Review

Optimising growth in phenylketonuria: Current state of the clinical evidence base

Katharina Dokoupila, Hulya Gokmen-Ozel, Anna Maria Lammardo, Kristina Motzfeldt, Martine Robert, Júlio César Rocha, Margreet van Rijn, Kirsten Ahring, Amaya Bélanger-Quintana, Anita MacDonald

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S U M M A R Y

Patients with phenylketonuria (PKU) must follow a strict low-phenylalanine (Phe) diet in order to minimise the potentially disabling neuropsychological sequelae of the disorder. Research in this area has unsurprisingly focussed largely on managing blood Phe concentrations to protect the brain. Protein requirements in dietary management of PKU are met mostly from Phe-free protein substitutes with the intake of natural protein restricted to patient tolerance. Several reports have suggested that growth in early childhood in PKU is sub-optimal, relative to non-PKU control groups or reference populations. We reviewed the literature searching for evidence regarding PKU and growth as well as possible links between dietary management of PKU and growth. The search retrieved only limited evidence on the effect of PKU and its dietary management on growth. Physical development in PKU remains an understudied aspect of this disorder.

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1. Introduction

The introduction of routine neonatal screening for hyperphenylalaninaemia from the 1960s onwards permitted early diagnosis of phenylketonuria (PKU). Prompt intervention with a phenylalanine (Phe)-restricted diet within the first weeks, or even days, of life has prevented most, of the adverse effects of this disorder on cognitive function. Maintaining adequate nutrition to support normal physical development for patients with PKU, is challenging, given the nature of the Phe-restricted diet, which restricts natural protein to patient tolerance and requires supplementation with a Phe-free protein substitute and specially manufactured low-protein foods. The relationship between diet and growth in PKU has been little studied compared with the large database of publications on the neuropsychological sequelae of PKU, especially in recent years. Little is also known about the development of obesity. The purpose of this review is to summarise the current state of the literature regarding physical development in patients with PKU; we provide our interpretation of this evidence base and also highlight future areas for research.

2. The evidence base for growth and diet in PKU

2.1. Publications

Publications were identified from a PubMed search using the terms “growth” and “phenylketonuria”. Other publications came from the reference list of other publications, and from the personal reference databases of the authors. A brief summary of key study features and results is given in Table 1. Other publications of interest that are less clearly relevant to physical development (e.g. published as a letter only, or dealing with overweight/obesity) are discussed separately.
Overview of studies of diet and growth in patients with phenylketonuria.

