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Prospective study of growth and bone mass in Swedish children treated with the modified Atkins diet

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ABSTRACT

Purpose: The modified Atkins diet (MAD) is a less restrictive treatment option than the ketogenic diet (KD) for intractable epilepsy and some metabolic conditions. Prolonged KD treatment may decrease bone mineralization and affect linear growth; however, long-term studies of MAD treatment are lacking. This study was designed to assess growth, body composition, and bone mass in children on MAD treatment for 24 months.

Methods: Thirty-eight patients, mean age (SD) 6.1 years (4.8 years), 21 girls, with intractable epilepsy ($n = 22$), glucose transporter type 1 deficiency syndrome ($n = 7$), or pyruvate dehydrogenase complex deficiency ($n = 9$) were included. Body weight, height, body mass index (BMI), bone mass, and laboratory tests (calcium, phosphorus, magnesium, alkaline phosphatase, cholesterol, 25-hydroxyvitamin D, insulin-like growth factor-I and insulin-like growth factor binding protein 3) were assessed at baseline and after 24 months of MAD treatment.

Results: Approximately 50% of the patients responded with more than 50% seizure reduction. Weight and height standard deviation score (SDS) were stable over 24 months, whereas median (minimum – maximum) BMI SDS increased from 0.2 (−3.3 to 4.5) to 0.7 (−0.9 to 2.6), $p < 0.005$. No effects were observed for bone mass (total body, lumbar spine and hip) or fat mass.

Conclusions: The MAD was efficient in reducing seizures, and no negative effect was observed on longitudinal growth or bone mass after MAD treatment for 24 months.

Abbreviations: BMAD, Bone mineral apparent density; BMC, Bone mineral content; BMD, Bone mineral density; DXA, Dual-energy X-ray absorptiometry; DXL, Dual-energy X-ray absorptiometry and laser; IGF-I, Insulin-like growth factor-I; IGFBP3, Insulin-like growth factor binding protein-3; LS, Lumbar spine; TB HE, Total body with head excluded; 25(OH)D, 25-hydroxyvitamin D.

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1. Introduction

In the majority of patients with epilepsy, antiepileptic drugs (AEDs) result in seizure remission; however, 20–30% will have refractory epilepsy and the chance of responding to medication falls dramatically after failure to respond to more than one drug.[1] For children with uncontrolled epilepsy, treatment options comprise epilepsy surgery, vagal nerve stimulation, and the ketogenic diet (KD).

During carbohydrate deprivation, the ketone bodies (3-beta-hydroxybutyrate, acetoacetate and acetone) generated by fatty acid oxidation, serve as an alternative energy source. Although the underlying mechanisms remain elusive, recent research indicates that the KD may involve many mechanisms.[2–4] In general, over 50% of patients on this diet achieve a seizure reduction of more than 50%, and 15–20% become seizure free.[5,6] Nonetheless, it is a restrictive treatment option, with drawbacks such as the need for strict weighing of foods and hospitalization at the initiation of treatment. Adverse events include kidney stones, hyperlipidemia, gastrointestinal disturbances, metabolic acidosis, and osteopenia.[7]

The modified Atkins diet (MAD) is a less strict treatment option that include 10–20 g of carbohydrates per day, no limit to the amount of protein and as much fat as possible.[8] It has been reported, that MAD is as efficacious as the classic KD in seizure reduction.[9] However, a recently published randomized study demonstrated a higher rate of seizure freedom for KD treatment than for MAD treatment in patients aged under 2 years.[7] Today, the indications for both classic KD and its variants have extended to several metabolic conditions in which the brain and mitochondria are unable to use glucose for ATP production.

Several factors (including genetics, gender, puberty, physical activity, nutrition, mineral homeostasis, and vitamin D) regulate mechanisms that determine bone modeling and remodeling in children and adolescents.[10] A reduced acquisition of bone mass during childhood could result in the development of osteoporosis and subsequent fractures. Children with intractable epilepsy are exposed to factors such as immobilization that contribute to an increased risk of poor bone health. Older AEDs can adversely affect bone remodeling by direct effects on bone-forming osteoblasts or by secondary effects on vitamin D metabolism and calcium homeostasis.[11] Newer AEDs have better side-effect profiles, but the effects on bone health in growing children have thus far not been thoroughly investigated. Some studies indicate that KD treatment may result in growth failure and alteration in body composition,[12,13] and osteopenia.[14] Reduced linear growth with unchanged weight has also been reported in children on KD treatment.[15] Linear growth is regulated by the combination of growth hormone and insulin-like growth factor-I (IGF-I),[16] which are instrumental in bone formation.[17] The latter may be suppressed by KD treatment.[18]

This prospective study was designed to assess linear growth, body composition, and bone mass in children and adolescents on MAD treatment over a 24-month period. We hypothesized that the MAD, as earlier described with KD, negatively affects growth and bone mass.

2. Materials and methods

2.1. Study design

This study was a prospective longitudinal cohort study of pediatric patients treated with the MAD between 2010 and 2017. Thirty-eight patients (21 girls, 17 boys) with disease onset before 18 years of age were included at the Queen Silvia Children's Hospital in Gothenburg, Sweden. Inclusion criteria comprised a treatment period of at least 6 months with the MAD, and there were no exclusion criteria. All children were followed up at the same epilepsy center at the Department of Pediatric Neurology. The study was approved by the Regional Research Ethics Committee of Gothenburg, Sweden, and written informed consent was obtained from all parents and from children if old enough.

Mean (standard deviation (SD)) age at MAD initiation was 6 years, 2 months (4 years, 9 months), and the median duration of epilepsy was 3.0 years (0–16 years). The etiologies were genetic epilepsy ($n = 6$), glucose transporter type 1 deficiency syndrome (GLUT1-DS) ($n = 7$), pyruvate dehydrogenase complex deficiency (PDHCD) ($n = 9$), cortical malformation ($n = 3$), other mitochondriopathies ($n = 2$), tuberous sclerosis ($n = 2$), encephalitis ($n = 2$), stroke ($n = 2$), Aicardi syndrome ($n = 1$) and unknown etiology ($n = 4$). Thirty patients (79%) had epilepsy (generalized epilepsy $n = 29$, and focal epilepsy $n = 1$). Twenty-three patients (71%) were ambulatory at inclusion. Auxiological and demographic data, including numbers and types of AEDs before and concomitant to MAD treatment, are presented in Table 1.

