OPEN ACCESS

University of Dundee

University of Dundee

Tolerance, adherence, and acceptability of a ketogenic 2.5:1 ratio, nutritionally complete, medium chain triglyceride-containing liquid feed in children and adults with drug-resistant epilepsy following a ketogenic diet

Griffen, Corbin; Schoeler, Natasha E.; Browne, Robert; Cameron, Tracy; Kirkpatrick, Martin; Thowfeek, Seema

Published in:
Epilepsia Open

DOI:
10.1002/epi4.12910

Publication date:
2024

Licence:
CC BY-NC-ND

Document Version
Publisher's PDF, also known as Version of record

Link to publication in Discovery Research Portal

Citation for published version (APA):
Griffen, C., Schoeler, N. E., Browne, R., Cameron, T., Kirkpatrick, M., Thowfeek, S., Munn, J., Champion, H., Mills, N., Phillips, S., Air, L., Devlin, A., Nicol, C., Macfarlane, S., Bittle, V., Thomas, P., Cooke, L., Ackril, J., Allford, A., ... Stratton, R. J. (2024). Tolerance, adherence, and acceptability of a ketogenic 2.5:1 ratio, nutritionally complete, medium chain triglyceride-containing liquid feed in children and adults with drug-resistant epilepsy following a ketogenic diet. *Epilepsia Open*, *9*(2), 727-738. https://doi.org/10.1002/epi4.12910

General rights
Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 04. Jul. 2024

Check for updates

Received: 17 November 2023 | Revised: 22 January 2024 | Accepted: 23 January 2024

DOI: 10.1002/epi4.12910

Epilepsia Open® Open Access

ORIGINAL ARTICLE

Tolerance, adherence, and acceptability of a ketogenic 2.5:1 ratio, nutritionally complete, medium chain triglyceride-containing liquid feed in children and adults with drug-resistant epilepsy following a ketogenic diet

Corbin Griffen[1] | Natasha E. Schoeler[2,3] | Robert Browne[1] | Tracy Cameron[4,5] | Martin Kirkpatrick[4] | Seema Thowfeek[6] | Judith Munn[6] | Helena Champion[7] | Nicole Mills[7] | Siân Phillips[8] | Linda Air[9] | Anita Devlin[9] | Claire Nicol[9] | Susan Macfarlane[4] | Victoria Bittle[10] | Phillipa Thomas[10] | Lisa Cooke[10] | Julia Ackril[11] | Astrid Allford[11] | Vanessa Appleyard[11] | Clare Szwec[1] | Kiranjit Atwal[12] | Gary P. Hubbard[1] | Rebecca J. Stratton[1,13]

[1]Clinical Research, Nutricia Ltd., Trowbridge, UK

[2]UCL Great Ormond Street Institute of Child Health, London, UK

[3]Great Ormond Street Hospital for Children, London, UK

[4]Tayside Children's Hospital, Dundee, UK

[5]Royal Aberdeen Children's Hospital, Aberdeen, UK

[6]The Barberry, Birmingham and Solihull Mental Health NHS Foundation Trust, Birmingham, UK

[7]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[8]Southampton Children's Hospital, Southampton General Hospital, Southampton, UK

[9]Great North Children's Hospital, Newcastle Upon Tyne, UK

[10]Bristol Royal Hospital for Children, Bristol, UK

[11]Birmingham Women's and Children's NHS Trust, Birmingham, UK

[12]Independent Researcher, Phoenix, Arizona, USA

[13]University of Southampton, Southampton, UK

Abstract

Objective: To investigate incorporating a ready-to-use 2.5:1 ratio liquid feed into a ketogenic diet (KD) in children and adults with drug-resistant epilepsy.

Methods: Following a three-day baseline, patients ($n = 19$; age: 19 years [SD 13], range: 8–46 years) followed a KD for 28 days (control period), then incorporated ≥200 mL/day of a ready-to-use liquid feed, made with a ratio of 2.5 g of fat to 1 g of protein plus carbohydrate and including medium chain triglycerides ([MCTs]; 25.6% of total fat/100 mL) for 28 days as part of their KD (intervention period). Outcome measures (control vs intervention period) included gastrointestinal (GI) tolerance, adherence to KD and intervention feed, dietary intake, blood ß-hydroxybutyrate (BHB) concentration, seizure outcomes, health-related quality of life (HRQoL), acceptability and safety.

Results: Compared to the control period, during the intervention period, the percentage of patients reporting no GI symptoms increased (+5% [SD 5], $p = 0.02$); adherence to the KD prescription was similar ($p = 0.92$) but higher in patients ($n = 5$) with poor adherence (<50%) to KD during the control period (+33% [SD 26], $p = 0.049$); total MCT intake increased (+12.1 g/day [SD 14.0], $p = 0.002$), driven by increases in octanoic (C8; +8.3 g/day [SD 6.4], $p < 0.001$) and decanoic acid (C10; +5.4 g/day [SD 5.4], $p < 0.001$); KD ratio decreased ($p = 0.047$), driven by a nonsignificant increase in protein intake (+11 g/day [SD 44], $p = 0.29$); seizure outcomes were similar ($p \geq 0.63$) but improved in patients ($n = 6$) with the worst seizure outcomes during the control period ($p = 0.04$); and HRQoL

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2024 Nutricia Ltd. *Epilepsia Open* published by Wiley Periodicals LLC on behalf of International League Against Epilepsy.

Correspondence
Gary P. Hubbard, Clinical Research, Nutricia Ltd., Trowbridge, UK.
Email: gary.hubbard@nutricia.com

Funding information
Nutricia Ltd.

outcomes were similar. The intervention feed was well adhered to (96% [SD 8]) and accepted (≥88% of patients confirmed).

Significance: These findings provide an evidence-base to support the effective management of children and adults with drug-resistant epilepsy following a KD with the use of a ready-to-use, nutritionally complete, 2.5:1 ratio feed including MCTs.

Plain language summary: This study examined the use of a ready-to-use, nutritionally complete, 2.5:1 ratio (2.5 g of fat to 1 g of protein plus carbohydrate) liquid feed, including medium chain triglycerides (MCTs), into a ketogenic diet (KD) in children and adults with drug-resistant epilepsy. The results show that the 2.5:1 ratio feed was well tolerated, adhered to, and accepted in these patients. Increases in MCT intake (particularly C8 and C10) and improvements in seizure outcomes (reduced seizure burden and intensity) and KD adherence also occurred with the 2.5:1 ratio feed in patients with the worst seizures and adherence, respectively.

