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Simplifying the diet for patients with phenylketonuria (PKU): unrestricted consumption of fruit and vegetables

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Summary

Over a period of three years, the phenylalanine content in fruit and vegetables was not taken into account in the daily phenylalanine balance for patients with phenylketonuria, a congenital metabolic disorder. In spite of a significantly higher intake of phenylalanine, no worsening of metabolic control could be detected.

Keywords: phenylketonuria, phenylalanine, metabolic disorder, diet, balancing, fruit consumption, vegetable consumption

Introduction

Phenylketonuria (PKU) (OMIM[1] 261600) is one of the most common congenital metabolic disorders. The phenylalanine (Phe) hydroxylase enzyme needed to break down phenylalanine exhibits significantly reduced activity as a result of mutations in the encoding gene. Untreated, it causes severe psychomotor retardation. Only thanks to early diagnosis as part of newborn screening and immediate commencement of treatment by means of a strict, protein-restricted diet will patients develop normally [1, 2].

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Dietary treatment is based on the principle of substrate reduction (Phe) and product supplementation (tyrosine, other amino acids, micronutrients). Metabolic control is monitored by regular determination of the Phe concentration in plasma or dried blood.

Depending on the residual activity of phenylalanine hydroxylase, each PKU patient has an individual Phe tolerance level. This is the amount of Phe, which can be introduced with food, without Phe plasma concentrations exceeding the therapeutic range. In patients with classical PKU, the average Phe tolerance is only approx. 200–400 mg/day, which corresponds to approx. 5–10 g protein/day.

PKU patients now have access to quite a wide range of low-protein speciality foods. Patients are able to satisfy their protein requirement only up to approx. 20 % from natural foods. Precise calculation of Phe content in foods by means of nutritional tables is essential. As a result of the very limited food choice, nutrient intake in these patients will be inadequate. They therefore depend on a nutrient supplement composed of amino acids and micro-nutrients, which must be taken several times a day. Patients are recommended to follow the diet throughout their lives [3], but it is of crucial importance primarily during the growth of the central nervous system, i.e. up to the age of 10 years [2].

Objective

Simplification of diet management without treatment losses would represent a huge relief for PKU patients, particularly for those with classical PKU, who have to follow a very strict diet regime. Most fruit and vegetable varieties are relatively low in protein in comparison to other foods such as e.g. grains or dairy products. A 4-week cross-over study [4] and a 1-year observation [5] studied the effects on Phe plasma concentrations as a result of not accounting for fruit and vegetables in the diet regime among children with classical PKU aged 2 to 10 years. The studies showed that, both in the short and medium term, the patients' metabolic control was also consistently good when fruit and vegetables were not accounted for. The data from long-term observation over three years is now available.

[1] OMIM= Online Mendelian Inheritance in Man (genetics database)

Methodology

Of the patients with classical PKU who had taken part in the previous studies [4, 5] (n = 19), all who had regularly sent in dried blood and food records could be included in the long-term observation over a three-year period. Valid data over this long period was evaluated from 9 patients. These patients observed a Phe-balanced diet, whereby fruit and vegetables with a Phe content of < 75 mg/100 g were not accounted for in the daily Phe intake. Plant foods with a higher Phe content e.g. pulses, broccoli, nuts, were calculated. During the observation period, the Phe concentrations in dried blood were regularly determined by means of tandem mass spectrometry [6]. In the evaluation of the metabolic control, all Phe concentrations were received from dried blood during a three-year period when fruit and vegetables were not accounted for and these were compared with the values from the previous one-year evaluation. In addition, the percentage of Phe plasma concentrations above the therapeutic target range was determined. The average fruit and vegetable intake, the average Phe intake from fruit and vegetables and the average total Phe intake before and after a three-year period of not accounting for these food groups were calculated using the respective 3-day food records (*Bundeslebensmittelschlüssel* [German Nutrient Database; BLS], version 3.0) [7] and compared (multivariable variance analysis [MANOVA]).

