Molecular Genetics and Metabolism Reports 5 (2015) 36–41

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: http://www.journals.elsevier.com/molecular-genetics-and-metabolism-reports/

# Effect of dietary regime on metabolic control in phenylketonuria: Is exact calculation of phenylalanine intake really necessary?

Carmen Rohde [a,*], Alena Gerlinde Thiele [a], Ulrike Och [b], Katrin Schönherr [c], Uta Meyer [d], Stefanie Rosenbaum-Fabian [e], Cornelia Maddalon [f], Sabine Matzken [g], Holger Blessing [h], Frauke Lang [i], Monika Jörg-Streller [j], Skadi Beblo [a]

[a] Hospital for Children and Adolescents, Department of Women and Child Health, University Hospitals, University of Leipzig, Liebigstraße 20 a, 04103 Leipzig, Germany
[b] Muenster University Children's Hospital, Albert-Schweitzer-Campus 1, 48149 Münster, Germany
[c] University Children's Hospital, Department of Clinical Genetics, Centre of treatment of metabolic diseases, Kochstr. 2, 07745 Jena, Germany
[d] Medical School Hannover, Clinic of Pediatrics, Carl-Neuberg-Straße 1, 30625 Hannover, Germany
[e] Center of Pediatrics and Adolescent Medicine, University Hospital, Department of Pediatrics, Hugstetter Straße 55, 79106 Freiburg, Germany
[f] University Children's Hospital, Steinwiesstrasse 75, 8032 Zürich, Switzerland
[g] Justus Liebig University, Department for General Pediatrics, Metabolic Unit, Rudolf-Buchheim-Straße, 35392 Giessen, Germany
[h] Department for Inborn Metabolic Diseases, Children's and Adolescents' Hospital, University of Erlangen-Nürnberg, Loschgestraße 15, 91054 Erlangen, Germany
[i] Departement of Pediatric and Adolscent Medicine, Villa Metabolica, University Medical Center, Johannes Gutenberg-University of Mainz, Langenbeckstr. 1, 55131 Mainz, Germany
[j] Clinic for Pediatrics I, Inherited Metabolic Disorders, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria

ARTICLE INFO

*Article history:*
Received 21 August 2015
Received in revised form 28 September 2015
Accepted 28 September 2015
Available online 22 October 2015

*Keywords:*
Dietary regime
Phenylketonuria
Phenylalanine
Metabolic control
Phe-intake

ABSTRACT

*Background:* A phenylalanine (Phe) restricted dietary management is required in phenylketonuria (PKU) to maintain good metabolic control. Nevertheless, five different models of dietary regimes, which differ in their accuracy of Phe documentation, are used. To investigate the effect of the dietary regime on metabolic control, a multicenter evaluation was performed.

*Patients/Methods:* 149 patients (max. 800 mg Phe-intake/day; 108 children aged 1–9 years and 41 adolescents aged 10–15 years) could be included. They were separated according to age and dietary regime, revealed by a questionnaire on dietary habits. Dietary regimes vary from daily strict calculation of all Phe-intake (group 1) to a rather loose regime only estimating Phe-intake and including high protein food (group 5). Data were analyzed with respect to metabolic control (Phe-concentrations, Phe-concentrations above upper recommended limit during 6 months before the interview), Phe-intake (mg/day) and age (years).

*Results:* Median Phe-concentrations in children did not differ significantly among diet groups (group 1: 161; 2: 229, 3: 236, 4: 249, 5: 288 μmol/l, $p = 0.175$). However, exact daily Phe calculation led to significantly lower percentage of Phe concentrations above the upper recommended limit (group 1: 17, 2: 50, 3: 42, 4: 50, 5: 75%, $p = 0.035$). All included patients showed good to acceptable metabolic control. Patients on the dietary regime with the least accuracy, consuming also high protein foods, showed the poorest metabolic control. Median Phe concentrations of all other groups remained within recommended ranges, including from groups not calculating special low protein foods, fruit and vegetables and using a simplified system of recording Phe-intake.
In adolescents no significant differences among diet groups were revealed.

