1 Introduction

Ketogenic diet therapy (KDT) is a group of high fat, low carbohydrate, low-to-moderate protein diets used as a treatment option for drug-resistant epilepsy, particularly in children. Despite encouraging efficacy rates in terms of seizure control – up to 85% children on the classical diet for 3 months achieved seizure reduction of at least 50%, with up to 55% achieving seizure freedom (Martin-McGill et al., 2020) – there is concern that KDT negatively affects growth in children. A significant decrease in height and weight z-scores in children following classical or medium-chain triglyceride (MCT) KDT has been reported (Neal et al., 2008), particularly in younger children. Similarly, Vining et al. (2002) demonstrated a negative impact on height and weight growth in children on KDT, again more marked in younger children and non-ambulatory children. However, both Numis et al. (2011) and Armeno et al. (2019) found no significant impact of the classical diet on height or weight, nor any significant effect of factors such as age or ambulatory status. The effect of KDT on growth in children, as well as factors which are potentially associated with adverse growth, therefore remains a contested topic.

The aim of this case note review was to determine the impact of KDT on linear growth and weight in children with epilepsy in the UK, as well investigating clinical, dietary, or demographic factors that may influence growth.

2 Material and methods

2.1 Method

Medical records of children following KDT at three UK centres were reviewed. All children who had followed KDT for at least one year, under the epilepsy KDT services at each of the three centres, from the onset of the service up until 2020 were included, except those with previous growth concerns. Length/height and weight measurements were included at baseline (pre-diet), 1, 2, 3, 4, 5, 6, 7 and 8 years on diet, and 1-year after discontinuation of KDT, where available. Individuals who were identified at baseline as needing to increase or decrease weight centile due to previous growth concerns were excluded.

Other variables recorded were epilepsy aetiology (grouped into genetic, structural, metabolic, infectious, immune or unknown, according to the International League Against Epilepsy classification (ILAE, 2020)), number of anti-seizure medicines (ASMs) trialled pre-KDT, number of ASMs taken at diet initiation, ambulatory status (ambulatory vs non-ambulatory), age at diet onset, feeding method (oral-fed vs tube-fed), KDT type (classical KD, MCT KD and modified KDs), and average protein intake per day (g/kg) at 1-year follow-up. In individuals who switched KDT type, growth data were only included up to the time of diet type change to avoid confounding.

2.2 Statistical analysis

Height and weight measurements were converted into z-scores using World Health Organisation (WHO) LMS reference values (WHO, 2020) and calculated in Excel using the formula $z\text{-}score = \frac{(observed\ value \div \mathrm{M})^{L} - 1}{L \times S}$ (WHO, 2008). The Growth Charts

UK-WHO app (Incubate, 2017) was used for children over the age of 10 as WHO references did not extend beyond this age. The change in z-score from the pre-diet value was calculated for each timepoint. SPSS 27 (IBM, 2020) was used to perform the statistical analysis. The Wilcoxon Signed Rank test was used to compare median z-scores at each timepoint to a hypothesised change of zero. Subgroup analyses were carried out for 1, 2 and 3 years on diet, as well as 1-year post-diet discontinuation, due to small sample sizes at later timepoints (n=1 in some subgroups). For categoric subgroup variables, either Mann-Whitney U or Kruskal-Wallis tests were used, and Spearman's Rank correlation was used for numeric variables. A Bonferroni-correction was applied for these subgroup comparisons, with a corrected p-value of 0.01 applied as the significance threshold.

2.3 Ethical approval

This project was registered as a case note review at participating centres: Great Ormond Street Hospital for Children (GOSH), Cambridge University Hospitals and Royal Manchester Children's Hospital.

2.4. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

3 Results

3.1 Cohort characteristics

A total of 265 individuals were included in the final analysis, of which 84 had 1-year post-diet data available. The cohort clinical/demographic characteristics are shown in Table 1.

Table 1
Cohort characteristics

Characteristic	
Epilepsy aetiology	
Genetic, n (%)	79 (29.8%)
Structural, n (%)	43 (16.2%)
Infectious, n (%)	5 (1.9%)
Metabolic, n (%)	23 (8.7%)
Immune, n (%)	1 (0.4%)
Unknown, n (%)	115 (43.0%)
Median age at diet onset in months (IQR)	55 (22 - 97)
Median number of failed anti-seizure medicines (IQR)	4 (3 - 6)
Diet type	
Classical, n (%)	158 (59.6%)
MCT, n (%)	56 (21.1%)
Modified, n (%)	45 (17.0%)
Unknown/mixed, n (%)	6 (2.3%)
Ambulatory status	
Ambulatory, n (%)	152 (57.7%)
Non-ambulatory, n (%)	102 (38.5%)
Unknown, n (%)	10 (3.8%)
Feeding method	
Oral, n (%)	159 (60.0%)
Tube, n (%)	84 (31.7%)
Both, n (%)	22 (8.3%)
Diet responder at 1 year (≥50% seizure reduction)	
Yes, n (%)	194 (73.2%)
No, n (%)	31 (11.7%)
Unknown, n (%)	40 (15.1%)
Median protein intake in g/kg (IQR)	1.30 (1 – 1.555)

