High prevalence of overweight and obesity in females with phenylketonuria

Lindsay C. Burrage a,b,d,* , Judy McConnell c , Rebecca Haesler a,b , Mary Ann O’Riordan d , V. Reid Sutton a,b , Douglas S. Kerr c , Shawn E. McCandless c

a Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA
b Texas Children’s Hospital, 6701 Fannin St., Houston, TX 77030, USA
c Department of Genetics and Genome Sciences, Case Western Reserve University and Center for Human Genetics, University Hospitals Case Medical Center, 11100 Euclid Ave., Cleveland, OH 44106, USA
d Division of Endocrinology and Metabolism, Rainbow Babies and Children’s Hospital, 11100 Euclid Ave., Cleveland, OH 44106, USA

1. Introduction

Newborn screening for presymptomatic diagnosis of PKU is one of the major public health success stories of the 20th century with dietary treatment at the center of that success. Early dietary restriction of phenylalanine prevents the major sequelae associated with untreated PKU: intellectual disability, seizures, behavior problems and microcephaly. Thus, PKU patients are advised to consume a low-phenylalanine diet together with an amino acid-based, phenylalanine-free formula. Thus, PKU patients tend to consume a diet enriched in carbohydrates which could predispose to obesity. Studies in the 1980s and 1990s demonstrated that school-age phenylketonuria (PKU) patients have a higher mean body weight compared to a control population. However, no recent studies in the United States PKU population have examined whether this trend has persisted or whether adolescents are also affected. To investigate whether pediatric PKU populations (ages 2–20 years) in two major metropolitan areas of the United States (Cleveland, OH and Houston, TX) have a higher than expected percentage of overweight (BMI ≥ 85th percentile) relative to the general population in the United States (NHANES), a retrospective chart review of PKU patients born between 1990 and 2008 and followed in Cleveland, OH (Rainbow Babies and Children’s Hospital/University Hospitals Case Medical Center) and in Houston, TX (Texas Children’s Hospital) was performed. Based on data from the U.S., 40% of pediatric PKU patients were overweight or obese. However, the percentage of overweight females (55%) and obese females (33%) is 1.8× and 2.1× higher respectively than expected based on comparison data from U.S. children. Further studies are necessary to identify potential strategies for prevention of excessive weight gain in children with PKU, especially in females.

Abbreviations: BMI, body mass index; PKU, phenylketonuria.

* Corresponding author at: Department of Molecular and Human Genetics, Baylor College of Medicine, Texas Children’s Hospital, 6701 Fannin St., Suite 1560, Houston, TX 77030, USA. Fax: +1 832 825 4294.
E-mail address: burrage@bcm.edu (L.C. Burrage).

© 2012 Elsevier Inc. All rights reserved.
non-US populations have not confirmed the tendency for PKU patients to become overweight nor have they found inherent differences in resting energy expenditure that would explain an increased risk for overweight in PKU patients. Although no difference in body composition was found in pediatric PKU patients relative to a control population in an Austrian study, a more recent study detected a higher fat mass in Dutch pediatric PKU patients relative to controls. The interpretation of data in patients with PKU is complicated by the fact that the prevalence of overweight has risen in the general pediatric population of the United States since the 1980s. According to recent data from the National Health and Nutrition Examination Survey (NHANES, 2007–2008), 11.9% of children ages 2–19 years have a body mass index (BMI) ≥97th percentile, 16.9% have a BMI ≥95th percentile (defined as obese), and 31.7% have a BMI ≥85th percentile (defined as overweight). Despite this rise in prevalence of obesity in the general pediatric population, no study has re-examined the prevalence of obesity and overweight in the United States school-age PKU population relative to the general population to determine if there has been a simultaneous rise in prevalence in this unique population. Furthermore, despite the high rates of obesity in adolescents, no recent study has examined the prevalence of overweight and obesity in a U.S. adolescent PKU population.