KEYWORDS
enteral feed, gastrointestinal tolerance, ketogenic diet, medium chain triglycerides, seizures

1 | INTRODUCTION

Ketogenic diets (KDs), a group of low-carbohydrate, high-fat, adequate protein diets that mimic the state of starvation, offer a nonpharmacological dietary alternative treatment option for patients with drug-resistant epilepsy.[1] KDs are recommended in the National Institute for Health and Care Excellence (NICE) guidelines [NG217] for consideration in children with 'certain childhood-onset epilepsy syndromes' and with 'drug-resistant epilepsy if other treatment options have been unsuccessful or are not appropriate'[2] and are used worldwide.[3]

There are different variants of the KD, such as the classical KD (CKD), medium chain triglyceride KD (MCT KD), and modified KDs (MKD).[1] The CKD is high in long chain triglyceride (LCT) fat and provides a specific ratio of fat to carbohydrate plus protein, usually up to a maximum of 4:1.[1] Due to the restrictiveness of the CKD, the MCT KD was designed in the 1970s[4] to allow individuals greater freedom with protein and carbohydrate intake and a lower fat intake, as MCTs yield more ketones per kcal than LCT fats.[5] Modified KDs, where carbohydrate intake is restricted to ~5% total energy or 10–20 g/day,[6] also aim to provide increased flexibility and palatability, with no restrictions on protein. More recently, a 2.5:1 ratio KD, which allows for higher intakes of protein to more easily meet requirements without a further restriction of carbohydrate intake, has been shown to be as efficacious as higher KD ratios in some patient groups, particularly younger children.[7]

Key points

- A 2.5:1 ratio feed including MCTs as part of a KD is well tolerated, adhered to and accepted in patients with drug-resistant epilepsy.
- The 2.5:1 ratio feed increased patients' MCT intake (particularly C8 and C10).
- The 2.5:1 ratio feed improved seizure outcomes (reduced seizure burden and intensity) and KD adherence in patients with the worst seizures and poorest adherence, respectively.
- The 2.5:1 ratio feed decreased patients' KD ratio, allowing for a higher protein intake.

While the abovementioned variants of the KD have been reported to be clinically effective in the dietary management of drug-resistance epilepsy,[8,9] with high effectiveness (≥50% reduction in seizures in 30–60% of children[9]), following such diets can be challenging, with low adherence (~45%) cited.[9,10] Poor adherence is often linked to psychosocial factors or the restrictiveness of the diet,[11] or related gastrointestinal (GI) side effects, particularly constipation.[12,13] Nutritional therapies that are clinically effective, improve KD adherence and are well tolerated are therefore essential.

There are a number of multinutrient medical nutritional feeds available for use as part of KDs. These include

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ep4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

powdered or liquid feeds providing either a 3:1 or 4:1 ratio of grams of fat to grams of carbohydrate plus protein and also modular feeds such as MCT emulsions. These feeds have been developed for children following a KD to provide variety and convenience, support adherence, and to help ensure nutritional needs are met. However, before now, there were no nutritionally complete feeds available which were suitable for older children, adolescents, and adults, despite the increasing use of KDs to manage drug-resistant epilepsy in these groups.[14,15] There is also a growing interest in MCTs, particularly octanoic (C8) and decanoic (C10) acids into medical feeds for drug-resistance epilepsy due to an increasing evidence of their antiseizure effects.[16] Consequently, a ready-to-use, 2.5:1 ratio, nutritionally complete liquid feed including MCTs (25.6% of total fat) has been developed, suitable for children from 8+ years, adolescents and adults as a sole source of nutrition or as a supplementary feed, and can be used as part of any of the variant forms of the KD.

This study aimed to assess GI tolerance (primary outcome), adherence, dietary intake, blood ketone (ß-hydroxybutyrate; BHB) concentration, seizure outcomes (frequency, intensity and burden), health-related quality of life (HRQoL), acceptability, anthropometrics, patient-specific study goals(s), and safety of a ready-to-use, 2.5:1 ratio, nutritionally complete liquid feed including MCTs when used as part of a KD in individuals aged 8+ years with drug-resistant epilepsy.

2 | MATERIALS AND METHODS

2.1 | Patients

Individuals were screened against an eligibility criteria (see Supplementary Materials S1) and recruited by Ketogenic Dietitians from 9 healthcare centres in the United Kingdom. All patients (or parents/carers, where applicable) provided written informed consent.

2.2 | Study design and ethics

This was a prospective, multicentre, single-arm pilot intervention study. The study was reviewed and approved by a UK National Health Service (NHS) Research Ethics Committee (South Central—Hampshire A Research Ethics Committee; reference number: 16/SC/0530) and was registered at clinicaltrials.gov as NCT03196271.

The study consisted of 3 phases: a baseline period, a control period, and an intervention period (Figure 1). After a 3-day baseline period where patients continued their usual diet (either KD or regular diet) and baseline data were collected, patients entered a 28-day control period. During this time, patients who were already following a KD continued their current KD and patients who had not yet started a KD were established on an appropriate KD by their Dietitian. Immediately following the 28-day control period, each patient incorporated at least 200 mL/day of a ready-to-use, nutritionally complete, vanilla flavor liquid feed (KetoCal 2.5:1 LQ; Nutricia Ltd., UK) into their KD for a further 28 days (intervention period). The intervention feed provided a 2.5:1 ratio of grams of fat (84% total energy) to carbohydrate (3% total energy) plus protein (12% total energy) and contained MCTs (contributing 25.6% of total fat and 19.5% total energy), fiber (1% of total energy), vitamins, and minerals (see Table S1 for nutritional composition). The appropriate feed prescription was determined on a per patient basis by the Dietitian responsible for the patient's nutritional management, based on their clinical requirements and preference. Patients could take the feed as a sole source of nutrition or as a supplementary feed, either orally or via an enteral feeding tube (the latter only for patients who were enterally tube fed at

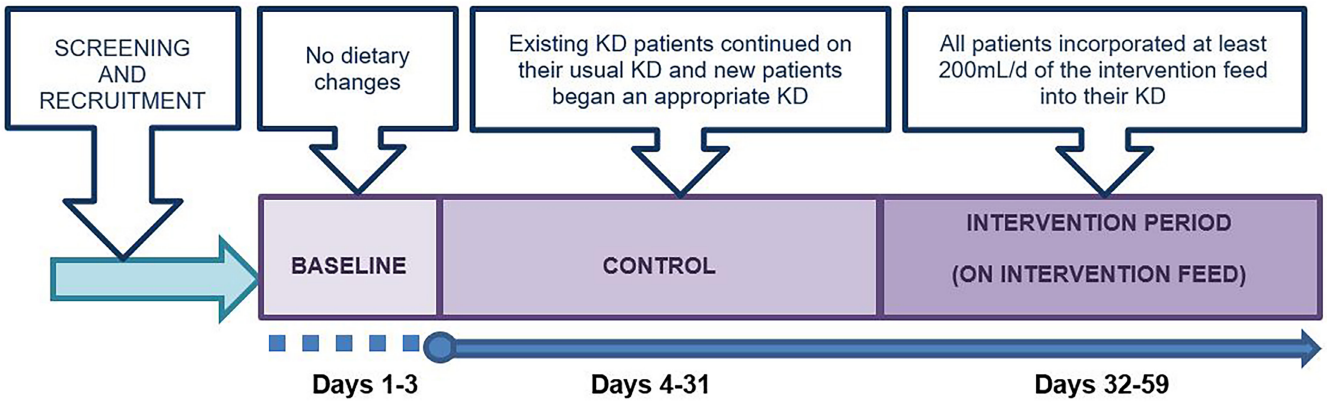

FIGURE 1 Schematic of the trial design.

