

Additional costs of a low-protein diet in children and adolescents with phenylketonuria

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Introduction

Phenylketonuria (PKU) is one of the most common disorders of the metabolism of aromatic amino acids [1]. People with PKU are unable, or have a limited ability, to break down the essential amino acid phenylalanine (Phe). The disease is congenital and inherited in an autosomal recessive manner [3]. PKU is one of the target diseases in advanced screenings of newborns and is identified by means of a blood test [4]. In Germany, the prevalence was 1:7,914 in 2016 [5].

In healthy humans, Phe, which is not required for endogenous functions, is converted into tyrosine with the help of the enzyme phenylalanine hydroxylase (PAH). This reaction requires tetrahydrobiopterin (BH4) as a co-factor [6]. In patients with PKU, various mutations of the coding gene result in changes in the PAH enzyme so that there is no – or very little – conversion of Phe into tyrosine [3]. For that reason, partially through alternative conversion methods of transamination and decarboxylation, Phe is converted into phenylpyruvic acid, phenyllactic acid and phenylacetic acid, among others, and excreted in urine [7]. Since not all Phe can be converted using these alternative methods, it accumulates in the blood and tissues (e.g. brain) [2]. In the absence of treatment, the Phe concentration in the blood increases and interferes with the transport of other essential amino acids to the brain [8]. This pathological situation results e.g. in a decreased share of neurotransmitters (e.g. serotonin and dopamine) and a reduction in the protein synthesis [2]. Typical clinical symptoms include retardation, epilepsy, behavioral problems, a “musty” body odor, eczema and reduced skin and hair pigmentation [9].

Abstract

Phenylketonuria (PKU) is a congenital disorder of the metabolism of aromatic amino acids. The impaired breakdown of phenylalanine (Phe) into tyrosine leads to an accumulation of Phe and the production of unwanted metabolites. At the same time, the lack of tyrosine results in the reduced formation of melanine and catecholamines. The therapy for avoiding the various clinical symptoms is based on a low-protein – or low-Phe – diet. In addition to comprehensive instructions by nutritional experts, this special diet requires the consumption of specific foods. As a result of the present study, it has been found that depending on the age group, the dietary treatment of PKU costs between 67 € and 164 € more per month than the diet of a healthy adolescent. Aside from the increased financial demand, the extra time spent on implementing the diet should also be considered.

Keywords: Phenylketonuria, low-protein diet, Phe reduction, nutritional therapy, costs

Citation

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The main treatment of patients with PKU is based on a dietary therapy. The diet consists of a protein restriction, i.e. the absorption of Phe is decreased as a result of reducing high-protein foods in the diet. To ensure the supply of indispensable amino acids, the patients also receive a Phe-free amino acid blend which is usually enriched with vitamins and minerals to further prevent vitamin and mineral deficiency [2].

There are different food groups that meet the desired dietary requirements. This includes foods that are naturally low in protein, such as sugar, oil, butter as well as various types of fruits and vegetables. Special low-protein products can also be ordered from different manufacturers to increase variety. The range of special products includes bread, pastries, flours, flakes, powdered mashed potatoes, milk and meat substitutes. Foods for other special target groups are also available, e.g. for vegans or patients with celiac disease, who sometimes have lower amounts of protein than their “normal” peers as a result of consuming animal protein alternatives and gluten-free substitutes (with the exception of e.g. soy products). Some of these foods contain such small amounts of protein that they can also be used in the diet of patients with PKU. Typical examples of vegan low-protein or low-Phe products include e.g. jackfruit as a meat substitute, almond/hemp/coconut yogurt alternatives, hard cheese substitutes, dairy-free cream cheese with vegetable oils as well as plant-based sandwich spreads and drinks (e.g. with a rice or rice-coconut base).

Since special products and those offered to certain target groups are usually more expensive than conventional foods, it may be assumed that adopting a PKU-specific diet is more expensive than a balanced diet for a healthy child.

For PKU patients, adherence to the Phe-restricted diet is essential to ensure their normal physical and mental development. High food costs can have a negative impact on dietary adherence and result in adverse health effects.

Studies that are already known have shown a much higher financial burden on patients with PKU [10, 11]. An update of these data is

urgently needed to represent the currently applicable additional costs of diets in cases of PKU.

