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Overweight in classical phenylketonuria children: A retrospective cohort study

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ABSTRACT

Purpose: This cohort study aimed to determine the frequency of overweight and obesity in classical phenylketonuria children and to identify the possible influence of metabolic control on the BMI of the studied patients.
Patients and methods: The study group included 63 classical phenylketonuria patients (40 girls and 23 boys; aged 5–16 years). Their z-score BMI, metabolic control, educational level of parents and socioeconomic status were determined.
Results: Twenty children were overweight or obese and only three were underweight. The percentages of overweight and obese children were 31.7% for the whole group, 21.7% (5 out of 23) for boys and 37.5% (15 out of 40) for girls. Overweight and obesity in these phenylketonuria patients was statistically significantly more frequent when compared to national reference studies ($p = 0.0031$).

The five-year index of dietary control and the percentage of spikes exceeding 6 and 12 mg/dl (Spikes 6 and 12) indicated better metabolic control in the case of normal weight children than those who were overweight and obese ($p < 0.049$, $p < 0.041$ and $p < 0.011$, respectively). The odds ratio of being overweight or obese for those having poorer metabolic control (values higher *vs* lower than mean) was statistically significantly higher than for the remaining patients (for Spikes 12: $6.926 <$ 95%CI: 2.011–23.854 $>$; $p < 0.002$). These results strongly suggest a link between overweight and diet non-compliance.
Conclusions: Children with classical phenylketonuria presented higher odds of being overweight or obese as compared with reference national studies, with girls only having a higher frequency of overweight.

1. Introduction

Phenylketonuria (PKU; OMIM 261600) is a rare, recessively inherited metabolic disease of phenylalanine (Phe) metabolism, caused mostly (98–99%) by deficient activity of the hepatic-based enzyme L-phenylalanine-4-hydroxylase (PAH; EC 1.14.16.1). The deficiency results in a complete or partial inability to convert Phe to tyrosine, with the loss of PAH activity leading to accumulation of Phe and its derivative metabolites, causing irreversible neurological damage if left untreated [1].

Available treatment aims to decrease the blood Phe concentration mainly with a low Phe diet, restrictive in natural protein, combined with Phe-free supplements and low protein commercial food products. New treatment options are being developed that might reduce the burden of such a difficult and restrictive diet, but the diet still remains the only effective treatment in all PKU patients. When diagnosed by newborn screening and treated immediately, patients essentially show normal development, although neuropsychological deficits as well as behavioural and social issues have been reported [2–4]. In the past, frequent side effects of the diet included malnutrition and growth disturbances. Indeed, in 1950s and 1960s, unsatisfactory physical growth in children with treated PKU was demonstrated [5,6]. In 1971, Schmidt [7] analysed data of 23 PKU children, finding that their height and weight were not normally distributed, but overrepresented below 10th

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and above 90th centile, with equal number of those below 10th and above 90th centiles. The first reports of the possibility of being overweight in PKU date back to 1979 and 1982 [8,9]. The latter study reported a higher risk of being overweight for girls and in patients with low socioeconomic status (SES) compared to the National Center for Health Statistic data [8]. There was no correlation between being overweight and the level of blood Phe. In similar studies conducted at the same time, the opposite results were obtained, growth disturbances concerned not only infants and toddlers [10–13], but also older children [14–17].

Growth in PKU patients remains a concern, particularly due to the changes that have occurred over the years in the patients' diet. The published results on overweight and obesity in PKU patients are contradictory, depending predominantly on what region the study group came from. Most American researchers indicated a risk of being overweight in PKU patients in different developmental stages [8,18–20], while European researchers usually observe the opposite [21–32]. However, in the case of Europe, there have been some reports of overweight PKU children in the past few years. In a multi-centre study conducted by Gokmen Ozel et al. [33] in eight centres in Europe and Turkey, the prevalence of overweight and obesity varied widely between countries, commonly following respective national trends. Since this study did not use uniform methodology and is the sum of the responses of participating centres with a different number of PKU patients examined, it is difficult to generalise the results. A recent study from the USA showed that 40% of paediatric PKU patients were overweight or obese [20], whereas the latest research from Australia documented no statistically significant difference in BMI between PKU children and their healthy peers [26]. Aldámiz-Echevarría et al. [34] documented that BMI values until 16 years of age, except for the age of 8, only deviated marginally from the population data, with a statistically significant difference at the age of 18, and only in girls.