Four patients dropped out before 12 months and five patients between 12 and 24 months after treatment start because of insufficient effect on seizures. Hence, 29 patients continued the MAD treatment for at least 24 months and were evaluated before inclusion and after 6, 12 and 24 months for growth parameters (height and weight), seizure frequency and laboratory parameters (ketosis, side effects). A flow chart describing inclusions and dropouts is presented in Fig. 1. The aim of the present study was to evaluate bone mineral density (BMD) and body composition with dual-energy X-ray absorptiometry (DXA) and with DXA and laser (DXL) in all patients at baseline and after 12 and 24 months.

2.2. The treatment modality of modified Atkins diet

All children started gradually on the MAD with 10–30 g of carbohydrates per day. All diets were calculated on an individual basis by the same dietician, taking into account the child's current food preferences. The initial calorie prescription was based on an average of the child's pre-diet intake and about 80% of the recommended energy requirements. Twenty-nine patients (76%) tolerated the MAD well and thus remained on this diet for 24 months. Diets were fully supplemented with vitamins and minerals according to the Nordic Nutrition Recommendations[19]: thiamine (in six patients), carnitine (in 20 patients), potassium citrate (in 14 patients), calcium (in 21 patients), vitamin D (in 14 patients), magnesium (in eight patients), and phosphorus (in nine patients).

Table 1 – Auxiological and demographic data.

Gender	Age at start of MAD	Epilepsy syndrome	Physical status	3-hydroxybutyric acid 0/6/12/24 months	Seizures per month 0/6/12/24 months	AEDs 0/24 months
Patients with intractable epilepsy						
M	3.8	LGS	A	<0.1/1.4/2.3/1.1	200/8/8/8	1,8,10/1,8,10
F	14.8	Gen. ep.	A	<0.1/2.6/1.0/–	15/3/3/–	1,4,9/–
F	3.6	Gen. ep.	NA	<0.1/4.7/3.8/3.6	200/20/20/10	5,7,8,9/5,7,8
M	2.3	LGS	NA	<0.1/2.2/1.4/3.6	500/300/300/300	4,8,12/4,8
F	16.3	LGS	A	<0.1/–/–/–	240/240/–/–	1,5,8/–
M	4.0	MAE	A	<0.1/3.0/2.8/2.1	200/0/0/0	1,8,10/1
M	8.5	LGS	NA	0.2/3.4/2.3/2.7	340/340/340/340	1,10/1,10
M	2.3	WS	NA	0.21/2.8/–/–	400/280/–/–	1,5,8/–
M	4.5	Gen. ep.	NA	0.1/2.3/1.9/2.1	150/100/75/75	9,11/9,11
M	5.7	LGS	NA	<0.1/1.8/–/–	400/250/250/250	3/3,2
M	1.6	WS	NA	<0.1/2.3/1.4/–	180/180/180/–	1,5,11/1,5,11
M	2.3	WS	NA	0.7/2.3/4.9/–	500/300/300/300	4,8,12/4,8,12
F	6.2	MAE	A	0.2/2.9/3.2/–	150/25/25/–	1/–
F	3.8	DS	A	<0.1/2.5/0.2/–	300/200/200/100	1,8,13/1,8,13
M	8.7	LGS	NA	0.13/2.3/–/–	500/500/–/–	1,8/–
F	3.0	MAE	A	<0.1/2.3/3.8/3.3	300/0/0/0	1,8,10/8,10
M	5.4	LGS	NA	0.2/3.8/3.4/2.9	1090/280/280/280	4,5,8,9/4,5,8,9
F	10.0	LGS	A	0.3/5.2/3.8/4.8	1532/50/50/50	1,3,8,11/1,3,8,11
F	3.7	LGS	NA	0.11/2.4/–/–	230/250/–/–	1,8/–
M	15.0	MAE	A	–/4.2/2.8/3.4	330/6/6/6	1,8,10,14/1,8,10,14
M	5.5	LGS	A	<0.1/3.4/2.0/2.4	60/10/10/10	1,3,11/1,3,11
F	4.8	LGS	A	0.39/2.6/2.3/2.6	36/22/22/22	1,9/1
Patients with GLUT1-DS						
F	17.2	Gen. ep.	A	<0.1/1.4/2.3/1.1	30/0/0/0	1/–
F	13.2	Gen. ep.	A	<0.1/1.2/2.7/1.7	5/0/0/0	1,4/–
F	3.6	Gen. ep.	A	<0.1/1.4/2.1/0.9	40/0/0/0	1/–
F	1.5	–	A	0.2/3.3/2.9/3.7	0/0/0/0	–/–
M	4.2	Gen. ep.	A	–/–/–/4.9	30/0/0/0	1/–
M	16.7	Gen. ep.	A	<0.1/3.5/4.2/1.8	11/0/0/0	1,4/–
M	0.4	–	A	<0.1/3.0/2.9/3.2	0/0/0/0	–/–
Patients with PDHCD						
F	4.2	WS	NA	0.2/0.7/0.3/–	90/20/20/–	1,5/5
F	2.6	–	NA → A	–/0.8/0.9/1.2	0/0/0/0	–/–
F	2.0	–	A	0.2/1.4/2.0/3.3	0/0/0/0	–/–
F	9.5	–	A	<0.1/0.4/0.9/0.2	0/0/0/0	–/–
M	6.0	–	A	2.2/1.5/–/2.3	0/0/0/0	–/–
F	6.1	–	A	<0.1/–/2.8/2.3	0/0/0/0	–/–
F	8.0	–	A	–/–/–/1.8	1/0/0/0	–/–
F	1.3	WS	NA	<0.1/1.1/1.8/1.6	150/110/60/60	11/11
F	1.1	–	NA	<0.1/2.4/2.9/2.0	0/0/0/0	–/–

DS = Dravet syndrome, Gen. ep. = Generalized epilepsy, LGS = Lennox Gastaut Syndrome, MAE = Myoclonic Atonic Epilepsy, WS = West syndrome, A = ambulatory, NA = non-ambulatory (Anti-epileptic drugs 1 = valproate, 2 = carbamazepine, 3 = oxcarbazepine, 4 = lamotrigine, 5 = levetiracetam, 6 = phenytoin, 7 = phenobarbital, 8 = benzodiazepine, 9 = topiramate, 10 = rufinamide, 11 = vigabatrin, 12 = zonisamide, 13 = stiripentol, 14 = felbamat).

