

Does Dietary Treatment Cause Obesity in Phenylketonuria? Comparison of Obesity Ratios of Patients Receiving Dietary Treatment and Tetrahydrobiopterin Treatment

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Abstract

Phenylketonuria is treated either with tetrahydrobiopterin (BH4) or with a phenylalanine-restricted diet. Patients in the diet group may tend to consume carbohydrate-rich foods which have a risk for obesity. In this study, the prevalence of obesity+overweight among phenylketonuria patients either treated with phenylalanine-restricted diet or with BH4 were compared. Patients with phenylketonuria were divided into two groups on dietary treatment and BH4 treatment. Body mass index (BMI), BMI-percentile, and z-score values of patients were calculated and classified as underweight, normal-weight, overweight, and obese according to their nutritional status. The annual mean phenylalanine level of each patient is also evaluated. The study was done retrospectively. A total of 130 patients was included. 77 were receiving diet (female (n,%):37, 48.1%; male (n,%):40, 51.9%) and 53 were receiving BH4 (female (n,%):33, 62.3%; male (n,%):20, 37.7%) respectively. According to BMI-z-score, the sum of the ratio of obesity+overweight was found to be 35.1% in the diet group, 16.9% in the BH4 group. Ratio was significantly higher in diet group ($p=0.02$). When obesity+overweight ratios were examined in terms of female/male distribution, no significant difference was found. Considering the correlation of obesity+overweight ratios with age in two groups, the median age of the patients with normal weight+underweight in the BH4 group were found as 46-months, and the median age of obese+overweight patients was 137-months ($p=0.001$). For the same situation, there was no significant difference in the dietary treatment group ($p=0.92$). Mean annual phenylalanine levels were significantly higher in obese+overweight patients ($p=0.047$) in the BH4 treatment group but this difference was not significant in the diet group ($p=0.051$). Patients on the phenylalanine-restricted diet have a risk of obesity or overweight. Therefore, attention should be paid not only to the phenylalanine levels of these patients but also to their weight control and dietary content.

Keywords: Phenylketonuria, diet, tetrahydrobiopterin, obesity, overweight



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Introduction

Phenylketonuria (PKU) is an inherited metabolic disorder that is caused by the deficiency of phenylalanine hydroxylase enzyme.¹ Due to phenylalanine hydroxylase enzyme deficiency, conversion of phenylalanine (Phe) to tyrosine is affected completely or partially, and the accumulated phenylalanine in untreated cases causes irreversible brain damage.¹ Phenylketonuria (PKU) is the most common inherited disorder of amino acid metabolism in Turkey.^{1,2} In the treatment of the disease, if patients are tetrahydrobiopterin (BH4) responsive, BH4 treatment is started and if unresponsive, patients are treated with a phenylalanine restricted diet.^{3,4}

Dietary treatment aims to keep the blood phenylalanine levels within the target values by applying a diet containing low phenylalanine which means low natural protein.⁵⁻⁷ Patients on dietary treatment tend to eat carbohydrate-rich foods and this situation creates a risk for obesity.⁵⁻⁷ Various studies are arguing that the prevalence of obesity in PKU patients are equal or increased to the general population of the related country.⁵⁻⁸

In this study, we aimed to compare the obesity ratios of our PKU patients receiving BH4 treatment and dietary treatment. We also compared the obesity ratios of our PKU patients with the overall obesity ratios in Turkish children.

Material and Method

Ethics committee approval was taken from local ethic committee (Decision No: 2021/470). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We included patients diagnosed with PKU, who were followed up at Erciyes University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Nutrition and Metabolism, and divided them into two groups according to their treatments, dietary treatment or BH4 treatment. Patients <19 years of age were collected. Our patients are from the city of Kayseri and the neighboring cities of Kayseri which reflects the population of, Central Anatolia Region, in Turkey. The PKU diagnosis was made by either measuring blood phe levels or both phe levels and genetic testing. BH4 responsiveness was defined as a 30% reductions of phe levels at the time of the 24th hour after 20 mg/kg/dose of BH4 administration. Patients receiving both BH4 and dietary treatment were excluded from the study. PKU patients without any treatment, with severe neurological problems, and patients who have additional diseases, were also excluded. Anthropometric measurements were done by using a Densi[®] branded digital weighing scale and stadiometer. Height of children under two years of age and those who are unable to stand stably enough were measured in the supine position on a measuring board. The weight and height of

