

## Original Article

# Overweight and Obesity in Children Under Phenylalanine Restricted Diet

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### Abstract

**Introduction:** The aim of this study is to determine the obesity and overweight frequency in children with phenylketonuria (PKU) and hyperphenylalaninaemia (HPA). **Methods:** From the patients' demographic data, diagnosis, type of diet, weight for height, body mass index, serum phenylalanine concentrations were obtained and recorded. **Results:** Four hundred and forty charts were evaluated and 288 of them were enrolled in the study. Two hundred and forty-six (85.4%) were under phenylalanine-restricted diet with protein support. Of those, 23 (9.3%) were obese and 16 (6.5%) were overweight. When we compared the obesity ratio of 246 patients with PKU and HPA to the obesity ratio in the Turkish population, the difference was statistically significant ( $p=0.025$ ). **Conclusion:** The frequency of obesity was higher in PKU and HPA children who underwent phenylalanine-restricted diet treatment than in the normal population in Turkey. Detailed studies are needed to increase the understanding of the obesity risk factors in this special disorder group.

### Key words

Hyperphenylalaninaemia; Obesity; Overweight; Phenylalanine restricted medical diet; Phenylketonuria

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### Introduction

Phenylalanine is an essential amino acid and most of it is converted into tyrosine by phenylalanine hydroxylase. For this chemical reaction, oxygen and tetrahydrobiopterine are needed, as well as the enzyme activity. If the enzyme or cofactor is deficient, phenylalanine levels are increased in the blood and clinical symptoms such as motor and mental retardation, convulsions, microcephaly and behavioural problems may develop. Phenylalanine-restricted diet is the most effective treatment.<sup>1,2</sup> It is thought that, obesity or overweight is a potential risk in these cases, since the daily calorie is supplied by fats and carbohydrates and, related eating behavioural problems in this disorder.<sup>3,4</sup>

The purpose of this study is to determine the obesity and overweight frequency in children with phenylketonuria (PKU) and hyperphenylalaninaemia (HPA), who are also under phenylalanine-restricted diet treatment.

## Methods

All patients with PKU and HPA, which were followed by Dokuz Eylul University Pediatric Metabolic Disease Department, were evaluated retrospectively. PKU defined as 'phenylalanine level is 6-10 mg/dl despite 400-600 mg/day phenylalanine intake', and HPA defined as 'phenylalanine level is <10 mg/dl despite >600 mg/day phenylalanine intake'. There was no patient, who was diagnosed with BH<sub>4</sub> (tetrahydrobiopterin) metabolism disorders. From the patients' medical records, demographic data, diagnosis, type of medical diet, weight for height, body mass index (BMI), serum phenylalanine, T<sub>4</sub>, TSH, insulin and cortisol levels were obtained and recorded. Weight for height and BMI were evaluated by relevant percentiles of the gender.<sup>5</sup> Weight for height was used for the patients 0-36 months old and BMI was used for the patients older than 36 months. According to these evaluations, lower than 85th percentile was considered as normal, 85-97th percentile was considered as overweight and higher than 97th percentile was considered as obese.

## Statistical Analysis

Statistical evaluation was performed by using SPSS software (version 15.0, SPSS Inc, Chicago, IL). Mann-Whitney U test was used to compare average values of the groups, exact Chi-square test or Fisher's exact test was used to compare rational values of the groups. Binominal test was used to compare obesity or overweight data with population data.  $p < 0.05$  values were regarded as statistically significant.

## Results

Four hundred and forty charts were evaluated and 288 of them had complete records and were enrolled in the study. The follow-up duration was between 2.5-5 years. The rest of them were excluded because of missing information of patients such as anthropometric measurements and inadequate follow-up. All patients were referred from the newborn screening program. There was no responsive patient to 48-hour BH<sub>4</sub> loading test. The patients were under phenylalanine-restricted diet by using PKU-formula without support of BH<sub>4</sub>.

Of the 288 patients, 141 (49%) were female and 147 (51%) were male. Two hundred and forty-six (85.4%) were under phenylalanine-restricted diet with protein support. Of those, 39 (15.9%) were obese ( $n=23$ ) and overweight ( $n=16$ ).

Mean age for obesity/overweight diagnosis was  $7.50 \pm 5.10$  years, and their PKU and HPA diagnosis age was  $1.7 \pm 0.8$  months. Of the 23 obese patients, 22 were PKU and one was a HPA patient.

When the obese/overweight and non-obese PKU children who underwent phenylalanine-restricted diet treatment groups were compared individually, no statistical significance was present on gender, recommended protein supplement doses, phenylalanine and protein amounts on diet (Table 1). When the obesity ratio of the 246 patients with PKU and HPA was compared to the overall Turkish population obesity ratio,<sup>6</sup> the difference was statistically significant ( $p=0.025$ ). Mean blood phenylalanine concentration in the obese/overweight group was  $10.70 \pm 5.70$  mg/dl, and this was  $9.70 \pm 7.71$  in the non-obese group. The difference was not statistically significant ( $p=0.156$ ).