The present study is a retrospective chart review that investigated whether PKU patients (ages 2–19 years) from two major U.S. metropolitan areas have a higher than expected percentage of overweight (BMI ≥85th percentile) and obesity (BMI ≥95th percentile) relative to published pediatric data from the general population in the United States. In addition, we investigated whether plasma phenylalanine concentration over the one year prior to the most recent metabolic appointment (a measure of dietary compliance), fraction of total calories consumed from formula, and initial plasma phenylalanine concentration (a marker for the severity of the enzymatic deficiency) are correlated with BMI in this pediatric PKU population.

2. Materials and methods

2.1. Study population

This retrospective chart review included all PKU patients born between 1990 and 2008 who were managed at University Hospitals Case Medical Center/Rainbow Babies and Children's Hospital or by the Department of Molecular and Human Genetics at Baylor College of Medicine/Texas Children's Hospital in Houston, TX. For the purposes of this study, PKU patients were defined as those patients who require a low-phenylalanine diet and/or phenylalanine-free supplemental formula to maintain plasma phenylalanine levels within the target range of 120–360 μmol/L. In Cleveland, the patients were identified with the assistance of the metabolic nutritionist who participates in the care of all PKU patients at the institution. At Texas Children's Hospital, patients were identified using the metabolic clinic patient database. Patients with hyperphenylalaninemia, who have elevated plasma phenylalanine relative to the general population but who do not require a low-phenylalanine diet and/or supplemental phenylalanine-free formula to maintain plasma phenylalanine levels within the target range, were excluded from the study. Likewise, patients with a second metabolic disorder (e.g. diabetes, hypothyroidism, other inborn errors or metabolism) and patients with no clinic visits after the age of 24 months were also excluded. For patients who became pregnant, only data prior to pregnancy was used. All procedures were approved by the University Hospitals Case Medical Center and Baylor College of Medicine Institutional Review Boards (IRB).

2.2. Data collection and analysis

For each patient, the initial plasma phenylalanine (newborn screen confirmatory sample) was recorded if available. In addition, for each patient and each clinic visit, age, weight (kg), length/height (cm), and BMI (kg/m²) were collected. For the most recent clinic visit as of December 31, 2010, all plasma phenylalanine levels (and plasma tyrosine levels in Houston patients) within the past year, the metabolic formula type, and the quantity of calories prescribed from the metabolic formula were recorded. The average daily caloric intake for each patient was estimated using previously published data assuming an activity level of moderate as total calorie prescriptions were not routinely provided to patients at either site. Formula prescriptions at both sites were typically based on protein not on total calories. In the Houston population, daily caloric intake as calculated from dietary records was used if available. Lastly, the use of sapropterin dihydrochloride or other treatment supplements was also noted.

Age, gender, height and body weight for each patient from the most recent clinic visit were entered into the nutrition module of Epi Info, a software program provided by the CDC (http://www.cdc.gov/epiinfo/), that provides height percentile and z-score, body weight percentile and z-score, and BMI percentile and z-score based on the 2000 CDC growth charts (http://www.cdc.gov/growthcharts/). Percentiles were rounded to the nearest whole number. Patients were classified as underweight (BMI <5th percentile), normal weight (BMI = 5th–85th percentile), overweight (BMI ≥85th percentile) or obese (BMI ≥95th percentile) to maintain consistency with the NHANES study. Consequently, percentages of overweight include overweight and obese patients. For a single patient born in 1990, the standard adult definitions of overweight (BMI ≥25 kg/m²) and obesity (BMI ≥30 kg/m²) were used.

2.3. Statistical analysis

2.3.1. Descriptive analysis

Continuous variables, such as body weight z-score, height z-score, BMI z-score, and age are described using mean ± standard deviation. Categorical variables such as weight classes (normal weight, overweight, and obese defined above) and compliance (defined as having greater than or equal to 50% of plasma phenylalanine concentrations over the year prior to the most recent clinic visit within the target range [≤360 μmol/L]) are described as percentages. For the cross-sectional analysis, historical data was used. For each patient, the BMI from the visit nearest to the age in years (±5 months) for ages 2–16 years was used for analysis.

