BONE STATUS IN PATIENTS WITH GLUT 1 DEFICIENCY SYNDROME (GLUT1D) TREATED WITH KETOGENIC DIET (KD): A CHILEAN COHORT

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INTRODUCTION:

Ketogenic diet has been used as a first line treatment in patients with GLUT 1D for fueling brain in a long-term basis. Bone health in children that use KD has been a concern due to the acid load associated with the diet, deficient calcium and vitamin D intake, and chronic antiepileptic drug (AED) use (1).

Dual energy X-ray absorptiometry (DEXA) has been recommended as a gold standard for assessing bone mineral density (BMD) in children because of its availability, reproducibility, speed, low exposure to ionizing radiation, and robust pediatric reference data (2,3).

However, other risk factors have to be considered for a thorough evaluation such as: chronic immobilization, low body weight, use of drugs that affect bone metabolism, hormonal abnormalities, personal and familial history of fractures (2,4).

In the pediatric age group, the diagnosis of osteoporosis requires both a low BMD (defined as a z score < −2 SD) and a clinically significant fracture (defined as a long-bone fracture of the lower extremity, a vertebral compression fracture, or 2 or more long-bone fractures of the upper extremity) for its diagnosis.

Earlier studies describe a progressive loss of bone mineral content in patients with refractory epilepsy subjected to multiple AED, the majority being non ambulatory. In long-term follow-up studies, approximately 20% of children treated with KD (≥ 6 years) experience an increased incidence of bone fractures (1,5,6).

Considering GLUT 1D patients use KD as a life-long therapy, monitoring bone health is important as part of a comprehensive follow-up management.

OBJECTIVE:

The purpose of this communication is to characterize bone status in 10 patients with GLUT 1D treated with KD, and other factors that may contribute to maintaining a healthy bone.

MATERIALS AND METHODS:

Cross-sectional study. We conducted a retrospective review of clinical records of 10 patients (6 males), who followed a KD as a treatment for GLUT 1D in Santiago de Chile. Children where between 5-19y of age. DEXA (GE Healthcare, Lunar iDXA.) was performed as part of our follow-up program for assessing bone status, by means of areal bone mineral density (g/cm²); results were adjusted for age and ethnicity. Ketosis, vitamin D levels (25 OH vit D), KD ratio, micronutrient intake and supplementation were collected from clinical and dietary record.

Anthropometric measures were registered according to its Z score SD, including height for age (HA) and body mass index (BMI).

Normal Bone Mineral Density Z score (BMDz) was defined as Z score > -1 SD

Low for age BMDz was defined with Z scores between -1 and -2.5 SD

CONCLUSIONS:

- In this GLUT1D cohort, patients with long term KD had conserved BMD, and the ones with low for age BMDz scores had no clinically significant consequences due to this alteration.
- Factors that potentially contribute to this outcome are adequate calcium supplementation and vitamin D sufficiency, as well as ambulation which was probably a protective factor.
- A comprehensive protocol that monitors bone health consdiering DEXA as well as other factors that have an impact on BMD must be considered in GLUT 1 patient

TABLE 1: Characteristics of children with GLUT 1D

Patient	Age at DEXA	BMD Z Score	Time on KD prior to DEXA (years)	Type of KD
1, F *	11y 2m	1.3	1y	2:1
2, F *	19y	0.0	18y 3m	2.1:1
3, F *	12y 4m	0.7	4y 10m	3:1
4, F *	6y 6m	1	5m	3:1
5, M +	15y 2m	-2.5	1m	2.5:1
6, M +	5y 5m	-1.2	5y	3:1
7, M +	11y 8m	-1.6	1y	2.5:1
8, M +	9y 1m	-1.6	2y	2:1
9, M *	8y 7m	1.3	1m	1.9:1
10, M +	5y 4m	-1.5	4m	3:1

* Group 1 : BMD Z score > -1
+ Group 2: BMD Z score < -1

RESULTS:

Four patients were on classic KD (3:1), and 6 patients were on a MAD diet with ketogenic ratios between 2-2.5:1 (Table 1). Betahydroxibutyrate (BOHB) levels ranged between 1.5 and 3.7 mmol/lt (x: 3.6, M: 2.5). At the time of DEXA, all patients but 1 had normal ambulation. Four subjects were overweight, 4 had normal weight and 2 were underweight at the time of DEXA. Just 1 subject was classified as short stature with HFA − 2 SD.

Whole body bone mineral density z score (BMDz) was measured: 5 patients had values above > -1SD (normal BMDz), and 5 patients had low for age BMDz. In the latter group, one patient had a fracture after a high-altitude fall, but none had fractures of clinical significance that could suggest osteoporosis. Patients with normal BMDz had been on KD between 1m and 18y (x: 5y, M: 1y) and those with low for age BMDz between 1m and 5y (x: 1.7y, M 1y).