*Conclusion:* Exact calculation of Phe content of all food is not necessary to achieve good metabolic control in children and adolescents with PKU. Excluding special low protein food, as well as fruit and vegetables from calculation of Phe-intake has no impact on metabolic control. However including protein rich food into the diet and simply estimating all Phe-intake appears insufficient. The simplification of dietary regime may be helpful in enhancing acceptability and feasibility.



*Abbreviations:* Phe, phenylalanine; PKU, phenylketonuria; Phe > limit, Phe-concentrations above the therapeutic limit; SD, standard deviation.

* Corresponding author at: Hospital for Children and Adolescents, Centre of Paediatric Research (CPR), Department of Women and Child Health, University Hospitals, University of Leipzig, Liebigstraße 20 a, D-04103 Leipzig, Germany.
*E-mail addresses:* Carmen.Rohde@medizin.uni-leipzig.de (C. Rohde), Alena.Thiele@medizin.uni-leipzig.de (A.G. Thiele), och@uni-muenster.de (U. Och), kathrin-schoenherr@med.uni-jena.de (K. Schönherr), Meyer.Uta@mh-hannover.de (U. Meyer), stefanie.rosenbaum-fabian@uniklinik-freiburg.de (S. Rosenbaum-Fabian), Cornelia.Maddalon@Kispi.uzh.ch (C. Maddalon), Sabine.Matzken@paediat.med.uni-giessen.de (S. Matzken), holger.blessing@uk-erlangen.de (H. Blessing), frauke.lang@web.de (F. Lang), monika.joerg-streller@uki.at (M. Jörg-Streller), Skadi.Beblo@medizin.uni-leipzig.de (S. Beblo).

http://dx.doi.org/10.1016/j.ymgmr.2015.09.006

## 1. Introduction

Phenylketonuria (PKU) (OMIN 261600) is one of the most common inborn metabolic disorders. The incidence across Europe varies between 1:3.000 and 1:30.000 [1]. PKU is caused by deficient activity of phenylalanine hydroxylase (EC 1.14.16.1) in most tissues, predominantly in the liver. Severe physical and mental disability appears in children with untreated PKU. Postnatal diagnosis by newborn screening, immediate initiation of a lifelong phenylalanine (Phe) restricted diet and supplementation of a Phe free amino acid mixture enriched with micronutrients result in almost normal cognitive development [2,3]. The individual daily Phe tolerance depends on residual phenylalanine hydroxylase activity and varies significantly among patients [2]. Poor dietary control results in high plasma Phe-concentrations, which lead to neurocognitive impairment and negatively affect attention span, mood [4] and cognitive performance [5]. Consequently, lifelong dietary therapy with good metabolic control is recommended [6].

Across Europe, two different systems are used to achieve a limited Phe-intake: Phe can either be allocated in total daily amounts or by Phe exchange systems, where portion sizes of Phe-containing foods are precalculated for a defined amount of Phe. The latter is used in the United Kingdom, Denmark and Italy. In most other European countries, the exact Phe content of individual serving sizes is calculated and taken into account [7]. Within this system, however, there are differences with respect to its degree of accuracy. So far, only few studies with small patient groups of children and adolescents were performed to examine the influence of dietary regimes on metabolic control [8–11].

The classical dietary approach consists in the exact calculation of the Phe content of all ingested foods and drinks without any exceptions (dietary regime 1). Patients under dietary regime 2 calculate their Phe ingestion but do not include foods with a very low Phe content, e.g. <10 mg/100 g food. Dietary regime 3 combines free consumption of low protein foods (<10 mg Phe/100 g), fruit and vegetables (<75 mg Phe/100 g) with calculating the exact Phe content of all other foods [9–12]. Dietary regime 4, the so-called “simplified diet”, consists of estimating the Phe content according to certain principles (free use of five portions of fruit and vegetables; free use of special low protein food including low protein bread, pasta and breakfast cereals; quantities of potatoes, rice and maize are discussed with the parents and then fixed for a period of time) [8]. Despite other instructions some patients only estimate their protein consumption and even consume varying amounts of protein rich foods e.g. meat, milk or eggs (dietary regime 5) [13,14]. This regime is self-selected by the families and was never recommended, dietary regimes 1–4 have been chosen by the different metabolic centres.

