with dietary treatment, and their initial assessments were taken at the start of the study, followed by the 2nd, 3rd and 4th controls. The time interval between the study periods was 1-1.5 months.

A face-to-face questionnaire was applied to the patients, personal and disease-related data were recorded in this form. In the first part of the survey, patients' blood phenylalanine and tyrosine levels were examined, and their food consumption records were used to calculate the total daily protein intake from their diet, the amount of protein from amino acid mixtures, phenylalanine intake, and daily energy intake. Additionally, anthropometric measurements were taken and evaluated. In the second part of the survey; socio-demographic characteristics such as parental age, profession, educational status, social security, and questions such as whether there are other patients with PKU in the family, and the presence of a kinship relationship are included.

In the third part of the survey; the consumption of the amino acid mixture used, the level of knowledge about its consumption, and the difficulties experienced in its consumption were questioned. In the fourth part of the questionnaire, the consumption of special products, and in the fifth part, the frequency of daily meals and the level of compliance with the diet regarding general eating habits were questioned.

Statistical Analysis

As descriptive statistics, mean and standard deviation were used for continuous data, frequency and percentage were used for categorical data. The conformity of continuous data to the normal distribution was checked by the Kolmogorov-Smirnov test. The relationship between two continuous variables was evaluated by Pearson and Spearman correlation analysis, the relationship between ordinal categorical variables was evaluated by Spearman correlation analysis, the relationship between categorical variables was evaluated by Cramer's V correlation coefficient, and the relationship between continuous and bi-category variables was evaluated by Point biserial correlation coefficient. The cut-off points used for the interpretation of the obtained correlation coefficients are 0.00-0.19 very weak, 0.20-0.39 weak, 0.40-0.69 moderate, 0.70-0.89 high and 0.90-1.00 very high. The data were analyzed with the IBM SPSS 21 (IBM SPSS Inc, Chicago, IL) package program. Statistical significance level was taken as $p<0.050$.

RESULTS

Of the 20 patients who participated in the study, 42.9% (n=9) were female and 57.1% (n=11) were male. The majority of patients (70%, n=14) were between the ages of 2-6, 20% (n=4) were between the ages of 6-10, and 10% (n=2) were between the ages of 10-13. The mean age of the patients was 4.7±3.22, the mean weight was 17.61±7.97 kg, the mean height was 103.38±27.00 cm.

It was observed that 57.1% (n=12) of the patients had a family history of phenylketonuria other than themselves. The majority of patients (70%, n=14) have a kinship relationship between their parents.

The mean blood phenylalanine level, blood tyrosine levels, daily phenylalanine, protein and energy intake level of the patients in 4 controls are shown in Table I.

The mean blood phenylalanine level of the patients was 356.95± 193.18 µmol/L at the first follow-up, 345.55±180.35 µmol/L at the second follow-up, 327.16±213.62 µmol/L at the third follow-up, and 274.77±205.66 µmol/L at the fourth follow-up. When blood tyrosine levels were examined, it was found to be 105.78±188.99 µmol/L in the first control, 59.65±31.24 µmol/L in the second control, 59.36±30.55 µmol/L in the third control, 49.37±17.57 µmol/L in the fourth control.

When the average amount of protein taken by the patients in the daily diet is examined, it is seen that it is 33.86±10.47 g in the first control, 35.01±10.62 g in the second control, 35.26±9.70 g in the third control, 35.47±9.89 g in the fourth control. When the average total energy they received with the daily diet was 1442.07±364.31 kcal in the first control, 1449.67±399.68 kcal in the second control, 1432.38±373.39 kcal in the third control, 1425.09±368.76 kcal in the fourth control. The mean daily dietary phenylalanine level of the patients was 276.09±188.85 mg at the first control, 257.71 ±130.09 mg at the second control, 254.86±174.43 at the third control, and 270.00±158.89 mg at the fourth control. Daily intake of protein, phenyalanine, tyrosine and energy was sufficient according to the recommended daily allowance of patients.

The nutritional habits of patients, including the consumption of amino acid mixtures and special products, as well as the number of main and snack meals, are presented in Table II.

When the daily meal consumption of the patients was examined, it was seen that 95% (n=19) made 3 main meals and 5% (n=1) made 2 main meals. When we look at the snack consumption, 10% (n=2) stated that they had 1 snack, 65% (n=13) had 2 snacks, 15% (n=3) had 3 snacks, 5% (n=1) had 4 snacks, and 5% (n=1) had 5 snacks.