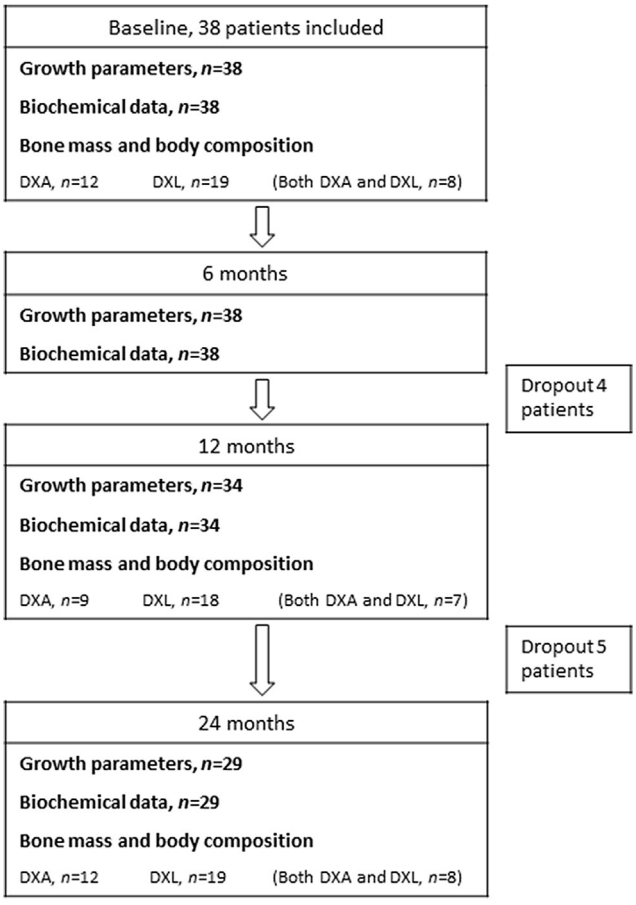

Fig. 1 – Flow chart describing inclusions and dropouts, and information about growth parameters, biochemical data, bone mass and body composition.

2.3. *Biochemical analyses*

Blood samples were analyzed in accordance with clinical routine at the SWEDAC-accredited laboratories of Clinical Chemistry at Sahlgrenska University Hospital, Gothenburg, and at the SWEDAC-accredited laboratories of Clinical Chemistry in Karlstad, Jönköping, Trollhättan, Skövde, Borås and Halmstad, Sweden.

Serum IGF-I and insulin-like growth factor binding protein 3 (IGFBP3) were measured using an IGFBP-blocked radioimmunoassay with an excess of IGF-II for determination of IGF-I and a specific radioimmunoassay for IGFBP3 (Mediagnost GmbH, Tübingen, Germany). Intra-assay and inter-assay CVs for IGF-I were 7–15% and 8–25% and for IGFBP3 7–9% and 10–20%, respectively. Results were converted into standard deviation scores (SDS) according to sex, pubertal stage, and age, and the IGF-I/IGFBP3 ratio SDS was calculated.

2.4. *Assessment of body composition and bone mass*

Body weight and height were measured with the same calibrated scale by a trained nurse at baseline and after 6, 12, and 24 months. Measurements were compared to reference values for healthy children[20] and BMI was calculated. BMD and bone mineral content (BMC) were measured with DXA (Lunar Prodigy, GE Lunar Corp., Madison, WI, USA) for total body with head excluded (TB HE), hip, and lumbar spine (L_1–L_4). Age- and gender-specific Z-scores were calculated automatically. Fat mass and lean mass were also assessed. Twenty healthy individuals (age 6–37 years) were scanned twice by the same examiner in order to assess the *in vivo* precision. For these measurements, the coefficients of variation (CV) were 0.5% for total body BMD and 0.7% for lumbar spine (LS) BMD (L_1–L_4). CV for body fat mass and lean mass was 2.4% and 0.9% respectively. All DXA measurements were performed by the same nurse. The last two measurements were made on a new device, Lunar iDXA (GE Lunar Corp.). A reliability study was performed with 25 individuals, comparing the old DXA with the new iDXA method for total BMC, total BMD, total fat mass, total lean mass, LS BMC, and LS BMD. The reliability was evaluated as acceptable, based on high intraclass correlation coefficient, >0.98 for all six parameters, and low CV, ranging between 1.34% and 3.33% (Table 2). The Bland–Altman plots revealed no heteroscedasticity in data points. However, the Lunar Prodigy DXA showed systematically lower values than the Lunar iDXA method for total BMC, mean difference −36.1 (95% CI −53.5 to −18.7), $p < 0.001$, and for LS BMD, mean difference −0.023 (95% CI −0.033 to −0.012), $p < 0.001$ (see Table 2).

In the DXL Calscan technique, calcaneal BMD is assessed by a combination of DXA and laser measurements of the total heel thickness of the left foot. The DXL Calscan (Demetech AB, Täby, Sweden) has been used in conjunction with measurements of axial DXA for the diagnosis of osteoporosis in adults[21,22] and has been modified for pediatric use; it measures BMD (g/cm^2) and BMC (g) with high accuracy. The DXL Calscan pediatric version includes a function that makes manual measurement of calcaneal height possible. This height, together with the BMD value, provides the opportunity to calculate volumetric bone mineral apparent density (BMAD) (g/cm^3). BMAD is valuable for longitudinal measurement of bones of different sizes, such as for growing individuals.[23]

2.5. *Statistical analysis*

Dichotomous variables were expressed as number and percentage and continuous variables were expressed as mean, SD, median, minimum, and maximum. The Wilcoxon signed rank test was used to measure changes in continuous variables over time within a group. The relation between two continuous variables was described by Spearman's correlation coefficient. For the purpose of evaluating the reliability between the old DXA and the new iDXA method, the following statistics were produced: mean difference between the methods and 95% limits of agreement, 95% CI for the mean difference, inter-individual SD, coefficient of variation (CV, inter-individual SD/mean), Wilcoxon signed rank test for systematic differences, and Shrout–Fleiss intraclass correlation coefficient two-way random single measures. The Bland-Altman method was used to test for methodological differences between the DXA and the iDXA methods. All tests were two-tailed and conducted at the 0.05 significance level. All analyses were performed by using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 2 – Reliability old DXA - new iDXA method.

