Practices in prescribing protein substitutes for PKU in Europe: No uniformity of approach


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Background: There appears little consensus concerning protein requirements in phenylketonuria (PKU). Methods: A questionnaire completed by 63 European and Turkish IMD centres from 18 countries collected data on prescribed total protein intake (natural/intact protein and phenylalanine-free protein substitute [PS]) by age, administration frequency and method, monitoring, and type of protein substitute. Data were analysed by European region using descriptive statistics.

Results: The amount of total protein (from PS and natural/intact protein) varied according to the European region. Higher median amounts of total protein were prescribed in infants and children in Northern Europe (n = 24 centres) (infants <1 year, 2–3 g/kg/day; 1–3 years of age, 2–3 g/kg/day; 4–10 years of age, 1.5–2.5 g/kg/day) and Southern Europe (n = 10 centres) (infants <1 year, 2.5 g/kg/day, 1–3 years of age, 2 g/kg/day; 4–10 years of age, 1.5–2 g/kg/day), than by Eastern Europe (n = 4 centres) (infants <1 year, 2.5 g/kg/day, 1–3 years of age, 2–2.5 g/kg/day; 4–10 years of age, 1.5–2 g/kg/day) and with Western Europe (n = 25 centres) giving the least (infants <1 year, 2–2.5 g/kg/day, 1–3 years of age, 1.5–2 g/kg/day; 4–10 years of age, 1–1.5 g/kg/day). Total protein prescription was similar in patients aged >10 years (1–1.5 g/kg/day) and maternal patients (1–1.5 g/kg/day).

Conclusions: The amounts of total protein prescribed varied between European countries and appeared to be influenced by geographical region. In PKU, all gave higher than the recommended 2007 WHO/FAO/UNU safe levels of protein intake for the general population.

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1. Introduction

Phenylalanine-free protein substitute is a primary source of protein in patients with PKU treated by a low phenylalanine diet only. This is predominantly based on phenylalanine-free L-amino acids. It is essential to prevent protein deficiency and optimize metabolic control [1–4], and it may block phenylalanine transport across the blood brain barrier [5,6]. Phenylalanine-free protein substitute is likely to supply 52 to 80% of the total protein intake [7–9], but there is no robust evidence base to support the optimal dose due to a lack of studies examining its utility. Nevertheless, developing universal guidelines on protein substitute dosage that are supported and agreed by health professionals are necessary to provide consistent, effective and cost efficient care to patients. However, there is little harmony between professionals on optimal amounts.

There have been different approaches for prescribing the dose of protein substitute.

1. Some PKU centres recommend a higher dose of protein equivalent than the FAO/WHO/UNU [10] safe levels of protein intake [11]. This may lead to an increase in nitrogen retention, prevention of protein insufficiency [12], improved phenylalanine tolerance [11,13,14], contribute to better phenylalanine control [1], as well as provide a higher intake of large neutral amino acids [15]. There is also evidence that L-amino acids may be poorly utilised and are less efficacious than the low phenylalanine-peptide based glycomacropeptide (GMP) both in subjects with PKU [16] and PKU mice [17,18]. Compared with a casein rich protein [19], there is suggestion of less efficient transfer of amino acids into tissue and plasma proteins with L-amino acid supplements [20,21].

2. Some centres advocate the same dose of protein equivalent (from a combined intake of phenylalanine-free protein substitute and natural/intact protein) as for the healthy population [22,23]. Protein substitute is expensive and adherence maybe suboptimal. Adults with PKU (excluding pregnancy) do not have higher protein requirements when the majority of dietary protein is provided by amino acids [24]. Also long term intake of phenylalanine-free L-amino acids has been linked to proteinuria and decreased GFR [9] but further study is required.

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It is possible that by examining the current European prescribing trends it may help unravel health professional attitudes and decision making processes on protein substitute dosing. Therefore, an internet questionnaire on dietary practices with protein substitute prescription (dosage, type, and administration) was sent to dietitians and physicians who were members of the Society for the Study of Inborn Errors of Metabolism Dietitians Group (SSIEM-DG).