When the number of meals consumed daily of the amino acid mixture used was questioned, it was seen that 20% (n=4) of the patients consumed 1 meal, 45% (n=9) consumed 2 snacks, 5% (n=1) consumed 3 meals, 5% (n=1) consumed 4 meals, 20% (n=4) consumed 5 meals, and 5% (n=1) consumed 6 meals. The amino acid mixture is consumed by 30% (n=6) of the patients with a bottle, 65% (n=13) by a glass and 5% (n=1) by a bowl. When it was questioned whether the daily recommended amount of amino acid mixture was followed, it was learned that 50% (n=10) of the patients always consumed all of them, 40% (n=8) consumed them most of the time, and 10% (n=2) rarely consumed them. When the emotional state of the families was questioned at the time of consumption of the amino acid mixture by the child, 60% (n=12) said that they felt comfortable, 5% (n=1) said that they were calm, 30% (n=6) said that they were nervous, and 5% (n=1) said that they were hectic.

While 60% (n=12) of the patients consumed the amino acid mixture with other individuals, 40% (n=8) did not. Likewise, when the consumption status of the amino acid mixture in kindergarten and/ or school was questioned, it was seen that 50% (n=10) did not consume it. When the reason for not consuming was questioned, 60% (n=6) of the patients stated that they did not consume it because they were ashamed, 20% (n=2) because it was difficult to carry, and 20% (n=2) because they hid their disease.

When the consumption status of special products was questioned, it was stated that 60% (n = 12) of the patients consumed, 40% (n = 8) of the non-consumers and 50% (n = 4) of the products were expensive and 50% (n = 4) of them tasted bad.

When parents were asked about their children's compliance with the diet, 85% (n=17) stated that they complied with the diet and 15% (n=3) stated that they were non-compliant. When the families who stated that there was no compliance with the diet were asked about the reason for this situation, 10% of them stated that the elders of the family were involved in the extended family, and 5% (n = 1) stated that the children did not want/like to diet.

The relationship between blood phenylalanine and tyrosine levels and daily phenylalanine intake is presented separately in Table III.

The relationship between the daily phenylalanine intake and blood phenylalanine level in the first measurement was a moderate negative correlation (r=-0.577) and was found to be statistically significant (p=0.006). The relationship between the daily phenylalanine intake and blood phenylalanine level in the second measurement was a strong negative correlation (r=-0.716) and

Table I: Blood phenylalanine(phe) and tyrosine levels and daily dietary phenylalanine, protein and energy intake of children with PKU

Blood Findings and Food Consumption	1.Control	2.Control	3.Control	4.Control
Blood phe level (µmol/L)*	356.95±193.18	345.55±180.35	327.16±213.62	274.77±205.66
Blood tyrosine level (µmol/L)*	105.78±188.99	59.65±31.24	59.36±30.55	49.37±17.57
Taken daily with diet amount of phenylalanine (mg/day)*	276.09±188.85	257.71±130.09	254.86±174.43	270.00±158.89
Total protein (g/day)*	33.86±10.47	35.01±10.62	35.26±9.70	35.47±9.89
Total Energy (kcal/day)*	1442.07±364.31	1449.67±399.68	1432.38±373.39	1425.09 ±368.76

***:** *mean ± SD*

Table II: Patients' eating habits, amino acid mixture and special product consumption status

	n (%)
Number of main meals consumed per day	
2	1 (5)
3	19 (95)
Number of snacks consumed per day	
1	2 (10)
2	13 (65)
3	3 (15)
4	1 (5)
5	1 (5)
Number of meals consumed daily of the amino acid mixture	
1	4 (20)
2	9 (45)
3	1 (5)
4	1 (5)
5	4 (20)
6	1 (5)
Consumption of amino acid mixture	
With a baby bottle	6 (30)
With glass	13 (65)
With bowl	1 (5)
Consumption of the amino acid mixture in the recommended amount per day	
All the time	10 (50)
Most of the time	8 (40)
Rarely	2 (10)
Consumption of amino acid mixture in the presence of other ındividuals	
Yes, it consumes	12 (60)
No, it does not consume	8 (40)
Consumption status of amino acid mixture in kindergarten/school	
Yes, it consumes	10 (50)
No, it does not consume	10 (50)
The reason why children who do not consume amino acid mixtures in the presence of other ındividuals and in kindergarten/school do not consume	
Ashamed	6 (60)
Difficult to carry	2 (20)
Hides the illness	2 (20)
Special product consumption status	
Yes, it consumes	12 (60)
No, it does not consume	8 (40)
The reason why children who do not consume special products do not consume	
Expensive prices	4 (50)
Bad taste	4 (50)
Families' children's feelings/emotional state during the consumption of amino acid mixtures	
Comfortable	12 (60)
Calm	1 (5)
Nervous	6 (30)
Hectic	1 (5)
According to parents, the compliance status of their children with their current diet	
Yes, it fits	17 (85)
No, it doesn't fit	3 (15)
The reason for non-compliance of patients who are thought to be non-compliant with the diet	
Involvement of family elders in the extended family	2 (10)
Unwilling/disliking dieting	1 (5)