To investigate the influence of the chosen dietary regime on metabolic control, a survey was performed with PKU children and adolescents from ten German speaking metabolic centres, eight from Germany, one from Switzerland and one from Austria using a structured questionnaire (Fig. 1). In addition, the influence of daily Phe-intake and patient's age on metabolic control in relation to the dietary regime was evaluated.

## 2. Methods

### 2.1. Study design

This open, multicentre, retrospective investigation followed the principles of the guidelines in the World Medical Association Declaration of Helsinki of 1975, as revised in 2000 and the harmonized ICH-Guideline for Good Clinical Practice. It was approved by the University of Leipzig's ethics committee (registration-number 372–12–05122012) and registered at the International Clinical Trials Registry Platform (DRKS00004732). Guardians of all included patients gave written informed consent.

The study was open to all German speaking metabolic centres willing to participate. Inclusion was restricted to PKU patients with a maximum Phe-intake of 800 mg/day. Patients older than 15 years, because of higher target reference values, [15] and patients with additional acute or chronic diseases, adhering to additional dietary treatments, or participating in other clinical trials over the past six months were excluded from the analysis.

Data collection was performed during routine clinic visits at the respective metabolic centres between December 2012 and November 2013.

### 2.2. Patients

A total of 149 PKU patients (77 male/72 female) aged 1–15 (mean ± SD: 7.0 ± 6.6; median = 7) years could be included. They were assigned to the group of children (1–9 years) or the group of adolescents (10–15 years) according to age at clinic visit; this resulted in 108 children (58 male/50 female, mean age ± SD: 4.5 ± 2.8) and 41 adolescents (19 male/22 female, mean age ± SD: 12.2 ± 1.7). All patients were advised to maintain their dried blood Phe-concentrations according to the current recommendations for the German speaking countries (upper therapeutic limit of Phe-concentrations: 240 μmol until the age of ten years, 900 μmol/l thereafter [15] by maintaining the prescribed Phe restricted diet.

### 2.3. Questionnaire

A two-part questionnaire was developed. The first part recorded patients' characteristics (gender, age, height, body weight, recommended daily Phe-intake, and the last six Phe-concentrations in dried blood prior study entry under routine and thorough dietary conditions, representing the metabolic control over about six months). All data were collected from medical records by trained dieticians and physicians. To verify Phe-intake (recommended versus actual Phe-intake), patients' most recent three-day diet records, documented once a year as part of routine care, were evaluated by the dietician.

In the second part, the patients or their caregivers were asked for information about their degree of accuracy in dietary management with respect to Phe calculation. Additional information about the amino acid mixture consumption and the psychosocial burden implied by the therapy was requested (entire questionnaire see Fig. 1). The second part of the questionnaire was completed anonymously after the clinic visit, and families handed in the questionnaire in a sealed envelope.

### 2.4. Data analysis

Since guidelines for metabolic control differ according to the patient's age, the entire cohort was divided into two age-groups (children, age 1–9 years, and adolescents, age 10–15 years) before data analysis.

Both age-groups were then assigned to the respective subgroups according to their dietary regime (Fig. 1, Tables 1a and 1b). Psychological burden of diet realisation and adherence to the intake of the Phe free amino acid mixture was expressed as value on a scale of one to five (Fig. 1).

Metabolic control, expressed as mean Phe-concentrations (μmol/l) as well as percent of Phe-concentrations above the therapeutic limit (Phe > limit) was investigated with respect to dietary regime, Phe-intake (mg/day) and age.

Possible associations between the dietary regime and the psychological burden of diet management were investigated, as well as dietary regime and adherence to the intake of the amino acid mixture.

### 2.5. Statistical analysis

All procedures were performed using IBM SPSS for Windows 20.