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Original Article

Effects of Short-Term Calcium Supplementation in Children and Adolescents with Phenylketonuria

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Abstract

Reduction of bone mineral density and the risk of osteopenia have been reported to occur in phenylketonuria (PKU) patients. This study aimed to evaluate the short-term effects of calcium supplementation in phenylketonuric children and adolescents. The study included 18 patients with PKU aged 5–18 yr (61% male) under clinical and nutritional treatment. Evaluation of food intake, anthropometry, and biochemical and phalangeal quantitative ultrasound were performed before (phase 1) and after (phase 2) calcium supplementation (1000 mg/d) for 34 d. Statistical analysis was performed using *t* test for paired samples, Wilcoxon's test, and McNemar's test ($p < 0.05$). There was an inadequate intake of phosphorus and vitamin D, the same occurring with serum concentrations of these nutrients. About 50% of the patients had an accumulation of adipose tissue measures, with a negative correlation between *Z*-score, body mass index, and phalangeal quantitative ultrasound (amplitude-dependent speed of sound [AD-SoS]). There was a significant difference in urinary phosphorus excretion with higher values before supplementation. Comparison of the two phases revealed significantly higher AD-SoS values after the supplementation ($p = 0.017$). The reduction in phosphorus excretion associated with increased AD-SoS between the two phases suggested increased bone formation, and showed no negative effects in relation to short-term calcium supplementation in children and in adolescents with PKU.

Key Words: Bone mass density; calcium; dietary supplementation; phenylketonuria.

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What is known? Reduction of bone mineral density and the risk of osteopenia have been reported to occur in phenylketonuria patients.

What is new? Short-term calcium supplementation improves bone quality, suggesting increased bone formation, in children and in adolescents with phenylketonuria.

Informed consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Author contributions: Design and conduct of the study: NYYT, OI, JSM. Data collection and analysis: NYYT, MFT, LDM, and OI. Data interpretation: NYYT, CBN, CG, GGS, and JSM. Manuscript writing: NYYT, CNF, JSM.

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Introduction

Phenylketonuria (PKU) is an inborn error in the metabolism of phenylalanine (Phe), genetically transmitted in an autosomal recessive manner. Generally, PKU results from the deficiency of the hepatic enzyme phenylalanine hydroxylase, which is responsible for the conversion of the amino acid Phe in tyrosine *(1)*. PKU occurs in all ethnic groups, and the incidence in newborns is on average 1:10,000 *(2)*. In Brazil, studies have estimated a ratio from 1:12,000 to 1:15,000 in newborns *(3)*. The severity of the enzymatic defect results in different forms of PKU, where the clinical results as plasma levels and tolerance to dietary Phe vary *(4)*.

Nutritional therapy is an important and decisive component in the treatment of PKU and consists of a severe restriction of Phe intake, which reflects directly in the supply of proteins from natural sources to the body. In this context, PKU requires lifelong nutritional management, with the control diet associated with a daily supply of free amino acids through Phe and enriched with a vitamin and mineral formula. This formula is responsible for providing around 75%–95% of protein and 90%–100% of vitamins and trace element needs *(5)*. The regular intake of this formula is essential to allow proper growth and development *(4)*.

Furthermore, recent studies suggest that patients with PKU show loss in the bone remodeling process and decreased bone mineral density (BMD) *(6,7)*, especially those older than 8 yr, with higher plasma Phe concentrations *(8)*. The etiology of BMD reduction is not fully elucidated, but it is believed that the damage in bone mass can occur as a result of a cumulative process related to the disease *(9)* or can be secondary to food restriction, which undertakes the formation of bone mass *(10)*. Therefore, it is not clear whether the deficit of bone mineralization is due to a primary defect in bone turnover caused by the disease itself or a result of dietary long-term treatment *(11)*. Some recent studies have highlighted the role of osteoclastogenesis in the pathogenesis of bone disease in patients with PKU *(12)*. Authors observed an increase in the excretion of bone resorption markers, suggesting increased osteoclastic activity, and concluded that bone formation seems active in childhood and deteriorating in adult patients *(13)*.

Bone mineral structure is the result of the balance between the maximum bone mass and loss rate associated with physiological events and disease. The main strategies to reduce the risk of osteoporosis consist in making bone mass reach its optimal level during childhood and adolescence *(14,15)*. A better quality of life in adulthood can be purchased with an adequate peak bone mass in adolescence, because osteoporosis is inversely proportional to the peak bone mass acquired during childhood *(16)*. In this context, calcium has a fundamental role in bone mineral formation *(17)*.

Despite several studies showing the existence of the relationship between PKU and the greatest risk for developing bone diseases, it is still unknown studies describing the real benefits of the use of calcium supplementation as a preventive strategy and indication of this procedure as a routine in clinic practice. The present study aimed to evaluate the effects of short-term calcium supplementation in children and adolescents with PKU.

Materials and Methods

This is a controlled and paired clinical trial with a convenience sample. The study was conducted at the PKU outpatient clinic of a university hospital. All patients were diagnosed with PKU by phenylalanine hydroxylase deficiency, aged 5–18 yr, and underwent clinical and nutritional treatment. Patients who did not adhere to the dietary treatment (evaluated by the food anamnesis) associated with no intake of elemental formula free of Phe in the recommended amount and those who were receiving a drug supplement of calcium were excluded. The study was approved by the ethical committee of the institution, and all participants or guardians provided written informed consent.

The participants underwent calcium supplementation (calcium carbonate) for 34 d. Assessment of food intake, anthropometric (weight, height, and body mass index [BMI]) and biochemical markers in the blood (Phe, calcium, magnesium, inorganic phosphorus, alkaline phosphatase, 25-hydroxyvitamin D [25-OH-D], and zinc), and urine (calcium and inorganic phosphorus) and quantitative ultrasound (QUS) of the phalanges were performed before and after supplementation.

Oral Calcium Supplementation

The patients received calcium carbonate capsules in sufficient quantity for a daily intake of 3 units (833 mg each), totaling 1000 mg of calcium a day, consumed during meals.

The patients were periodically followed up at the PKU outpatient clinic of the hospital by the responsible nutritionist or dietitian. In the outpatient clinics, as well as during the evaluation period of the study, the researcher made a record of the number of capsules ingested, certifying that the protocol of supplementation was being followed correctly, ensuring adherence to treatment.

Anthropometric Assessment

The body weight was measured by an electronic Filizola® (Filizola, S.A., Brazil) balance, Personal Line model, with an accuracy of 0.1 kg and a maximum capacity of 150 kg. Height was measured using a vertical shaft equipped with a centesimal scale with markings every half centimeter, with a minimum capacity of 95 cm and a maximum capacity of 190 cm. BMI was calculated using the formula weight (kg)/height $(m)^2$.

The classification of anthropometric indices height for age (H/A) and BMI for age (BMI/A) was performed using WHO AnthroPlus® software (World Health Organization), referencing the *Z*-score.