Table 1
Overview of studies of diet and growth in patients with phenylketonuria.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year (N)</th>
<th>Ages (y)</th>
<th>Follow-up</th>
<th>Where?</th>
<th>Measured growth parameters</th>
<th>Study design and key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1979 (693)</td>
<td>0–17</td>
<td>NA*</td>
<td>USA</td>
<td>Height, head circ.</td>
<td>Retrospective cross-sectional survey. Significant ( p &lt; 0.01 ) to ( p &lt; 0.001 ) height (-0.7 to -0.8 SD) vs. normal controls at 1.3–1.4 y; head circ. was ( 0.78 ) SD vs. normal controls at 1.2 y ( p &lt; 0.01 ).*</td>
</tr>
<tr>
<td>16</td>
<td>1979 (124)</td>
<td>0–4</td>
<td>4 y</td>
<td>USA</td>
<td>Height, wt, head circ.</td>
<td>Longitudinal study. No significant difference in height, weight, head circ. between PKU and normal controls at any age. However, there was a significant trend towards weight gain over time in girls with PKU ( p &lt; 0.005 ), but not in other groups. Overall, growth in PKU was as expected.</td>
</tr>
<tr>
<td>10</td>
<td>1984 (67)</td>
<td>0–6</td>
<td>6 y</td>
<td>USA</td>
<td>Height, head circ. wt</td>
<td>Longitudinal study of early diet-treated children. Normal growth was observed in children with PKU, compared with the general population.</td>
</tr>
<tr>
<td>18</td>
<td>1991 (133)</td>
<td>2–10</td>
<td>8 y</td>
<td>USA</td>
<td>Height, head circ. wt</td>
<td>Longitudinal study of early diet-treated children. No significant differences for height of head circ. for PKU vs. reference population. Weight was significantly ( p &lt; 0.05 ) higher for PKU vs. reference standards for the general population at most ages.</td>
</tr>
<tr>
<td>7</td>
<td>1994 (25)</td>
<td>'Infants'</td>
<td>6 months</td>
<td>USA</td>
<td>Length, head circ., wt</td>
<td>Comparison of growth parameters in children receiving different protein supplements ( 38% ) difference in protein intake between study groups. Higher protein intake was associated with higher growth percentiles for length ( 55 ) vs. ( 28 ), head circ. ( 50 ) vs. ( 29 ), weight ( 73 ) vs. ( 39 ).</td>
</tr>
<tr>
<td>13</td>
<td>1994 (137)</td>
<td>0–10</td>
<td>10 y</td>
<td>NL</td>
<td>Height, head circ. wt</td>
<td>Longitudinal study. PKU infants were 141 g smaller at birth, on average, than reference control; z scores for height remained significantly smaller for PKU vs. control, though there were no significant differences in z scores for height for age ( &gt; )1 y, and no differences for weight.</td>
</tr>
<tr>
<td>19</td>
<td>1994 (82)</td>
<td>0–6</td>
<td>6 y</td>
<td>Germany</td>
<td>Height, head circ. wt</td>
<td>Longitudinal study. Height declined up to age 2.5 y in boys and girls, and head circ. decreased in boys up to 2.5 y, compared with a reference population. Weight-for-height SD score remained close to zero for boys and girls.</td>
</tr>
<tr>
<td>11</td>
<td>1995 (94)</td>
<td>0–8</td>
<td>8 y</td>
<td>France</td>
<td>Height, head circ., wt/BMI</td>
<td>Longitudinal study at a single centre. The z score for height-by-age was decreased vs. normal values at ages up to 8 y ( \text{only seen for patients born after 1981} ). Above this age, height-by-age and weight-by age increased to above normal values by 10 years.</td>
</tr>
<tr>
<td>20</td>
<td>1995 (30)</td>
<td>Mean 9.6</td>
<td>NA*</td>
<td>AUS</td>
<td>Wt</td>
<td>Cross-sectional comparison of children with PKU and control children. No excess weight, and no difference in resting energy expenditure was observed between groups.</td>
</tr>
<tr>
<td>14</td>
<td>1997 (103)</td>
<td>0–3</td>
<td>NA*</td>
<td>NL</td>
<td>Height (z score)</td>
<td>Study correlated the strictness of diet treatment (blood Phe levels) with growth parameters. No effect on growth was associated with the strictness of dietary control.</td>
</tr>
<tr>
<td>8</td>
<td>1998 (35)</td>
<td>'Infants'</td>
<td>6 months</td>
<td>USA</td>
<td>Length, head circ., wt</td>
<td>Longitudinal study. Intake of protein, energy and Tyr correlated with growth indices at 3 months; neither Phe nor Tyr concentrations in the blood correlated with growth.</td>
</tr>
<tr>
<td>9</td>
<td>2002 (38)</td>
<td>Mean 8.9</td>
<td>NAd</td>
<td>USA</td>
<td>BMI, height</td>
<td>Chart review of early and continuously diet-treated children with PKU. Mean height was at the 46th percentile; protein insufficiency ( \text{low pre-albumin} ) correlated with impaired growth.</td>
</tr>
<tr>
<td>6</td>
<td>2003 (58)</td>
<td>2–12</td>
<td>1 y</td>
<td>USA</td>
<td>Height, BMI*</td>
<td>One-year non-randomised comparison of three medical foods. All children received adequate nutrition; normal growth was observed. BMI z scores were ( &gt; 0.5 ) in 40/58 children at study end, suggesting many were overweight.</td>
</tr>
<tr>
<td>12</td>
<td>2003 (20)</td>
<td>1–7</td>
<td>NA*</td>
<td>France</td>
<td>Height, wt, FFM</td>
<td>Cross-sectional study. Patients with PKU were shorter ( \text{mean height-for-age z-score} &gt; -0.49 ) and lighter ( \text{mean weight-for-age z-score} &gt; -0.471 ) than the French reference population. There were no effects of PKU on body composition, IGFl, IGFBP3, or thyroid hormone. Plasma Phe did not predict growth.</td>
</tr>
<tr>
<td>15</td>
<td>2005 (174)</td>
<td>0–3</td>
<td>NA*</td>
<td>NL</td>
<td>Height, head circ.</td>
<td>Retrospective analysis. Head circ. increased in line with natural or total protein intake ( \text{regression coefficients adjusted for Phe and energy intake of 0.28 and 0.22, respectively} ), but not with intake of protein substitute ( \text{adjusted regression coefficient 0.07} ). Height did not vary with intake of protein from natural sources, substitute, or both.</td>
</tr>
<tr>
<td>17</td>
<td>2007 (34)</td>
<td>Mean 8.7</td>
<td>1 y</td>
<td>Austria</td>
<td>Height, wt</td>
<td>Longitudinal study. No difference in growth or body composition for PKU vs. reference population.</td>
</tr>
</tbody>
</table>