the patients were recorded routinely in their files in our clinic. The weight measurements were done with light clothes and the height measurements were done without shoes. Anthropometric calculations of the body mass index (BMI) (kg/m²), BMI percentile (%), and z-score values were evaluated retrospectively from the files of patients by using the age and gender-specific charts of the World Health Organisation (WHO).⁸

The overweight classification was as follows: for patients <5 years: BMI z score ≥ 2 and <3 SD, for patients 5-18 years; BMI z score ≥ 1 and <2 SD.⁸

Obesity classification was for patients <5 years: BMI z score ≥ 3 and for patients 5-18 years: BMI z score ≥ 2 SD.⁸ Percentages of overweight+obesity and obesity were calculated respectively from BMI z scores and compared with the overall obesity prevalence of children in Turkey. Underweight status was defined as BMI z score < -3 SD.⁹ Annual mean phenylalanine levels were evaluated from the blood phenylalanine amino acid measurements (mg/dl) with the high-performance liquid chromatography (HPLC) analysis. The mean value of at least three measurements was calculated.

Statistical analysis was done with SPSS 15.0. Descriptive criteria are presented as mean, median, and percentage distribution. The compliance of the data to normal distribution was checked with the Kolmogorov-Smirnov test. To determine the mean differences between the groups, student t-test was used when parametric conditions were met, Mann Whitney U test in cases where they could not be met, and Pearson Chi-square to compare the differences between percentages were used when necessary, and also Fisher's exact test was used. Pearson Correlation Analysis was used to evaluate the correlation. For the significance level, $p < 0.05$ was taken.

Results

A total of 130 patients were included to the study. There were 77 patients (female (n,%): 37, 48.1%; male (n,%): 40, 51.9%) receiving dietary treatment and 53 patients (female (n, %): 33, 62.3%; male (n,%): 20, 37.7%) receiving BH4 treatment.

The distribution of nutritional status of the patients in the dietary treatment group and BH4 treatment group according to BMI z-score is given in table 1 below.

According to the BMI z-score, the ratio of obesity and overweight was found to be significantly higher in the dietary treatment group and it is shown in **Figure 1** (dietary treatment group 35.1%, BH4 treatment group 16.9%, $p = 0.02$).

When obesity and overweight ratios were examined in terms of female / male distribution, no significant difference was found in both groups ($p = 0.33$ in the group receiving dietary treatment and $p = 0.49$ in the BH4 treatment group).

Highlights

- PKU patients on dietary treatment may tend to be overweight or obese more than the normal population.
- Therefore attention should be paid not only to the phenylalanine levels of these patients but also to their weight control and dietary content.

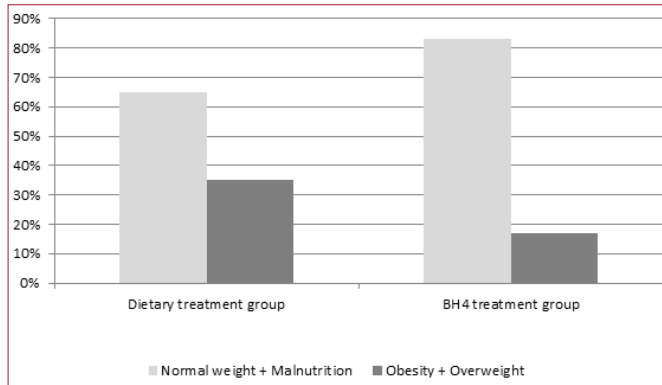


Figure 1. Percentage distribution of obesity + overweight status among the patient groups receiving dietary treatment and BH4 treatment

When the median age of the group receiving dietary treatment and the group receiving BH4 treatment was compared with the Mann-Whitney U test, the median age of the group receiving BH4 drug was found to be significantly lower ($p=0.002$) (**Table 1**).