Eight patients had 25-OH-vitamin D values measured (x: 46.5, M:40 ng/ml), only 1 patient in the low for age BMDz group had insufficient levels. All patients complied with calcium RDA at the time of DEXA (x: 1181 mg/d, M 1150).

Statistical analysis (Wilcoxon Test), showed no significant difference between BMDz of patients on KD for > 2y when compared to patients on KD for < 2y (p=0.74) Fig 1.

No difference was found when comparing vitamin D levels (p=0.59) Fig 2, and type of KD Fig 3, (p=0.66) with DEXA BMDz values.

Although 9/10 patients had sufficiency levels of vitamin D, there was a significant difference between vitamin D levels and type of KD (Fig 4) (p=0,024) with higher levels (60-77 ng/ml) occurring on the group with higher ratios (>2.5:1).

DISCUSSION:

The preservation of adequate bone health in patients on long term KD has been demonstrated as a difficult task, mostly in patients with neurological impairment.

In this cohort with GLUT 1D patients, BMDz measured by DEXA was used for bone status assessment. Even though half of the subjects presented with BMDz values below the norm, no subject had clinically significant morbidity. This could be explained because the risk of bone fragility is not only dependent on BMDz values, but also on age of onset and severity of the underlying condition and the number of associated risk factors (such as poor nutrition or inactivity) (2). Bergqvist et al (5) studied patients with refractory epilepsy and demonstrated poor bone health and suboptimal growth status with progressive loss of bone mineral content with KD treatment despite improved serum vitamin D concentrations; however most at risk were young, non-ambulatory children with low BMI status.

In this sample, the majority of subjects had an adequate nutritional status, and only 2 of them had a low BMI, both of them having low for age BMDz along with one of them being non-ambulatory.

The effect of mechanical loading and exercise on bone accretion has been described previously (4,7); with exercise intervention leading to 0.6%-1.7% greater annual increase in bone accrual. In patients with neurological impairmen' Finbraten(8) demonstrated that non-walkers had lower mean BMDz that walkers i a study of 51 patients with cerebral palsy.

Further analysis demonstrated that there were no differences in BMDz regardin duration of KD and type of diet. This could be associated with adequate calciur and VitD consumption, which was prevalent in our cohort. Moreover, the BOH levels were alongside a conservative range (1.5-3.7 mmol/lt).

Interestingly, the group with higher KD ratio (>2.5:1) had significantly greate vitamin D levels. In our group vitD supplementation is not universal, but targete according to vitamin D dietary intake, considering all GLUT 1D patients ar entitled to fortified ketogenic formula as part of a National Supplementary Foo Program. Intake varies among them according to preference for cooking c drinking. This result could reflect that a greater intake of fats in the higher rati diet has a direct impact on serum vitamin D. This finding could be significant i patients with poor adherence to pharmacologic supplementation, in whom we ca use dietary sources to improve vitamin D levels and should be further explored.

Finally, bone health is a very important long-term issue in patients with GLUT 1D treated with KD and a thorough evaluation should be included as part of a a comprehensive protocol for monitoring adverse effects. The evaluation considers DEXA but also assessment of nutritional status, physical activity, pubertal stage, ambulation, patient and family fracture history, and long-term AED exposure, which is not a regular practice in some centers, as demonstrated by Fong et al (9), who reported 84% of neurologists infrequently performed bone health screening investigations routinely.

