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Review

Over twenty-five years of ketogenic diet therapy: Supporting children and adults with drug-resistant epilepsy using nutritionally complete ketogenic formulations: A scoping review

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ABSTRACT

Purpose: Ketogenic diet therapy (KDT) has been successfully used as an effective management option for drug resistant epilepsy (DRE) since the 1920 s. The ketogenic formulation studied here (KetoCal) is nutritionally complete, very high in fat, and low in carbohydrates and has played a crucial role in supporting the implementation of KDT for over twenty-five years. This scoping review aims to synthesise the existing literature regarding the safety, acceptability, and efficacy of the ketogenic formulation in supporting the management of DRE.

Methods: PubMed, Google Scholar and Cochrane databases were searched from January 1998 to November 2024. English and Dutch language studies involving paediatric or adult participants with epilepsy who used the ketogenic formulation were included if the outcomes for the ketogenic formulation group were reported separately and could be extracted. Data extracted included: demographics, type of KD, ratio and volume of ketogenic formulation used, reported outcomes and time points at which measured.

Results: Searches identified a total of 645 articles, 41 met the inclusion criteria. Several reports suggest additional benefits of KDT plus the studied ketogenic formulation versus KDT alone on seizure frequency reduction and seizure severity. Compliance and retention rates varied across studies but appeared higher in those treated with KDT plus the ketogenic formulation. The ketogenic formulation was well tolerated with no major adverse effects reported. Palatability and convenience/ease of use was generally rated highly by patients and parents/caregivers.

Conclusions: This review highlights the integral role of the studied ketogenic formulation in enhancing compliance, convenience, palatability, and efficacy of KDT for children and adults with DRE. In addition, an unexpected but important finding was the growing evidence for this particular ketogenic formulation's use in intensive care settings, particularly for the management of (super-)refractory status epilepticus.

1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures, affecting approximately 50 million people worldwide [1]. Early seizure control is necessary to support optimal developmental outcomes [2], as seizure freedom safeguards

Abbreviations: ASMs, Anti-Seizure Medication(s); BM, Breastmilk; CKD, Classic Ketogenic Diet; DRE, Drug Resistant Epilepsy; EEG, Electroencephalogram; FIRES, Febrile Infection-Related Epilepsy Syndrome; FSMP, Food for Special Medical Purposes; GCS, Glasgow Coma Scale; GI, Gastrointestinal; IL, Intralipid; ITU, Intensive Therapy Unit; IV, Intravenous; KD, Ketogenic Diet; KF, Ketogenic formulation; KDT, Ketogenic Diet Therapy; LQ, Liquid; MAD, Modified Adkins Diet; MCT, Medium Chain Triglycerides; MKD, Modified Ketogenic Diet; Mth(s), Month(s); RCT, Randomised Controlled Trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RSE, Refractory Status Epilepticus; SE, Status Epilepticus; SFR, Seizure Frequency Reduction; SRSE, Super Refractory Status Epilepticus; TPN, Total Parenteral Nutrition; VNS, Vagus Nerve Stimulation; Yrs, Years.

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psychomotor development. The primary goal of epilepsy management is seizure freedom together with maintaining quality of life, and minimising adverse events [3,4]. Although many individuals with epilepsy achieve seizure freedom with one or more anti-seizure medications (ASMs), approximately 40 % of children and adults experience drug-resistant epilepsy (DRE) and do not respond sufficiently to ASMs [5]. DRE is characterised as the failure of two appropriately chosen and tolerated ASMs [6,7]. Clinical consensus demonstrates that the likelihood of seizure control diminishes with each successive ASM trialled [8]. For individuals with DRE, alternative management options such as vagus nerve stimulation (VNS), epilepsy surgery, and ketogenic dietary therapy (KDT) are considered. The ketogenic diet (KD) is a very high-fat, low-carbohydrate, adequate protein regimen which has been successfully used as an effective management option for DRE since the 1920s [3,7]. The International Ketogenic Diet Study Group recommends that KDT be considered as one of the treatment options following the unsuccessful trial of two to three ASMs. Several epilepsy syndromes and conditions have demonstrated a higher responsiveness to KDT, warranting its consideration earlier in the treatment pathway. These include infantile epileptic spasms syndrome, Early-infantile developmental and epileptic encephalopathy, super refractory status epilepticus (SRSE), febrile infection-related epilepsy syndrome (FIRES), new onset refractory status epilepticus (NORSE), Dravet syndrome, Doose syndrome, Angelman syndrome, infants/children who are enterally fed [9,10] and adults [10,11]. Moreover, KDT is the main management option for glucose transporter type 1 (GLUT-1) deficiency syndrome and pyruvate dehydrogenase complex (PDHC) deficiency [9,11].