3.2 Height and weight change

As individuals followed KDT for varying lengths of time, and not all individuals had growth measurements recorded at each timepoint when on diet, the numbers of individuals with data available for analysis at each timepoint varied and, overall, decreased with time.

Table 2
Median weight and height z-score changes

Timepoint	**Median weight z-score change *(sample size, p-value)***	**Median height z-score change *(sample size, p-value)***
1 year	-0.0430 *(n=277, p= .428)*	**-0.1300 *(n=139, p= .018)****
2 years	-0.1200 *(n=185, p= .126)*	**-0.5275 *(n=86, p< .0005)****
3 years	-0.2400 *(n=101, p= .159)*	**-0.5800 *(n=27, p= .001)****
4 years	**-0.9650 *(n=15, p= .020)****	-1.0120 *(n=7, p= .310)*
5 years	-1.0725 *(n=10, p= .074)*	-0.5060 *(n=3, p= .109)*
6 years	**-1.0830 *(n=8, p= .025)****	-1.1070 *(n=4, p= .068)*
7 years	-1.3540 *(n=3, p= .109)*	-0.9650 *(n=1, p= .317)*
8 years	-0.7410 *(n=1, p= .318)*	*(n=0)*
1-year post-diet	-0.0940 *(n=84, p= .459)*	-0.1810 *(n=33, p= .823)*

*Asterisk (*) and **bold** indicates significance results at the 5% level*

Median height z-scores significantly decreased at 1 year, 2 years and 3 years on diet (Table 2). There was a significant decrease in median weight z-scores at 4 years and 6 years on diet, although the sample size was very limited for these timepoints (n=14 and n=8 respectively). There was no significant change from pre-diet values 1 year after diet discontinuation.

3.3 Subgroup analyses

The results for the subgroup analyses of change in weight z-score is shown below in tables 3 and 4 and for height z-score in tables 5 and 6.

Table 3
Comparison of weight z-scores across subgroups

Characteristic	Test statistic, sample size, p-value			
	1 year	**2 years**	**3 years**	**1-year post-diet discontinuation**
Oral-fed	-0.0125, n=132	-0.0700, n=107	-0.1100, n=56	-0.1255, n=54
Tube-fed	-0.1700, n=76	-0.2925, n=62	-0.5600, n=39	-0.0410, n=22
Difference	0.1575	0.2225	0.4500	0.0845
p-value[€]	*p= .142*	*p= .0210*	*p= .314*	*p= .927*
Ambulatory	-0.1000, n=131	-0.1100, n=108	-0.2565, n=54	-0.2695, n=48
Non-ambulatory	0.0400, n=90	-0.1900, n=73	-0.2400, n=47	0.0990, n=34
Difference	0.1400	0.0800	0.0165	0.3685
p-value[€]	*p= .797*	*p= .252*	*p= .814*	*p= .194*
Classical diet	-0.0600, n=134	-0.1540, n=106	-0.2100, n=51	-0.2800, n=47
MCT diet	-0.1700, n=49	-0.1300, n=41	-0.2790, n=21	-0.0420, n=15
Modified diets	0.0585, n=38	-0.0950, n=33	-0.2010, n=26	-0.0955, n=20
p-value[≠]	*p= .126*	*p= .747*	*p= .945*	*p= .624*

*Asterisk (*) and **bold** indicates significant results at the 1% level (significance threshold post-Bonferroni correction)*

[€] Mann-Whitney U test comparing median z-score change across subgroups
[≠] Kruskal-Wallis test comparing median z-score change across subgroups

Table 4
Spearman's Rank correlation of age at diet onset/average protein intake at with change in weight z-score

Characteristic	Correlation coefficient, sample size *(p-value)*			
	1 year	**2 years**	**3 years**	**1-year post-diet discontinuation**
Age at diet onset (months)	-0.210, n=227	0.087, n=185	0.228, n=101	-0.024, n=84
p-value	*p= .755*	*p= .238*	*p= .022*	*p= .831*
Average daily protein intake at 1 year (g/kg)	0.169, n=149	n/a	n/a	n/a
p-value	*p= .040*			