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/epi4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

baseline), depending on their nutritional requirements and mode of feeding.

2.3 | Gastrointestinal tolerance

GI symptoms (diarrhea, constipation, nausea, vomiting, abdominal discomfort or pain, bloating, flatulence, and burping) and severity rating (none, mild, moderate, or severe) were recorded on the final day of the control and intervention periods using a standardized GI tolerance questionnaire, which was completed by the patient and/or their parent/carer. Patients and/or their parent/carer and Dietitians were also asked at the end of the study to record if they were satisfied with their/the patient's tolerance of the intervention feed.

2.4 | Adherence

Adherence with the KD prescription during the control and intervention periods was assessed by comparing the percentage difference in ratio of fat to carbohydrate plus protein intake from 24-h dietary recalls, to that prescribed by the patient's Dietitian, or percentage difference in carbohydrate for patients on a MKD. Adherence with the intervention feed (mean daily percentage over the intervention period) was determined as the volume of intake (recorded daily by the patient and/or their parent/carer) relative to the amount prescribed by the Dietitian.

2.5 | Dietary intake

Dietary intake (including all food, drink, and medical foods, including the intervention feed) was recorded at the end of the control and intervention periods by the dietitian, using 24-h dietary recalls. Data were analyzed for assessment of total energy, fat (including MCT), carbohydrate and protein intakes, fiber, KD ratio (ratio of grams of fat to carbohydrate plus protein), and the overall contribution of the intervention feed to total macronutrient intake using Nutritics (v5.026 Research Edition, Dublin).

2.6 | Blood ß-hydroxybutyrate concentration, seizure outcomes, and health-related quality of life

Blood BHB concentration was measured upon waking and in the evenings of the final 3 days of the control and intervention periods by a capillary blood sample, taken by the patient or their parent/carer using a home blood ketone monitor (Freestyle Optimum Neo, Abbott Laboratories, Berkshire, UK). Mean morning and evening blood BHB concentrations were calculated over the 3 days during the control and intervention periods.

HRQoL was assessed on the last day of the control and intervention periods with a 7-point Likert scale questionnaire (see Table S2). A composite HRQoL score was calculated by summing the scores of all HRQoL outcomes for each patient divided by the number of HRQoL outcomes.

The number of seizures (for all seizure types) was recorded daily throughout the control and intervention periods by patients and/or their parents/carer. At the end of each week, patients and/or their parent/carer were also asked to rate on a 7-point Likert scale (ranging from: 1 = not at all/very mild; 4 = moderate; 7 = severe/a lot) how intense the patient's seizures had been (seizure intensity) and how much their seizures had bothered them (seizure burden). Each seizure outcome was analyzed separately, and individual scores were also transformed into z-scores ((value-mean)/standard deviation (SD)) using the mean and SD of the total sample at baseline as the reference population. Individual seizure z-scores were clustered into a composite score using the following equation: $Z_{\text{seizure number}} + Z_{\text{seiure intensity}} + Z_{\text{seizure burden}}/3$.

2.7 | Acceptability

Patients and/or their parent/carer completed a questionnaire at the end of the intervention period to indicate their acceptability of the intervention feed (5-point Likert scale: Strongly Agree, Agree, Don't Know, Disagree, Strongly Disagree, to indicate: ease of use, ease of taking the full amount, whether the feed fitted into their routine, enjoyment of the taste, overall liking, and if taking the intervention feed made it easier to follow their prescribed KD).

2.8 | Anthropometry

At the end of the control and intervention periods, body weight and height were measured by the Dietitian using standard methods.

2.9 | Dietetic goals

During the baseline period, the dietitian recorded KD and intervention feed goal(s), which were set individually and

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/epi4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

could relate to overall tolerance, adherence, liking, acceptability, seizure control, blood BHB concentration, or any other goal the Dietitian felt was suitable. At the end of the study, the Dietitian indicated whether these goals had been met (via Yes/No response).

2.10 | Safety

Adverse (AEs) and serious adverse events (SAEs) were recorded throughout the study by Dietitians to assess potential safety issues related to the KD and the intervention feed. For all AEs, information regarding the intensity (mild, moderate, or severe) and potential relatedness (definitely related, possibly related, or not related) to the KD and/or intervention feed was recorded.

2.11 | Statistics

The complexity and paucity of data from studies of similar feeds rendered an a priori power calculation difficult. As such, a sample size calculation was not conducted for this study. Nevertheless, post hoc analysis using the effect size obtained from the primary outcome measure, percentage of patients reporting absent GI symptoms (Cohen's $d = 1.0$), revealed the sample size achieved in this study ($n = 19$) had sufficient statistical power ($\beta = 0.98$) to detect a minimal detectable statistically significant difference ($p < 0.05$) of 2.5% between the control and intervention periods. The sample size of this study is also consistent with prior studies that investigated the tolerability of KD in patients with drug-resistant epilepsy.[17–19]

Statistical analysis was performed on a per-protocol (PP) basis using SPSS v27 (IBM Corp., New York, USA). Although not planned in the original study protocol, to reduce any risk of bias, an intention-to-treat (ITT) analysis was performed for all patients who started the intervention period for the outcomes GI tolerance, intervention feed adherence and acceptability, and safety. For the ITT analysis, outcomes were collected on each patient's final day of the study. Data were checked for normality using the Shapiro–Wilk test. Paired samples t-tests were used for comparisons of two time points (control vs intervention period). For nonparametric data relating to changes over time, the Wilcoxon Signed-rank test was used. Exploratory subanalyses were also conducted (e.g., tertile analyses) on certain outcomes. Post hoc correlation analysis was performed on the prescribed volume of the intervention feed and changes in outcomes from the end of the control to the end of the intervention period using Pearson's correlation. Statistical significance was accepted as $p < 0.05$. Data are presented as means (SD) unless stated otherwise.