Methods

Preparation of a dietary plan according to optiMIX® and for PKU

For healthy children and adolescents as well as patients with PKU, the weekly plans were prepared in line with the concept of the optimized mixed diet (optiMIX®) by the Research Institute for Children’s Nutrition (*Forschungsinstitut für Kinderernährung* [FKE]) [12]. The age-appropriate intake of the individual food groups for children and adolescents with low physical activity levels was used as the basis for the plan [12, 13]. The program Prodi 6 expert®, version 6.7, was applied to calculate the dietary values. This program is based on the nutritional value table by the German Nutrient Data Base (*Bundeslebensmittelschlüssel* [BLS]), version III.02. To implement a diet that limits daily Phe intake, equivalent low-protein products or replacements were used. A maximum amount of Phe/day to be consumed as a weekly average was defined during the preparation of the weekly plans. The maximum Phe intake was calculated on the basis of the daily Phe requirement per kg body weight (BW) and the average body weight according to the KiGGS study [13, 14]. The studies by van Spronsen et al. and Wendel et al. (♦ Table 1) were used as the basis to calculate the average daily Phe supply [15, 16].

The ingredients of the foods that were not listed in the BLS were entered into the database according to the information from the manufacturers. Products that lacked information about the Phe content were calculated at 30 mg Phe/g protein for predominantly fruit-based and 40 mg Phe/g protein for vegetable-based foods [17, 18]. A standard value of 50 mg Phe/g protein was used for other products [2]. A program-controlled comparison of the required micro- and macronutrients for the respective age groups was performed on the basis of the D-A-CH reference values. In selecting the manufacturers for specific dietary foods to use in PKU, only manufacturers whose products are available in Germany were considered (e.g. *Hammermühle*®, *Huber*, *Poensgen GmbH*, *metaX Institut für Diätetik GmbH*, *Mevalia*, *Loprofin*).

Age (years)	Weight (kg)	Phe (kg BW/day)	Phe (mg/day)
1 ^a	9.7	28.5	276
2–3 ^a	13.5	24	324
4–6 ^a	19.1	19	363
7–9 ^a	27.5	15.5	426
10–12 ^a	39.3	11.8	464
13–14 (w)	52	9.3	483
13–14 (m)	52.2	9.9	516
15–18 (w)	58.7	8.6	505
15–18 (m)	67.1	9.4	631

Tab. 1: Calculation of Phe requirements per day based on average weight according to KiGGS (German Health Interview and Examination Survey for Children and Adolescents) and the recommendations for the amount of Phe per kg BW/day

^a male and female combined. Patients in the age groups 13–14 years and 15–18 years were subdivided by gender.

BW = body weight; f = female; m = male; Phe = phenylalanine

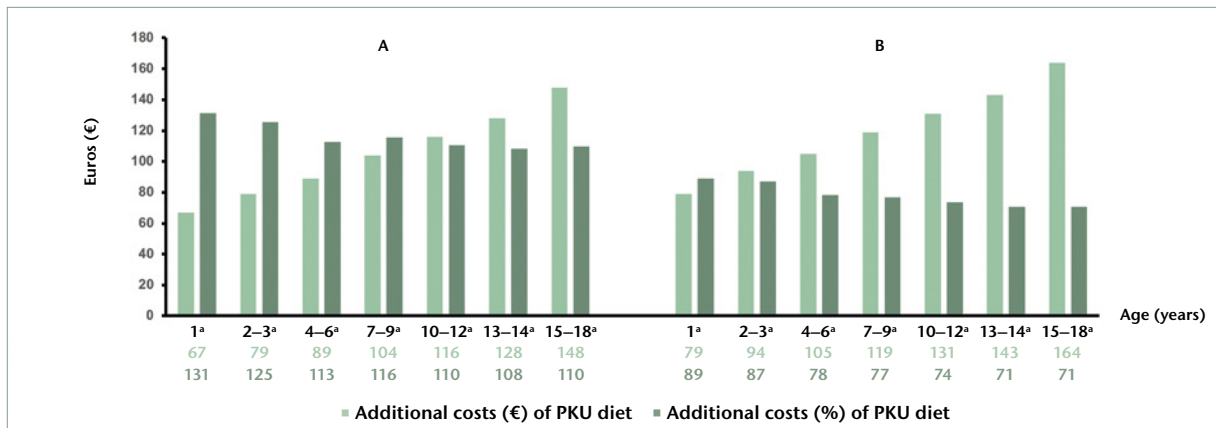


Fig. 1: Representation of the monthly additional costs (€, %) of the inexpensive (A) and expensive (B) variants of a diet with phenylketonuria (PKU) depending on the respective age group
^a male and female combined

Among the amino acid blends on the market, there are so-called “pure” amino acid blends that contain only the amino acids (except for Phe) along with vitamins and minerals. Mixtures that are enriched with carbohydrates, e.g. maltodextrin, are also available. Amino acid blends without carbohydrate supplements and with a low total energy content (40 kcal/10 g protein) were selected for the calculation of the meal plans, since PKU patients, just like healthy people, should cover their energy requirements by eating food.