Table III: Relationship between blood phenylalanine and tyrosine levels of children with pku and the amount of phenylalanine taken in the daily diet

Daily intake of phenylalanine	Blood phenylalanine level*	Blood tyrosine level*
1. Control	r=-0.577 p=0.006	r=0.297 p=0.191
2. Control	r=-0.716 p<0.001	r=0.097 p=0.676
3. Control	r=-0.739 p<0.001	r=-0.093 p=0.687
4. Control	r=-0.534 p=0.013	rho=0.088 p=0.704

***:** *1st, 2nd, 3rd, 4th follow-up visits, respectively,* ***r:** Pearson correlation coefficient,* ***rho:** Spearman correlation coefficient*

Table IV: Relationship between blood phenylalanine level and amino acid mixture consumption and diet adherence of children with PKU

Blood phenylalanine level	Consumption of the entire amino acid mixture*	Daily consumption frequency of amino acid mixture, meal consumption*	Compliance with the diet*
1. Control	rho=0.138 p=0.550	rho=-0.011 p=0.962	rpb=-0.267 p=0.242
2. Control	rho=-0.155 p=0.501	rho=-0.108 p=0.641	rpb=-0.225 p=0.326
3. Control	rho=-0.280 p=0.219	rho=-0.014 p=0.953	rpb=0.086 p=0.710
4. Control	rho=-0.231 p=0.314	rho=-0.093 p=0.689	rpb=-0.237 p=0.301

***:** *1st, 2nd, 3rd, 4th follow-up visits, respectively,* ***rpb :** Point double series correlation coefficient,* ***rho:** Spearman correlation coefficient.*

Table V: Relationship between diet adherence and daily consumption frequency of amino acid mixture

	Compliance with the diet	p
Daily meal consumption of the amino acid mixture	Cramer's V =0.667	p=0.025

***Cramer's V:** Cramer's V correlation coefficient*

was found to be statistically significant (p<0.001). The relationship between the daily phenylalanine intake and blood phenylalanine level in the third measurement was a strong negative correlation (r=-0.739) and was found to be statistically significant (p<0.001). The relationship between the daily phenylalanine intake and blood phenylalanine level in the fourth measurement was a moderate negative correlation (r=-0.534) and was found to be statistically significant (p=0.013).

No statistically significant relationship was found between dietary phenylalanine levels and blood tyrosine levels measured in four consecutive controls during follow-up (p=0.191, p=0.676, p=0.687 and p=0.704, respectevily).

The relationship between blood phenylalanine levels and the complete consumption of the amino acid mixture, diet compliance, and the number of daily meals of the amino acid mixture is presented in Table IV.

No statistically significant relationship was found between blood phenylalanine levels and consumption of the amino acid mixture measured in four consecutive controls during follow-up (p=0.550, p=0.501, p=0.219 and p=0.314, respectevily).

No statistically significant relationship was found between blood phenylalanine levels and daily meal consumption of amino acid mixture measured in four consecutive controls during follow-up (p=0.962, p=0.641, p=0.953 and p=0.689, respectevily).

The relationship between diet compliance and the daily meal consumption of amino acid mixtures is presented in Table IV.

The relationship between daily meal consumption of amino acid mixture and dietary adherence was examined with Cramer's V correlation coefficient, and a statistically significant relationship was found at a positive moderate level (Cramer's V=0.667) (p=0.025).

DISCUSSION

In phenylketonuria, a number of barriers such as time, management and economic reasons can make it difficult for both patients and families to comply with the diet, which is the most important step of treatment. Problems in compliance with the diet cause blood phenylalanine levels to rise and this negatively affects long-term neurocognitive development. Considering the positive effects of phenylalanine intake at the recommended level with the diet on the prevention of neurological disorders and the achievement of normal intelligence coefficients by patients, the importance of compliance with the diet emerges (9,10).

In recent studies, it has been emphasized that better metabolic control is achieved by keeping blood phenylalanine levels at lower limits, and it is reported that limit values can be kept higher for adolescence. In our study, the target blood phenylalanine level was determined as 120–360 µmol/L (2-6 mg/dL) for all age groups in order to ensure metabolic control (11,12).