3 | RESULTS

3.1 | Recruitment and patient characteristics

Twenty-six patients met the eligibility criteria and consented to participate. Nineteen patients completed the full 59-day study period, and seven patients either withdrew or were withdrawn from the trial (see Figure S1 for patient flow and reasons for withdrawal). Consequently, 19 patients were included in the PP analysis and 25 patients were included in the ITT analysis of GI tolerance, intervention feed adherence and acceptability, and safety.

Baseline characteristics of the 19 patients ($n = 10$ male, $n = 9$ female; age: 19 years [SD 12.9]; range: 8–46 years) who completed the study are shown in Table 1. Most patients ($n = 17$) were already following a KD at the time of recruitment, the majority ($n = 13$) for a duration of ≥6 months. Sixteen of these patients remained on their prescribed baseline KD during the study. Whilst 2 patients were not following a KD at the time of recruitment, analysis excluding these patients (data not reported for each outcome) did not alter statistical interpretation of outcomes. During the study, 11 patients were prescribed an MKD and eight patients were prescribed a CKD with ratios between 2.75:1 and 4:1. No changes to any patients' KD or intervention feed prescription occurred during the intervention period.

3.2 | Gastrointestinal tolerance

Most GI symptoms were absent during the control period (PP: 81% (SD 10); ITT: 84% (SD 8) of patients across all GI symptoms) with a few occurrences of mild–moderate symptoms reported (5–13% of patients across all GI symptoms for both PP and ITT analyses). Two incidences of severe symptoms ($n = 1$ patient: bloating and $n = 1$ patient: constipation) were reported during the control period. No significant differences occurred during the intervention compared to the control period for any individual GI symptom (PP: $p > 0.32$; ITT: $p > 0.25$). Likewise, across all GI symptoms pooled, no significant differences in the percentage of patients reporting mild, moderate, or severe symptoms occurred between the control and intervention periods ($p > 0.68$). Percentage of patients reporting absent symptoms significantly increased by 5% (SD 5, $p = 0.02$, Figure 2)

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/epi4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Baseline characteristics of patients who completed the study ($n = 19$).

Patient #	Age (years)	Sex	Weight (kg)	Seizure frequency (*n*/day)	Primary diagnosis	On a KD diet prior to the study (yes/no)	Prescribed KD	Intervention feed prescription (mL/day [route])
1	13	Male	44.0	12	Cerebral palsy with severe learning disability	Yes	3:1 CKD	800 (enteral tube)
2	10	Male	33.1	8	Juvenile Batten Disease	Yes	3.5:1 CKD with added MCT	565 (enteral tube)
3	10	Female	30.1	1	Lissencephaly – Deletion of exons 2–11 on LISI gene	Yes	CKD	690 (enteral tube)
4	8	Male	30.5	1	Epilepsy – No specific syndrome classification	Yes	CKD	750 (enteral tube)
5	9	Female	26.7	–[a]	Dyskinetic cerebral palsy	Yes	3.5:1 CKD with added MCT	565 (enteral tube)
6	8	Male	27.0	6	Drug-resistant epilepsy secondary to bilateral lissencephaly	Yes	MKD	600 (enteral tube)
7	9	Male	25.3	7	Cerebral palsy	Yes	3.2:1 CKD	795 (enteral tube)
8	16	Male	67.1	2	Quadriplegic cerebral palsy	Yes	4:1 CKD with added MCT + protein	900 (enteral tube)
9	9	Female	30.3	0	GLUT1 deficiency syndrome	Yes	2.75:1 CKD	200 (oral)
10	14	Male	64.7	10	Absence epilepsy with perioral myoclonia and generalized tonic–clonic seizures	Yes	MKD with added MCT	200 (oral)
11	16	Female	41.7	1	Epilepsy – No specific syndrome classification	Yes	MKD	400 (oral)
12	43	Female	53.9	1	Localisation-related epilepsy	Yes	MKD	200 (oral)
13	38	Male	79.5	0	Primary Generalized Epilepsy	Yes	MKD	200 (oral)
14	46	Female	70.5	0	Intractable Epilepsy	Yes	MKD	200 (oral)
15	17	Male	58.7	0	GLUT1 deficiency syndrome	Yes	MKD	200 (oral)
16	37	Male	93.6	1	Localisation-related epilepsy (temporal lobe epilepsy)	Yes	MKD	400 (oral)
17	29	Female	62.3	2	Drug-resistant epilepsy	Yes	MKD	400 (oral)
18	12	Female	55.9	–[a]	Structural focal frontal lobe epilepsy	No	MKD	200 (oral)
19	12	Female	40.8	75	Frontal lobe epilepsy	No	MKD	200 (oral)
	Mean (SD)	Total	Mean (SD)	Mean (SD)	Total	Total (Yes/No)	Total	Mean (SD) dose Total (route)
	19 (12.9)	Male (10) Female (9)	49.2 (20.1)	7 (18)	Epilepsy (11), Cerebral palsy (4), GLUT1 Deficiency yndrome (2), Juvenile Batten Disease (1), Lissencephaly (1)	17/2	MKD (11) CKD (8)	445 (252) 8 (Enteral tube) 11 (Oral)

Abbreviations: CKD, classical ketogenic diet; MCT, medium chain triglycerides; MKD, modified ketogenic diet.

[a]Missing data.

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/epi4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

between the control and intervention periods in the PP analysis, though remained unchanged in the ITT analysis ($p = 0.44$). Three severe symptoms of nausea and abdominal pain ($n = 1$ patient) and flatulence ($n = 1$ patient) were reported during the intervention period. Dietitians reported that patients tolerated the intervention feed as expected (PP: 100%; ITT: 92%) and patients (PP: 89%; ITT: 85%), confirmed by themselves or their parent/carer, strongly agreed or agreed that they tolerated the intervention feed well.

3.3 | Adherence

Adherence to the KD prescription during the control and intervention periods was similar (78% (SD 30) vs. 77% (SD 25), $p = 0.92$). In patients with adherence <50% to their prescribed KD during the control period ($n = 5$), adherence significantly increased during the intervention period (31% (SD 12) to 64% (SD 26), $p = 0.049$). Mean adherence to the intervention feed was high (PP: 96% (SD 8); ITT: 89% (SD 25)), with a mean prescribed intake of 445 mL/day (SD 252) and a mean actual intake of 422 mL/day (SD 264). Patients who received the feed via an enteral feeding tube ($n = 8$, of which $n = 2$ received as a sole source of nutrition) had a higher intake (708 mL/day [SD 124]) compared to those who consumed the feed orally ($n = 11$; 255 mL/day [SD 93], $p < 0.001$), although adherence was similar between the two groups ($p = 0.10$).

