Nutrition, Metabolism & Cardiovascular Diseases (2016) **26**, 171–177

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

REVIEW

Diet in children with phenylketonuria and risk of cardiovascular disease: A narrative overview

E. Verduci*, G. Banderali, F. Moretti, C. Lassandro, G. Cefalo, G. Radaelli, E. Salvatici, M. Giovannini

Department of Pediatrics, San Paolo Hospital, Department of Health Science, University of Milan, Via A. Di Rudinì 8, I-20142 Milan, Italy

Received 19 May 2015; received in revised form 18 September 2015; accepted 11 October 2015
Available online 3 November 2015

KEYWORDS
Phenylketonuria;
PKU diet;
Cardiovascular risk;
Nutrition;
Obesity;
Lipid profile

Abstract *Aims:* The aim of this paper is to review the possible relationship of restricted phenylalanine (Phe) diet, a diet primarily comprising low-protein foods and Phe-free protein substitutes, with major cardiovascular risk factors (overweight/obesity, blood lipid profile, plasma levels of homocysteine, adiponectin and free asymmetric dimethylarginine (ADMA), oxidative stress and blood pressure) in PKU children.
Data synthesis: In PKU children compliant with diet, blood total cholesterol, low-density lipoprotein cholesterol (LDL-C), plasma ADMA levels and diastolic pressure were reported to be lower and plasma adiponectin levels to be higher compared to healthy controls. No difference was observed in overweight prevalence and in high-density lipoprotein cholesterol (HDL-C) levels. Inconsistent results were found for plasma homocysteine levels and antioxidant status.
Conclusions: PKU children compliant with diet seem to display non-different cardiovascular risks compared with the healthy population. Well-designed longitudinal studies are required to clarify the potential underlying mechanisms associated with PKU and cardiovascular risk factors.

Introduction

Phenylketonuria (PKU; OMIM 261 600) is an autosomal recessive disorder of phenylalanine (Phe) metabolism [1], primarily due to mutations in Phe hydroxylase (PAH) gene, which facilitates conversion of the essential amino acid Phe to tyrosine. Loss of PAH activity results in increased Phe concentrations in the blood (hyperphenylalaninaemia, HPA) and therefore in toxic concentrations in the brain. Various combinations of mutations [2] result in a full spectrum of metabolic phenotypes ranging from severe, moderate and mild PKU (blood Phe concentration >360 μmol/L), which require dietary management, to mild HPA (blood Phe concentration: 120–360 μmol/L), wherein dietary restriction is not necessary [3]. A minority of HPA

Abbreviations: ADMA, asymmetric dimethylarginine; BH4, tetrahydrobiopterin; BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HPA, hyperphenylalaninaemia; LDL-C, low-density lipoprotein cholesterol; NO, nitric oxide; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria.

* Corresponding author. Department of Pediatrics, San Paolo Hospital, University of Milan, Via A. Di Rudinì 8, I-20142 Milan, Italy. Tel.: +39 0281 844 508.
E-mail addresses: elvira.verduci@unimi.it (E. Verduci), giuseppe.banderali@unimi.it (G. Banderali), francesca.moretti@unimi.it (F. Moretti), carlotta.lassandro@unimi.it (C. Lassandro), graziella.cefalo@unimi.it (G. Cefalo), giovanni.radaelli@unimi.it (G. Radaelli), elisabetta.salvatici@tin.it (E. Salvatici), marcello.giovannini@unimi.it (M. Giovannini).

http://dx.doi.org/10.1016/j.numecd.2015.10.005
0939-4753/

cases (1–2%) are due to mutation of one of the enzymes involved in the synthesis or recycling of PAH gene cofactor, tetrahydrobiopterin (BH4) [4,5].

In developed countries, PKU subjects are identified at birth through newborn screening programmes and classified by their clinical phenotype. The minimum pretreatment Phe levels, requiring a Phe-restricted diet, vary among different countries [6]. Differential diagnosis between the two major forms of HPA (PAH or BH4 deficiency) is performed by BH4 loading test, analysis of urinary pterins, determination of dihydropteridine reductase activity in blood, analysis of pterins, folates and neurotransmitter metabolites in cerebrospinal fluid and enzyme activity measurement.