Variable	Difference Lunar Prodigy DXA – Lunar iDXA		CV %	Inter individual SD(IISD)	Intraclass correlation coefficient(ICC)
	Mean (95% CI Limits of agreement) (SD) Median (min; max), n = 25	Systematic changes *p*-value			Shrout-Fleiss reliability: random set
TB BMC (g)	−36.1 (−118.9; 46.7) (42.3) −38.0 (−115.0; 31.0)	<0.001	2.00	38.84	0.997
TB BMD (g/cm^2)	−0.007 (−0.044; 0.031) (0.019) −0.012 (−0.040; 0.030)	0.07	1.34	0.014	0.996
Total fat mass (%)	−0.136 (−2.727; 2.455) (1.322) 0.100 (−2.700; 2.700)	0.56	3.33	0.921	0.984
Total lean mass (g)	80.1 (−1932.6; 2092.8) (1026.9) −140.0 (−1154.0; 2221.0)	0.84	2.00	714.00	0.998
LS BMC (g)	−0.595 (−4.794; 3.604) (2.142) −0.460 (−6.860; 3.280)	0.13	3.06	1.54	0.995
LS BMD (g/cm^2)	−0.023 (−0.073; 0.027) (0.026) −0.025 (−0.082; 0.056)	<0.001	2.35	0.024	0.991

CV is coefficient of variation (intra-individual SD × 100/mean). Wilcoxon signed rank test was used to test the difference. For difference mean (95% CI, limits of agreement)/(SD)/median (minimum; maximum)/n = is presented.

3. Results

3.1. *Clinical efficacy*

Thirty-eight patients were started on the MAD: 22 patients as a treatment for intractable epilepsy, seven patients as a treatment for GLUT1-DS and nine patients as a treatment for PDHCD. Thirty patients had seizures before MAD initiation; median seizure frequency at baseline was 200 seizures per month (1–1532 seizures per month). At 6, 12, and 24 months, the proportion of children with over 50% seizure frequency reduction was 57%, 63%, and 53%, respectively. Nine patients (30%) were seizure free after 6 months on MAD treatment, and remained seizure-free during the study period. Among these are all five patients with GLUT1-DS and seizures at baseline. The number of AEDs was reduced in 10 out of 29 patients treated with AEDs at MAD initiation and the AEDs were withdrawn in all of the five patients with GLUT1-DS and seizures. One of the non-ambulatory patients was able to walk after 6 months on the MAD.

3.2. *Growth*

There was no change in median weight SDS during the study period. Median height SDS was −0.4 (−4.0 to 2.5) at baseline and unchanged at 6 months, −0.4 (−3.0 to 2.5), $p = 0.50$, then decreased to −0.3 (−3.4 to 1.9), $p < 0.05$, at 12 months. There was a further decrease in height SDS from 12 to 24 months −0.3 (−2.9 to 1.4), $p = 0.02$, but no significant change between height SDS at baseline and 12 or 24 months ($p = 0.08$ and $p = 0.10$, respectively). Hence, there was no significant effect on height over 24 months.

Median BMI SDS was 0.2 (−3.3 to 4.5) at baseline, 0.4 (−1.8 to 3.8) at 6 months, 0.5 (−1.4 to 3.9) at 12 months, and 0.7 (−0.9 to 2.6) at 24 months. The increase from baseline to 24 months was significant ($p = 0.005$). Individual growth parameters are illustrated in Fig. 2.

Median IGF-I SDS was −0.2 at baseline and decreased to −0.9 at 6 months ($p = 0.003$) and to −1.0 at 12 months ($p = 0.02$). From 12 to 24 months, median IGF-I SDS increased to 0.1 ($p = 0.009$). Median IGFBP3 SDS at baseline was 1.0 and stable at 6 months, 0.6 ($p = 0.24$), then decreased at 12 months to 0.1, $p = 0.0029$. From 12 to 24 months, IGFBP3 SDS increased to 0.6 ($p = 0.03$). The change in IGF-I SDS from 0 to 24 months correlated to the changes in weight and height SDS for the same time period ($p = 0.02$ and $p = 0.03$, respectively) (Table 3).

3.3. *Bone mass and body composition*

In 23 patients (12 girls, 11 boys) out of the 29 who completed the study, DXA and/or DXL measurements were performed (Fig. 1). Because DXA reference Z-scores are only available for children over 5 years of age, and because there were artefacts from movements during DXA scans with younger children, we only have reliable DXA results for baseline and after 24 months in 12 of these 23 patients. Three patients were <5 years at the time for the baseline DXA. In contrast, even children under 2 years of age could easily perform the measurement of calcaneal BMD with the pediatric DXL Calscan technique, owing to its simplicity and short scan time, resulting in adequate scans at baseline and 24 months without artefacts in 19 patients. In comparison with the reference interval for DXL measurements for children under the age of 8 years,[23] most patients had levels below the lower limit of the reference interval for BMAD. The median calcaneal

Table 3 – Bone mass, body composition, and biochemical assessments.