3.4 | Dietary intake

The intervention feed contributed 47% (SD 34) of patients' total energy intake. Intakes of total energy, fat, carbohydrate and fiber were similar during control and intervention periods ($p \geq 0.11$, Table 2), whereas total MCT, C8 and C10 intakes were significantly higher during the intervention period ($p \leq 0.002$). The KD ratio of patients significantly decreased during the intervention compared to the control period ($p = 0.047$, Figure 3). This was primarily driven by an 11 g/day (SD 44) increase in protein intake, albeit non-significant ($p = 0.29$).

3.5 | Blood ß-hydroxybutyrate concentration, seizure outcomes and health-related quality of life

Three-day mean morning and evening blood BHB concentrations were similar during the control (morning: 1.7 mmol/L (SD 1.4; range: 0.2–3.6 mmol/L); evening: 1.8 mmol/L (SD 1.6; range: 0.2–4.8 mmol/L)) and intervention periods (morning: 1.6 mmol/L (SD 1.3; range: 0.1–5.2 mmol/L); evening: 1.9 mmol/L (SD 1.4; range 0.2–4.3 mmol/L, $p > 0.84$)).

Seizure frequency ($p = 0.98$), intensity ($p = 0.63$) and burden ($p = 0.94$), and composite seizure z-score ($p = 0.74$) were similar during the control and intervention periods. Tertile analysis of patients ($n = 6$) with the lowest seizure z-score during the control period (i.e., patients with the worst seizure symptoms) showed that composite seizure z-score significantly improved during the intervention period compared to the control period ($p = 0.04$, Figure 4) in the absence of an increase in 3-day mean morning ($p = 0.78$) and evening blood BHB concentration ($p = 0.76$). This improvement was driven by reductions in seizure burden (−0.45 [SD 0.35] $p = 0.03$) and intensity (−0.43 [SD 0.48] $p = 0.08$) whilst seizure frequency remained unchanged ($p = 0.66$).

There were no significant differences in scores for any of the individual questions regarding HRQoL, or composite HRQoL score (Supplementary Table S2).

3.6 | Acceptability

Most patients agreed or strongly agreed that the intervention feed was easy to use (89%), easy to take the full amount (94%), fitted into their routine (94%), and liked overall (88%). Patients (50%) who orally consumed the intervention feed agreed or strongly agreed that they enjoyed the taste of the intervention feed. Patients (63%) agreed or strongly agreed that the intervention feed made following their prescribed KD easier.

3.7 | Anthropometry

Body weight and height were maintained during control and intervention periods ($p > 0.08$).

3.8 | Dietetic goals

The KD goals set by Dietitians during the baseline period (more than one goal may have been set per patient) were to: maintain or improve seizures ($n = 12$), improve non-seizure-related outcomes ($n = 3$), maintain or increase ketone concentration ($n = 6$), improve vitamin and mineral intake or meet nutritional requirements ($n = 3$), improve tolerance to KD ($n = 1$), continued growth development ($n = 1$), and improved HRQoL ($n = 1$). At the end of the study, 89% of patients' KD goals were met.

The Dietetic goals set by Dietitians relating to the use of the intervention feed included: tolerating the intervention

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/epi4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

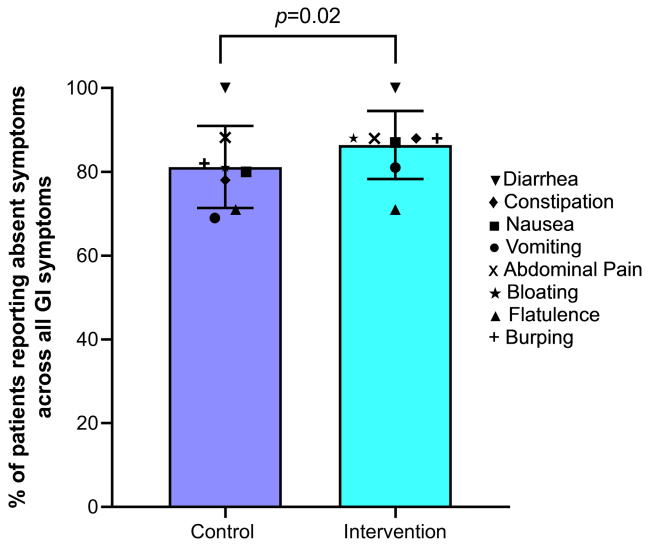

FIGURE 2 Percentage of patients reporting absent symptoms across all gastrointestinal (GI) symptoms during the control and intervention periods (means (SD), PP analysis ($n=19$)). Symbols represent mean value for respective symptom.

feed well ($n=4$), easy feed preparation, reduce time preparing meals, or to make the KD diet easier ($n=4$), improved convenience/variety ($n=3$), increased protein intake or reduced need for additional protein feeds ($n=1$), high compliance ($n=1$), and increased MCT intake ($n=5$). At the end of the study, 94% of patients' Dietetic goals relating to the use of the intervention feed were met.

3.9 | Safety

There were 11 AEs recorded throughout the study by eight patients ($n=3$ patients recorded 2 AEs each). Most AEs ($n=9$) were not related ($n=7$) or unlikely related ($n=2$) to the KD or intervention feed. One AE was classified as an SAE but unrelated to the KD or intervention feed (pneumonia, leading to hospital admission). Most AEs ($n=7$) were of either mild or moderate intensity. Two moderate intensity AEs ($n=1$: loose stools and $n=1$: GI upset) were recorded as highly probably related to the intervention feed and resulted in intervention feed discontinuation. Three AEs were classified as severe intensity ($n=1$ patient: first generalized and second tonic clonic seizures, and $n=1$ patient: nosebleed). These AEs were either not related or unlikely related to the KD or intervention feed.

3.10 | Correlation analysis

Significant positive correlations were observed between volume of prescribed intervention feed and changes in intakes of total MCTs ($r=0.67$, $p=0.003$), C8 ($r=0.73$, $p<0.001$), and C10 ($r=0.71$, $p<0.001$) between the control and intervention periods. A significant inverse correlation was observed for volume of prescribed intervention feed and change in seizure burden z-score ($r=-0.52$, $p=0.04$). No other significant correlations were observed.

TABLE 2 Daily total macronutrient intakes during the control and intervention periods (means (SD)).

	Control	Intervention	*p* value
Energy (kcal/day)	1663 (719)	1814 (920)	0.29
Carbohydrate (g/day)	17 (10)	21 (13)	0.11
Protein (g/day)	61 (46)	72 (53)	0.29
Fat (g/day)	149 (63)	160 (83)	0.38
Total MCTs (g/day)	12 (17)	24 (22)	0.002
C8 (g/day)	4.9 (8.9)	13.3 (12.9)	<0.001
C10 (g/day)	4.2 (6.7)	9.6 (9.4)	<0.001
Fiber (g/day)	13.8 (10.5)	13.0 (6.8)	0.66

Abbreviations: C8, octanoic acid; C10, decanoic acid; MCTs, medium chain triglycerides.

