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The effect of the ketogenic diet on the developing skeleton

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ABSTRACT

The ketogenic diet (KD) is a medically supervised, high fat, low carbohydrate and restricted protein diet which has been used successfully in patients with refractory epilepsy. Only one published report has explored its effect on the skeleton. We postulated that the KD impairs skeletal health parameters in patients on the KD.

Patients commenced on the KD were enrolled in a prospective, longitudinal study, with monitoring of Dual-energy X-ray absorptiometry (DXA) derived bone parameters including bone mineral content and density (BMD). Areal BMD was converted to bone mineral apparent density (BMAD) where possible. Biochemical parameters, including Vitamin D, and bone turnover markers, including osteocalcin, were assessed. Patients were stratified for level of mobility using the gross motor functional classification system (GMFCS).

29 patients were on the KD for a minimum of 6 months (range 0.5-6.5 years, mean 2.1 years). There was a trend towards a reduction in lumbar spine (LS) BMD Z score of 0.1562 ($p = 0.071$) per year and 20 patients (68%) had a lower BMD Z score at the end of treatment. While less mobile patients had lower baseline Z scores, the rate of bone loss on the diet was greater in the more mobile patients (0.28 SD loss per year, $p = 0.026$). Height adjustment of DXA data was possible for 13 patients, with a mean reduction in BMAD Z score of 0.19 SD. Only two patients sustained fractures. Mean urinary calcium-creatinine ratios were elevated (0.77), but only 1 patient developed renal calculi.

Children on the KD exhibited differences in skeletal development that may be related to the diet. The changes were independent of height but appear to be exaggerated in patients who are ambulant. Clinicians should be aware of potential skeletal side effects and monitor bone health during KD treatment. Longer term follow up is required to determine adult/peak bone mass and fracture risk throughout life.

1. Introduction

It is recognized that anti epileptic drug (AED) use is associated with lower bone mineral density (BMD) in both adults and children (Sheth et al., 1995; Petty et al., 2005; Babayigit et al., 2006; Sheth et al., 2008). Adults with epilepsy treated since childhood have lower bone mass than those who commenced treatment in adult life, suggesting a specific effect of AEDs on the developing skeleton (El-Hajj Fuleihan et al., 2008),and also pointing to a possible cumulative effect of AED use on the skeleton.

The ketogenic diet (KD) is a well-established therapeutic intervention for patients with refractory epilepsy (Keene, 2006, Hartman and Stafstrom, 2013). By maintaining a high fat, low carbohydrate and restricted protein intake, systemic ketosis results, which can have a beneficial effect on raising seizure threshold (Neal et al., 2008). However, chronic ketoacidosis results in increased demand on bone minerals for buffering capacity and decreased renal conversion of 25 OH Vitamin D to 1, 25 (OH)2 Vitamin D (Sampath et al., 2007). Other comorbidities in this patient group such as cerebral palsy further increase the risk of low bone density. In adults, however, there is no evidence of increased bone turnover when inducing a ketotic state (Carter et al., 2006). There is only one published report exploring the effect of the ketogenic diet on the developing skeleton (Bergqvist et al., 2008). This study demonstrated reduced bone mineral content in patients on the ketogenic diet, with follow up after 15 months. Despite increasingly widespread use of the KD for refractory epilepsy and a

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range of other disorders, no further studies have investigated its effect on bone health.

We aimed to document any sequelae on the skeleton for patients on the KD, given that this group is already at risk of poorer skeletal outcomes due to their AED use and related comorbidities. We hypothesised that treatment with the KD impairs bone mass accrual, and that subjects with higher degrees of comorbidity would have poorer bone health outcomes.

2. Methods

63 patients on the KD were enrolled in a prospective, longitudinal study between 2002 and 2009. Details of the KD as prescribed for this cohort can be found in previous publications from our group (Thammongkol et al., 2012). In brief, the Classical KD was initiated as an inpatient following a modified Johns Hopkins protocol with dietary ratio ranging from 2:1 to 4:1. The energy-intake prescription was based on a 3-day food diary and adjusted for ideal body weight, height and the child's physical activity level. The protein content of the diet was calculated to meet the child's RDI for ideal body weight and normal growth. Energy and protein content, and ketogenic dietary ratio (fat to carbohydrate and protein combined) were adjusted throughout the treatment to respond to identified issues regarding weight gain and loss, and optimizing ketosis for better seizure control. Subjects underwent monitoring of their bone health using dual energy X-ray absorptiometry (DXA). The scanner was an Hologic QDR-4500A densitometer (Hologic, Bedford, Massachusetts, USA). Areal BMD, bone mineral content (BMC) and soft tissue composition were assessed with scans taken at the right total hip (TH), and lumbar spine (LS). Z-scores were calculated using age- and sex-specific normative data provided by Hologic.