DXA and DXL measurements	Baseline	12 months	24 months	Delta values, 0–12 months	Delta values, 12–24 months	Delta values, 0–24 months
TB BMC HE (g)	428 (323; 2291) $n = 10$	755 (218; 1955) $n = 6$	542 (325; 1963) $n = 7$	85.8 (−116.9; 378.7) $n = 5$, $p = 0.44$	62.7 (7.3; 106.7) $n = 4$, $p = 0.13$	129.5 (−19.8; 257.6) $n = 6$, $p = 0.16$
TB BMD (g/cm^2)	0.836 (0.539; 1.223) $n = 7$	0.877 (0.721; 1.197) $n = 4$	0.716 (0.583; 1.188) $n = 6$	0.041 (−0.079; 0.183) $n = 4$, $p = 0.63$	−0.009 (−0.139; 0.013) $n = 3$, $p = 0.75$	−0.035 (−0.114; 0.044) $n = 5$, $p = 0.44$
TB BMC (g)	680 (553; 2800) $n = 7$	1413 (471; 2472) $n = 4$	827 (584; 2466) $n = 6$	76.2 (−82.2; 385.4) $n = 4$, $p = 0.63$	107.5 (−6.4; 113.5) $n = 3$, $p = 0.50$	123.8 (−24.1; 277.6) $n = 5$, $p = 0.13$
TB BMD, HE (g/cm^2)	0.612 (0.409; 1.095) $n = 10$	0.649 (0.507; 1.064) $n = 6$	0.530 (0.410; 1.062) $n = 7$	0.037 (−0.041; 0.124) $n = 5$, $p = 0.44$	−0.007 (−0.097; 0.040) $n = 4$, $p = 0.63$	0.000 (−0.083; 0.058) $n = 6$, $p = 0.88$
TB BMD HE Z-score	−0.60 (−2.50; 1.40) $n = 7$	−0.15 (−3.00; 1.00) $n = 6$	−0.50 (−2.90; 1.00) $n = 7$	−0.10 (−1.10; 0.70) $n = 5$, $p = 0.81$	−0.05 (−0.70; 0.10) $n = 4$, $p = 0.75$	−0.60 (−1.00; 0.10) $n = 4$, $p = 0.25$
LS BMD (g/cm^2)	0.605 (0.474; 1.318) $n = 12$	0.704 (0.496; 1.289) $n = 7$	0.630 (0.463; 1.247) $n = 8$	0.029 (−0.046; 0.181) $n = 7$, $p = 0.33$	0.004 (−0.042; 0.009) $n = 5$, $p = 0.81$	0.025 (−0.071; 0.089) $n = 8$, $p = 0.55$
LS BMD Z-score	−0.70 (−2.20; 2.00) $n = 9$	−0.20 (−2.00; 2.00) $n = 7$	−1.05 (−2.50; 0.60) $n = 8$	0.00 (−1.10; 0.90) $n = 7$, p = 0.88	−0.30 (−0.70; 0.00) $n = 5$, $p = 0.13$	−0.50 (−1.80; 0.70) $n = 6$, $p = 0.41$
LS BMC (g)	14.5 (10.7; 77.9) $n = 12$	20.1 (11.9; 74.3) $n = 7$	16.8 (11.8; 74.0) $n = 8$	1.39 (−3.55; 11.53) $n = 7$, $p = 0.47$	0.550 (−0.350; 0.970) $n = 5$, $p = 0.31$	2.37 (−3.90; 4.85) n = 8, $p = 0.15$
Total hip BMD (g/cm^2)	0.589 (0.349; 1.257) $n = 10$	0.746 (0.340; 1.246) $n = 5$	0.582 (0.335; 1.223) $n = 7$	0.007 (−0.011; 0.095) $n = 5$, p = 0.63	−0.005 (−0.023; 0.055) $n = 3$, $p = 1.00$	−0.007 (−0.154; 0.062) $n = 6$, $p = 1.00$
TB Fat mass (g)	10,927 (3016; 23,218) $n = 9$	9000 (6828; 18,704) $n = 6$	11,128 (4007; 21,552) $n = 8$	−1261.0 (−4514.0; 5084.0) n = 5, $p = 1.00$	2043 (913; 3594) $n = 4$, $p = 0.13$	1128 (−1666; 3942) $n = 6$, $p = 0.56$
TB Lean mass (g)	14,008 (11,095; 43,579) $n = 9$	16,095 (13,342; 40,531) $n = 6$	17,139 (12,348; 37,621) $n = 8$	2247 (615; 5808) $n = 5$, $p = 0.06$	105.5 (−2910.0; 1984.0) $n = 4$, $p = 1.00$	2446 (−2295; 4167) $n = 6$, $p = 0.16$
Calcaneal BMC (g)	0.083 (0.001; 0.233) $n = 19$	0.089 (0.001; 0.233) $n = 16$	0.101 (0.001; 0.313) $n = 18$	0.005 (−0.055; 0.049) $n = 16$, $p = 0.79$	0.017 (−0.022; 0.105) $n = 15$, $\mathbf{p = 0.03}$	0.020 (−0.024; 0.109) $n = 18$, $\mathbf{p = 0.01}$
Calcaneal BMD (g/cm^2)	0.113 (0.016; 0.318) $n = 19$	0.121 (0.013; 0.326) $n = 16$	0.135 (0.009; 0.310) $n = 18$	0.007 (−0.076; 0.069) $n = 16$, $p = 0.73$	0.021 (−0.026; 0.136) n = 15, $p = 0.12$	0.021 (−0.049; 0.128) $n = 18$, $\mathbf{p = 0.047}$
Calcaneal height (mm)	22.6 (14.9; 36.0) $n = 19$	24.4 (15.7; 37.0) $n = 16$	24.2 (17.1; 39.3) $n = 18$	1.68 (−1.90; 7.14) $n = 16$, $\mathbf{p < 0.001}$	0.900 (−4.530; 2.300) $n = 15$, $\mathbf{p = 0.04}$	2.63 (−0.60; 7.20) $n = 18$, $\mathbf{p < 0.001}$
Calcaneal BMAD (mg/cm^3)	42.7 (7.7; 96.3) $n = 19$	51.9 (6.5; 112.1) $n = 16$	53.4 (4.1; 94.7) $n = 18$	−0.31 (−34.88; 28.82) n = 16, $p = 0.43$	4.68 (−18.21; 40.33) $n = 15$, $p = 0.25$	0.078 (−34.008; 32.675) $n = 18$, $p = 0.80$

Biochemical assessments	Baseline	6 months	12 months	24 months	Delta values, 0–6 months	Delta values, 6–12 months	Delta values, 12–24 months	Delta values, 0–24 months
Lactate (mmol/L)	1.50 (0.50; 4.40) $n = 37$	1.10 (0.60; 4.10) $n = 35$	1.20 (0.76; 1.90) $n = 29$	1.20 (0.70; 3.10) $n = 26$	−0.10 (−3.50; 2.60) $n = 34$, $\mathbf{p = 0.04}$	0.10 (−2.50; 0.80) $n = 26$, $p = 0.35$	0.00 (−1.01; 1.80) $n = 21$, $p = 0.97$	−0.20 (−1.50; 1.50) $n = 25$, $p = 0.13$
3-hydroxybutyric acid (mmol/L)	0.05 (0.05; 2.20) $n = 34$	2.35 (0.42; 5.20) $n = 34$	2.30 (0.18; 4.90) $n = 29$	2.30 (0.16; 4.90) $n = 28$	2.25 (−0.70; 4.90) $n = 32$, $\mathbf{p < 0.001}$	−0.20 (−2.32; 2.60) $n = 28$, $p = 0.67$	−0.20 (−2.40; 2.20) $n = 23$, $p = 0.54$	2.13 (0.10; 4.50) $n = 24$, $\mathbf{p < 0.001}$
pH	7.38 (7.23; 7.51) $n = 36$	7.38 (7.30; 7.43) $n = 35$	7.39 (7.33; 7.47) $n = 31$	7.39 (7.34; 7.45) $n = 28$	−0.02 (−0.15; 0.19) $n = 34$, $p = 0.09$	0.03 (−0.05; 0.09) $n = 29$, $\mathbf{p = 0.01}$	0.00 (−0.10; 0.06) $n = 25$, $p = 0.21$	−0.01 (−0.10; 0.20) $n = 26$, $p = 0.45$
Base Excess	−1.00 (−7.30; 7.00) $n = 36$	−2.30 (−6.90; 3.00) $n = 37$	−1.70 (−5.60; 5.00) $n = 31$	−2.00 (−7.20; 6.00) $n = 28$	−1.80 (−12.00; 3.30) $n = 36$, $\mathbf{p = 0.004}$	0.70 (−2.20; 4.70) $n = 31$, $\mathbf{p = 0.014}$	0.50 (−4.80; 4.60) $n = 25$, $p = 0.77$	−1.00 (−13.00; 5.20) $n = 26$, $p = 0.17$
Calcium (mmol/L)	2.46 (2.13; 2.85) $n = 35$	2.45 (1.99; 2.78) $n = 37$	2.43 (2.00; 2.59) $n = 31$	2.43 (2.29; 2.62) $n = 29$	0.03 (−0.46; 0.20) $n = 34$, $p = 0.34$	0.01 (−0.48; 0.55) $n = 30$, $p = 0.49$	0.04 (−0.16; 0.21) $n = 26$, $p = 0.23$	−0.02 (−0.46; 0.31) $n = 26$, $p = 0.92$
Phosphorus (mmol/L)	1.60 (0.67; 2.00) $n = 34$	1.53 (1.00; 1.85) $n = 36$	1.50 (0.12; 1.80) $n = 32$	1.50 (1.00; 1.89) $n = 25$	−0.10 (−0.50; 0.63) $n = 32$, $p = 0.15$	0.00 (−1.48; 0.50) $n = 31$, $p = 0.07$	0.00 (−0.30; 0.47) $n = 24$, $p = 0.50$	−0.10 (−0.55; 1.13) $n = 22$, $p = 0.09$