The elements of the recommended diet in PKU are low Phe and high energy foods to promote anabolism and prevent protein insufficiency [15]. According to Rocha et al. [35], such a diet may lead to obesity, but the lack of proper metabolic control could be potentially related to malnutrition. Dobbelaere et al. [14] did not report a link between growth retardation and Phe levels. Similarly, no correlation between Phe levels and linear growth was found by Arnold et al. [15], and no correlation between Phe levels and loss of height by Weglage et al. [10].

The present study aimed to determine the frequency of overweight and obesity in classical PKU children and to identify the possible influence of metabolic control (expressed by Phe concentrations) and socioeconomic factors on the BMI of the study participants.

2. Material and methods

2.1. Patients & data collection

This retrospective cohort study included all PKU patients born between May 1999 and June 2012 who were treated at the Department of Pediatric Gastroenterology and Metabolic Diseases, of the Poznan University of Medical Sciences (Poland) - a reference unit for PKU patients from western Poland. The inclusion criteria were: classical PKU diagnosed in the neonatal screening programme, continuous treatment and age above 5 years. For the purposes of our analysis, patients with classical PKU were defined as those who, at diagnosis, required a low Phe diet to maintain plasma Phe levels within the target range of 2–6 mg/dL (120–360 μmol/L) and whose Phe levels without diet exceeded 20 mg/dL (1200 μmol/L) [1,36,37]. The exclusion criterion was chronic or acute disease which may influence PKU treatment. At the time of the study, our department was taking care of 64 PKU patients (40 girls and 24 boys) born between May 1999 and June 2012, of which, all but 1 participated in the study. The excluded PKU boy was suffering from spina bifida and hydrocephalus.

The studied PKU group was followed by a multi-disciplinary team (medical doctor, dietician, psychologist). Phe intake was based upon individual tolerance and ranged from 200 to 900 mg/day. The patients were followed to obtain Phe concentrations recommended for their age, and Phe-free supplements (PKU formula in the form of liquid or powder) constituted 60–80% of their daily protein intake.

From the clinical documentation, the last anthropometric record of all patients was collected. For each patient, weight (kg) and height (cm) were recorded to calculate BMI (kg/m^2), which was expressed as z-scores using the most recent regional growth charts [38]. Patients were classified as underweight (BMI < 5th percentile), normal weight (BMI = 5–85th percentiles), overweight (BMI ≥ 85th percentile) or obese (BMI ≥ 95th percentile). Consequently, percentages of overweight include overweight and obese PKU patients. Information about the socioeconomic position and educational level of the parents of all patients was also obtained. All data were collected in the years 2013–2017.

All blood Phe concentrations gathered during the first 5 years of the patients' lives were evaluated, with the exception of the 1st month, because Phe concentrations in this period are unstable. The 5-year index of dietary control (IDC) was calculated as the mean of the 12-month medians. The percentage of Phe concentrations which were within the therapeutic range was analysed for each patient. Similarly, the percentages of Phe concentrations exceeding the therapeutic range of 6 mg/dL (SPIKE 6) and its doubled value (SPIKE 12) were calculated.

Percentages of overweight/obesity and obesity in the PKU patients were compared with published national population ranges in the general population [39–41].

2.2. Ethical issues

The study design was compliant with the Helsinki Declaration of 1975 as revised in 1996 and it was approved by the Bioethical Committee at the Poznan University of Medical Sciences (Poland) (approval number: 268/15).

2.3. Statistical analysis

The Shapiro-Wilk test was applied to determine the normality of the data distribution. Wilcoxon signed rank test was used to assess differences in BMI mean rank between PKU patients and the general population. The frequency of overweight/obesity in PKU patients and the general population was compared using Fisher's exact test.

The relationship of BMI and metabolic control in PKU patients was tested in three ways:

1) Spearman correlation coefficient Rho was used to evaluate associations between the metabolic control and the continuous measure of BMI z-score;
2) then, it was tested whether metabolic control (as measured by Phe levels in the blood) was associated with the categorical variable, normal weight *vs* overweight (including obese). The objective was to determine if there was a link between a patient's inclusion in the normal weight *vs* overweight group and all the parameters of metabolic control measured as odds of being over/below mean for particular Phe blood levels (*i.e.* IDC, % of normal Phe concentrations, SPIKE 6, SPIKE 12). The 95% confidence intervals were calculated to estimate the precision of the odds ratios (ORs);
3) finally, multiple linear regression analysis, multiple forward and backward stepwise logistic regression analysis were performed. In all analyses, socioeconomic factors (SES and educational level of parents), age, sex and parameters of metabolic control (IDC, % of normal Phe concentrations, SPIKE 6, SPIKE 12) were included. As genotypes were not available for all PKU patients, the highest plasma Phe level from the period before the diet was used as a surrogate marker of PAH deficiency.