Table 1. Number of patients, demographic features and analysis of nutritional status according to treatment groups

	Dietary treatment group	BH4 treatment group	P value
Gender			
Male (n,%)	40 (51.9)	20 (37.7)	
Female (n,%)	37 (48.1)	33 (62.3)	
Total (n)	77	53	
Mean Age (month)			0.002
Mean±SS	101.7±64.9	66.1±49.2	
Median (IQR)	97 (103)	56 (62)	
Nutritional Status			
Underweight (n,%)	0 (0)	3 (5.7)	
Normal weight (n,%)	50 (64.9)	41 (77.4)	
Overweight (n,%)	15 (19.5)	7 (13.2)	
Obesity (n,%)	12 (15.6)	2 (3.8)	
Nutritional Status Subgroups			0.02
Underweight+normal weight (n,%)	50 (64.9)	44 (83.1)	
Overweight+obesity (n,%)	27 (35.1)	9 (16.9)	

When the correlation between age (in months) and BMI z-score was examined in the BH4 treatment group, it was found that they were positively correlated with a low degree and this correlation was statistically significant ($R: 0.33$ and $p: 0.017$).

In the BH4 treatment group, the median age of the patients in the normal weight+underweight subgroup were found 46 months, and in the overweight+obesity subgroup 137 months ($p=0.001$). In the dietary treatment group, the median age of the patients in the normal weight+underweight subgroup were found at 96 months, and in the overweight+obesity subgroup at 99 months ($p=0.92$) (**Table 2**).

When the median annual phe level of the patients in the dietary treatment group and BH4 treatment group were compared, the mean annual phe level of the group that received the diet was found to be higher; 9,6 mg/dl and 4,5 mg/dl, respectively ($p < 0.001$).

Table 2. Comparison of the median age of normal weight+underweight and obese+overweight children in treatment groups

Groups	Normal weight+ Underweight Mean±SS Median (IQR)	Overweight+ Obesity Mean±SS Median (IQR)	p value
BH4 treatment group, mean age (month)	51.2±34.6 46 (45)	138.7±46.4 137 (84)	0.001
Dietary treatment group, mean age (month)	100.8±67.7 96 (112)	103.4±60.4 99 (77)	0.92

Considering the annual median phe levels in normal-weight patients and obese+overweight patients in the dietary treatment group, the annual median phe levels in obese+overweight patients were higher, but the difference was not statistically significant ($p=0.051$).

Discussion

Obesity ratios vary within the countries. According to 2011-2012 National Health and Nutrition Examination Survey (NHANES) data in the United States of America, the prevalence of overweight in children and adolescents was reported as 31.8% and obesity prevalence as 16.9% (obesity+overweight 48.7%).¹⁰

In Turkey, these ratios are lower. The prevalence of overweight is 14.3% and obesity is 6.5% (overweight+obesity, 20.8%).¹¹ This may be because fast-food consumption is less in Turkey and homemade food is widespread. Another reason for this may be the socioeconomic status of the families in Turkey is worse and there may be restrictions in consuming fast-food.

Studies in the literature, the prevalence of obesity and overweight in patients with PKU on dietary treatment was compared with the obesity prevalence of the related country or within the healthy control group.⁶⁻⁸ In this study, obesity and overweight ratios of patients with PKU on dietary treatment were compared with patients with again PKU patients on BH4 drug treatment. The fact that both of the groups had PKU, showed the positive side of the study, while the median ages of the BH4 treatment group in the study were significantly younger than the dietary treatment group (diet group median age 97 months, BH4 group median age 56 months, $p=0.002$) constitutes the limitation of the study. BH4 treatment is approved for adults and pediatric patients of 4 years of age and over in 2008.¹² BH4 treatment under age 4 is approved in Turkey in 2015 and this situation causes the BH4 treatment group to be younger than the dietary treatment group.¹²

In this study, the ratio of obesity+overweight in the dietary treatment group was found to be statistically higher 35.1% and the BH4 treatment group was 16.1% ($p=0.02$). The obesity+overweight prevalence in PKU patients on the dietary treatment group was also higher than the overall obesity prevalence in Turkish children (obesity+overweight ratio of the dietary treatment group was 35.1% and overall obesity+overweight

ratio of Turkish children was 20.8%).¹¹ Because of a restricted natural protein diet, PKU patients tend to consume carbohydrate rich foods and this may cause excess caloric intake and obesity. In the BH4 treatment group, which they have no diet, the obesity+overweight ratio is lower than the dietary treatment group and also lower than the overall obesity prevalence of Turkish children.