2.3.2. Comparisons between sites

A Student's t-test was used to compare continuous variables (BMI z-score and height z-score) between Cleveland and Houston stratified by gender. Fisher's exact test was used to compare the proportion of normal weight, overweight and obese patients in the Cleveland vs. Houston patient populations.

2.3.3. Associations with BMI

Because of the differences in percentages of overweight and obese patients in the female vs. male populations, all additional comparisons were stratified by gender. A Student’s t-test was used to compare the BMI z-score in patients who were compliant with diet vs. non-compliant with diet. A chi-square test was used to compare the percentage of normal weight vs. overweight patients in the compliant vs. non-compliant patients. Pearson product-moment correlation coefficients were used to evaluate for associations between BMI z-score and the following traits: initial plasma phenylalanine, percentage of energy intake prescribed from formula, percentage of formula calories from fat, percentage of formula calories from protein, and percentage of formula calories from carbohydrates. For statistical analysis, Graphpad Prism software, version 4.0 and SAS, 9.2 (The SAS Institute, Cary, NC) were used. The level of significance was set at p = 0.05.
3. Results

3.1. PKU population

In Cleveland, a total of 38 PKU patients were identified. Of these, five patients were excluded from the study: two because adequate interpretable data were not available, two because of a second metabolic disorder (juvenile diabetes mellitus and propionic acidemia), and one with a significant chromosomal anomaly. Thus, 33 patients (19 females, 14 males) were included in the study (Table 1). The mean age for the patients was 10.1 years with a range of 2.3 years to 19 years. Only one patient was taking sapropterin dihydrochloride.

In Houston, a total of 55 PKU patients were identified with one patient excluded because of inadequate data. Thus, 54 patients (23 females, 31 males) were included in the study (Table 1). The mean age of the patients in Houston was 9.4 years with a range of 2.1 years to 20.5 years. Seven patients were taking sapropterin dihydrochloride.

3.2. Prevalence of overweight and obesity in PKU patients

Of the 87 patients, 60% (n=52) were normal weight whereas 40% (n=35) were overweight at their most recent visit to the metabolic clinic. Of the 35 overweight patients, 24 were classified as obese (28%). There were no significant differences in the percentage of overweight or obesity between the Cleveland vs. Houston populations (chi square, p=0.78) so the two groups were combined, where possible, for data analysis. Thus, the prevalence of overweight and obesity in both PKU populations was similar to expected based on data from the United States [14].

Eight PKU patients (2 females, 6 males) were taking sapropterin dihydrochloride. Of these eight patients, 38% (n=3) were overweight or obese. Although the sample size is small, this result suggests that the prevalence of overweight and obesity was similar in the patients taking sapropterin dihydrochloride as in the larger population.

However, when the PKU populations were analyzed by gender, differences were observed. Of the 45 male patients, 73% (n=33) were normal weight and 27% (n=12) were overweight. Of these 12 overweight patients, 10 were classified as obese (22%). Thus, the percentage of overweight and obesity in the male patients was similar to expected based on data from the general population (Table 2A) [14].

No significant differences were detected in the percentages of normal weight, overweight or obesity (p=0.26), mean BMI z-score (p=0.72), height z-score (p=0.91), and weight z-score (p=0.87) in the Houston vs. Cleveland male patients (Fig. 1).

In contrast, of the 42 female PKU patients, 45% (n=19) were normal weight and 55% (n=23) were overweight. Of the 23 overweight patients, 14 (33%) were also categorized as obese. Therefore, more than half of the female PKU population was either overweight or obese, and the prevalence of overweight and obesity in the female patients was 1.5 to 1.8 times higher than expected based on data from the general population in the United States (Table 2B) [14]. No significant differences were detected in the percentage of overweight or obesity (p=0.92), mean BMI z-score (p=0.55), height z-score (p=0.72), and weight z-score (p=0.42) in the Houston vs. Cleveland female patients (Fig. 1). Cross-sectional analysis of the pooled data set by age indicates a similarity in prevalence of overweight in females and males until approximately 11 years of age. Although the analysis of older patients is limited by sample size, the prevalence of overweight rises at approximately 11 years of age in females but not in male patients (Supplementary Table 1).