High blood Phe levels are neurotoxic mainly because of their inhibitory effect on the blood–brain barrier transport of free L-amino acids (leucine, isoleucine, valine, tyrosine, tryptophan and lysine) that are necessary for the synthesis of proteins and neurotransmitters (dopamine and serotonin) [3,5]. PKU children, if untreated, can exhibit microcephaly, epilepsy, a musty body odour, decreased skin and hair pigmentation, eczema, severe intellectual disability and behaviour problems as well as structural brain changes visible on magnetic resonance imaging [7]. Prognosis and outcome depend on both time of diagnosis and type of mutation [8].

Despite the new advancements and treatment strategies (e.g. large neutral amino acids, BH4, gene therapy, Phe ammonia lyase), dietary intervention remains the mainstay of PKU therapy [8].

PKU: dietary treatment

The main treatment for PKU is an early Phe-restricted diet, which aims at reducing blood Phe to non-toxic levels [8]. During infancy, breastfeeding is recommended to provide natural proteins according to the individual Phe tolerance, and/or whether necessary a Phe-free infant formula is used. With the introduction of solid foods, PKU infants have to avoid foods rich in protein (meat, fish, eggs, dairy products, standard bread, nuts and seeds). Therefore, PKU diet mainly comprises low-protein natural foods (vegetables, fruits and some cereals), to reach the ideal Phe levels necessary for growth processes. The allowed intake of low-protein natural foods is commonly calculated on the basis of their Phe content. Nowadays, low-protein variants of some foods are commercially present, such as low-protein bread and low-protein pasta [9]. The overall required amount of daily protein intake is obtained consuming additional Phe-free protein substitutes that supply essential amino acids in suitable proportions [3,8].

This type of dietary regimen usually includes high carbohydrate content, low saturated and long-chain polyunsaturated fat, cholesterol, carnitine, taurine, iron, zinc, selenium, calcium, folates, A, C, D, E and B2, B6, B12 vitamins, because of the very low consumption of Phe-containing animal foods [8,10,11]. Indeed, a study observed that PKU children compliant with diet consumed $<$ 7% of saturated fats including $<$50 mg cholesterol per day [12]. Moreover, PKU subjects must rely on the endogenous synthesis of long-chain polyunsaturated fatty acids from their precursors; the content of these acids is often suboptimal in dietary products for patients with PKU, particularly of α-linolenic acid, precursor of docosahexaenoic acid [8,10,13]. These characteristics of the diet for subjects with PKU may resemble those of a vegan diet with respect to the composition of permitted natural foods. Vegan diet has been recently considered within healthy populations for the presumed health benefits, including potential effects on cardiovascular health [14]. However, consumption of some foods of the usual vegan diet, rich in micronutrients (cereals, nuts, etc.), is restricted in PKU subjects because of their high protein content. PKU subjects need therefore nutritional supplements (by Phe-free protein substitutes or given separately) to meet the dietary reference intakes for micronutrients. Besides, it is worth noting that patients with severe PKU are provided with a significantly high percentage of dietary supplements such as folic acid and vitamin B12 [15–17].

Overall, while there is a general agreement that PKU patients need long-term dietary counselling and daily nutritional supplementation [8], particular attention should be paid concerning the micronutrient intake [17].

Cardiovascular disease

Cardiovascular disease (CVD) remains to be the major cause of deaths worldwide. More than 3 million of these deaths occurred before the age of 60, which could have largely been prevented. The percentage of premature deaths from CVD ranges from 4% in high-income countries to 42% in low-income countries [18].

The burden of disease will increase with an ageing population and increasing levels of obesity and sedentary lifestyles [18]. Diet has long been implicated in managing and reducing the risk of CVD [19]. The assessment of CVD risk factors relies mainly on the evaluation of dietary habits, anthropometric measurements, blood lipid profile, homocysteine and inflammatory biomarker levels, blood pressure as well as genetic and psychosocial factors [20].

Topic of review

This paper reviews the literature published over the past 15 years and discusses the potential relationship of restricted Phe diet in PKU children with cardiovascular risk factors (overweight/obesity; blood lipid profile; plasma levels of homocysteine, adiponectin and free asymmetric dimethylarginine (ADMA); oxidative stress; and blood pressure).

Methodology

Publications were identified from a PubMed search using the terms ‘obesity’, ‘overweight’, ‘lipid profile’, ‘cholesterol’, ‘long-chain polyunsaturated fatty acids’, ‘homocysteine’, ‘micronutrients’, ‘adiponectin’, ‘asymmetric dimethylarginine’, ‘nitric oxide’, ‘oxidative stress’, ‘blood