Studies from the USA and European countries, it was emphasized that the obesity prevalence was higher in girls in patients with PKU on dietary treatment, whereas in our study, the ratio of obesity+overweight was higher in boys (female 27%; male 42.5% $p=0.33$) but this was not statistically significant.^{7,8} Considering the overall ratio of childhood obesity in Turkey, the ratio is higher in the male gender which is overweight+obesity ratio in male gender 22.6% and 18.9% in the female gender.¹¹

In another multicenter study which is also including Turkey, 8 centers participated in the study with 397 patients.⁸ Gokmen Ozel et al.⁸ from the Ankara group gave the obesity+overweight ratio lower than our study 19.8%, 35.1% respectively. In the same study, the ratio of obesity was found to be higher in girls, contrary to our study (21.3% girls; 18.7% boys).⁸ The study of the Ankara group was done in 2014 but our study was done in 2019. Obesity and the overweight problem is increasing problem over the years. The 5-year difference between the two studies may have caused this difference. Ankara group was the first group that initiates neonatal screening program for phenylketonuria. Their patients are from Ankara and also from the Eastern Anatolia region which socioeconomic status is below the average of Turkey. Nutrition patterns vary from country to country, as well as from region to region within the same country. This may explain the different ratios of obesity among studies conducted in different regions. Kayseri and its surrounding provinces have a diet rich, especially in pastry foods. This situation may have been effective in the high rates of obesity in our study.

In addition, in our patient group, it was observed that the phe levels of the dietary treatment group were higher than the BH4 treatment group (9,6 mg/dl and 4,5 mg/dl, respectively ($p < 0.001$)). The reason for this may be that the BH4 treatment group does not require any dietary treatment. The dietary treatment group has a strict protein-restricted diet and many patients have difficulties in strict compliance with this diet. They can not fully comply with the diet so their phe levels are higher than the BH4 treatment group.

In another study from Portugal, it was found that the ratios of obesity or overweight and the risk of developing metabolic syndrome were higher in the PKU dietary treatment group when compared with the control group but the difference was not statistically significant.⁵ There are different results from different countries. This situation may be explained by the fact that different countries have different nutrition styles.

In this study when the relationship between the obese or overweight patients and age was examined, a significant correlation was not found in the dietary

treatment group, but a statistically significant correlation was found in the BH4 treatment group in the direction of increasing obesity with increasing age (median age of the normal weight group was 46 months, the median age of the obese/overweight group was 137 months, $p=0.001$). This situation raises the question of whether if the age of the BH4 treatment group was equal to the age of the dietary treatment group, would there be no statistical difference between obesity rates? However, to reveal this, it is necessary to follow the obesity rates of the same BH4 group in the following years prospectively. It is also important to do more studies that are comparing both the BH4 treatment group and dietary treatment group to see the differences. We also have not much information on how the phenylalanine restricted diet affects the PKU patients in a long-term period.

Conclusion

Obesity and overweight risk of PKU patients on the dietary group are higher than society and also higher than PKU patients who were not on diet. Therefore, attention should be paid not only to the phenylalanine levels of these patients but also to their weight control and dietary content. In the early period, if necessary, calorie restriction should be applied in their diets, or alternative solutions should be produced to increase the compliance of patients who do not comply with the diet. It is necessary to prevent the perception in the patients and also the parents that the phenylalanine restriction in diet is to be seen as the main aim in dietary treatment. It is also important to mention that phenylalanine-free high-calorie foods may not be consumed limitless in patients.

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