All patients were assessed on the same scanner according to the manufacturer's specifications. The scans were performed by a single observer who undertook daily phantom scans to ensure reproducibility of results. From these scans, bone parameters were measured including bone mineral density (BMD), bone mineral content (BMC) and bone area. In order to minimize the confounding effect of short stature on the DXA result (Binkley et al., 2008), areal BMD scores were converted to bone mineral apparent density (BMAD) where possible (Ward et al., 2007).

Subjects were scanned at baseline, prior to commencement of the KD, and then at 6 monthly intervals.

During the study period, all children were routinely supplemented with elemental calcium and Vitamin D3 to meet recommended daily requirements.

In addition to DXA scanning, biochemical parameters were assessed at baseline and 3 month intervals, including serum Ca^{2+}, PO_4, 25OH-Vitamin D, PTH, bone turnover markers including ALP, osteocalcin and urine Ca^{2+}/creatinine ratio.

In order to assess the impact of mobility on bone mass, we utilized the gross motor functional classification system (GMFCS). Patients were dichotomised to Level 1 (normal mobility) vs Level 2-5 (mobility problems) for purpose of further exploring the interaction of ambulant vs less/non-ambulant states with the KD.

Given the observational, exploratory nature of the study, no sample size calculation was undertaken. Two mixed effects models were fitted. The first captured the overall population effect of the time spent on KD on the BMD Z score. It has fixed effects for the time spent on KD, represented by the time since the first scan, as well as the (dichotomised) GMFCS. The model included random intercepts and random time-on-diet slopes. In addition to the terms in the first model, the second model contained a fixed effect for the interaction between mobility status and time-on-diet. Thus, the second model captured the average effect of time-on-diet within each mobility class. All random effects are independently normally distributed with zero mean. Their standard deviations were estimated during model fitting. Models with correlated error terms were fitted but provided no additional explanatory power.

Table 1
baseline characteristics of subjects. Values expressed are means unless otherwise stated.

Number of patients	29
Time on KD	2.1 (range 0.5–6.5 years)
Age of initiation of KD	6.4 (range 3.3–17.8)
Female/male	15/14
GMFCS	2.55
Baseline lumbar spine BMD score	−0.99 (median)
Mean vitamin D score during the study period	82 nmol/L (range 42–133)
Mean number of AEDs prescribed at baseline	2.1 (range 0–5)
Mean number of inducer AEDs prescribed at baseline	0.7 (range 0–2)

The study was approved by the Royal Children's Hospital (HREC 25055A) and Austin Health (H2005/02257) Human Research Ethics Committees.

3. Results

3.1. Baseline results (see table one)

Twenty-nine (46%) of 63 patients Table 1 who were initiated on the KD during the study period continued treatment for a minimum of 6 months (range 0.5-6.5 years, mean 2.1 years). Those 29 patients were then included in the analyses of bone health outcomes. Median age at initiation was 6.4 years (3.3 years to 17.8 years, 25th percentile = 4.4 years, 75th percentile = 8.3 years) with 52% of subjects female. The mean GMFCS score was 2.55, representing a spread of mobile and less mobile subjects. 2 patients were on glucocorticoid therapy at the commencement of the study, but were both weaned off, one after 5 months and one after 9 months.

The baseline (prior to commencement of KD) lumbar spine BMD Z score showed a median of −0.99 SD (see the left panel of Fig. 1). Less mobile subjects (GMFCS 2-5) had a lower baseline BMD Z score than normally mobile patients (see the right panel of Fig. 1) with a mean difference = 1.99 (p-value = 0.000016).

3.2. Change in BMD over time on diet:

On average, subjects on the KD demonstrated a decrease of 0.16 (p = 0.071) units per year relative to age-matched children. When the progression of lumbar spine Z scores was stratified by mobility, more mobile patients had a greater decline in lumbar spine BMD Z scores (Fig. 2).

On further analysis, it was found that the GMFCS 1 subjects (n = 11) had a rate of decline of 0.28 SD (95% confidence interval −0.52, −0.04) per year (p-value = 0.026), compared with the GMFCS 2–5 (n = 18) group, who had a rate of decline of 0.05 SD (95% CI −0.26, 0.16) per year (p-value = 0.65). Therefore, there was no evidence for decline in less mobile subjects.

Given the confounding effect of height on BMD as measured using DXA, where possible, we generated a height adjusted BMAD (n = 13), which also showed a mean reduction in BMAD Z score of 0.19 SD compared with age-matched children over total time on diet. Height adjustment was limited due to patients needing to be between 6 and 17 years old, as per the Ward reference charts (Ward et al., 2007). Due to issues with serial height measurements, it was not possible to estimate change in height SDS whilst on the diet.

3.3. Biochemical findings

The subjects' mean ALP levels were in the normal range (mean 150 IU/L), while the mean Vitamin D was 81 nmol/L (range 42-133). 5 patients were vitamin D deficient at baseline (< 50 nmol/L). This reflects that the vast majority of subjects were Vitamin D sufficient as