Only products consisting of L-amino acids were used, not those manufactured on the basis of glycomacropeptide (GMP). These amino acid supplements were not considered because they are based on whey protein and thus contain Phe. Additionally, the total Phe content differs according to manufacturer or product. A further aspect to bear in mind is that the market volume in Germany of GMP-based products is currently considerably lower than that of amino acid blends. The overall calculation took into account the fulfillment of daily protein requirements as well as an adequate supply of micronutrients.

Cost calculation

To calculate the daily costs of food, specific products were selected from each food group that can be used by any age group. To identify the widest possible range of food products and their costs, several basic products were defined in most food groups. The foods were divided into inexpensive and expensive variants to determine the costs. For the cheap variants, the calculations were based on prices from discount stores, while the usual market prices of brand-name products were used for the expensive variants. The median or average value of the determined product costs was used for the special foods in order to categorize the price segment. Special offers, fresh products (e.g. butcher, bakery items) and home-made meals were excluded, since their production is subject to drastic individual fluctuations.

For all fruit and vegetable products that were not prepared for direct consumption, the consumable portion was determined by means of a list called Monica quantity list (*Monica-Mengenliste*)

and/or the average weights were compared with a study by the Federal Office of Consumer Protection and Food Safety (*Bundesamt für Verbraucherschutz und Lebensmittelsicherheit* [BVL]) [19, 20].

The total calculation was prepared with a table in the Microsoft program Excel 2003, in which prices for 1 kg of the product were entered. 30.5 days were defined as the average month for the determination of the monthly costs. In addition to the food costs, shipping costs required for low-Phe special products were included in the amount of 15 € per month, since those special products must be ordered directly from providers. The costs of special amino acid supplements were not included in the calculation, since they are reimbursed by patients’ health insurance.

Results

For the calculated weekly plans, the foods were subdivided into inexpensive and expensive variants. In total, up to 89 different foods were included in the diet according to the optimized mixed diet, depending on the age group. Up to 100 foods were included in the low-protein diet for PKU.

The evaluation of the weekly plans showed that, depending on the age group, the dietary treatment of PKU costs between 67 € and 164 € more per month than a diet based on standard products. The average additional costs of the PKU diet amounted to 116 ± 9% in the cheaper variant and 78 ± 7% in the