In our study, although the average blood phenylalanine level was found to be between 120-360 µmol/L in all controls of the patients; it is seen in the Table I that the upper level of the standard deviation is well above 360 µmol/L. When the relationship between the phenylalanine level taken in the daily diet and the blood phenylalanine level is considered;A moderate positive correlation was found in the 1st and 4th controls,and a high positive correlation was found in the 2nd and 3rd controls (p=, 0.006, p<0.001, p<0.001, p=0.013). It is thougt that the cause of this situation is due to the deficiencies and errors in the information obtained from the patients' families. If the daily recommended phenylalanine level is followed, it is seen that blood phenylalanine levels remain at the target level and metabolic control is achieved. In the literature, as in our study, there are studies in which blood phenylalanine levels are seen in target ranges with compliance with diet, but there are also studies in which blood phenylalanine values are seen above the target range. In a study conducted on 85 patients diagnosed with phenylketonuria in various age groups, the mean phenylalanine values of the patients were found to be 342 µmol/L in patients under 18 years of age and 440.4 µmol/L in patients over 18 years of age (13). In another study in which 144 children and their mothers were evaluated with phenylketonuria between the ages of 1-15, it was determined that the average blood phenylalanine values of 60.4% of the patients were above the recommended range of 120-360 µmol/L, and dietary compliance was worse in school-age children (5).

When the relationship between daily phenylalanine levels and blood tyrosine levels was examined, no statistically significant relationship was found in all 4 controls (p=0.191, p=0.676, p=0.687, p=0.704). Phenylalanine-free amino acid mixtures provide the other essential amino acids required by the body and sustain growth and development (14).

While 40% of the patients did not want to consume amino acid mixtures with other individuals, 50% stated that they did not consume them at school. When the reason for not consuming was questioned, answers such as embarrassment, not wanting to carry, and hiding one's illness were received. Similarly, studies show that children have taste and flavor problems while consuming amino acid mixtures, and they do not want to consume them for reasons such as not needing them at school and being embarrassed (15,16).

When the number of daily meals taken with amino acid mixture and diet compliance parameters (such as blood PHE level) were examined, a positive moderate statistically significant relationship was found (p=0.025). As the number of meals taken with amino acid mixture during the day increases, diet Phe level remains within target ranges and fluctuations in blood Phe level are prevented. It is observed that compliance increases. In a study conducted on 41 patients between the ages of 8 and 19 with phenylketonuria, it was observed that consuming amino acid mixtures at least three meals provided better metabolic control (17). With the advancement of age, the number of daily meal consumption of the amino acid mixture decreases in children, which makes it difficult to comply with the diet (16). There are studies showing that dividing amino acid mixtures into at least 3-4 meals during the day prevents fluctuations in blood phenylalanine levels (18).

When the relationship between blood phenylalanine level and consumption of the entire amino acid mixture (p=0.550, p=0.501, p=0.219, p=0.314), blood phenylalanine level and compliance with diet (p=0.242, p=0.326, p=0.710, p=0.301), blood phenylalanine level and the number of daily meals consumed of the amino acid mixture (p=0.962, p=0.641, p=0.953, p=0.689), no statistically significant relationship was found in all 4 controls.

In 40% of patients who do not consume special products, the reasons for not consuming them are that the products are expensive and taste bad. When we look at the literature, in parallel with our study, among the reasons why special products are not consumed, are that they taste and smell badly, and at the same time they are high cost (8,19).

When parents were asked about their children's level of compliance with the diet, 85% said that they followed the diet, while 15% said that they were non-compliant with the diet; As a reason, they stated that the family elders in the extended family interfered and that their children did not want and did not like to diet. Studies have shown that patients' social lives and ages are related to their compliance with diet. It is stated that each age group and social life should be evaluated within itself, and the effect of mood changes on diet should not be ignored (20-22).

In our study, when the emotional state of the families was questioned during the consumption of amino acid mixtures by the child during the day, 60% stated that they were relaxed, 5% were calm, 30% were nervous, and 5% were hectic. In a study conducted on the parents of 36 healthy children with 61 phenylketonuria and a control group, it was shown that the mothers of children with phenylketonuria had higher anxiety levels and depression scores than the control group. Studies have shown that the tension between parents in child care makes it difficult to comply with the diet (23). It has been emphasized that with the provision of education plans for parents about the disease, compliance with diet and diet success will increase in patients with phenyleketonuria (24).

CONCLUSION

Phenylketonuria is one of the hereditary metabolic diseases for which medical nutrition therapy is of great importance. With early diagnosis and treatment, it should be ensured that a nutritional therapy that is limited from natural proteins, amino acid mixtures and artificial proteins, and adequate energy intake is provided for life. Many factors such as the age of the patients, their presence in the school age period, the variability of their eating habits with age, living in a large family, and intervening recurrent infections make it difficult to adapt to diet and metabolic control. For this reason, it should not be forgotten that there are multiple parameters at the point of providing metabolic control and each of them also affects the process of adaptation to the diet.

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