Bone 97 (2017) 216–221

Contents lists available at ScienceDirect

Bone

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

Full Length Article

The relationship of maternal bone density with nutritional rickets in Nigerian children☆

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ARTICLE INFO

Article history:
Received 10 August 2016
Revised 3 January 2017
Accepted 21 January 2017
Available online 23 January 2017

Keywords:
Nutrition
Vitamin D
Calcium
Heredity
Metabolic bone disease

ABSTRACT

Factors that affect maternal bone mineral density may be related to the risk of nutritional rickets in their offspring. Our aim was to determine the relationship between maternal areal bone mineral density (aBMD) and rickets in Nigerian children. Using a case-control design, we measured forearm aBMD in 56 and 135 mothers of children with and without nutritional rickets, respectively. Active rickets was confirmed or excluded in all children radiographically. Using logistic regression, we assessed the association of maternal aBMD, adjusted for parity, pregnancy and lactation status, duration of most recent completed lactation, age of menarche, height, body mass index, and maternal age with nutritional rickets. The median (range) age of all mothers was 30 years (17–47 years), and parity was 4 (1 − 12). A total of 36 (19%) were pregnant and 55 (29%) were currently breast feeding. Mean (±SD) metaphyseal forearm aBMDs were 0.321 ± 0.057 and 0.316 ± 0.053 g/cm^2 in mothers of children with and without rickets, respectively (P = 0.60). Diaphyseal forearm aBMDs were 0.719 ± 0.071 and 0.715 ± 0.072 g/cm^2, respectively (P = 0.69). In an adjusted analysis, maternal forearm aBMD, bone mineral content and bone area at metaphyseal and diaphyseal sites were not associated with rickets in the child. In the adjusted analysis, rickets was associated with shorter duration of most recently completed lactation (aOR 0.91 for each additional month; 95% CI 0.83–0.99), older maternal age (aOR 1.07 for each additional year; 1.00–1.14), and less frequent maternal use of lead-containing eye cosmetics (aOR 0.20; 95% CI 0.05–0.64), without any difference in maternal blood lead levels. Maternal age, parity, age of menarche, height, and body mass index were not associated with having had a child with rickets in multivariate analysis. Nutritional rickets in Nigerian children was not associated with maternal forearm aBMD. Other unidentified maternal characteristics and practices likely contribute to the risk of rickets in Nigerian children.

1. Introduction

Nutritional rickets is an important cause of disability among children in low-income countries. It remains prevalent in African, Middle Eastern, and Asian countries [1–3], and has increased in prevalence in high-income countries [4] like the United States, United Kingdom, Netherlands, Denmark, Australia, and New Zealand [5–9], mainly in dark-skinned, immigrant populations [10]. In addition to causing deformities of the long bones, stunted growth, muscle weakness, and delayed motor development, nutritional rickets is a risk factor for life threatening hypocalcemia, pneumonia, and cardiomyopathy [11]. Nutritional rickets has traditionally been associated with vitamin D deficiency. Yet, despite sufficient sunlight, rickets is still prevalent in many tropical countries. Dietary calcium deficiency as a cause of nutritional rickets has been observed in South Africa [12], Bangladesh [13], India [14], and Nigeria [15–17] and even in the United States [18].

Maternal nutritional factors affect fetal and infant skeletal growth and development and may be related to the risk of nutritional rickets in their children. Maternal diet in the first trimester has been associated with childhood bone mass [19]. Mothers with limited sun exposure due to climate, cultural practices, or lifestyle factors, and who do not consume vitamin D fortified foods, are predisposed to decreased vitamin

Abbreviations: aBMD, areal bone mineral density; aOR, adjusted odds ratio; BMC, bone mineral content; 25(OH)D, 25-hydroxyvitamin D.

☆ Disclosures: JH, PRF, JMP have nothing to declare. TDT is a consultant for Biomedical Systems, Inc. and has received a speaking honorarium from Sandoz.

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http://dx.doi.org/10.1016/j.bone.2017.01.026
8756-3282/

D stores [20]. This may result in neonatal vitamin D deficiency. Mothers of Arab children with rickets were more likely to be vitamin D deficient themselves than mothers of children without rickets [21]. Maternal vitamin D deficiency is common during pregnancy and has been variably associated with decreased bone mineral accretion in their offspring [22,23]. Korean newborns born in the winter had an 8% lower bone mineral content, lower cord serum 25-hydroxyvitamin D [25(OH)D], and greater bone resorption markers than infants born in the summer [24]. Low maternal vitamin D status has been associated with fetal growth restriction and an increased risk of preterm birth and small size for gestational age at birth [25].

Other maternal factors affect the bone mineral content of newborns. Maternal insulin-dependent diabetes mellitus is associated with roughly a 10% reduction in bone mineral content of newborns [26]. The Southampton Women's survey examined maternal predictors of neonatal bone size. Maternal smoking was associated with reduced neonatal bone mass, whereas maternal birthweight, height, and parity were all associated with a greater neonatal bone mineral content and bone area [27].