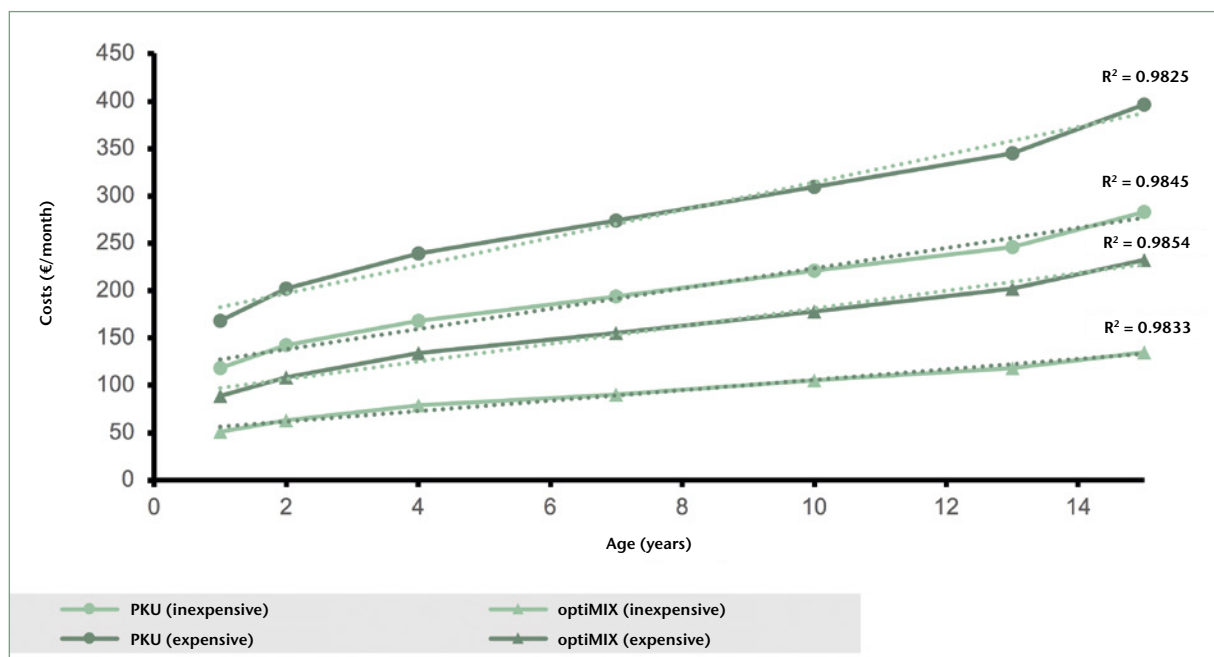


Fig. 2: Correlation between the cost increase with advancing age while eating a healthy diet according to the optiMIX® concept and a PKU diet in two price variants each
PKU = phenylketonuria

high-priced variant. In none of the age groups were the costs lower compared to the optimized mixed diet. Owing to increased energy requirements with advancing age, a consistent increase in the absolute additional costs is apparent. The conversion into the additional cost percentage produces contrary findings and is highest in infancy (♦ Figure 1).

On the whole, there was a linear cost increase for both types of costs and the underlying variants of the shopping behavior ($r^2 > 0.98$; ♦ Figure 2).

A combined calculation of the inexpensive and expensive variant presented additional food costs of $97 \pm 21\%$, corresponding to 112 ± 29 € per month.

In an analysis of individual food groups, starchy side dishes showed the highest price differences of 117–392% additional costs compared to standard products. The dairy substitutes also showed a significant difference in cost (221–223%). The lowest additional costs were found between the meat substitutes and meat/sausage products. Some food groups such as beverages, fruit, spreadable fats and oils showed no price differences between the compared types of diets, since the same products were used.

Discussion

The optiMIX® concept was selected because it is the only concept in Germany that represents the overall diet of various age groups and corresponds to the current state of knowledge about the healthy diet of adolescents. However, some aspects of the concept are not entirely plausible, for example in respect to the quantity increases in the food groups with advancing age. The conversion factors in the concept can sometimes result in discrepancies regarding the recommended intake by the respective age group. In a comparison with the reference values for energy supply issued by the German Nutrition Society (DGE), it can be seen that the optiMIX® concept lies below the recommended amounts for children up to 10 years of age and above the recommendations for children over 10 years of age. The recommendations for fruit and vegetables are also different. While a total of five portions of fruit and vegetables are mentioned in the optiMIX® concept, the DGE recommendations differentiate between three portions of vegetables and two portions of fruit per day. In the present concept, there is no difference in the quantities of fruit and vegetables to be consumed – in other words, contrary to the DGE specifications, the amounts are equivalent.

The amount of Phe that can be tolerated per day varies from patient to patient and is regularly adjusted to take account of changes. Age, growth phases or acute illnesses (infections) are some of the factors that influence the amount of Phe a patient can tolerate [2]. Accordingly, there are no standard specifications for all patients regarding the permitted amount of daily Phe intake. For this reason, this study has attempted to derive recommenda-

tions for daily Phe intake for different age groups from existing studies. Only few studies have a larger group of patients on which to base their findings, and there is a high variability in individual Phe requirements or Phe tolerance [2, 15, 16]. It should also be noted that the target ranges for the Phe content in the blood show significant differences at the international level [21]. The critical aspects highlighted above make it difficult to define specific recommendations for each age group. For the present analysis, only the average data from the studies by van Spronsen et al. and Wendel et al. were used [15, 16]. There are potential sources of errors due to the used data because of the high standard deviations and study population (children ≤ 10 years) [19, 20]. An extrapolation was performed for the age groups that could not be covered by the study data, which may thus lead to inaccuracies. The values were checked by means of a comparison with data for the daily Phe requirements of children and adolescents in order to minimize errors [22]. For practical reasons, a precise Phe amount was determined for each age group. This factor is not relevant for practical applications, since the objective was only to show the average costs of a specific diet while the individual Phe tolerance is generally determined or considered in the dietary plans for each child. The nutritional information used here is based on the BLS or information from the manufacturers. In both cases, deviations from the actual food e.g. on the basis of natural fluctuations may occur, although these fall into the range of the usual deviations in nutritional evaluations.