Several randomised controlled trials have demonstrated the efficacy of KDT in reducing seizure frequency among children [12–21] and adults [22]. The most recent Cochrane review concluded that children treated with KDT were up to three times more likely to achieve seizure freedom and up to six times more likely to achieve $\geq$ 50 % seizure frequency reduction (SFR) compared to children receiving their usual care [7]. Similarly, adults were up to five times more likely to achieve $\geq$ 50 % SFR. KDT has also been shown to positively impact upon non-seizure-related outcomes, including sleep [19,23], quality of life [24–26], cognition and behaviour [19,27,28]. Although KDT has demonstrated therapeutic benefits, the precise mechanisms underlying its effects remain incompletely understood [29]. Adverse effects of KDT can occur and are generally classified as either; short-term, most often gastrointestinal disturbances that require minimal intervention, or long-term complications, which may include dyslipidaemia, nephrolithiasis, bone fractures, impaired growth, and micronutrient deficiencies [9].

KDT demands substantial resources and commitment from patients, their families and healthcare professionals [25,30]. Specialised nutritional formulations are traditionally used when oral intake is inadequate, contraindicated or when exclusive enteral nutrition is required. In the context of inherited metabolic disorders and DRE, however, their role differs. These formulations are often introduced earlier and used as adjuncts to dietary regimens, rather than just as sole sources of nutrition. Their use is driven by factors such as convenience, palatability, accessibility, dietary compliance, and the need for precise macronutrient manipulation in KDT. In 1998, KetoCal was developed as a food for special medical purposes (FSMP) to support the dietary management of DRE. As the first nutritionally complete very high-fat, low-carbohydrate ketogenic formulation, it aimed to offer a convenient and practical option for families and healthcare professionals, thereby supporting adherence to KDT [31,32]. Originally developed as a powdered 4:1 ratio (fat to protein plus carbohydrate combined) formulation, it supports attainment of full macro and micronutrient requirements for enteral tube feeding or as an oral supplement within KDT.

Today, multiple powdered and liquid (LQ) nutritionally complete variants of this ketogenic formulation exist, with varying fat to carbohydrate plus protein ratios. These ketogenic formulations support the implementation of KDT in infants, children, teenagers, and adults with DRE and other epilepsy syndromes. They can be used as a sole intervention for enterally fed patients following the classical KD or as a combined therapeutic approach when used to supplement all oral KDs. In 2022, 854 patients in the UK and Ireland were being managed with KDT, of whom 329 (38.5 %) had an enteral feeding tube and 251 (76 % of those) were exclusively enterally fed [33]. At a global level, however, data on enteral and oral KDT remain limited and have not yet been comprehensively consolidated. Notably, an all-liquid KD for tube fed children demonstrated improved compliance compared to an oral solid food KD [31,32] likely due to easier administration via the tube, consistent macronutrient dosing and sustained ketosis.

This scoping review aims to map and synthesise current evidence to answer the research question 'how does the use of the ketogenic formulation (KetoCal) in ketogenic diet therapy impact the safety, acceptability, palatability, and efficacy in the management of drug-resistant epilepsy among children and adults?' We seek to provide a comprehensive understanding of the studied ketogenic formulation's role in facilitating KDT and identify gaps in the current research for future investigation.