Table 1
Group characteristics.

	Age (years)	Z-score BMI	IDC* (mg/dL)	Normal Phe concentrations (%)	SPIKE 6 (%)	SPIKE 12 (%)
Range	5-16	−1.6-4.2	2-17.5	3-90	1-83	0-68
Median (IQR)	9	0.1	4.6	41	35	3
	(5-11)	(-0.56-1.38)	(3.2-6.8)	(23-55)	(17-64)	(1-15)
Mean (SD)	9.5	0.42	5.4	41	38	11
	(3.5)	(1.19)	(3)	(21)	(25)	(16)

* IDC (five-year index of dietary control was calculated as the mean of the 12-month medians).

The level of significance was set at $p < 0.05$ and statistical analysis was performed using STATISTICA 12 (StatSoft Inc., Tulsa, USA).

3. Results

The 63 participants (43 girls and 20 boys) were children with PKU aged 5–16 yearsand their characteristics are presented in Table 1.

The z-score BMI distribution in the PKU patients was not normal and differed (p = 0.049) from the general population data [38], with a mean standardised BMI of 0.42 (95% CI: 0.12–0.72). The percentages of overweight and obese children were 31.7% for the whole group, 21.7% (5 out of 23) for boys and 37.5% (15 out of 40). The differences between sexes were not statistically significant.

The comparison of our PKU data with the results of three large national studies in which the frequency of overweight and obesity was assessed is presented in Table 2. The conducted analysis revealed that overweight and obesity in our PKU patients is statistically significantly more frequent when compared to older groups of patients: 6–16 years *vs* 7–18 years [39] or 11–15 years [40] or the difference was almost statistically significant when compared to younger patients: 6–16 years *vs* 7–12 years [39] or 8 years [41]. However, the observed differences were determined exclusively by female gender. Moreover, overweight and obesity in PKU girls is also statistically significantly more frequent when compared to younger patients aged 7–12 years [39].

Phe concentrations were higher and less frequently normal in overweight and obese children than normal weight children (Table 3). Phe concentrations, IDC values and the number of spikes seem to indicate better diet compliance in the case of normal weight children.

Poor metabolic control was associated with higher OR of being overweight or obese (Table 4). The Phe concentrations, IDC values and the number of spikes implied better compliance in normal weight subjects.

There was a weak (p = 0.032) positive correlation between BMI and SPIKE 12, but no other relationship between standardised BMI and the metabolic control results or socioeconomic factors was found. Multiple regression logistic analysis revealed that the patients' BMIs were independently positively associated with SPIKE 12 (p = 0.007) and patients' age when anthropometric data were considered (p = 0.035). However, the observed relationships were weak (Pseudo $R^2 = 0.38$, p = 0.04 - for the whole model).

Table 2
Overweight and obesity percentages in the studied PKU patients as compared with national general population.

Comparative study	Study years	Subjects' age (years)	% of population from the study who were classed as overweight (statistical comparison with our PKU patients)		
			All children	Boys	Girls
Kułaga et al. [39]	2007-2009	7-18	12.3% (0.0031)*	19.3% (N.s.)	13.9% (0.0002)*
		7-12	21.6% (0.065)	24.6% (N.s.)	18.6 % (0.0068)*
Dzielska [40]	2016	8	22.8% (0.0976)	24.4% (N.s.)	21.2% (0.0642)
Oblacinska [41]	2013-2014	11-15	14.6% (0.0005)*	19.2% (N.s.)	10.4% (0.0001)*

* statistical significance.

Table 3
The comparison of Phe concentrations in normal weight and overweight/obese subjects.