Suboptimal linear growth is one possible explanation for the higher than expected prevalence of overweight in PKU females. The mean z-score for height in the PKU females was −0.35±1.18 with no significant differences between the Cleveland and Houston data (t-test, p=0.72). Previous studies of non-Hispanic females in the NHANES study (1999-2004) showed a mean height z-score of 0.23 [17]. Interestingly, similar trends were observed in males with a mean height z-score of −0.26±0.93 (no significant differences between the Houston and Cleveland data t-test, p=0.91) compared to 0.30 in previously published studies [17]. Comparatively, the mean BMI z-score was 1.1±0.8 in PKU females and 0.56±1.01 in PKU males with no significant differences in the Cleveland and Houston populations (females: t-test, p=0.55; males: t-test, p=0.72). Thus, the mean height z-scores for both males and females were lower than expected but the BMI z-score in females was more than 1.5 times that of males. Although suboptimal linear growth may be a contributing factor to overweight in PKU patients, if decreased height accounted for the high prevalence of BMI in PKU patients, one would expect that males, who are as short as females, would have a similar prevalence of overweight and obesity. Supplementary Table 1 provides mean height z-scores by age for the study population.

3.3. Relationship of diet and formula compliance with BMI

We tested the relationship of compliance with the low phenylalanine diet and BMI in PKU patients in two ways. First, we tested whether there is an association between compliance with diet and the continuous measure of BMI z-score. Then, we tested whether compliance with diet is associated with the categorical variable, normal

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Total patients</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Age in years (all patients)</td>
</tr>
<tr>
<td>Initial PHE (µmol/L)</td>
</tr>
<tr>
<td>% on sapropterin (n)</td>
</tr>
</tbody>
</table>

![Fig. 1. BMI z-score in male and female PKU patients. BMI z-score for each patient is plotted by gender. The mean for each group is indicated with a bar.](image-url)
weight vs. overweight or obese. To assess compliance with the low phenylalanine diet, the plasma phenylalanine concentrations over the one-year period prior to their most recent visit to the metabolic clinic were collected. Then, each patient was categorized as "compliant with diet" (n = 25 females, n = 24 males) or "non-compliant with diet" (n = 17 females, n = 20 males). Data were unavailable for one patient.

Analysis of the continuous variable revealed that the BMI z-score was higher in female patients who were categorized as non-compliant. However, this difference did not reach statistical significance in our study (p = 0.07). Likewise, a similar comparison of BMI z-scores in compliant vs. non-compliant male patients revealed no significant differences (p = 0.30).

Analysis of the categorical variable, normal weight vs. overweight in compliant vs. non-compliant patients revealed similar results. Of the compliant female patients, 35% were overweight or obese compared to 68% of the non-compliant patients (chi square, p = 0.04). In contrast, no significant differences were observed in the male patients. Because several patients had two or fewer phenylalanine levels, we repeated the above analysis by only using patients with three or more phenylalanine levels available. Although the sample size was smaller and the p values were not significant, similar trends were observed with 43% of compliant females overweight or obese compared to 67% of non-compliant females (chi square, p = 0.18).

To evaluate compliance with formula in the Houston cohort, plasma tyrosine concentrations over the one year prior to the most recent metabolic clinic visit were collected. Plasma tyrosine concentrations were not measured routinely in the Cleveland cohort. Patients were classified as "compliant with formula" if ≥50% of their plasma tyrosine levels were ≥44 μmol/L (n = 38) and "noncompliant with formula" if <50% of their plasma tyrosine levels were ≥44 μmol/L (n = 14). Every female (n = 7) categorized as "non-compliant with formula" was overweight or obese. This trend was only observed in females. Because a subset of patients had two or fewer tyrosine levels available, the analysis was repeated in patients with three or more tyrosine levels available. With this repeat analysis, four female patients were categorized as non-compliant with formula and all four were overweight or obese.