2. Methods

2.1. Study design

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [34] and The Joanna Briggs Institute (JBI) methodology for scoping reviews [35]. A scoping review was deemed appropriate to comprehensively map existing evidence on the use of KetoCal (hereafter referred to as ketogenic formulation) in KDT for DRE. The inclusion and exclusion criteria, search strategy, screening, data extraction and synthesis practices were agreed *a priori* among authors. Ethical approval was not required for this review.

2.2. Eligibility criteria

The inclusion criteria followed JBI recommended structure of Participants, Concept and Context.

Participants

Children or adults with a diagnosis of DRE.

Concept

The concept of interest was the use of the ketogenic formulation in a ketogenic diet regimen as a sole source of nutrition or to supplement the KD. All types of ketogenic diet were considered for inclusion; classical KD, medium chain triglyceride KD, modified Atkins diet, modified ketogenic diet and low glycaemic index treatment. Studies were excluded if they did not use the studied ketogenic formulation or if outcomes related to this ketogenic formulation were not reported separately and thus could not be extracted.

Context

The review considered studies from any setting (e.g., home, hospital) and any geographical location.

Types of studies

A wide range of study designs were included: clinical trials, observational studies and case reports. Grey literature, conference abstracts, narrative and opinion pieces were excluded. The ketogenic formulation under investigation was first launched in 1998, so English or Dutch language papers published after that year were considered.

2.3. Search strategy

An initial search identified key words and index terms which in turn were used to construct a detailed search strategy. Electronic databases including PubMed, Google Scholar, Cochrane Central and the Prospero Register were searched (November 29th, 2024). The full search strategy for PubMed is included (Appendix 1). Reference lists of all included studies were manually screened to identify additional studies. Citations

were collated and de-duplicated using Microsoft Excel.

2.4. Data extraction and synthesis

Typically, title and abstract screening is undertaken first, followed by a critical review of the full texts of a smaller subset of papers. However, this approach proved ineffective in this case, as there was often no indication of i) whether a ketogenic formulation was used, and ii) the specific brand of the formulation in the titles and abstracts. Consequently, two reviewers (JC, DH) independently screened the full text of all identified papers to determine eligibility using the predetermined inclusion and exclusion criteria. A standardised data extraction form was developed and piloted by both reviewers capturing key variables including study design, location, journal of publication, patient demographics, attrition, type of KD used, type and volume of feed used, reported outcomes and time points at which measured. If the brand of ketogenic formulation was not specified in an article, the corresponding author was contacted for clarification. Each reviewer extracted relevant data from 50 % of the included studies, as well as a portion from each other's extractions to ensure consensus. Altogether, data was doubly extracted from 33 % of all included papers with full agreement reached for all. The resulting data were charted and summarised in tabular and narrative format, focusing on patterns in intervention use, reported outcomes and study characteristics.

3. Results

3.1. Identification of studies

The search identified a total of 645 articles (see Fig. 1). 558 articles remained after duplicates were removed. After removal of 429 records that did not match the scope of this review, the full text of 129 articles were screened for suitability against the inclusion criteria, yielding a total of 41 articles for full text analysis. Eighty-eight articles were excluded for reasons outlined in Fig. 1.

3.1.1. Studies utilising the ketogenic formulation in the management of epilepsy with KDT

A total of 72 studies utilised the ketogenic formulation under investigation, (KetoCal) administered either enterally or orally, as part of the ketogenic diet prescription. However, only 41 of these studies, published between 2010 and 2024, met the inclusion criteria for this scoping review. Study characteristics and participant demographics are presented in Table 1. Of these, 33 studies included children only, seven focussed exclusively on adults and one study included both adults and children. In total, data from 1083 participants were assessed, of whom 628 received the ketogenic formulation, most commonly the 4:1 formulation as part of a classical ketogenic diet. The mode of administration (oral or enteral) was not specified in 17 studies; although oral