AUS: Australia; FFM: fat-free mass; NA: not applicable; NL: Netherlands; Wt: body weight. All studies measured Phe intake in addition to parameters shown. 'Year' refers to year of publication. N: total number of patients.

* Cross-sectional or retrospective study.

Data shown for treated PKU only \( \text{data on untreated PKU not shown as this is not relevant to current management of PKU} \), and deficits in growth parameters are for a subset of patients with measurements before and after treatment.

Regression analysis based on retrospective analysis of the most recent nutritional assessment.

z-scores for length/height or body mass index (BMI).
2.2. Study characteristics/designs

The majority of the reports in Table 1 recruited study populations consisting exclusively or mostly of children aged 12 years or lower (i.e. before the teenage growth spurt). A retrospective USA study from 1979 collected data via a questionnaire from a large population of 693 patients with PKU. However, it included untreated, institutionalised patients with mental retardation due to PKU, and its definition of "treated" was intervention with diet before 121 days (4 months) of age, which is known now to be too late for intervention to protect cognitive function. Another, cross-sectional, study applied an upper age limit of 18 years. However, the mean age was below 9 years, and the report did not include information on the age distribution of subjects whose data were included.

Most of the data originated in only a small number of countries, particularly the USA, the Netherlands, France and Germany. There were differences between studies in the anthropometric parameters considered, although most included measurements of height (length), weight and/or body mass index (BMI), and head circumference. Few studies measured parental height. Some studies employed longitudinal measurements of parameters related to growth (follow-up periods ranged between 1 and 9 y (see Table 1)), while others had a cross-sectional or retrospective design.

Finally, most of the studies are not recent, with publication dates of 1998 or earlier for 11 of the 16 studies included in the table.

2.3. Summary of findings from studies of physical development in PKU

Although, a minority of studies found little or no effect of PKU on growth outcomes, usually height (see Table 1), the majority of studies detected differences in parameters related to physical development between these populations. A longitudinal study in France found that height in patients with PKU was restricted according to standardised growth charts for that country during the first 8 years of life, when dietary restriction was relatively stringent; however, height caught up and even surpassed normal values after the age of 8 years, when the diet was relaxed. Incomplete growth catch-up in height in later childhood, after an early decline in height relative to controls (mainly during the second year of life), was reported in Germany. Also, head circumference SD score decreased during the first year of life in boys but not girls, and did not catch up in later years.

Higher total protein intake has been associated (see Table 1) with increased height or crown–heel length, head circumference, or weight. Data from a study in Austria showed that fat-free mass correlated significantly with ingestion of natural protein, but not with total protein (natural protein plus medical protein supplement). A study on infants in the Netherlands indicated that the natural protein intake correlated positively and significantly with head circumference, although no correlation was found between total protein intake and height. Higher protein intake (24% vs. 9% above recommended daily intake) was associated with better maintained growth (crown–heel distance and head circumference) in a US study comparing two different Phe-free protein substitutes.