*Asterisk (*) and **bold** indicates significant results at the 1% level (significance threshold post-Bonferroni correction)*

Table 5
Comparison of height z-scores across subgroups

Characteristic	Test statistic, sample size, p-value			
	1 year	**2 years**	**3 years**	**1-year post-diet discontinuation**
Oral-fed	-0.2200, n=99	-0.5120, n=62	-0.5750, n=16	-0.3180, n=27
Tube-fed	-0.1200, n=26	-0.7100, n=15	-1.2420, n=8	0.4850, n=2
Difference	0.1000	0.1980	0.6670	0.8030
p-value[€]	*p= .376*	*p= .021*	*p= .528*	*p= .650*
Ambulatory	-0.1650, n=102	**-0.4940, n=69**	-0.5750, n=20	-0.2435, n=30
Non-ambulatory	-0.0700, n=32	**-0.9300, n=15**	-1.790, n=7	1.600, n=3
Difference	0.0950	**0.4360**	1.2150	1.8435
p-value[€]	*p= .301*	***p= .009****	*p= .400*	*p= .260*
Classical diet	-0.2490, n=66	**-0.6800, n=37**	-1.453, n=11	-0.1810, n=13
MCT diet	-0.2800, n=42	**-0.5090, n=28**	-0.5600, n=10	-0.1490, n=12
Modified diets	-0.0130, n=25	**-0.2725, n=16**	-0.2400, n=3	-0.3060, n=7
p-value[≠]	*p= .033*	***p= .006****	*p= .240*	*p= .919*

*Asterisk (*) and **bold** indicates significant results at the 1% level (significance threshold post-Bonferroni correction)*

[€] Mann-Whitney U test comparing median z-score change across subgroups
[≠] Kruskal-Wallis test comparing median z-score change across subgroups

Table 6
Spearman's Rank correlation of age at diet onset/average protein intake with change in height z-score

Characteristic	**Correlation coefficient, sample size *(p-value)***			
	1 year	**2 years**	**3 years**	**1-year post-diet discontinuation**
Age at diet onset (months)	0.0410, n=139	0.435, n=86	0.501, n=27	0.398, n=33
p-value	*p= .041*	*P <.005**	*p= .008**	*p= .022*
Average daily protein intake at 1 year (g/kg)	-0.0100, n=82	n/a	n/a	n/a
p-value	*p= .929*			

Asterisk (*) indicates significant results at the 1% level (significance threshold post-Bonferroni correction)

There were no significant differences in weight z-score change at any timepoint across feeding method, ambulatory status, diet type, protein prescription or age at diet onset. Non-ambulatory children showed a greater height z-score decrease compared with ambulatory children at 2 years. There was also a significantly greater decrease in height z-score in individuals following a classical diet compared with modified diets at 2 years. Age at diet onset showed a significant positive correlation with change in height z-score at 2 and 3 years on diet.

4 Discussion

Our results showed a consistent decrease in linear growth in children for the first 3 years on KDT. Whilst there was no significant change in height z-score beyond the 3-year timepoint, the limited sample sizes may have contributed to this. However, with the exception of individuals with glucose transporter type 1 deficiency syndrome, discontinuation of KDT tends to be considered after 2 to 3 years in individuals with epilepsy and so any longer-term impact on growth may be less

clinically relevant. Linear growth did not appear to be affected 1-year after discontinuation of KDT, meaning there may be some element of ‘catch-up growth’.

There was no consistent impact of KDT on weight z-score, with only the 4- and 6-year timepoints showing significant change from baseline. However, it is important to note that due to the small sample size at 4 years and beyond, there are limited conclusions that can be drawn from these timepoints. Energy intake on KDT is carefully calculated and monitored by specialist dietitians, ensuring daily requirements are met and weight trajectories followed. In some previous studies, calorie intake was restricted to 75% of daily requirements (Vining et al., 2002) and/or KDT prescriptions that accounted for pre-existing poor or excessive weight gain were not excluded (Neal et al., 2008; Vining et al., 2002), unlike in our cohort, which perhaps accounts for varying conclusions. There may be a greater likelihood of weight being impacted by KDT when followed for prolonged periods, although further research with larger sample sizes and long-term follow-up is required.