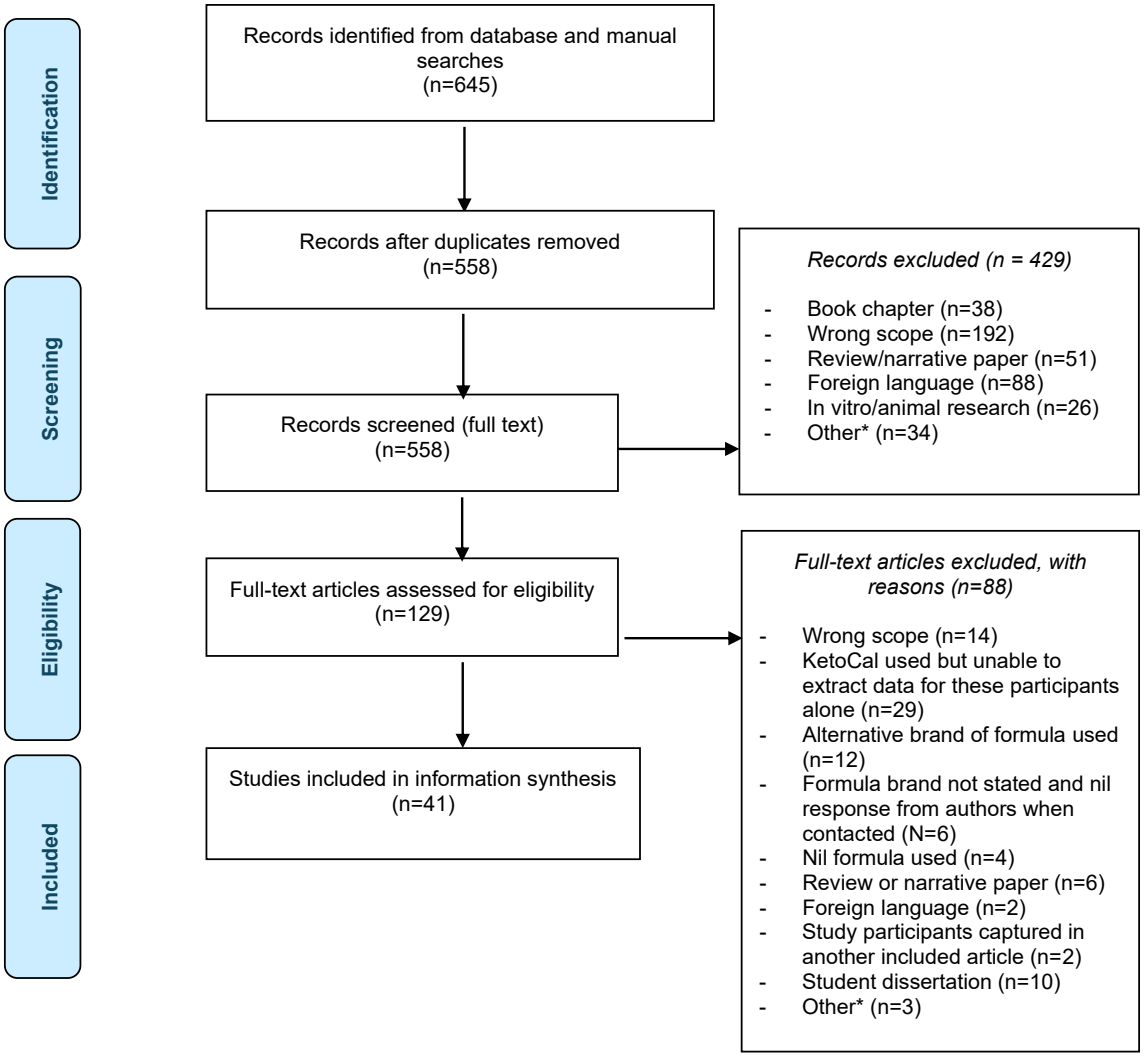

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the scoping review search. ** For example: opinion piece, study protocol, newsletter, NHS information sheet, cookbook, recipes, conference proceedings).*

Table 1
Demographics of included studies and mapping of assessed outcomes.