2. Materials and methods

A cross-sectional computer questionnaire was distributed to all European dietitian members of the Society for the Study of Inborn Errors of Metabolism (SSIEM-DG). SSIEM-DG members then cascaded the questionnaire to dietitians and/or physicians within their own country between July and December 2013. The questionnaire consisted of 26 multiple choice and short answer questions. The following data were collected by age group: total protein intake prescribed (sourced from natural/intact protein and protein substitutes), use of protein substitutes (including type, dose and method of administration) and biochemical monitoring of protein substitute. The age groups chosen represented infants (<1 year of age); pre-school children (1–3 years of age); primary school children (4–10 years of age); and teenagers and adults.

Clinical outcome data or patient specific data were not included in this questionnaire. Therefore, ethical approval was not required.

3. Results

Sixty three questionnaires were completed by dietitians/physicians from PKU centres from 18 countries. The countries were (n = centre number): Austria (n = 1); Belgium (n = 7); Denmark (n = 1); France (n = 2); Germany (n = 6); Hungary (n = 1); Ireland (n = 1); Italy (n = 2); Netherlands (n = 7); Norway (n = 1); Poland (n = 2); Portugal (n = 4); Spain (n = 2); Sweden (n = 5); Switzerland (n = 2); Turkey (n = 2); United Kingdom (n = 16); and Russia (n = 1). The countries were then divided into 4 European regions: Eastern, Western, Northern, and Southern (Table 1). Patient numbers in each centre varied from 1 to 100 patients, 57% centres (n = 36); >100–200; patients, 24% centres (n = 15); >200–300, 6% centres (n = 4); >300–400, 3% centres (n = 2); >400–500, 5% (n = 3); and >500, 5% centres (n = 3). The PKU centres were: children’s hospitals/units only, 29% (n = 18); adult hospitals/units only, 14% (n = 9); and children and adult units combined, 57% (n = 36).

3.1. Total protein (from protein substitute and natural/intact protein) prescribed

The median amounts of total protein intake prescribed (determined by calculating the median prescribed protein intake of the PKU centres from the 4 European regions) in different age categories are given in Table 1. Overall higher amounts of total protein/protein equivalent were prescribed (particularly in infancy and early childhood) in Northern and Eastern Europe, followed by Southern Europe with centres from Western Europe generally giving the least. Total protein amounts between European centres were similar in patients >10 years of age.

Only 46% (n = 29) of centres indicated that they calculated an ‘inefficiency’ factor for the utilisation of amino acids, with a mean 20% (range 10% to 100%) additional amino acids given in compensation. Fifty nine percent (n = 37/63) of all European centres calculated vitamin, mineral, and trace element intake from protein substitutes, but this was only conducted by 18% (n = 3) of UK and Irish centres.

3.2. Administration of protein substitute

In children over 1 year of age, 65% (n = 41) of centres recommended that protein substitute be given three times daily and 17% (n = 11) 4 times daily. Only 5% (n = 3) recommended administration <3 times daily and only one centre (1.5%) recommended that it be administered 6 times daily. The four major factors influencing the frequency of administration were: blood phenylalanine control, patient adherence, patient and caregiver lifestyle, and patient age.

Almost 41% of centres (n = 26/63) routinely recommended giving additional water with the protein substitute mainly to reduce osmolality of product. In direct contrast, a further 41% of centres (n = 26/63) said they would routinely give a protein substitute more concentrated than recommended by the manufacturer. The major reason associated with this practice was to improve adherence with protein substitute presumably because it reduced product volume.

3.3. Monitoring of protein substitute

Ninety five per cent (n = 60/63) of centres monitored growth and BMI with protein substitute. Eighty three percent (n = 52/63) would monitor biochemical nutritional status, 52% of centres (n = 33/63) said they would monitor patients for gastrointestinal upset such as abdominal discomfort and constipation but only 19% (n = 12/63) said they would monitor renal function.