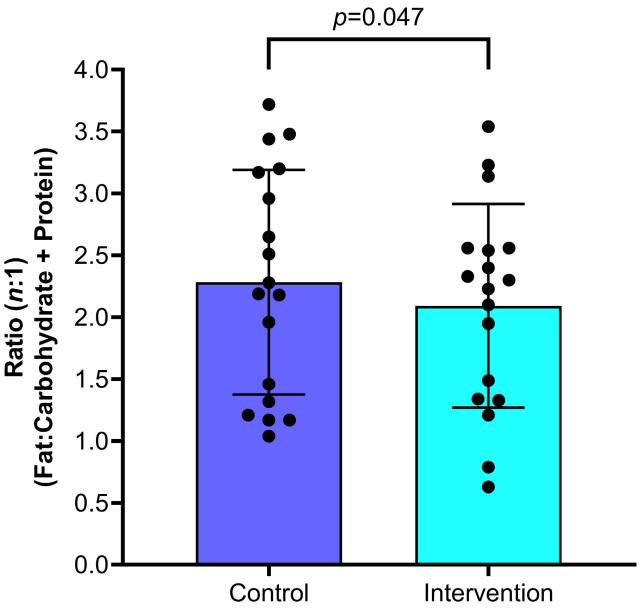

FIGURE 3 Ketogenic diet (KD) ratio (means (SD)) during the control and intervention periods. Circles represent individual patients.

4 | DISCUSSION

This prospective, multi-centre, single-arm pilot intervention study demonstrates that a ready-to-use, nutritionally complete, 2.5:1 ratio feed including MCTs as part of a KD (either a MKD or various ratios of a CKD) is well tolerated, highly adhered to and accepted in children and

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/epi4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

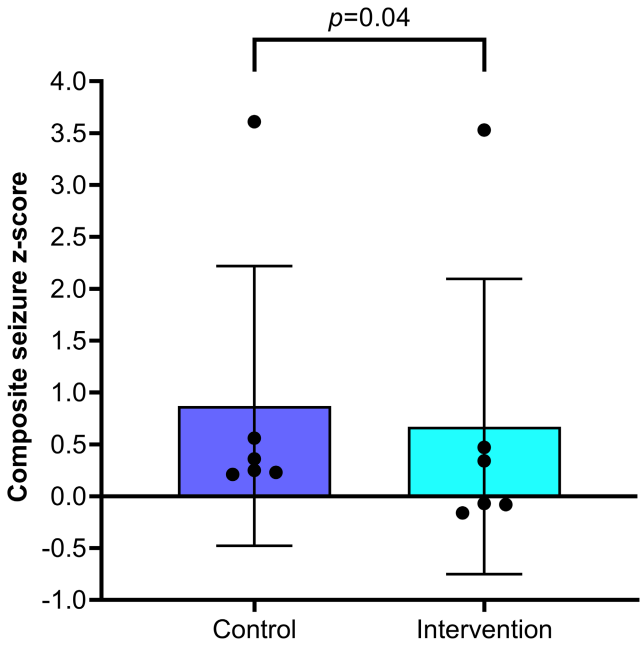

FIGURE 4 Tertile analysis of composite seizure z-score during the control and intervention periods (means (SD)) in patients ($n = 6$) with the lowest seizure z-score during the control period (i.e., patients with the worst seizure symptoms). Circles represent individual patients.

adults with drug-resistant epilepsy. This study also highlights that such a feed increases MCT intake (particularly C8 and C10), improves seizure outcomes and KD adherence in those with the worst seizures and poorest adherence, respectively, and decreases KD ratio, allowing for a higher protein intake to more easily meet the increased requirements of older children and adults without a further restriction of carbohydrate intake.

The majority of patients did not report any GI symptoms throughout the study; however, some patients reported GI symptoms with various levels of severity whilst on the KD during the control period, at a similar level to that report in both randomized controlled trials[13] and uncontrolled studies[12] of the KD, and in other studies of the use of nutritional support in various disease areas.[20–23] More absent symptoms were reported during the intervention period with the use of the 2.5:1 ratio feed compared to the control period. This is encouraging and was predominantly driven by the lower incidence of mild and moderate GI side effects. MCTs have been cited as having the potential to cause GI discomfort,[24] but have also been reported to be more easily digested and absorbed than LCTs.[25] Therefore, either the amount present in the 2.5:1 ratio intervention feed or its overall composition showed it to be well-tolerated compared to a 'usual' KD (which, for some patients, already contained some intake of MCTs). Constipation, the most commonly reported GI side effect of KDs,[12] was not particularly prevalent in this study and was reported slightly less (though not significantly) whilst patients took the 2.5:1 ratio feed compared to patients' control KD, despite similar fiber intakes during both study periods.

Adherence to the KD prescription was similar during the control and intervention periods (~78%) and higher than that previously reported in the literature (~45%).[9,10] This may be related to patients mostly being prescribed a lower KD ratio, therefore less restrictive than a 3:1 or 4:1 ratio KD, and/or the fact that patients in this study tolerated their KD well. Of importance, however, is the convenience of ready-to-use feeds such as the 2.5:1 ratio feed investigated in this study, as such a feed is likely to be particularly useful for patients at risk of (or with actual) poor adherence to a KD in the first place. This is confirmed in the present study by: the high compliance to the 2.5:1 ratio feed; the 63% of patients who agreed that the intervention feed made following their prescribed KD easier; and those patients who reported <50% adherence to their KD during the control period, who reported a 33% increase in adherence to their KD prescription with the 2.5:1 ratio intervention feed.

Although assessed over a relatively short period of time, the impact of the 2.5:1 ratio feed on nutritional intake is encouraging. The decrease in prescribed KD ratio caused by the 2.5:1 ratio feed was likely driven by the, albeit non-significant, increase in protein intake. An increase in protein intake may be of particular use when prescribing a KD for patients with low energy requirements, or children to support growth,[26] or older adults with increased protein requirements.[27–29]

The 2.5:1 ratio intervention feed elicited some positive impacts on seizures, particularly seizure burden and intensity, in patients with the worst seizure control on KD. Interestingly, a higher prescribed volume of the intervention feed also correlated with a reduction in seizure burden. The maintenance of response (or, for some patients, improvement in seizure outcomes) during the intervention period compared to the control period was observed despite similar blood BHB concentration and, except for a few isolated cases, below suggested therapeutic concentrations for infants and adults (2-6 mmol/L).[30,31] However, it is important to note that there is high individual variability in the therapeutic BHB concentration required for optimal seizure response, and some individuals achieve optimal seizure control with lower concentrations.[30] There is also uncertainty over the long-term correlation between blood BHB concentration and seizure reduction.[32,33] Consequently, we hypothesize that the improvements in seizure outcomes observed in certain patients may be due to improved adherence, potentially, the addition (or a different formulation) of MCTs. The evidence for a possible role of MCTs, specifically C8 and C10, in the anti-seizure effect of KDs has

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/epi4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

been growing over the past decade.[16] This is relevant not just for the MCT version of the KD, although there may be different mechanisms of action in different KD types and, indeed, in different patients.