Study	Reference	Design and duration	Participants Gender Age (mean)	Type of KD and mode of feeding (MOF)	Ketogenic formulation (KF) ratio and volume	Seizure outcomes	Non seizure outcomes	KD outcomes	Adverse events, SAE or other
Paediatric studies									
Appavu 2016	[36]	Retrospective F/up 0-39mths	N = 10 6 M, 4F 12-16yrs	CKD 9 enteral 1 TPN/IL	4:1 Initially: 50 % dietary intake; then: increases of intake of 10 %	Resolution of SRSE Weaning from anaesthesia ASM and steroid use		Time to ketosis Duration of KD post ITU Reasons for KD discontinuation	Biochemistry GI tolerance Survival
Ashrafi 2016	[37]	Open label trial 20mths	N = 27 16 M, 11F 1-5yrs (35mths ± 17)	CKD MOF not specified	4:1 Started at 60–80 mL, increased by 40–60 mL/day until desired ketosis levels achieved; final volumes not specified	SFR EEG changes		Adherence to KD Ketosis Palatability of the KF	Anthropometry Biochemistry GI tolerance
Bashiri 2018	[38]	Case report F/up to 1 yr	N = 1F 13mths	CKD enteral	3:1 Volume not specified	ASM use SFR EEG changes		Time to ketosis	Anthropometry
Breu 2021	[39]	Retrospective 4.2mths (mean 8.4, IQR 1.6–12.3)	N = 8 4 M, 4F 1.9mths to 8.9yrs (13.6mths)	CKD 3 enteral 2 combined enteral/IV 2 IV then enteral 1 IV	3:1/4:1 Volume not specified	SFR Time to resolution of SRSE Time to withdrawal of anaesthetic drugs		Time to clinically relevant ketosis (>2mmol/L) Ketosis Duration of KD post ITU admission	Anthropometry Biochemistry GI tolerance Survival
Byler 2013	[40]	Case report F/up to 1 yr	N = 1 M 5yrs	CKD MOF not specified	4:1 100 % dietary requirements	Time to extubation			Biochemistry GI tolerance
Caraballo 2014	[41]	Prospective 6mths with f/up to 3yrs	N = 10 6 M, 4F 2-9yrs (5yrs)	CKD Enteral with transition to oral KD (n = 7)	4:1 Volume not specified	SFR EEG changes		Ketosis Reasons for KD discontinuation Tolerability	Biochemistry Lethargy Other
Caraballo 2015	[42]	Case report	N = 2 2 M 17-23mths (20mths)	CKD Enteral to oral	4:1 Volume not specified	SFR EEG changes ASM use	Motor development Cognition	Ketosis	Anthropometry Biochemistry
Coppola 2010	[43]	Unclear F/up to 12 months on KD. Mean 10.3mths ± 7.4wks	N = 38 22 M, 16F 8mth – 5yrs (37.2mths ± 16.5)	CKD with fasted start MOF not specified	4:1 80–100 % of daily caloric intake	SFR ASM use			Anthropometry Biochemistry Fatigue, irritability GI tolerance Other
Dressler 2015	[44]	Retrospective cross sectional. Mean 1 yr ± 1.16 (0.25–8.03) yrs	N = 115 56 M, 59F 0–16.8yrs (2.86 ± 3.1yrs)	CKD MOF not specified	Ratio and volume not specified	SFR Seizure relapse post KD termination		Compliance Retention	Anthropometry Biochemistry GI tolerance
Dressler 2020	[45]	Retrospective	N = 79 45 M, 34F 14.6 days-12mths (6.2mths)	CKD MOF not specified	3:1/4:1 Mixed with BM/formula, volume dependent on individual response	ASM use SFR		Time to therapeutic ketosis (≥2 mmol/L) Ketosis Continuation of breast feeding Dietary intake	Anthropometry Biochemistry GI tolerance
El-Rashidy 2013	[12]	Prospective case control. 6mths	N = 40 19 M, 21F 12-36mths (27.13 ± 6.63mths)	CKD MAD MOF not specified	4:1 Volume not specified	SFR Seizure severity		Ketosis Reasons for KD discontinuation	Anthropometry Biochemistry GI tolerance Fatigue

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Table 1 (*continued*)