Results

A summary of the results is shown in ◆ Table 1. The average Phe plasma concentration rose from 203 µmol/L before the three-year period of not accounting for fruit and vegetables to 215, 219 or 216 µmol/L, and remained stable for the three years in the therapeutic range of 42–240 µmol/L. This still represented a very good metabolic control [2]. The number of values above the therapeutic range did not significantly alter. The fruit and vegetable intake measured as a percentage of the recommendations of the *Forschungsinstitut für Kinderernährung* (Research Institute of Child Nutrition; FKE) remained unchanged. The patients' Phe tolerance increased by 83 mg as a result of the unrestricted intake of fruit and vegetables. This is an increase of 25 %.

Discussion

During the three-year observation period, in which fruit and vegetables were not calculated, the patients were able to maintain good metabolic control. The percentage of Phe plasma concentrations above the therapeutic range remained unchanged, although, in addition to the age-related increase in Phe tolerance, an average of 83 mg of Phe was consumed from the fruit and vegetables that were not counted. This is in line with observations made in both previous studies with shorter study periods [4, 5]. The reason for consistently good metabolic control in spite of a significant increase in Phe intake is not definitively established. The high fibre content of fruit and vegetables and the associated poorer protein absorption [8] or the generally poorer bioavailability of amino acids from plant proteins [9] are possible causes.

These results confirm the observations made in two other studies, which however also included patients over 10 years of age and patients with milder PKU forms. In those studies, no treatment losses were shown when fruit and vegetables were not accounted for in the administration of standardised mealtimes [10] and when a fixed rate of fruit and vegetable intake was allowed [11].

Interestingly, fruit and vegetable eating habits had not changed in this study. The newly-established latitude in Phe tolerance was used for other foods. In comparison with the eating habits of healthy 6 to 10 year olds, this is not surprising, as the fruit and vegetable intake among the PKU patients studied with 91, 90, or 92 % of the FKE recommendations [12] was already significantly higher than the amount consumed by healthier children (48 %) [13].

The PKU patients in this study thus indirectly gained a higher Phe tolerance. Of far greater significance is the fact that an entire food group is freely available to patients.

Even though data already exists for a larger group of PKU patients [11], this data largely comprises adults, often with mild forms of PKU. It would therefore be desirable to confirm the data produced in a larger group of children with classic PKU.

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Conflict of Interest
The authors declare no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

	B (basis) (-1 year) calculated fruit/ vegetable intake n = 9	1 (1st year) unrestricted fruit/vegetable intake n = 9	2 (2nd year) unrestricted fruit/vegetable intake n = 9	3 (3rd year) unrestricted fruit/vegetable intake n = 7	p*
Phe concentrations average in µmol/L (SD)	203 (77)	215 (65)	219 (55)	216 (55)	0.894
Phe concentrations above the therapeutic target range average in % (SD)	34 (26)	28 (20)	40 (22)	26 (20)	0.623
total Phe intake average in mg (SD)	333 (90)	382 (69)	–	457 (62)	B vs. 1: < 0.001*1 B vs. 3: 0.001*1 1 vs. 3: 0.012*1 B vs. 1: < 0.001*2 B vs. 3: < 0.001*2 1 vs. 3: 0.628
Phe intake from fruit/ vegetables average in mg (SD)	76 (43)	49 (22)	–	83 (24)	B vs 1:0 .020* B vs 3: 0.953 1 vs 3: 0.013*
fruit/vegetable intake intake average as a % of FKE recommendations (SD)	91 50	90 (33)	–	92 (28)	0,858

Tab. 1: **Comparison of PKU diet management with and without accounting for fruit and vegetables after 1, 2 and 3 years**
FKE = *Forschungsinstitut für Kinderernährung Dortmund* (Research Institute of Child Nutrition), Phe = phenylalanine, PKU = phenylketonuria, SD = standard deviation

* Wilk's multivariable analysis of variance (MANOVA) with "time" as the within-subject factor over 4 study phases. Significance was assumed at p < 0.05.
*1 Comparison of Phe intake without consideration of age-related increase in Phe tolerance
*2 Comparison of Phe intake with consideration of age-related increase in Phe tolerance
– valid food records not available for all patients

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