Patients with PKU in some studies tended to be overweight relative to subjects without PKU, particularly in studies in the USA (see Table 1). The phenomenon of "BMI rebound", an increase in BMI at about age 6 y, has been described as a predictor of subsequent overweight or obesity in the general population. The same phenomenon appears to apply to children with hyperphenylalaninaemia or PKU: an early BMI rebound in hyperphenylalaninaemic children increased the likelihood of overweight at the age of 8 y in an Italian study, and excess weight for height at age 2 y was significantly associated with overweight at age 4 y in the PKU Collaborative study in the USA. Parental overweight was also a significant risk factor for overweight among children with PKU in both of these studies, and low socioeconomic status was a significant risk factor for overweight in the US study. Boys and girls with or without PKU had similar ranges of body fat content in a study in Australia. This study also showed that resting energy expenditure (measured using indirect calorimetry) did not differ between children with or without PKU. It should be noted that caution may be required in interpreting some measurements of resting energy expenditure in this population, as a recent study has shown that the Schofield equation, often used for estimating resting energy expenditure, underestimates this parameter in female adolescents with PKU.

It is well known that the prevalence of obesity is high, and rising in many countries, and some underlying factors related to increased risk of obesity, such as sedentariness and increased intake of high-energy foods, may apply equally to populations with or without PKU. Indeed, adults with PKU, unlike children, are free to make their own decisions relating to dietary and activity choices and often lose contact with healthcare professionals, leading to reduced opportunities for healthy living. The published in abstract form suggest a higher prevalence of overweight in adult patients with PKU in European countries, relative to the general population, although there may be no increased prevalence of obesity-associated cardiovascular risk factors. However, full peer-reviewed reports of these data are required, and further research is required to define the magnitude of the problem posed by overweight and obesity, and its impact on health, in patients with PKU.

3. Interpreting the current evidence base

The studies described in this article are heterogeneous, and the fragmented nature of the current evidence base precludes a meaningful overall assessment of individual aspects of dietary management on outcomes related to physical development. Nevertheless, more than half of the studies described in Table 1 reported that indices of growth were abnormal in patients with PKU compared with reference populations, particularly with regard to reduced head circumference and/or height, or increased body weight.

There are important limitations to the evidence available. Many were small, and few studies were completed recently. Considerable changes in dietary practices in recent years, including more acceptable protein substitutes. Thus, the current evidence base for optimising growth in PKU is based largely on outdated dietary practices. For example, current intensive management of biochemical parameters or micronutrients may affect physical development of patients with PKU. Also, most studies recruited infants, with little longitudinal data (or studies of a duration insufficient to measure changes in growth adequately, e.g. the 6 month follow-up in Refs. 7,8), and essentially no data in older subjects. In addition, the studies were conducted in different countries, with differences in access to Phe-free protein substitutes and special foods, dietary approaches, cultural factors and healthcare systems (e.g. reimbursement). The selection of a suitable reference population also poses a challenge in the design of studies evaluating growth in children (new standards for child growth from the World Health Organisation may be useful here). Determining protein requirements in PKU is not straightforward: patients with PKU appear to handle dietary protein in a similar manner to subjects without PKU but the anabolic response to ingested amino acid mixtures differs from that to
dietary protein. Experimental data suggest that amino acids delivered as dietary protein (casein) may support whole-body protein metabolism better than ingestion of crystalline amino acids, casein hydrolysates or soy protein. In a prospective, controlled trial, ingestion of protein rather than an amino acid mixture resulted in lower nitrogen excretion for the same energy and amino acid intake. Accordingly, differences in the amounts of amino acid mixtures prescribed, or different patterns of ingestion throughout the day could, in principle, affect growth outcomes in PKU. Manufacturers of protein substitutes should be urged to provide information on the anabolic response to their products, especially as these are classified as “functional foods” specifically designed to optimise nutrition. While some studies indicated that growth parameters varied with intake of natural protein (but not protein substitutes), these studies were generally small, or involved limited follow-up, and could not be used to make definite recommendations on optimisation of protein intake. Long-term longitudinal studies examining the impact of Phe-free protein substitutes on growth are needed. A reliable analytical marker of sub-optimal protein ingestion would also be valuable. Preliminary evidence suggests that pre-albumin, a marker of plasma protein status, may be a useful marker of growth in this population.