Previous work has indicated that HRQoL is poor in patients with drug-resistant epilepsy.[34–36] Whilst a recent randomized-controlled trial (RCT) has shown for the first time that a KD may improve HRQoL compared to a habitual diet,[37] HRQoL of individuals with drug-resistance epilepsy following a KD is still generally poor.[38] In agreement, in this study, HRQoL reported by patients and/or their parent/carer during both the control and intervention periods was poor-to-fair. Interestingly, whilst not significant, the 2.5:1 ratio intervention feed did seem to improve the HRQoL of patients >16 years in employment, in particular, being able to work more.

Whilst the present study provides novel preliminary data and has several strengths, including the collection of an array of highly relevant outcomes in real-world, the study has limitations. These include using a design that was single-arm, non-randomized and without a control, the small sample size, and the short intervention period. Nevertheless, post-hoc analysis revealed the sample size was statistically powered to detect a significant difference in the primary outcome and other significant improvements in key outcomes were reported over this intervention period with this sample size, therefore providing essential evidence for future studies. Furthermore, standardized assessments of HRQoL and seizure outcomes were not used, although this would be challenging in this complex, heterogeneous population. Due to the difficulties in obtaining seizure diary data in studies including patients with drug-resistant epilepsy and the limitations of taking seizure frequency as the sole indicator of treatment 'response', it is a strength of this study that an assessment of seizure burden and intensity was attempted. The potential reporting bias from 24 hr dietary recalls is well-documented, including under- and/or over-reporting,[39] particularly considering that patients or parents/carers were aware that their Dietitian could see what was recorded. Although such methodology allows for a community-based study with minimal invasiveness for patients and families, these pitfalls should be considered when interpreting nutritional intake data in this study.

In conclusion, these study findings provide an evidence-base to support the effective management of patients with drug-resistant epilepsy following a KD with the use of a ready-to-use, nutritionally complete, 2.5:1 ratio feed including MCTs, widening the repertoire of ketogenic feeds at Dietitians' disposal. As a convenient ready-to-use feed, it may be particularly of use for those in whom adherence to a KD may otherwise be challenging and/or for young patients and adults who do not require or want a higher KD ratio and have higher protein requirements. Furthermore, the study findings suggest that generally the KD is well tolerated, complied with and does not negatively impact HRQoL.

AUTHOR CONTRIBUTIONS

Conceptualisation, R.B., K.A., G.P.H., R.J.S.; methodology, R.B., K.A., G.P.H., R.J.S., C.S.; trial site management, R.B.; data collection, T.C., M.K., J.M., H.C., N.M., S.P., L.A., A.D., C.N., S.M., V.B., P.T., L.C., J.A., A.A., V.A.; writing—original draft preparation, C.G., N.S.; writing—review and editing, C.G., N.S., R.B., G.P.H., R.J.S.; funding acquisition, G.P.H. and R.J.S.; All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

The authors would like to thank all patients recruited to this study (and their families/carers) for their generous commitment, effort and understanding for the conduct of this trial. The authors would also like to thank Denise Hofman (Nutricia) and Rebecca Capener (Nutricia) for their support in reviewing the manuscript, and Rachel Ahmed (Cambridge University Hospitals NHS Foundation Trust) and Debbie Rice (Tayside Children's Hospital) for their support in data collection.

FUNDING INFORMATION

This research was supported by Nutricia Ltd.

CONFLICT OF INTEREST STATEMENT

C.G., R.B., C.S., G.P.H., R.J.S. are employees of Nutricia Ltd. K.A. is a former employee of Nutirica Ltd. N.S was previously supported for a research post by Vitaflo (International) Ltd, she has received grants from Nutricia Ltd., Vitaflo (International) Ltd. and Matthew's Friends Charity, and honoraria from Nutricia Ltd., Vitaflo (International) Ltd. and Dr Schaer. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the South Central – Hampshire A Research Ethics Committee (reference number: 16/SC/0530).

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/epi4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

INFORMED CONSENT

Informed consent was obtained from all subjects involved in the study.

ORCID

Corbin Griffen https://orcid.org/0000-0002-8269-1401
Natasha E. Schoeler https://orcid.org/0000-0001-6202-1497
Gary P. Hubbard https://orcid.org/0000-0001-6029-6446
Rebecca J. Stratton https://orcid.org/0000-0003-3811-3847