Study	Reference	Design and duration	Participants Gender Age (mean)	Type of KD and mode of feeding (MOF)	Ketogenic formulation (KF) ratio and volume	Seizure outcomes	Non seizure outcomes	KD outcomes	Adverse events, SAE or other
El-Shafie 2023	[46]	Prospective randomised 2yrs	N = 30 13 M,17F 4-144mths (36mths CKD group, 72mths MAD group)	CKD MAD MOF not specified	4:1 Volume not specified	ASM use Time to SFR SFR Seizure severity EEG changes	Attention		Anthropometry GI tolerance
Farias-Moeller 2017	[47]	Retrospective F/up to 6mths	N = 9 4 M, 4F 2–8 years (5.4yrs)	CKD 7 enteral, 1 IV then enteral, 1 IV	3:1 or 4:1 Volume not specified	ASM use and anaesthetics Steroid use SFR		Time from diagnosis to KD initiation Time to ketosis Duration of KD Adherence to KD Reasons for KD discontinuation	Biochemistry Survival
Fung 2015	[48]	Case series	N = 4 2 M,2F 12-21yrs	CKD MOF not specified	4:1 Volume not specified	Anaesthetic use ASM use Resolution of SRSE		Duration of KD Ketosis Reasons for KD discontinuation Compliance	Biochemistry GI tolerance Other
Hussain 2016	[49]	Retrospective F/up to 1 yr	N = 22 11 M, 11F (33.1mths)	CKD MOF not specified	3:1 33, 66 and 100 % dietary requirements on day 1, 2 and 3, respectively	SFR		Retention	Anthropometry Biochemistry GI tolerance Lethargy
Karimzadeh 2019	[50]	Prospective with random allocation 6mths	N = 45 Gender and age not stated	CKD MOF not specified	4:1 1-2yrs: 50 % of requirements 2-3yrs: 30 % of requirements	SFR EEG changes	Cognition	Retention Attrition and reasons	Biochemistry
Kossoff 2010	[51]	Open label, non-blinded prospective study. 2mths	N = 30 11 M, 19F 3-16yrs (7yrs)	MAD MOF not specified	4:1 300 mL / day	SFR		Duration of KD Time to ketosis Ketosis Dietary intake Tolerability of diet and KF Reasons for restarting the KF	Anthropometry Biochemistry GI tolerance Fatigue
Le Pichon 2019	[52]	Cohort study F/up to 24mths	N = 9 Not stated 1.2-13mths (6.7mths)	CKD Oral	4:1 90–95 % caloric intake (5–10 % BM)	ASM use SFR	Quality of life	Duration of continued breastfeeding Ketosis	Anthropometry Biochemistry GI tolerance Other
Mahesan 2024	[53]	Open label RCT 6mths	N = 83 78 M, 5F 6-24mths	CKD MOF not specified	4:1 Volume not specified	SFR Relapse rate		Compliance	Biochemistry GI tolerance Other
Merino-Hernandez 2023	[54]	Case report 32 days	N = 1 M, 14 days	CKD MOF not specified	3:1 100 % dietary requirements	ASM use SFR		Time to ketosis	Anthropometry Biochemistry GI tolerance Other
Mir 2020	[55]	Retrospective case note review 3–5 days	N = 66 (M27, F39) 7mths – 13yrs (48mths)	CKD 48 oral 18 enteral	4:1 Volume not specified	ASM use		Ketosis	GI tolerance Lethargy
Nabbout 2010	[56]	Retrospective F/up to 2yrs	N = 9 4 M,5F 54-98mths (74mths)	CKD Enteral	4:1 Volume not specified	Time to resolution of SRSE Time to seizure recurrence		Ketosis Duration of KD post ITU admission	Survival
Phitsanuwong 2022	[57]	Case report F/up to 6mths	N = 2F (twins) 24 days	CKD Enteral	4:1 100 % dietary requirements	SFR		Time to ketosis	Anthropometry Biochemistry
Pires 2013	[58]	Prospective 6mths	N = 17 11 M,6F 2-11mths (9.4 ± 1.1)	CKD MOF not specified	4:1 Volume not clearly specified	SFR EEG changes ASM use	Psychomotor development and social interactions		Anthropometry Biochemistry Tolerability