Magnesium (mmol/L)	0.87 (0.71; 1.00)	0.82 (0.63; 1.10)	0.80 (0.57; 0.90)	0.80 (0.60; 0.95)	−0.07 (−0.24; 0.08)	−0.02 (−0.33; 0.13)	0.02 (−0.08; 0.07)	−0.09 (−0.27; 0.08)
	$n = 34$	$n = 37$	$n = 32$	$n = 26$	$n = 33$, $\mathbf{p < 0.001}$	$n = 32$, $p = 0.10$	$n = 25$, $p = 0.06$	$n = 22$, $\mathbf{p < 0.001}$
25(OH)D (nmol/L)	85.7 (29.8; 175.0)	117.5 (32.5; 271.0)	113.5 (14.3; 192.0)	98.0 (36.3; 204.0)	27.0 (−29.0; 114.0)	3.00 (−32.00; 64.70)	−10.20 (−95.70; 52.00)	20.1 (−76.7; 101.0)
	$n = 24$	$n = 24$	$n = 22$	$n = 24$	$n = 20$, $\mathbf{p = 0.002}$	$n = 19$, $p = 0.42$	$n = 17$, $p = 0.47$	$n = 17$, $p = 0.13$
ALP (µkat/L)	3.40 (0.89; 5.10)	2.95 (1.10; 4.40)	2.80 (1.20; 4.40)	2.70 (1.00; 5.70)	−0.50 (−1.90; 1.20)	0.00 (−1.60; 0.90)	−0.10 (−2.10; 1.00)	−0.70 (−3.30; 2.00)
	$n = 36$	$n = 36$	$n = 33$	$n = 28$	$n = 35$, $\mathbf{p = 0.01}$	$n = 31$, $p = 0.50$	$n = 27$, $p = 0.06$	$n = 26$, $\mathbf{p = 0.01}$
Cholesterol (mmol/L)	4.30 (2.80; 5.50)	4.20 (2.80; 6.90)	4.10 (1.90; 7.00)	4.25 (2.80; 5.60)	0.30 (−1.30; 2.70)	−0.10 (−2.00; 1.60)	−0.20 (−2.28; 1.50)	0.00 (−1.40; 1.50)
	$n = 35$	$n = 37$	$n = 33$	$n = 28$	$n = 34$, $p = 0.15$	$n = 32$, $p = 0.22$	$n = 27$, $p = 0.80$	$n = 25$, $p = 0.68$
TG (mmol/L)	0.98 (0.38; 4.20)	0.90 (0.27; 3.20)	0.90 (0.31; 2.40)	0.92 (0.37; 2.30)	−0.10 (−3.10; 0.74)	−0.07 (−2.46; 1.85)	0.00 (−0.60; 0.86)	0.00 (−3.30; 0.82)
	$n = 34$	$n = 38$	$n = 30$	$n = 25$	$n = 34$, $p = 0.20$	$n = 30$, $p = 0.46$	$n = 24$, $p = 0.73$	$n = 22$, $p = 0.28$
LDL (mmol/L)	2.40 (1.14; 3.40)	2.65 (1.40; 5.50)	2.60 (0.30; 5.30)	2.70 (0.80; 4.50)	0.35 (−1.30; 2.90)	−0.10 (−1.40; 2.00)	−0.15 (−1.60; 1.50)	0.30 (−1.40; 1.80)
	$n = 34$	$n = 38$	$n = 33$	$n = 27$	$n = 34$, $\mathbf{p = 0.049}$	$n = 33$, $p = 0.47$	$n = 26$, $p = 0.35$	$n = 24$, $p = 0.08$
HDL (mmol/L)	1.40 (0.61; 2.30)	1.30 (0.54; 2.60)	1.30 (0.16; 2.90)	1.23 (0.78; 2.30)	−0.10 (−0.80; 0.80)	0.00 (−0.70; 0.69)	0.10 (−0.55; 0.50)	−0.05 (−0.70; 0.80)
	$n = 35$	$n = 37$	$n = 33$	$n = 28$	$n = 34$, $p = 0.15$	$n = 32$, $p = 0.74$	$n = 27$, $p = 0.49$	$n = 25$, $p = 0.29$
IGF-I SDS	−0.15 (−3.00; 3.30)	−0.85 (−3.40; 2.60)	−1.00 (−4.70; 2.20)	0.05 (−5.00; 2.20)	−0.65 (−3.00; 3.90)	−0.70 (−3.00; 1.40)	0.70 (−2.30; 3.70)	−0.50 (−4.10; 4.20)
	$n = 32$	$n = 26$	$n = 25$	$n = 22$	$n = 26$, $\mathbf{p = 0.003}$	$n = 22$, $\mathbf{p = 0.02}$	$n = 20$, $\mathbf{p = 0.009}$	$n = 20$, $p = 0.16$
IGFBP3 SDS	1.00 (−5.10; 2.50)	0.60 (−3.40; 3.10)	0.10 (−4.30; 2.80)	0.60 (−1.10; 2.90)	−0.35 (−2.80; 5.90)	−0.60 (−4.00; 2.60)	0.40 (−0.60; 3.70)	−0.10 (−2.20; 5.20)
	$n = 31$	$n = 26$	$n = 25$	$n = 22$	$n = 26$, $p = 0.24$	$n = 22$, $\mathbf{p = 0.003}$	$n = 20$, $\mathbf{p = 0.03}$	$n = 20$, $p = 0.86$

Values are given as median with minimum and maximum values in parentheses. For comparison over time, the Wilcoxon signed rank test was used for continuous variables. Bold numbers indicate significant p-values.