Figure 1 **Time on KD at DEXA**

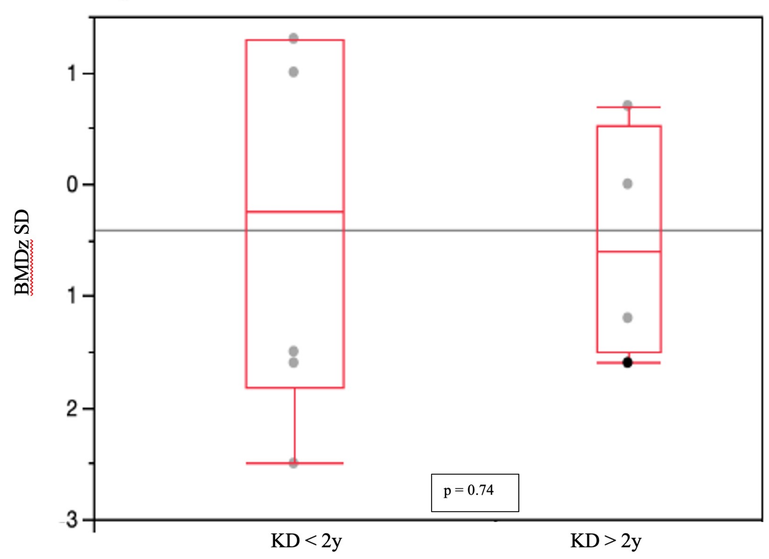


Figure 2. **Vitamin D levels and DEXA**

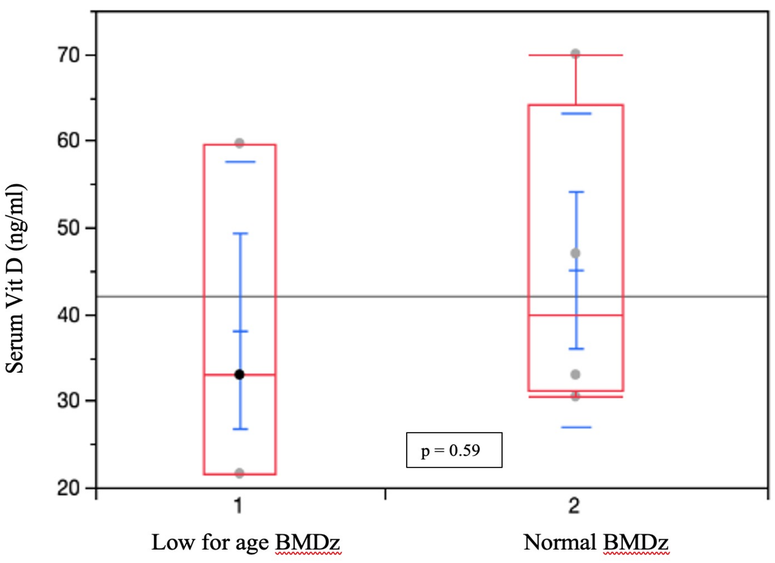


Figure 3. **Type of KD at DEXA**

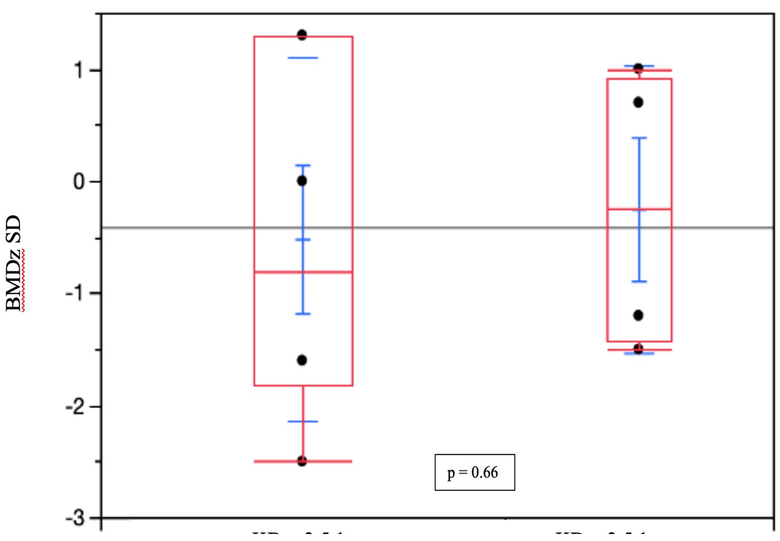
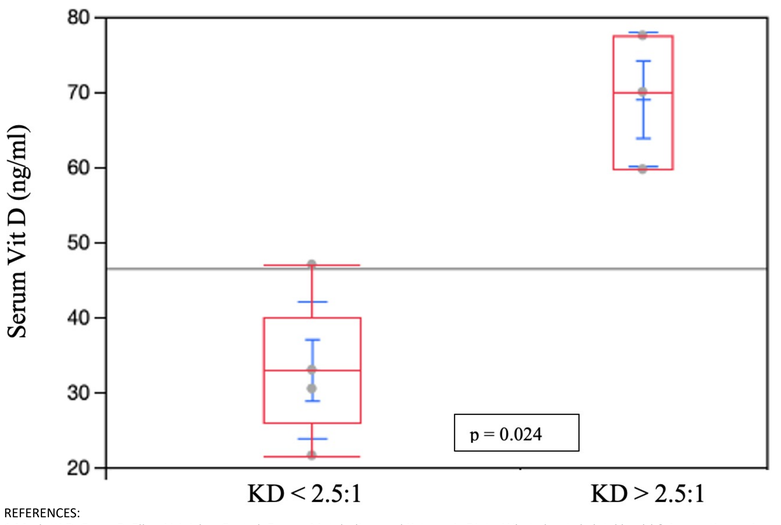


Figure 4. **Vitamin D and Type of KD**



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