Low areal bone mineral density (aBMD) in mothers may be associated with low aBMD in their infants. Several studies have reported a major gene effect and familial correlation on aBMD [28,29]. As much as 30% and 51% of the variance in lumbar spine and femoral neck aBMD, respectively, were attributable to genetic factors [30]. Maternal nutritional or genetic factors could account for the observation of nutritional rickets in multiple offspring within the same family. These factors could be shared by both the mother and her offspring with possibly similar effects on both maternal and infant bone mass, and thus on measured aBMD.

While studies have examined the relationship between maternal nutrition and fetal aBMD, no studies have examined the relationship between maternal aBMD and rickets in their offspring. We postulated that lower maternal aBMD would increase the risk of rickets in their offspring. Our objective was to determine the relationship between maternal aBMD and nutritional rickets in Nigerian children.

2. Methods

2.1. Study subjects and measurements

The study was conducted at the Jos University Teaching Hospital in Jos, Nigeria, located at a latitude approximately 10° N of the equator. We used a case-control study design without matching. The study subjects were mothers of children with and without rickets, who had been enrolled in clinical studies of nutritional rickets [31–33]. All children with rickets had clinical symptoms and signs suggestive of rickets, which was confirmed by radiographs of the wrists and knees [34]. Control mothers were recruited from a study of calcium supplementation to prevent nutritional rickets in healthy children residing in the same community [31]. These children all had radiographs that excluded active rickets.

Using an interview questionnaire, we recorded the following data for each mother: age, parity, age of menarche, duration of most recently completed lactation, eye cosmetic use, and current pregnancy or lactation status. We measured weight with a floor scale and standing height with a wall-mounted stadiometer. Blood was collected by lancing the finger for measurement of lead level (some eye cosmetics contain lead), with blood spots as previously described [35] (LeadTech Corporation, North Bergen, NJ). In mothers of children with rickets, the child who most recently completed lactation did not always correspond with the child who had rickets, but for 42 mothers (75%) the duration of most recently completed lactation was within 3 months of the duration in their child with rickets. Although the radiation exposure from forearm bone densitometry is negligible and similar to background radiation, forearm aBMD measurements were not performed in the first trimester of pregnancy.

A single investigator (TDT) measured aBMD with dual energy X-ray at the distal and proximal 1/3 of the left radius and ulna with a portable densitometer (Norland pDEXA, Model 476A110). The distal site was located at the site of minimal bone density proximal to the distal bone edge, representing the metaphyseal bone of the radius and ulna. The proximal 1/3 site was located at 1/3 the distance from the wrist to the elbow and represents diaphyseal bone of the radius and ulna. Each site was 1 cm in length, and bone mineral content (BMC) measured in each section was divided by the bone area to calculate aBMD. The machine was calibrated daily, and long-term in vitro precision of aBMD assessed with a bone phantom, was 0.11 g/cm^2 (1.1%). Duplicate scans in 37 children demonstrated short-term in vivo aBMD precision of 0.007 g/cm^2 at the distal radius and ulna and 0.013 g/cm^2 at the proximal 1/3 radius and ulna.

Participation was voluntary, and written informed consent was obtained from all subjects. The study was approved by the Ethical Committee of the Jos University Teaching Hospital and the Mayo Clinic Institutional Review Board. The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Statistical analysis

Statistical analysis was performed using JMP Pro 9.0.1 (SAS Institute, Cary, NC). We conducted both univariate and multivariable regression analyses to test the association of aBMD, bone mineral content, and bone area of mothers with rickets in their offspring. Using logistic regression, we assessed the association of maternal forearm aBMD with nutritional rickets in their offspring, controlling for parity, pregnancy and lactation status, duration of most recently completed lactation, age of menarche, and maternal age. The influence of pregnancy and lactation status, duration of most recently completed lactation, maternal age, parity, age of menarche, height, weight, body mass index, and use of eye cosmetics on maternal bone densitometry measures were examined by linear regression analysis in the entire group of mothers. Only significant covariates were retained in the linear regression models. The results of a multivariate analysis restricted to the 100 women who were not currently pregnant or lactating were similar to the analysis that included women who were pregnant (data not shown). Because aBMD is not a true volumetric bone density, we performed a sensitivity analysis by adjusting for bone area in the final multivariate model for aBMD to determine if adjusting for bone area altered the interpretation of the results.

3. Results

3.1. Comparison of mothers of children with and without rickets

We studied 191 mothers: 56 had children with rickets and 135 had children without rickets (Table 1). Compared with mothers of children without rickets, mothers of children with rickets were an average of two years older. The duration of most recently completed lactation was significantly shorter in mothers of children with rickets than in mothers of children without rickets (16.3 ± 6.3 and 18.9 ± 3.2 months, respectively, $P < 0.001$). Mothers of children with rickets had an earlier age of menarche than mothers of children without rickets (14.4 ± 1.4 and 15.1 ± 1.8 years, respectively, $P = 0.03$). Mothers of children with rickets were less likely than mothers of children without rickets to use eye cosmetics (77% and 92%, respectively, $P = 0.004$), without any difference in blood lead levels (Table 1). Parity, height, weight, body mass index, interval since last delivery, pregnancy and lactation status in mothers of children with and without rickets were similar. The median age of index children at the time of mother's enrollment was greater in the group of children with rickets than in those without rickets. The last child birth was less likely to be the index child in the group with rickets than in those without rickets. Metaphyseal and