**Table 1** Comparison of clinical, demographic features in obese and non-obese children with phenylketonuria (PKU)/hyperphenylalaninaemia (HPA) who underwent phenylalanine-restricted diet ( $n=246$ )

	Obese/overweight ( $n=39$ )	Non-obese ( $n=207$ )	p values
Age of the children at the time of diagnosis PKU/HPA (mean $\pm$ SD; months)	1.7 $\pm$ 0.8	1.9 $\pm$ 1.5	0.41
Gender (F/M)	99/108	20/19	0.60
Recommended PA concentration in dietary (mg/kg/day)	28,1 $\pm$ 20,2	26,3 $\pm$ 13,2	0,782
Recommended natural protein in dietary (g/day)	1,2 $\pm$ 0,3	1,5 $\pm$ 0,4	0,437
Mean serum phenylalanine concentrations (mg/dl)	10.7 $\pm$ 5.7	9.7 $\pm$ 7.7	0.156
Age of the children at the time of diagnosis obesity/overweight (mean $\pm$ SD;years)	7.5 $\pm$ 5.1		

There was a correlation between individual mean blood phenylalanine concentration and individual mean BMI value ( $r=0.362$ ;  $p=0.023$ ) in the obese/overweight group.

## Discussion

Obesity is a very important health problem and its frequency is increasing worldwide. According to data provided by the Ministry of Health of the Republic of Turkey, the frequency of obesity among children has increased ten-fold compared with the frequency in the seventies. In a study named "The Pro Children", which was carried out in 9 countries in Europe in 2003, the frequency of overweight was found to be 17% in males and 14% in females.<sup>7</sup> In the United States, prevalence of obesity among children 2-19 years old was reported to be 16.3-17%.<sup>8,9</sup> There are few studies about obesity prevalence among children with PKU and on a phenylalanine-restricted diet. In a study of 236 adults with PKU, the percentages of participants reported having obesity or overweight, were 31% and 24%, respectively.<sup>10</sup> Although those ratios are in accordance with their normal population values, they are two-fold the values that are obtained from previously mentioned larger studies. In a study carried out in Spain, 160 children with PKU were evaluated and, it was found that girls older than 13 years have significantly higher BMI.<sup>11</sup> In a study that evaluates 87 PKU patients from United States, it is reported that girls have two-fold the frequency of obesity and overweight.<sup>12</sup> In our study, we could not find difference between males and females.

In a study that was carried out in 0-18 year-old children, in our country in 2010, the frequency of obesity was 6.9%, and overweight was 14.4%.<sup>6</sup> Subsequent to comparison of these results, we found that obesity frequency is increased in children with PKU. We speculate that, phenylalanine-restricted medical diet with protein supplements and eating disorders which are associated with PKU may be responsible for this increased obesity frequency. However, we currently have no direct evidence to support this thought. Among important limitations of this study, there is no assessment of dietary energy intake of subjects. However, we can say for now, it should be kept in mind that general risk factors for obesity are also relevant for the PKU patient group.

Regarding to blood phenylalanine level and increased obesity risk, conflicting results have been obtained in the literature. In Robertson et al's study, a positive correlation was found between blood phenylalanine levels and BMI; however, no correlation was found in the study carried out on Spanish children with PKU.<sup>10,11</sup> In our study, we also have found a correlation between blood phenylalanine concentrations and BMI values in obese/overweight children with PKU/HPA who underwent phenylalanine-restricted diet treatment.

The effect of phenylalanine-restricted diet on patients' metabolism is not clear. One of the most popular explanations is increased carbohydrate intake.<sup>10,12</sup> Robertson et al stated that they, especially adult patients, consume much more instant foods, prefer fatty food instead of fresh vegetables and fruits and were not willing to exercise. More interestingly, studies on patients on diet show that calorie intake were very close or lower than suggested calorie intake.<sup>1,13</sup> But the latest data suggest patients' declarations may not be trustworthy. Therefore, dietary compliance may be followed by growth charts, BMI and/or weight for height. Limitations of our study are the retrospective design, and limited data about dietary compliance and daily exercise levels.

The frequency of obesity, an important health problem, is increasing. In the literature, there are very few studies evaluating obesity and overweight frequencies in PKU patients. According to our results, children with PKU under phenylalanine-restricted diet are at risk for obesity.

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## Authors Contributions

PG prepared the manuscript. BE, YT, İI, SBA collected the data. YO is co-corresponding author.

## Declaration of Conflicting Interest

The authors declared no potential interest with respect to the research, authorship, and/or publication of this article.

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## Ethical Approval

The local ethics committee approved this study.

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