Parameter	IDC* (mg/dL)	Normal Phe concentrations (%)	SPIKE 6 (%)	SPIKE 12 (%)
Normal weight (n = 40)				
Range	2.0-9.9	8-90	2-80	0-42
Median (IQR)	4.1	47	25	2
	(3.2-5.3)	(34-57)	(17-40)	(1-5)
Mean (SD)	4.6	45	32	6
	(1.9)	(20)	(22)	(9)
Overweight and obese (n = 20)				
Range	2.8-17.5	3-86	1-83	0-68
Median (IQR)	5.9	32	54	14
	(3.4-8.8)	(16-44)	(19-72)	(2-29)
Mean (SD)	6.9	34	48	20
	(4.1)	(23)	(27)	(22)
p	0.049*	0.022*	0.041**	0.011**

* IDC (five-year index of dietary control was calculated as the mean of the 12-month medians).
** statistical significance.

4. Discussion

This is the first PKU study in Europe that found an elevated BMI in a uniform group of paediatric patients with classical PKU, establishing a clear link between overweight and lack of metabolic control, as evidenced by high Phe concentrations, which could be attributed to dietary non-compliance. Few studies have examined the relationship between diet non-compliance and BMI in children with classical PKU, especially analysing the impact of blood Phe levels during the first 5 years of life on the later occurrence of being overweight or obesity. In this study, a wide range of parameters was used to estimate the correlation between Phe blood levels and BMI, and the relationship was established regardless of the parameter used.

Increased standardised BMI values in the patients studied suggested that overweight and obesity in our PKU group is more frequent than in the general healthy local peer population. Regional growth charts prepared at the same University were used to obtain the most reliable results, and they were compared with the results of our study group. Observed potential gender differences between the female and male PKU patients were not statistically significant, but this may have been due to the small number of boys.

The comparison of our data to large national studies [39–41] indicated that PKU females were more likely to be overweight than their healthy peers. In these three studies, conducted in the general population, overweight and obesity were more frequent in younger children (7–12 years old) than in older children and adolescents (13–18 years old), concordant with our PKU data. However, normal body weight was more common in girls than in boys. The definition of the overweight

Table 4
Comparison of patient's risk of being overweight or obese considering their metabolic control.

	IDC*	% of normal Phe concentrations*	SPIKE 6*	SPIKE 12*
OR	4.210	3.500	4.896	6.926
95% CI	1.330 to 13.320	1.112 to 11.017	1.548 to 15.486	2.011 to 23.854
p	0.014	0.032	0.007	0.002

* values higher *vs* lower than mean.

and obesity was based upon CDC standards (85th and 95th percentile), rendering the present study most comparable to that conducted by Kułaga et al. [39], whereas the studies by Oblacinska [40] and Dzielska [41] referred to WHO and IOTF definitions, respectively.

Studies that assessed the phenomenon of overweight and obesity in PKU patients differ in terms of several methodological issues. A wide range of inclusion criteria were applied: classical PKU only, all forms of PKU, PKU + HPA, non-specified PKU. There were also different modalities of treatment resulting from the historical context, 40 years of observation and more recently, from therapeutic options available and applied due to different forms of PKU in different countries (*e.g.*, low Phe diet, BH4 only, both options combined). In some studies, the BMI of PKU patients was referred to that of a control group or national growth charts, whereas in the others, the frequencies of overweight between PKU patients and general population were compared. Control groups were based on small groups of healthy peers [22,31,32] or siblings [26]. Rocha et al. [27] enrolled a relatively larger, as compared to the other studies, control group comprising 78 subjects, 74% of which were close relatives (siblings or cousins) and compared the frequency of overweight/obesity in PKU patients and healthy controls. In several studies, body mass and/or BMI were compared to national reference values: US National Center for Health Statistics (NCHS) reference data [8,9,18,19], not specified reference group of French children [17], official Spanish percentiles/reference values [23,25] or reference values from another country [21,42]. Such an approach allows for the comparison with growth standards and may be suggestive of potential overweight/obesity but does not allow for the assessment of the phenomenon of overweight/obesity in comparison to healthy peers. Holm et al. [8] also compared their PKU data to an external control group, documenting higher body mass percentiles, however, no difference in comparison to 184 children assessed by the Fels Research Institute Group was revealed.

