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Dietary glycemic index, glycemic load and metabolic profile in children with phenylketonuria

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Abstract *Background and aims:* No data exist in the current literature on the glycemic index (GI) and glycemic load (GL) of the diet of phenylketonuric (PKU) children. The aims of this study were to examine the dietary GI and GL in PKU children on a low-phenylalanine (Phe)-diet and to evaluate whether an association may exist between the carbohydrate quality and the metabolic profile.
Methods: Twenty-one PKU children (age 5–11 years) and 21 healthy children, gender and age matched, were enrolled. Dietary (including GI and GL) and blood biochemical assessments were performed.
Results: No difference was observed for daily energy intake between PKU and healthy children. Compared to healthy controls, PKU children consumed less protein ($p = 0.001$) and fat ($p = 0.028$), and more carbohydrate (% of total energy, $p = 0.004$) and fiber ($p = 0.009$). PKU children had higher daily GI than healthy children (mean difference (95% confidence interval), 13.7 (9.3–18.3)) and higher GL (31.7 (10.1–53.2)). PKU children exhibited lower blood total and low density lipoprotein cholesterol (LDL) levels ($p < 0.01$) and higher triglyceride level ($p = 0.014$) than healthy children, while glucose and insulin concentrations did not differ. In PKU children the dietary GL was associated with triglyceride glucose index (Spearman's correlation coefficient = 0.515, $p = 0.034$).
Conclusion: In PKU children a relationship of the dietary treatment with GI and GL, blood triglycerides and triglyceride glucose index may exist. Improvement towards an optimal diet for PKU children could include additional attention to the management of dietary carbohydrate quality.

Abbreviation list: BMI, body mass index; GI, glycemic index; GL, glycemic load; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; ICQC, International scientific consensus summit from the International Carbohydrate Quality Consortium; LDL, low-density lipoprotein; MHP, mild hyperphenylalaninemia; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; QUICK, quantitative insulin sensitivity check index; TyG, triglyceride glucose index; WHO, World Health Organization.

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Introduction

Phenylketonuria (PKU; OMIM 261 600) is an autosomal recessive disorder of phenylalanine (Phe) metabolism mainly due to mutations of the phenylalanine hydroxylase (PAH) gene, which is needed to convert the essential amino acid phenylalanine to tyrosine [1]. The loss of PAH activity results in accumulation of Phe to neurotoxic levels [1]. Various combinations of mutations result in a full

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spectrum of metabolic phenotypes ranging from mild hyperphenylalaninaemia (MHP, blood Phe 120–360 μmol/L) – in which dietary restriction is not necessary, to mild, moderate and classical phenylketonuria (blood Phe levels >360 μmol/L) which require dietary management [1].

The main goal of treatment for PKU is to maintain the blood Phe within safe limits to prevent mental retardation and ensure normal growth and life with good health through adulthood [2–4]. The dietary treatment usually begins immediately after confirmation of PKU diagnosis in newborns and should be continued throughout their lifetime [3,4].

Patients with PKU have to avoid foods rich in protein (meat, fish, eggs, conventional bread, dairy products, nuts, and seeds) [3]. Accordingly, the PKU diet is mainly made up of low-protein natural foods (vegetables, fruits) and special low protein products, which are low-protein variants of some foods such as bread, pasta and biscuits with a protein content <1 g/100 g [3]. In Italy, the quantities of the permitted natural foods are calculated from a method of Phe equivalence (dependent upon how much Phe a food contains for a given weight) [5]. The required amount of daily protein is obtained from Phe-free protein substitutes providing essential amino acids in suitable proportions [3].

In PKU patients the issue of overweight and obesity has been highlighted [6], although the prevalence of obesity was observed similar to general populations both in PKU children [7] and adults [8,9]. The metabolic profile of PKU patients has been studied in the past (e.g. Refs. [8–10]). Only a study compared the metabolic syndrome between PKU and healthy subjects and no difference in the prevalence was reported [8].

The high energy content of Phe-free protein substitutes and the “avoidance” of sporting activities have been suggested to be factors influencing the tendency to overweight/obesity in the PKU population [6]. The uncontrolled consumption of special low protein products could be another factor predisposing to obesity [6]. In severe PKU phenotypes (with natural protein tolerance less than 10 g/day), the special low protein products may provide up to 50% of energy requirements [6]. Moreover, Rocha et al. [6] highlighted that in some low protein products it is common to add glucose, dextrose or sugar as ingredients, and this may increase the sugar intake in PKU [6].

The glycemic index (GI) was developed to systematically classify foods according to their ability to raise postprandial glycemia [11]. Since the overall impact of one food on postprandial response is due to the combination of GI and the amount of carbohydrates in that food, a derived index has been proposed, namely glycemic load (GL) [11]. Subsequently, GL was standardized to the energy of the food portion consumed (GL/1000 kJ) for a better representation of carbohydrate-based foods combined with fat and protein [11].

In 2015 the International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC) [12] recommended that low GI and low GL should be considered in the context of a healthy diet [12]. The ICQC stated that low GI/GL diets reduce the risk of type 2 diabetes and could reduce total body fat mass [12]. No data exist in the current literature on GI and GL in PKU children.

The primary aim of the present study was to examine the dietary glycemic index and glycemic load in PKU children on low-Phe diet. Secondary aim was to evaluate whether an association may exist between the carbohydrate quality and their metabolic profile.

Methods

This observational case-control study examined 21 PKU primary school children (age 5–11 years) gender and age (±6 months) matched with 21 healthy controls, consecutively admitted to the Department of Pediatrics, San Paolo Hospital, Milan, from January 2014 to September 2014. Inclusion criteria were: gestational age 37–42 week inclusive, weight at birth ≥2500 g, single birth, no congenital malformation, white parents. Exclusion criteria were: having endocrine disorders, chronic liver diseases or overweight/obesity. PKU children non-compliant with the recommended diet were also excluded. Overweight/obesity was defined in accordance with the International Obesity Task Force [13]. PKU children were defined as compliant to the diet when the annual mean Phe levels, monitored monthly by the Guthrie test [14], was within the range 120–360 μmol/L. Phenylketonuric children were detected by a newborn screening test and periodically monitored in our department since diagnosis.

A medical history was collected at recruitment from parents by a standardized questionnaire during a personal interview conducted by the same pediatrician that also saw the children for a general examination, and evaluated the Tanner stage of puberty [15]. Moreover, the pediatrician took anthropometric measurements of children, assisted by an experienced operator. Body weight and height were measured using a mechanical column scale (seca 711; seca GmbH & KG, Hamburg, Germany) with an integrated measuring rod (seca 220; seca GmbH & KG). The body mass index (BMI) was calculated from the ratio of weight to height squared (kg/m^2). BMI z-scores were calculated and adjusted for age and gender by using Cole’s LMS method [16] and Italian reference data [17]. The parents of eligible children or their legal guardian received a detailed explanation of the study, and signed a consent form. The hospital Ethics Committee approved the study protocol and gave ethical clearance.

Dietary assessment and daily GI and GL

For each child, the dietary intake, including beverages, was recorded by means of a food diary filled out by parents for three consecutive days (two weekdays and one weekend day). Parents received instructions about the method for weighing and recording food. They were trained by a dietitian to weigh each food item offered to their child before consumption, to weigh leftovers and to record the weights each time [18]. Quantification and analysis of the energy intake and nutrient composition were performed