The tendency to be overweight in the USA requires explanation. Higher natural protein intake was associated with overweight in some studies. Overweight may have been associated with poor dietary compliance, as suggested by one report. More data on the prescription of protein substitutes, and compliance with them, in the USA and Europe are required. Protein substitutes used in the USA often have higher energy content, for a given protein content, than those used in Europe which would be consistent with a higher risk of overweight or obesity in American relative to European populations. Conversely, in a study in the USA, the actual intake of protein substitutes was lower than the amount prescribed, and self-reported by patients. The effects of optimised nutrition on growth patterns, together with data on physical activity in this population, would be another interesting area for further study.

A subset of patients with PKU demonstrate a tetrahydrobiopterin (BH4)-sensitive clinical phenotype, in which pharmacological doses of BH4 increase dietary Phe tolerance and/or reduced blood Phe concentrations. A pharmaceutical formulation of BH4 (sapropterin dihydrochloride) has been associated with an increased intake of natural protein and growth when 6 patients were studied longitudinally for 2 years. If future research in PKU demonstrates that natural protein is better than Phe-free protein substitute in maintaining growth, then a relaxation of the Phe-restricted diet may be of benefit in preserving a normal growth trajectory.

Genetic influence (as shown by parents’ growth patterns) is an area requiring further study, as parental overweight has been identified as a risk factor for overweight in children with PKU. In general, the studies did not detect an effect of PKU status on growth, although blood Phe concentrations, Phe intake, dietary compliance, and natural protein intake are closely interwoven. Data on patterns of growth in patients with different severities of hyperphenylalaninaemia/PKU are lacking; particularly as the prescription of L-amino acid mixtures and natural protein restriction varies with severity of the disorder. Table 2 summarises some potential areas for future research based on issues identified in this review.

### 4. Conclusions

Growth does not appear to be markedly affected in infants, although there is variability within published data, and several reports described reduced height and/or head circumference in young children. The clinical evidence base describing physical development in PKU is limited, particularly for adolescent or adult patients. A number of unanswered questions relating to nutrition and growth remain in this area, particularly with regard to the effects of natural versus artificial sources of protein, and the correct balance between protein, fats and carbohydrates. Further prospective, multicentre evaluations of growth in children and adolescents with PKU are necessary.

### Conflict of interest

Katharina Dokoupil has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU.

Hulya Gökmen-Özçel has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU.

Anna Maria Lammardo has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU.

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Amaya Bélanger-Quintana has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU and the Scientific Advisory Board on PKU.

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Table 2
Summary of potential areas for new research into growth in PKU.

<table>
<thead>
<tr>
<th>Area</th>
<th>Research issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in PKU</td>
<td>• Macronutrient composition of Phe-free protein substitutes and impact on growth in PKU</td>
</tr>
<tr>
<td>management</td>
<td>• Impact of new sources of dietary protein (e.g. glycomacroprotein) on growth</td>
</tr>
<tr>
<td></td>
<td>• New pharmaceutical approaches (e.g. sapropterin)</td>
</tr>
<tr>
<td>Optimising therapy</td>
<td>• Growth responses to natural vs. Phe-free protein substitute.</td>
</tr>
<tr>
<td></td>
<td>• Micronutrient status</td>
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<tr>
<td></td>
<td>• Analysis of body composition (e.g. bioimpedance spectroscopy)</td>
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<tr>
<td></td>
<td>• Role of metabolic control</td>
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<tr>
<td></td>
<td>• Anabolic/catabolic responses to oral amino acids</td>
</tr>
<tr>
<td></td>
<td>• Markers of protein metabolism</td>
</tr>
<tr>
<td>Cultural/behavioural influences</td>
<td>• Cultural influences on diet</td>
</tr>
<tr>
<td></td>
<td>• Lifestyle/activity</td>
</tr>
<tr>
<td></td>
<td>• Prevention/management of overweight/obesity</td>
</tr>
<tr>
<td></td>
<td>• PKU genotype</td>
</tr>
<tr>
<td></td>
<td>• Other genetic background</td>
</tr>
</tbody>
</table>

See text for discussion and references.
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References