3.4. Preferred types of protein substitute

The most popular type of protein substitute used by all European regions was L-amino acids with added vitamins and minerals (Table 2). Forty percent (n = 25) of centres also used L-amino acids without vitamins and minerals (and so used separate vitamin and mineral supplements) but mainly in adult centres (67%; n = 6 out of 9 centres) or combined paediatric and adult centres (42%; n = 15 of 36). Only 3 centres (all in Portugal) used GMP (peptide supplemented with L-amino acids) and 17% (11 of 63 centres) used large neutral amino acids but mainly from centres in Northern and Southern Europe.

Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>Belgium (N = 16)</th>
<th>Germany (N = 9)</th>
<th>United Kingdom (N = 17)</th>
<th>Norway (N = 7)</th>
<th>Southern Europe (N = 10)</th>
<th>Eastern Europe (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &lt;1 year</td>
<td>2-2.5&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2-2.5&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2.5-3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2-2.5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2.5</td>
</tr>
<tr>
<td>1-3 years</td>
<td>1.5-2&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1.5-2&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2.5-3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2-2.5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2</td>
<td>2-2.5</td>
</tr>
<tr>
<td>4-10 years</td>
<td>1-1.5&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1-1.5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2-2.5&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>1.5-2</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>1-1.5&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1-1.5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1-1.5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1-1.5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1-1.5</td>
<td>1.5-2&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maternal patients</td>
<td>1-1.5&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1-1.5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1-1.5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1-1.5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1-1.5</td>
<td>1-1.5</td>
</tr>
</tbody>
</table>

Suffix numbers are the number of centres who did not provide data in each age category.

** Turkey belongs to Southeastern Europe, but is categorized in this overview in Southern Europe.

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4. Discussion

In PKU, l-amino acid supplements remain the most extensive protein substitute used by European countries with GMP still not widely available in Europe. In children ≤ 10 years of age the amounts of total protein prescribed for each age category were variable and strongly influenced by European location. Overall most Western European PKU centres prescribed less total protein than other regions in Europe. In children under 1 year of age, Swiss centres prescribed a total protein intake of less than 2 g/kg/day, in children 1–3 years of age from centres from Austria, Germany, Netherlands, Spain, Switzerland, Turkey, and Russia prescribed less than 2 g/kg/day. In patients >10 years of age and with maternal PKU, there was less variation in total protein intake prescription.

Despite these differences, it was evident that for all ages, for each European region the median total protein (per kg/body weight) prescribed was in excess of the FAO/WHO/UNU [10] safe levels of protein intake. Overall an extra median 65% protein (range 10 to 177%) was given over the FAO/WHO/UNU [10] guidelines. This was interesting, as only 46% (n = 29) of centres said they calculated an ‘inefficiency’ factor for the provision of extra l-amino acids to compensate for their poor bioavailability.

In PKU it is unclear how much additional protein should be allocated to allow for ineffective digestibility of natural/intact protein mainly derived from plant protein, and poor utilisation of l-amino acids [25], or sub-optimal energy intake (protein synthesis and possibly turnover) requires energy and is sensitive to energy deprivation. In children, growth is an important parameter to establish the safe, minimum protein intakes. In PKU, growth is an issue [26], and relationships between growth and protein intake have been investigated [27], but results are as yet inconclusive. Even so, any previous studies on growth in PKU have compared protein intakes with the WHO/FAO/UNU [28] safe levels of protein intake. These former guidelines recommended a higher amount of protein than the current WHO/FAO/UNU [10] which have reduced the safe levels of protein intake (in infants under one year by approximately 34 to 38%, children 1–5 years by 26 to 27% and children 6–10 years by 9 to 11%). No studies in children with PKU have examined growth in PKU on such a low total protein intake. In patients with PKU treated by diet only, natural/intact protein sources usually supply anything from 20 to 50% of total protein intake and are mainly supplied by plant protein associated with a low protein digestibility of approximately 80% when compared with egg or milk protein that have 100% digestibility [28]. Furthermore, l-amino acids supplements are rapidly absorbed [21,29] with increased oxidation particularly when taken in large single doses [30], although most centres recommended frequent administration of amino acids to reduce oxidation losses.