(*continued on next page*)

Table 1 (*continued*)

Study	Reference	Design and duration	Participants Gender Age (mean)	Type of KD and mode of feeding (MOF)	Ketogenic formulation (KF) ratio and volume	Seizure outcomes	Non seizure outcomes	KD outcomes	Adverse events, SAE or other
Sampaio 2017	[59]	Retrospective 3mths	N = 10 6 M, 4F 9mths – 16yrs (6.3yrs)	CKD 7 oral 3 enteral	3:1 and 4:1 Oral: 2 feeds/day Enteral:100 % dietary requirements	SFR	Attention and activity	Ketosis Acceptability of KD and KF	Fatigue GI tolerance Other
Serrano-Tabares 2022	[60]	Retrospective case series 6mths	N = 7 Gender not stated 9 days –4mths (24 days)	CKD 3 oral 4 enteral	4:1 Volume not specified	ASM use SFR		Reasons for KD discontinuation	GI tolerance
Singh 2015	[61]	Case report F: 4mths M: 20mths	N = 2 1 M 20mths 1F 4mths	CKD Enteral	4:1 100 % dietary requirements	SFR	Cognition	Time to ketosis	Anthropometry
Sort 2013	[62]	Retrospective case series Varies	N = 3 2 M, 1F 3-11yrs	CKD Enteral	4:1 Volume not specified	ASM use SFR		Time to ketosis Reasons for KD discontinuation	Anthropometry Biochemistry
Suo 2013	[63]	Prospective 1 day to 48mths (mean 5.7mths)	N = 317 206 M,111F 2mths to 17yrs 8mth (39.6mths)	CKD MOF not specified	Ratio and volume not specified	SFR		Retention Reason for withdrawal	Biochemistry GI tolerance Survival
Urbizu 2010	[64]	Case series. Unclear	N = 2 2 M 11yrs	CKD MOF not specified	4:1 Volume not specified	SFR EEG changes ASM use	Paroxysmal dyskinesia Writer's cramp	Compliance	Occurrence of headaches
Weijenberg 2018	[65]	Prospective. 12mths	N = 16 10 M, 6F 1 yr 11mths-14yrs 11mths	CKD 8 oral 8 enteral	4:1 100 % dietary requirements for first 6 weeks, after this supplemental for oral eaters (volume not specified)	SFR Hospital admissions		Time to KD response Time to stable ketosis (≥2.5 mmol/L for 2 days) Retention Reasons for KD discontinuation Reasons for continuing KD	Anthropometry GI tolerance
Wijaya 2019	[66]	Case report	N = 1 M 29mths	CKD Oral	4:1 8x125mL / day	ASM use SFR			GI tolerance
Yildirim 2022	[67]	Retrospective case review 20mths	N = 18 7 M, 11F 5-192mths (70mths)	CKD 11 oral 7 enteral	4:1 Volume not specified	SFR		Time to ketosis	Anthropometry Biochemistry GI tolerance Other
Adult studies									
Cervenka 2011	[68]	Case report	N = 1 1 M, 49yrs	CKD (enteral), transitioned to MAD (oral)	4:1 100 % dietary requirements	ASM use EEG changes		Ketosis	Biochemistry GI tolerance
Cervenka 2017	[69]	Prospective open label F/up to 21mths	N = 15 5 M,10F 18-82yrs	CKD (enteral), transitioned to MAD (oral) if able	4:1 100 % dietary requirements	SRSE resolution SFR ASM use Steroid use	Level of consciousness Degree of disability/dependence	Time to therapeutic ketosis (>2mmol/L) Duration of KD post ITU	Anthropometry Biochemistry GI tolerance Survival
Griffen 2024	[70]	Prospective multicentre pilot study. 59 days	N = 26 *10 M, 9F (8-46yrs)	MKD and CKD 11 oral 8 enteral	2.5:1 ≥ 200 mL/day; mean 422 mL/day Oral: mean 255 mL/day Enteral: mean 708 mL/day	SFR Seizure severity and burden	Health related quality of life	GI tolerance Adherence Dietary intake Ketosis Acceptability of the KF Dietetic goals	Anthropometry GI tolerance and severity of GI symptoms Safety
Kaul 2022	[71]	Retrospective multicentre cohort 4–26 days	N = 12 M5, F7 23-74yrs (58yrs)	2:1 CKD Enteral with transition to oral if able	4:1 100 % dietary requirements (supplemented with protein, MCT etc. as needed)	Time to SRSE resolution		Nutritional adequacy Ketosis	Biochemistry GI tolerance