### 3.4. Correlation of fraction of energy from formula and BMI z-score

We next tested whether the percentage of energy (caloric) intake derived from metabolic formula was correlated with BMI. To calculate the percentage of prescribed energy intake from formula, the total number of calories prescribed in the form of metabolic formula was calculated for each patient and divided by recommended caloric intake for a child of their particular age and gender assuming moderate activity [15]. For a subset of the Houston patients (n = 11), energy intake as calculated based on diet records provided by the patient was used rather than predicted energy intake. A Pearson product-moment correlation coefficient for percentage of recommended energy (calories) from formula and BMI z-score was −0.44 (p = 0.0027) in males but not significant in females (p = 0.50). Thus, a higher percentage of prescribed total energy from formula was correlated with a lower BMI z-score, but only in the male subjects. The fraction of formula calories derived from fat (p = 0.16), carbohydrate (p > 0.99), and protein (p = 0.13) was not significantly correlated with BMI z-score.

### 3.5. Correlation between initial phenylalanine concentration and BMI z-score

Lastly, we tested whether initial plasma phenylalanine (newborn screening confirmatory sample), a surrogate marker of severity of the enzymatic deficiency, was associated with BMI z-score. The initial plasma phenylalanine was available for 67 patients and ranged from 200 μmol/L to >5000 μmol/L. A Pearson product-moment correlation coefficient did not detect a significant correlation between initial plasma phenylalanine and BMI z-score in either the male or female subjects.

### 4. Discussion

Although previous studies have demonstrated that school-age PKU patients in the U.S. have a tendency to be overweight, no study has examined this trend in the U.S. population of PKU patients including adolescent patients. Our results demonstrate that the prevalence of overweight in the female PKU population is 1.5 to 1.8× higher than expected based on data from United States children with overweight or obese [14].

Both Texas and Ohio have a high prevalence of pediatric overweight and obesity [18,19]. For example, in 2000–2001, 21.3% of Texas 4th grade females were obese, 16.7% of 8th grade females were obese, and 11.7% of 11th grade females were obese [18]. Even compared to the Texas data, the 30% prevalence of obesity in PKU females in the Houston area is higher than expected. Likewise, according to the 2008 Ohio Family Health Survey, 29.5% of Ohio female children ages 10–17 years were overweight or obese and 14.8% were obese [19]. Thus, our finding of 58% of PKU females who were overweight and 37% of PKU females who were obese in the Cleveland PKU population is higher than expected when compared to Ohio data [19].

Our longitudinal data suggests that the prevalence of overweight increases in female patients after 10 years of age which is near the start of puberty. At this age, the patients may have less supervision regarding formula consumption and meal preparation which could result in higher calorie consumption. Studies have demonstrated that mothers of young children with PKU report more abnormal feeding behaviors compared to mothers of unaffected children [3,4]. Whether these abnormal feeding behaviors affect feeding behavior and food choice in later childhood and adolescence has not been determined.

The explanation for the differences in prevalence of overweight and obesity between female and male PKU patients remains unclear. As discussed previously, higher prevalence of overweight and obesity was demonstrated in female patients at 11 years of age and older. However, we have fewer male patients with age ≥11 years (n = 12) as compared to female patients (n = 22) in this age range. A recent study of PKU patients in Spain demonstrated elevated z-scores for weight and BMI in severely affected females older than age 13 years and males older than 18 years [10]. Thus, the male population should be followed over time to determine if the prevalence increases as the male population ages.

Overweight and obesity are complex, multi-factorial phenotypes with genetic and environmental contributions. One hypothesis was that the low phenylalanine diet, which is typically rich in carbohydrate content, contributes to overweight in PKU patients [12]. However, caloric intake calculated from diet records of PKU patients has revealed caloric intake that is similar to or lower than recommended, but the accuracy of the diet records cannot be determined [19,20]. Interestingly, in this study population, the mean BMI z-score trended higher in non-compliant female patients as compared to compliant female patients. In addition, there was a higher percentage of overweight and obesity among female patients who were non-compliant with the PKU diet. Although this trend fell short of significance in the most conservative analysis (patients with three or more phenylalanine levels
available), this finding suggests that the low-phenylalanine diet does not contribute to the overweight and obesity in this population. More studies are needed to investigate the potential relationship between dietary compliance and overweight in female PKU patients.