Our findings that linear growth may be adversely impacted in the first few years on diet, but not in the longer-term (particularly post-diet), is consistent with other published literature. Kim et al. (2013) reported no significant change in height or weight percentile 1-year after diet discontinuation, despite significant reduction in height and weight whilst on the diets. Despite this, the study did report a significant decrease in height and weight percentile 1-year post-diet in younger children (under 3 years). There was a similar trend in our study, with younger children more adversely impacted in terms of linear growth compared with older children at 1-year post-diet, although these results did not meet the significance threshold after

Bonferroni-correction. It is therefore possible that catch-up growth may not occur to the same extent as in older children, at least during the first year after stopping KDT, although further prospective studies and larger sample sizes with long-term follow-up are indicated to explore this. We did, however, identify significantly reduced linear growth in younger children at 2 and 3 years on diet. This is supported by Neal et al. (2008) and Vining et al. (2002), suggesting that linear growth may be more impacted in those who are started on KDT at a younger age, particularly when following the diet for a prolonged period of time.

Individuals following modified ketogenic diets were less negatively affected in terms of linear growth compared with those on classical diets at 2 years. There was a similar trend between classical and modified diets and the MCT and modified diets at 1 year, although these results did not meet the significance threshold after Bonferroni-correction. Modified ketogenic diets may impact height to a lesser extent, perhaps due to typically less measurement or restriction of protein compared to the more traditional KDT types (Martin-McGill et al., 2019).

We found non-ambulatory children to have a greater height z-score decrease compared with ambulatory children at 2 years on diet, perhaps due to the inherent limitations in bone turnover and bone accrual, but this association was not found at other timepoints. This finding may also be related to the inherent difficulties in accurately measuring non-ambulatory children's height, as well as potentially increased incidence of hip dislocation and spine curvature (either diagnosed or undiagnosed). Ambulatory children have been previously reported to have a more significant decrease in height z-score at 1 year on KDT, although the mean gradient

of the line of best fit for serial z-scores was not significantly different in ambulatory versus non-ambulatory groups (Neal et al., 2008).

Other clinical and demographic variables showed a trend for association with decreased height or weight z-scores but did not consistently meet the Bonferroni-corrected significance threshold over time. The conservative nature of the Bonferroni correction means that potential associations should not be discounted but, at least, associations with a large, clinically relevant effect were not found in our cohort.

The main limitation of this study is the retrospective data collection. With the exception of children with glucose transporter type 1 deficiency syndrome, discontinuation of KDT is often considered after 2 to 3 years, so sample sizes were further minimised at later timepoints, and missing data were particularly common for height measurements. As previously mentioned, the sample sizes for the timepoints 4 years and onwards were very small, with only 1 individual having height measurements at 7 years and weight measurements at 8 years. This means the value of the conclusions drawn from this is very limited, and the significant change in weight at 4 and 6 years needs to be interpreted with great caution. However, further study with larger sample sizes at these later timepoints would be indicated to identify any impact on growth that may be related with increased time on diet. Anthropometric measurements were not standardised, with height and weight often taken being taken in the community. Similarly, as well as being highly tailored to the individual, the way in which KDT is implemented and which particular diet is selected varies between centres. Other factors that were not recorded may also impact growth, such as level of ketosis, ASMs pre-diet or on-diet and vitamin D status. The

latter is important as enzyme-inducing ASMs have been shown to be related to vitamin D deficiency, potentially due to increased vitamin D metabolism via CYP450 enzyme induction (Menninga et al., 2020). As the median number of ASMs our cohort had trialled was 4, this could have affected growth and was not accounted for. Furthermore, underlying diagnoses such as metabolic bone diseases and genetic conditions that may impact fuel metabolism and nutritional status, and predispose to short stature,were not factored in.Eschbach et al. (2017) demonstrated altered hormones (insulin-like growth factor 1 and testosterone) in children with Dravet syndrome, as well as reduced height and weight growth patterns. This may also be contributing to reduced growth and has not been considered in our study.

5 Conclusion

Linear growth may be impacted in children on KDT up to 3 years on diet, although catch-up growth may occur post-diet as suggested in our cohort, with no significant change in height z-score from baseline 1 year after diet discontinuation. Younger children may be more vulnerable to impacted linear growth, with a potential lasting effect 1-year after diet discontinuation, although this needs exploration with wider collaboration to generate larger sample sizes with longer-term follow-up. Where appropriate, modified ketogenic diets may be considered in place of more traditional KDT types, particularly for those with pre-existing growth problems or who are at risk of impacted growth. The potential impact of KDT on linear growth should be discussed with individuals with epilepsy considering KDT and included as a factor when deciding how long to stay on KDT, particularly in younger children and those following more traditional KDT types.

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Declaration of interest

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