REFERENCES

1. Barzegar M, Afghan M, Tarmahi V, Behtari M, Rahimi Khamaneh S, Raeisi SJN. Ketogenic diet: overview, types, and possible anti-seizure mechanisms. Nutr Neurosci. 2021;24:307–16.
2. National Institue for Health and Care Excellence (NICE). Epilepsies in children, young people and adults. https://www.nice.org.uk/guidance/ng217. Accessed 23 Feb 2023
3. Kossoff EH, McGrogan JR. Worldwide use of the ketogenic diet. Epilepsia. 2005;46:280–9.
4. Huttenlocher PR, Wilbourn AJ, Signore JM. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. Neurology. 1971;21:1097–103.
5. Liu Y-M, Wang H-S. Medium-chain triglyceride ketogenic diet, an effective treatment for drug-resistant epilepsy and a comparison with other ketogenic diets. Biom J. 2013;36:9–15.
6. Martin-McGill KJ, Lambert BA, Whiteley VJ, Wood S, Neal EG, Simpson ZR, et al. Understanding the core principles of a modified ketogenic diet: a UK and Ireland perspective. J Hum Nutr Diet. 2019;32:385–90.
7. Raju KV, Gulati S, Kabra M, Agarwala A, Sharma S, Pandey RM, et al. Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study. Epilepsy Res. 2011;96:96–100.
8. Sondhi V, Agarwala A, Pandey RM, Chakrabarty B, Jauhari P, Lodha R, et al. Efficacy of ketogenic diet, modified atkins diet, and low glycemic index therapy diet among children with drug-resistant epilepsy: a randomized clinical trial. JAMA Pediatr. 2020;174:944–51.
9. Ye F, Li XJ, Jiang WL, Sun HB, Liu J. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. Neurology. 2015;11:26–31.
10. Payne NE, Cross JH, Sander JW, Sisodiya SMJE. The ketogenic and related diets in adolescents and adults—a review. Epilepsia. 2011;52:1941–8.
11. Nei M, Ngo L, Sirven JI, Sperling MR. Ketogenic diet in adolescents and adults with epilepsy. Seizure. 2014;23:439–42.
12. Cai QY, Zhou ZJ, Luo R, Gan J, Li SP, Mu DZ, et al. Safety and tolerability of the ketogenic diet used for the treatment of refractory childhood epilepsy: a systematic review of published prospective studies. World J Pediatr. 2017;13:528–36.
13. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020;6:CD001903.
14. Zarnowska IM. Therapeutic use of the ketogenic diet in refractory epilepsy: what we know and what still needs to be learned. Nutrients. 2020;12:2616.
15. Operto FF, Labate A, Aiello S, Perillo C, de Simone V, Rinaldi R, et al. The ketogenic diet in children with epilepsy: a focus on parental stress and family compliance. Nutrients. 2023;15:1058.
16. Augustin K, Khabbush A, Williams S, Eaton S, Orford M, Cross JH, et al. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. Lancet Neurol. 2018;17:84–93.
17. Seo JH, Lee YM, Lee JS, Kang HC, Kim HD. Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios – comparison of 3:1 with 4:1 diet. Epilepsia. 2007;48:801–5.
18. El-Rashidy OF, Nassar MF, Hamid IA, Shatla RH, Hamid MH, Gabr SS. Modified Atkins diet vs classic ketogenic formula in intractable epilepsy. Acta Neurol Scand. 2013;128:402–8.
19. Lambrechts DA, Wielders LH, Aldenkamp AP, Kessels FG, de Kinderen RJ, Majoie MJ. The ketogenic diet as a treatment option in adults with chronic refractory epilepsy: efficacy and tolerability in clinical practice. Epilepsy Behav. 2012;23:310–4.
20. Griffen C, Delsoglio M, Syed R, Cookson T, Saliba H, Vowles A, et al. A ready to drink, plant-based oral nutritional supplement is highly complied with, palatable and tolerated in community-based patients at risk of disease-related malnutrition. Clinical Nutrition ESPEN. 2023;54:706.
21. Green BP, Wong E, Andrews S, Hampshire-Jones K, McKinnon S, Brooks C, et al. Increased protein intake is associated with improved hand grip strength and quality of life in home enterally tube fed adults using a high-energy, high-protein feed. Clinical Nutrition ESPEN. 2020;35:208.
22. Hubbard GP, Fry C, Sorensen K, Casewell C, Collins L, Cunjamalay A, et al. Energy-dense, low-volume paediatric oral nutritional supplements improve total nutrient intake and increase growth in paediatric patients requiring nutritional support: results of a randomised controlled pilot trial. Eur J Pediatr. 2020;179:1–10.
23. Delsoglio M, Griffen C, Syed R, Cookson T, Saliba H, Vowles A, et al. A multi-centre prospective study of plant-based nutritional support in adult community-based patients at risk of disease-related malnutrition. Front Nutr. 2023;10:1297624.
24. Liu YM, Wang HS. Medium-chain triglyceride ketogenic diet, an effective treatment for drug-resistant epilepsy and a comparison with other ketogenic diets. Biom J. 2013;36:9–15.
25. Muscaritoli M, Pradelli LJ. Medium-chain triglyceride (MCT) content of adult enteral tube feeding formulas and clinical outcomes. A systematic review. Front Nutr. 2021;8:697529.
26. Switkowski KM, Jacques PF, Must A, Fleisch A, Oken EJ. Associations of protein intake in early childhood with body composition, height, and insulin-like growth factor I in mid-childhood and early adolescence. Am J Clin Nutr. 2019;109:1154–63.
27. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN expert group. Clin Nutr. 2014;33:929–36.
28. Griffen C, Duncan M, Hattersley J, Weickert MO, Dallaway A, Renshaw D. Effects of resistance exercise and whey protein supplementation on skeletal muscle strength, mass, physical function, and hormonal and inflammatory biomarkers in

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ep4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

healthy active older men: a randomised, double-blind, placebo-controlled trial. Exp Gerontol. 2022;158:111651.
29. Griffen C, Renshaw D, Duncan M, Weickert MO, Hattersley J. Changes in 24-h energy expenditure, substrate oxidation, and body composition following resistance exercise and a high protein diet via whey protein supplementation in healthy older men. Physiol Rep. 2022;10:e15268.
30. Schoeler NE, Cross JH. Ketogenic dietary therapies in adults with epilepsy: a practical guide. Pract Neurol. 2016;16:208–14.
31. van der Louw E, van den Hurk D, Neal E, Leiendecker B, Fitzsimmon G, Dority L, et al. Ketogenic diet guidelines for infants with refractory epilepsy. Eur J Paediatr Neurol. 2016;20:798–809.
32. van Delft R, Lambrechts D, Verschuure P, Hulsman J, Majoie M. Blood beta-hydroxybutyrate correlates better with seizure reduction due to ketogenic diet than do ketones in the urine. Seizure. 2010;19:36–9.
33. Schoeler NE, Cross JH, Sander JW, Sisodiya SM. Can we predict a favourable response to ketogenic diet therapies for drug-resistant epilepsy? Epilepsy Res. 2013;106:1–16.
34. Akdemir V, Sut N, Godlike B. Factors affecting the quality of life in drug-resistant epilepsy patients. Acta Neurol Belg. 2016;116:513–8.
35. Lu H-H, Tsai C-Y, Chou I, Tsai J. The impact of parenting stress on parents of school-age children with drug-resistant epilepsy. Front Pediatr. 2022;10:948286.
36. Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. Epilepsia. 1997;38:353–62.
37. Kverneland M, Nakken KO, Hofoss D, Skogan AH, Iversen PO, Selmer KK, et al. Health-related quality of life in adults with drug-resistant focal epilepsy treated with modified Atkins diet in a randomized clinical trial. Epilepsia. 2023;64:e69–e74.
38. Sourbron J, Klinkenberg S, van Kuijk SM, Lagae L, Lambrechts D, Braakman HM, et al. Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis. Childs Nerv Syst. 2020;36:1099–109.
39. Beaton GH, Milner J, McGuire V, Feather TE, Little JA. Source of variance in 24-hour dietary recall data: implications for nutrition study design and interpretation. Carbohydrate sources, vitamins, and minerals. Am J Clin Nutr. 1983;37:986–95.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Griffen C, Schoeler NE, Browne R, Cameron T, Kirkpatrick M, Thowfeek S, et al. Tolerance, adherence, and acceptability of a ketogenic 2.5:1 ratio, nutritionally complete, medium chain triglyceride-containing liquid feed in children and adults with drug-resistant epilepsy following a ketogenic diet. Epilepsia Open. 2024;9:727–738. https://doi.org/10.1002/epi4.12910

24709239, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/epi4.12910 by University of Dundee, Wiley Online Library on [17/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License