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Original Research

Normal vitamin D levels and bone mineral density among children with inborn errors of metabolism consuming medical food–based diets

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ARTICLE INFO

Article history:
Received 5 August 2015
Revised 6 November 2015
Accepted 11 November 2015

Keywords:
Humans
Vitamin D
Medical foods
Bone mineral density
Inborn errors of metabolism
Phenylketonuria

ABSTRACT

A higher incidence of osteopenia is observed among children with inherited metabolic disorders (inborn errors of metabolism, or IEMs) who consume medical food–based diets that restrict natural vitamin D–containing food sources. We evaluated the vitamin D status of children with IEMs who live in the Pacific Northwest with limited sun exposure and determined whether bone mineral density (BMD) in children with phenylketonuria (PKU), the most common IEM, correlated with diet or biochemical markers of bone metabolism. We hypothesized that children with IEMs would have lower serum vitamin D concentrations than controls and that some children with PKU would have reduced bone mineralization. A retrospective record review of 88 patients with IEMs, and 445 children on unrestricted diets (controls) found the 25-hydroxyvitamin D concentrations were normal and not significantly different between groups (IEM patients, 27.1 ± 10.9; controls, 27.6 ± 11.2). Normal BMD at the hip or spine (–2 < z score < 2) was measured in 20 patients with PKU. There was a correlation between lumbar spine BMD and dietary calcium intake. We saw no evidence of low serum vitamin D in our population of children with IEMs compared with control children. We also found no evidence for reduced BMD in children with PKU on specialized diets, but BMD was associated with calcium intake. Dietary intake of essential nutrients in medical food–based diets supports normal 25-hydroxyvitamin D levels and BMD in children with IEMs, including PKU. The risk of vitamin D deficiency among patients consuming a medical food–based diet is similar to the general population.

Abbreviations: BMD, bone mineral density; DEXA, dual-energy x-ray absorptiometry; HPLC-MS/MS, high-pressure liquid chromatography tandem mass spectrometry; IEM, inborn errors of metabolism; iPTH, intact parathyroid hormone; OHSU, Oregon Health & Science University; PAH, phenylalanine hydroxalase; PKU, phenylketonuria.

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http://dx.doi.org/10.1016/j.nutres.2015.11.007
0271-5317/

1. Introduction

Vitamin D, calcium, and phosphorous are essential for proper bone growth and integrity in children, and deficiency of any of these nutrients can lead to rickets [1]. Children with inborn errors of metabolism (IEMs) consume specialized diets that restrict natural food sources of vitamin D and calcium, which places them at an increased risk for micronutrient deficiencies and bone disease [2]. Patients obtain most, if not all, of their vitamin D and much of their calcium and protein from medical formulas containing mixtures of free amino acids (synthetic protein). Adults with IEMs are also at risk because most clinics recommend lifelong adherence to these strict diets. In addition, children from northern latitudes, including those treated in our clinic in Portland, Oregon, have very limited sun exposure during the winter months, which limits endogenous vitamin D synthesis by the skin.

Phenylketonuria (PKU) is an inherited disorder of amino acid metabolism that results from mutations in the gene for phenylalanine hydroxylase (*PAH*) and is the most common IEM that requires treatment with a specialized diet, which includes restriction of foods that supply natural vitamin D and calcium. Multiple studies in children and adults with PKU suggest patients may have a decreased bone mineral density (BMD) [3]. The etiology of low BMD among patients with PKU is unknown, but in addition to a potentially inadequate intake of micronutrients in the diet, it has also been postulated that *PAH* mutations which result in loss of PAH activity inherently predispose patients to osteoporosis, independent of diet [4], and that elevations in plasma phenylalanine concentrations may decrease BMD [5–7].

The Metabolic Clinic of the Child Development and Rehabilitation Center at Oregon Health & Science University (OHSU) treats children and adults with IEMs. Because of its northern location and frequent winter time cloud cover, all residents of Northwestern Oregon are at risk for vitamin D deficiency, which further increases the risk for patients with IEMs on specialized diets. We hypothesized that children with IEMs would have lower serum vitamin D concentrations than control children and that some children with IEMs and low serum 25-hydroxyvitamin D (25[OH]D) would have reduced bone mineralization. The objective of this study was to compare serum 25(OH)D concentrations in children with IEMs consuming a medical food–based diet to those in a group of control children on unrestricted diets. Our second objective was to evaluate BMD in a group of PKU patients living in the Northwest compared with age reference values and determine whether BMD was correlated with dietary nutrient intake and/or biochemical markers of bone metabolism, including 25(OH)D.

2. Methods and materials

2.1. Electronic medical record review

This cross-sectional medical record review was deemed exempt by the OHSU Institutional Review Board (eIRB no. 7556). Patients with the diagnosis of an IEM on a specialized diet (IEM patients) were identified via a search of the OHSU electronic medical records system for the *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes listed in Table 1. All identified records were then queried for the presence of at least 1 25(OH)D level. Records were subsequently reviewed individually, with documentation of age, sex, and date on which the blood sample(s) for vitamin D was drawn. Vitamin D levels of age and sex matched controls on an unrestricted diet were also identified via an electronic medical record search. Control patients were excluded if their record included an *ICD-9* diagnosis code associated with abnormal bone health (eg, osteopenia, osteoporosis, and rickets), a disorder known to affect nutritional status (eg, intestinal malabsorption and anorexia nervosa), or serum 25(OH)D or mineral status (renal disease; Fig. 1). If multiple serum 25(OH)D concentrations were provided for a patient, only the earliest draw date was considered. Patients who resided outside Oregon and Washington or had missing data such as age and zip code were excluded from the medical record review. A total of 918 potential patients were obtained from the initial query, of which 533 (88 IEM patients, 445 controls) were included in the analysis. The age range of patients in both groups was 8 to 20 years (Table 2).

Patients were assigned to 1 of 4 geographic regions (Northwest, Southwest, Northeast, and Southeast), according to postal zip code. The Cascade mountain range formed the east/west dividing line, and the 45th parallel was used as the north/south division.

To assess possible seasonal variation in 25(OH)D levels, blood draw dates were categorized as either "winter" (October 1–May 31) or "summer" (June 1–September 30).

Table 1 – *ICD-9* codes

Diagnosis	*ICD-9* [a]	No. of patients identified [b]
Disorders of urea cycle metabolism	270.6	5
Galactosemia	271.1	7
Glutaric aciduria, type I	270.7	0
IVA	276.2	4
Homocystinuria	270.4	2
Hyperphenylalaninemia, PKU	270.1	62
Lysinuric protein intolerance	270.0	1
MSUD	270.3	4
Methylmalonic acidemia/cobalamin C and D	276.2	1
MCD	270.7	0
PA	270.6	0
Tyrosinemia, type I/II	270.2	2

A list of the *ICD* codes used to query the electronic medical record system to identify patients with the diagnosis of an IEM requiring a medical food–based dietary intervention. Diagnosis codes were selected based on the need for medical food–based diet therapy.
Abbreviations: IVA, isovaleric acidemia; MSUD, maple syrup urine disease; MCD, multiple carboxylase deficiency; PA, propionic acidemia.
[a] *ICD-9* is used in electronic medical record systems to designate a diagnosis.
[b] No. of patients identified refers to the number of patients with that diagnosis included in the analysis.