Another hypothesis that we explored was whether formula compliance was associated with overweight and obesity in the PKU population. Interestingly, all female PKU patients who were not compliant with formula (based on low plasma tyrosine concentration) were overweight or obese. Obviously, patients who are non-compliant with formula but who have a normal tyrosine concentration from diet would not be identified with this approach. In addition, the fraction of energy prescribed in the form of metabolic formula was significantly negatively correlated with BMI z-score in the male subjects but not in the female subjects. Thus, there may be a relationship between formula consumption and BMI z-score with a tendency for patients who are not consuming formula (or who are prescribed a smaller fraction of their total daily caloric intake from formula) to have a higher BMI z-score, but more studies are needed to investigate this possibility. One hypothesis that explains why patients who are not consuming formula (or who consume a smaller fraction of total energy from formula) may have a tendency to be overweight is that the formula may induce satiety in patients. In fact, Gokmen-Ozel et al. reported that children with PKU (ages 1–5 years) consumed less calories from food when taking a higher calorie (more carbohydrate rich) formula vs. a lower calorie formula although these differences were not significant [21]. Thus, patients who consume a large fraction of total energy in the form of metabolic formula may consume fewer calories in the form of calorically dense, (protein-free) “free foods” compared to patients who do not consume their formula regularly. However, more studies of energy consumption in compliant vs. non-compliant PKU patients are necessary to test this hypothesis.

Our analysis of the percentage of calories prescribed in the form of metabolic formula has some limitations. First, we calculated the calories prescribed from formula not the calories actually consumed from formula as these data were unavailable to us. Obviously, patients may not be consuming the entire quantity of formula prescribed. Furthermore, we used recommended caloric intake based on published reference standards rather than actual caloric intake from dietary records for most patients. Lastly, although the majority (>90%) of patients were on complete metabolic formulas which provide all the necessary nutrients (e.g. vitamins, minerals, amino acids, carbohydrate, and fat) except phenylalanine, a small subset of patients was consuming incomplete formulas which do not provide all necessary nutrients. More studies are needed to investigate this potential association between type of medical formula and risk of overweight and obesity in PKU patients.

Although no association was found between initial plasma phenylalanine, a surrogate marker for the severity of the phenylalanine hydroxylase activity, and BMI z-score, there were also a few limitations to this analysis. First, initial plasma phenylalanine may be influenced by the day of life on which the sample is drawn. For example, in patients with more severe enzyme deficiency, the plasma phenylalanine will continue to rise as the patient continues to consume regular infant formula or breast milk. In contrast, in patients with a milder enzymatic deficiency, the initial plasma phenylalanine may level off. Furthermore, siblings of affected children often have earlier measurements than children with no affected siblings which could confound the results. Perhaps, other surrogate measures of biochemical severity such as phenylalanine allowance could be analyzed to confirm these results. Although our results suggest that biochemical severity is not associated with BMI z-score, these limitations must be considered.

5. Conclusions

Overall, we demonstrated that overweight and obesity are highly prevalent in U.S. females with PKU managed at two different metabolic centers. The difference in prevalence of overweight and obesity in females vs. males relative to the general pediatric population is unclear [14]. In addition, our data provides preliminary evidence suggesting that poor compliance with the low phenylalanine diet and phenylalanine-free formula may be associated with increased risk for overweight in female PKU patients. A humbling conclusion is that despite the generally more intense nutritional supervision of these PKU patients relative to the general population, they had a greater probability of becoming overweight or obese. The high prevalence of overweight and obesity indicates that anticipatory guidance for all PKU patients, particularly females, should include the risk for overweight and obesity and methods for reducing this risk such as increased activity, healthy food selection, and possibly improved compliance with supplemental formula. Lastly, further studies are needed to investigate overweight and obesity as these patients become older and to evaluate for other factors associated with obesity in this population.

Conflicts of interest statement

There are no conflicts of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ymgme.2012.07.006.

References