When searching for suitable products, it became apparent that the food selection was greatly limited by the “low-protein” condition and that the time spent on procuring the appropriate food was much higher than that for the diet of a healthy child. Additionally, the portions for the PKU patient must be calculated and weighed in such a way that the Phe amount per day is neither too low nor too high. On top of the additional costs of the diet, which are also partly due to shipping costs from special providers, these added burdens for the patients and parents should be kept in mind.

A total calculation of the micronutrient supply was not possible due to a lack of available information about the special foods. The amino acid blend used for the calculation was supplemented with micronutrients, according to the guideline [2]. Because of the existing supplementation, it is not necessary to rely on foods enriched with vitamins and minerals. No modification was required for the macronutrients fat and carbohydrates. The overall analysis showed that the quality of carbohydrates tends to be worse in a PKU diet than in the diet of healthy persons. The reasons for the loss of quality include e.g. that whole-grain products have a high protein content which means they cannot be included in the diet; instead, they are replaced with special foods with a higher starch and sugar content.

The underlying calculation was based on a survey of the current market situation. Accordingly, price changes within the survey period could only be considered to a limited extent.

Especially for families with a low income, the additional burden imposed by the special diet can result in great financial strain, even with very frugal shopping behavior (67–148 €). An allowance

for special dietary foods as per the German Social Security Code, which is possible with some illnesses, is not defined for PKU [23, 24]. The increase in the standard rate is generally in the range of 10–20% [25]. This allowance would not cover the requirements for the PKU diet; according to each age group, it should be between about 30 and 50%. Despite cost-effective shopping, added financial burdens – especially as a result of having to buy special foods – are unavoidable.

In comparison to existing surveys, this study showed an increase in the costs of food that also corresponds to the data from the Federal Statistical Office. There are a total of two previous evaluations concerning the additional costs for PKU by Peul from 2004 and 2007. The cited publications also undertook a comparison with the optiMIX® concept, meaning it is almost possible to make a direct comparison (♦ Table 1) [10, 11]. The presented differences in cost between the surveys are within a realistic range, which can e.g. be explained by the rising costs of living. Differences that arose from a divergent product selection within the surveys cannot be ruled out.

In summary, it can clearly be seen that since 2004, the costs of the special diet are consistently higher than that of a normal mixed diet of healthy persons and that they have continued to increase. The monthly costs depend on which foods or food amounts are selected. A sharp reduction of daily Phe intake, i.e. stricter adherence to the diet, can once more significantly increase the costs arising from the added need for special foods [26]. The high costs of PKU diet food can jeopardize adherence and thus endanger the health of the patients. Mandating reimbursements for special foods for patients in need of medically indicated diets could greatly help alleviate this problem.

Age (years)	Peul 2004 [10]			Peul 2007 [11]			own data (2018)		
	€/month optiMIX®	€/month PKU diet	Additional costs (€) PKU diet	€/month optiMIX®	€/month PKU diet	Additional costs (€) PKU diet	€/month optiMIX®	€/month PKU diet	Additional costs (€) PKU diet
1 ^a	45	75	30	50	85	35	89	168	79
2–3 ^a	90	145	55	90	165	75	108	202	94
4–6 ^a	115	175	60	115	220	105	134	239	105
7–9 ^a	135	195	60	140	245	105	155	274	119
10–12 ^a	165	230	65	170	285	115	178	309	131
13–14 ^a	165	230	65	180	315	135	202	345	143
15–18 ^a	195	265	70	200	335	135	232	396	164

Tab. 2: Comparison of the established costs including additional costs of a diet according to the optiMIX® concept and a special diet for phenylketonuria (PKU)

The calculated costs already include the added expenditures of shipping costs during a PKU diet.

^a male and female combined; note: Peul 2004/2007 [10, 11] calculates 10 € worth of shipping costs for children aged 1 year; for other age groups, 15 €.

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Conflict of Interest

At the invitation of Nutricia GmbH, Vitaflo®, Dr. Schär, BioMarin Pharmaceutical, and metaX Institut für Diätetik GmbH, Ulrike Och has held continuing education courses and lectures and created brochures.

The other authors declare that there is no conflict of interest.

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