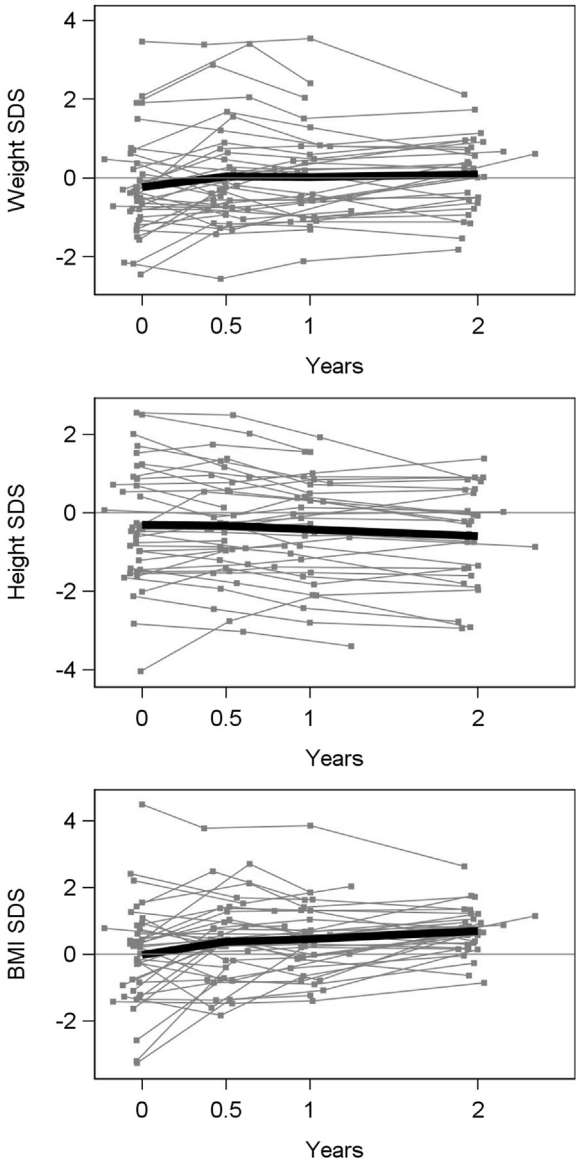

Fig. 2 – Individual growth parameters at start, 0.5, 1 and 2 years on treatment. Weight SDS, height SDS, and BMI SDS during the study period of 24 months, $n = 38$. The bold line represents the median value.

BMD increased after 24 months ($p = 0.047$). Calcaneal BMC and calcaneal height increased from baseline to 24 months ($p = 0.01$ and $p < 0.001$), thus the BMAD was not affected ($p = 0.80$) (Table 3).

There were no changes in total body BMD with head excluded (TB BMD HE) Z-scores: median −0.6 at baseline, −0.2 after 12 months, and −0.5 after 24 months ($p = 0.25$). LS BMD Z-scores did not change either: median −0.7, −0.2, and −1.1 at the same time points. TB BMD HE Z-score was below −1.0 in two patients at baseline (in one of those, below −2.0), and in three patients after 24 months (in one of those, below −2.0). LS BMD Z-score was below −1.0 in three patients at baseline (in one of those, below −2.0), and in four patients after 24 months (in two of those, below −2.0). Total hip BMD was unaffected after 24 months. There were no changes in

TB BMC HE or LS BMC from baseline to 12 or 24 months. The amount of total fat mass, trunk fat mass and total lean mass did not change significantly from baseline to 12 or 24 months. Individual values of bone mass and body composition are illustrated in Fig. 3. During the study period, only one child had a fracture (femur fracture), after MAD treatment for more than 1 year.

3.4. *Association analyses*

There were no significant differences in auxiological and demographic data between the patients continuing the diet for 24 months ($n = 29$) and the dropouts ($n = 9$), except the type of epilepsy.

4. Discussion

The present study investigated long-term effects on growth, body composition, and bone mass in children on MAD treatment. Our results support earlier findings that the MAD is efficient in reducing seizures, and indicate that both longitudinal growth and bone mass remained stable. Hence, our data suggest that MAD treatment is an effective and safe treatment option in childhood and adolescence.

In this study, 22 patients were treated with the MAD for intractable epilepsy. Nine of these stopped the treatment due to insufficient effect on seizures. Approximately 50% responded well to the diet, with over 50% seizure reduction. These results are similar to most studies of the classic KD[5,6,24] as well as previously published results for the MAD.[9,25] All patients with GLUT1-DS in the present study remained on the MAD after 24 months and the five patients with seizures in this group all became seizure-free within 6 months on this diet, which corresponds to previous results for GLUT1-DS patients reported elsewhere.[26]

Weight and height SDS were unchanged during treatment with the MAD, but BMI SDS increased over the whole study period. In another study an increase in Z-scores for both weight and height were observed in children with refractory epilepsy treated with the MAD for 9 months.[27] However, other studies have demonstrated a decrease in both weight and height Z-scores after 12 months on the KD[28,29] and a decrease in height after 15 months on the KD was reported by Bergqvist et al.[14] Similarly and interestingly, we found a slight negative impact on height SDS after 12 months but not at 24 months. IGF-I levels showed the same trend over time, which correlated to longitudinal skeletal growth. Thus, based on the results, we reject our initial hypothesis that the long-term growth would be affected by MAD treatment. One explanatory mechanism, behind the lack of negative effect on growth, could be a higher energy intake and a more liberate protein intake associated with MAD in comparison with KD. Another mechanism, related to skeletal development, could be that the 3-hydroxybutyric acid levels in our patients were stable near 2 mmol/L, which is lower than the target level of > 3–4 mmol/L in the KD. In our study a compensatory mechanism on the metabolic acidosis with a long-term adjustment to the changed metabolic conditions during MAD treatment was confirmed by normal and stable pH during the study period.