It is a concern that vitamin and mineral intake of patients was routinely assessed by only 59% of centres. The most common l-amino acid supplements used by the centres contain added vitamins and minerals, with the aim of meeting the nutritional requirements for a product specific age targeted population. However, it is difficult to formulate vitamin and mineral concentrations of protein substitute, when different dosages are prescribed and natural/intact protein tolerance is variable. It is possible that centres prescribing higher amounts of protein equivalent from protein substitute could be exceeding upper tolerable amounts of some vitamins and minerals [31] and so intake should clearly be monitored. Prescribing higher doses of protein substitute necessitates a lower ‘vitamin–amino acid’ content ratio and in contrast a lower dosage of protein substitute requires a higher ‘vitamin–amino acid’ content ratio.

Irrespective of protein substitute dosage, it is likely that insufficient attention was also given to potential side effects associated with l-amino acids, particularly when administered more concentrated than recommended. l-amino acid supplements are hyperosmolar, e.g. products designed for children range from 600 to 2700 mOsmol/kg H2O (manufacturers data cards), depending on their dilution with water and so may cause gastrointestinal upset [32]; Abdominal pain, diarrhoea, and constipation have been reported in a small series of young children [33]; this could have been related to a lack of fluid with l-amino acid supplements. Results from the current survey indicate that renal function was seldom monitored despite being a potential complication due to increased oxidation of l-amino acids [34], l-amino acid formulas provide a high dietary acid load [35] and chronic ingestion may have a potentially negative impact on the kidney [34] and bone health in PKU [36]. There have also been recent concerns that a higher protein intake in infancy may contribute to a higher BMI and risk of obesity in children [37]. Given that obesity has been reported in PKU, particularly in female patients [38–40], additional study is required investigating total protein intakes in infancy and its long term effect on the development of obesity.

This study is limited to data reporting prescribed protein intakes rather than actual intakes and does not include clinical outcome data such as biochemical monitoring, metabolic control or phenylalanine tolerance. In addition, some centres only cared for either children or adults so could not provide data for all age ranges, and not all European countries and centres are represented. However it is the first time that collective data of this nature have been collated and this provides supporting data for the development of European PKU guidelines.

In conclusion, there have been no definitive studies that have characterised protein requirements in patients with PKU. It is clear that practices for total protein prescription vary widely and this appears to be influenced by European region. However, all centres prescribe in excess of the FAO/WHO/UNU safe levels of protein intake for every age group. In PKU, further randomised, controlled studies examining the efficacy of protein substitutes and natural/intact protein sources are important to establish requirements. This should help direct management guidelines to define minimal protein requirements and ensure that consistent treatment is given to patients.

Conflicts of interest

Kirsten Ahring — a member of the European Nutrition Expert Panel (Merck Serono International).

Table 2

<table>
<thead>
<tr>
<th>Type of protein substitute used by European IMD centres</th>
<th>Western Europe (N = 25)</th>
<th>Northern Europe (N = 24)</th>
<th>Southern Europe (N = 10)</th>
<th>Eastern Europe (N = 4)</th>
</tr>
</thead>
</table>
| Belgium Netherlands Germany Austria Switzerland | 16 (100%) 9 (100%) | 17 (100%) 7 (100%) 9 (90%) | 4 (100%) | **
| France (N = 16) Ireland (N = 17) Denmark Sweden (N = 7) Spain Turkey** | | | | **
| Turkey | | | | **
|具体描述和分析|**

**IMD**: inherited metabolic disease; **vit/min**: vitamins/minerals.

****: Turkey belongs to Southeastern Europe, but is categorized in this overview in Southern EU.
Authors’ contributions

All authors were involved in data collection, interpretation of data, critical revision of the paper for important intellectual content and final approval of the version to be published. FVJ and AM were additionally involved in the initial conception and design and AM and SE in the collation of data and drafting of the initial article. AM will serve as a guarantor for the article.

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References