The other option applied in some studies was to compare the frequency of overweight/obesity in PKU patients to large national studies. Burrage et al. [20] classified patients as overweight (BMI $\geq$ 85th percentile) or obese (BMI $\geq$ 95th percentile) to maintain consistency with the NHANES study; of the 87 patients, 60% (n = 52) were normal weight, whereas 40% (n = 35) were overweight or obese. The prevalence of overweight and obesity in the studied PKU population was similar to what could be expected according to the data from the United States. However, when patients were analysed by gender, statistically significant differences were observed. In a multi-centre study, Gokmen Ozel et al. [33] classified overweight in children as follows: for patients aged below 5 years of age BMI z-score $\geq$ 2 and < 3 SD, for patients older than 5 years of age BMI z-score $\geq$ 1 and < 2 SD and obesity BMI z-score $\geq$ 3 and $\geq$ 2SD. The frequency of overweight/obesity in PKU patients was calculated and compared with the general population ranges [43]. However, in the reference data, surveys that collected self-reported data were included. Moreover, definitions of obesity in children from the general population varied between IOTF and WHO standards. The small groups of PKU patients included in some centres suggest that the report only covers a part of the patients remaining under control. In addition, the median age differs statistically significantly between centres. In a very recent study, Ozturk et al. [42] compared the obesity ratio of their 246 patients with PKU and HPA to the general Turkish population obesity ratio, reporting a statistically significant difference (p = 0.025). However, no information about the applied definition of obesity and age of the control subjects was given.

The present study revealed that poor metabolic control was statistically significantly linked to being overweight and obese. McBurnie et al. [18] suggested a positive correlation of Phe values with body weight in girls with PKU, although their presentation of the results does not allow for any deeper analysis. Similarly, Burrage et al. [20] suggested that poor compliance with Phe-restricted formula may be associated with an increased risk of being overweight in female patients. However, they divided the patients into only 2 categories (compliant *vs* non-compliant), whereas we performed analyses treating data as binary (ORs), but also outlining Phe concentrations as a continuum. Moreover, our results suggest that the same phenomenon is present in the whole population of PKU patients, not only limited to female patients. A positive relationship between Phe levels and body weight in the early stages of physical growth was also revealed by Aldámiz-Echevarría et al. [34]. However, the mean BMI in their PKU group did not differ from the general population data. Albersen et al. [43] did not find an association between mean blood Phe level and body fat percentage in young patients with PKU, whereas Ozturk et al. [42] documented a statistically significant correlation (r = 0.362; p = 0.023) between mean blood Phe concentration and BMI in the obese/overweight group.

Still, it is not certain whether non-compliance and excessive Phe levels lead to higher calorie intake, or whether the higher Phe levels demonstrate inadequate parental care in many aspects, including negligence regarding the weight of the child. The present knowledge does not clarify the main etiological reasons for being overweight in PKU. Moreover, there are no evidence-based studies to indicate if overweight or obesity is related to the disorder itself, to the low Phe diet, or to patient's lifestyle behaviour. There is a lack of research regarding potential risk factors in PKU, and it can only be speculated if there are important causes of overweight and obesity [35]. One hypothesis is that the low Phe diet, which is typically rich in carbohydrate content, contributes to weight gain in PKU patients [44,45]. In the study by Acosta et al. [19], overweight occurred despite reported energy intakes that appeared to be less than recommended. From the point of view of technology, there are ongoing attempts to optimise taste, content and energy value of low Phe diet, but undesirable eating habits and patterns prevail. Currently, the main risk factors for young people, if pathological cases are disregarded, are inadequate diet and low physical activity.

The presence of increased body weight in PKU patients still remains a controversial issue. Excess weight may have an impact on future life in view of published data documenting increased oxidative stress [46,47] and higher concentrations of atherosclerotic markers [48] in PKU patients. Therefore, all overweight PKU children should receive thorough dietetic advice. Nonetheless, the potential impact of PKU diet and non-compliance demands further studies.

4.1. *The limitations of the study*

The limitations of our study are mainly related to the retrospective data collection, running several correlation analyses, lack of a direct control group, and sample size (especially for boys) that could limit expected results as well as the fact that it is a single centre study. Nonetheless, the strength of our study is the enrolment of all patients

treated in our clinic who met the inclusion criteria and the comparison to a large national study assessing the frequency of overweight in the general population in which a comparable methodological approach was applied. It is of note that the lack of data on caloric intake did not allow the investigation of its possible links with BMI in our study group. Well-planned large multi-centre studies are warranted to confirm our findings.

5. Conclusions

In conclusion, children with classical PKU presented higher odds of being overweight or obese as compared with the reference national studies. However, a higher frequency of overweight was only documented in girls. Our data strongly suggest a link between being overweight and poor metabolic control which implies diet non-compliance.

Declaration of Competing Interest

Dariusz Walkowiak, Michał Musielak, Mariusz Ołtarzewski, Jerzy A. Moczko, Rafał Staszewski declare that they have no competing interests.

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