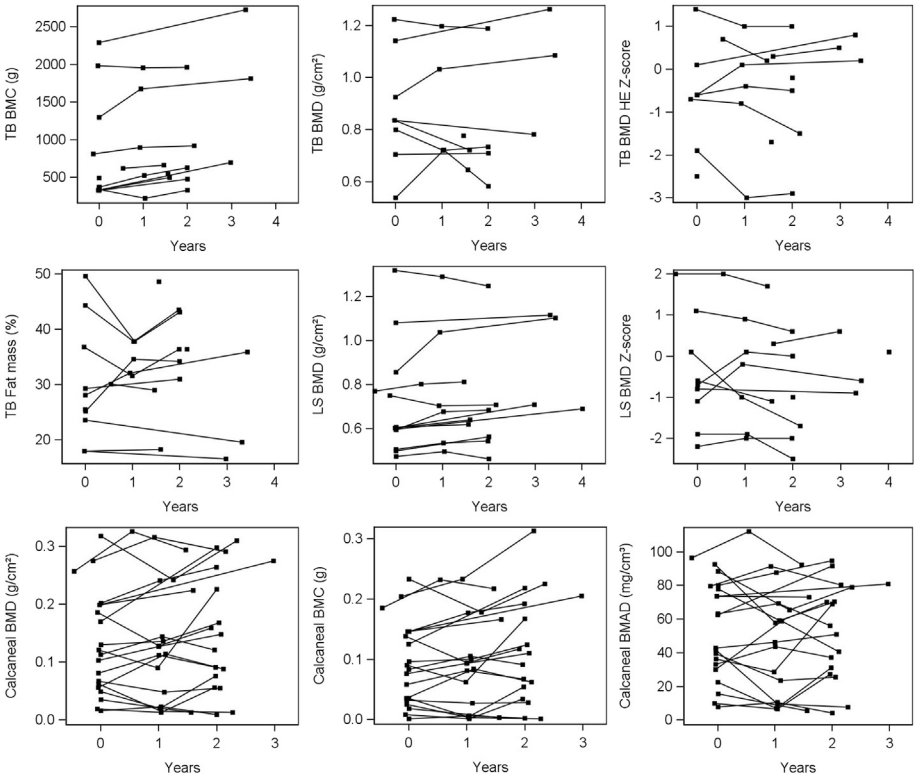

Fig. 3 – Individual values of bone mass and body composition at start, 0.5, 1 and 2 years of treatment. Bone mass measurements (DXA and DXL Calscan) during the study period of 24 months.

Another protecting factor could be the treatment with potassium citrate, a mild alkaline compound used to prevent nephrolithiasis due to aciduria and hypocitraturia induced by KD and MAD. Thus, the 14 patients on potassium citrate treatment were in a less ketotic state, but the effect on seizures was nonetheless satisfactory and consistent with previously published results.[5]

Children with intractable epilepsy have compromised bone health before initiation of KD and suboptimal longitudinal growth, as described by Bergqvist et al.[14] They found a progressive loss of BMC in both total body and lumbar spine with KD treatment. A progressive loss of BMC, associated with poor bone health status, has previously been described as a consequence of the chronic acidic environment that may be preventing the normal accumulation of BMC and also affect linear growth.[12–14] Our results, favorably, indicate that bone mass remains stable during treatment with the MAD for 24 months. The lack of negative effect on bone acquisition in our patients could probably be explained by the stable pH and lower 3-hydroxybutyric acid level mentioned above. In addition patients were carefully evaluated for and substituted with minerals such as phosphate, calcium and magnesium, although the diet with MAD, is less restrictive than the KD. The reduction in seizure frequency may lead to more daily physical activity for the children, and consequently increasing the mechanical loading and muscle forces, which in turn is favorable for bone acquisition.

As shown before, BMAD could be used as a more relevant parameter for comparing bone mass over time.[23] This could be particularly relevant in longitudinal studies of growing individuals with changing skeletal dimensions. In our study, both calcaneal BMC and BMD increased over the treatment period. However, the calcaneal heel height also increased, reflecting general longitudinal skeletal growth. Thus, the finding that BMAD was unchanged over time indicates that the increases in both BMC and BMD are not true increases, but a reflection of the new bone acquisition of the growing child. This fact also indicates that MAD treatment does not affect bone mass negatively. The adequate vitamin D levels were probably another contributing factor for the unaffected bone mass during MAD treatment. Bergqvist et al.[30] presented deficient vitamin D levels (<10 ng/mL) in 4% and insufficient levels (<30 ng/mL) in 55% of children with intractable epilepsy before KD. In our study, in contrast, mean 25(OH)D was adequate both before and during MAD treatment. No patient was vitamin D deficient (<12 ng/mL) prior to or after 24 months, while 8% had an insufficient 25(OH)D level (<20 ng/mL) before MAD initiation, according to global consensus recommendations for classification of vitamin D status.[31]

This is the first study to assess the long-term effects on growth and bone mass in children treated with the MAD. Another strength is that patients were well controlled and monitored regularly at the same center. The small number of patients limits the statistical power in the current study. In addition, the heterogeneous nature of this patient group, with a variety of etiologies and wide age range, makes the interpretation more complex. A longer study period, than 24 months, would have been favorable in order to study the long-term consequences on bone health. Another shortcoming is the lack of a control group matched for age, gender, diagnosis, height, BMI, bone age and puberty. It would, however, not be ethically motivated to withhold MAD treatment from children with severe epilepsy by assigning them to a control group. Moreover, for bone mass there are robust reference values from healthy children which can be used; however, it would have been preferable to adjust bone mass data for size and height. Unfortunately, we were unable to perform DXA scans in many of the patients, but this was inevitable given their low age and artefacts from movement related to seizures or spasticity. Due to the present lack of long-term data on bone mass in children on MAD treatment, our results still provide new knowledge in this area.

This longitudinal study supports that the MAD is effective for seizure reduction. The absence of negative effects on longitudinal growth or bone mass despite the major nutritional changes was unexpected, but can be explained both by the increase in BMI and stable body composition and the lower level of acidosis. The MAD could thereby be considered a safe and effective treatment option in childhood and adolescence. The transient, large metabolic changes that are a consequence of MAD treatment (reflected by the changes in IGF-I) are stabilized over time and the result is a positive net effect that is reflected by the fact that the children are growing.

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Conflict of interest

The authors wish to confirm that we have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.04.001.

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