(*continued on next page*)

Table 1 (*continued*)

Study	Reference	Design and duration	Participants Gender Age (mean)	Type of KD and mode of feeding (MOF)	Ketogenic formulation (KF) ratio and volume	Seizure outcomes	Non seizure outcomes	KD outcomes	Adverse events, SAE or other
McDonald 2018	[72]	Randomised crossover 2mth trial and 6mth f/up	N = 80 25 M, 55F 38.1yrs control, 32.4yrs intervention group	MAD MOF not specified	4:1 237 mL (1 tetra)/ day	SFR		Ketosis Dietary intake Adherence Convenience of MAD ± KF Taste, texture and tolerance of MAD ± KF KF use	Anthropometry Biochemistry GI tolerance Other
Noviawaty 2020	[73]	Case report F/up to 1 yr	N = 1 1 M 38yrs	CKD (enteral) transitioned to MAD (not specified)	4:1 Volume not specified	SFR EEG changes		Ketosis	Not reported
Strzelczyk 2013	[74]	Case report 4mths f/up	N = 1 1F 21yrs	CKD IV then enteral	4:1 5x 237 mL/day	SRSE resolution EEG changes SFR		Ketosis	Not reported
Wusthoff 2010	[75]	Case report 1 yr post discharge	N = 2 1 M, 29yrs 1F, 37yrs	CKD Enteral with transition to oral	4:1 Volume not specified	SFR ASM use		Ketosis KD duration post discharge from ITU	Not reported

ASM; antiseizure medication, BM; breastmilk, CKD; classical ketogenic diet, EEG; Electroencephalogram, F; female, GI; gastrointestinal, IL; intralipids, ITU; intensive therapy unit, IV; intravenous, KD; ketogenic diet, KF; ketogenic formulation (KetoCal), M; male, MAD; modified Atkins diet, MCT; medium chain triglycerides, MOF; mode of feeding, Mth(s); month(s), SAE; serious adverse event, SFR; seizure frequency reduction, TPN; total parenteral nutrition, Wks; weeks, Yrs; years.
*Gender only stated for those who completed.
Example 'GI tolerance' outcomes; nausea, vomiting, abdominal cramping, gastro oesophageal reflux, diarrhoea and constipation.
Example 'Other' outcomes; encompasses a range of additional adverse effects such; rash, hypoactivity, pancreatitis, irregular menses, headaches, brittle hair or nails, vaginal odour, hospitalisation for adverse effects, sepsis, jaundice and nephrolithiasis.

intake was likely, this cannot be assumed with certainty. The contribution of the ketogenic formulation to the KD was often not specified in detail. Studies that did provide information on ketogenic formulation consumption/ administration either specified volumes (mL) or expressed ketogenic formulation intakes as a percentage of dietary requirements or caloric intake. The study designs were as follows: 13 retrospective studies, 12 case series and 16 prospective studies. Among the prospective studies, two were multicentre, two employed random allocation to either KD alone or a formulation based/ supplemented KD, and one was an open label RCT.

A wide range of outcomes were assessed (Table 1), which can be broadly categorised as follows:

1. Seizure-related outcomes: seizure frequency, seizure freedom, seizure severity, adjustments to ASM and resolution of refractory status epilepticus (RSE), SRSE and FIRES
2. Non-seizure-related outcomes: quality of life and functional performance
3. Ketogenic diet-related outcomes: dietary intake, acceptability, compliance, ketosis, and growth
4. Adverse events or other: encompassed the broad range of adverse events including gastrointestinal symptoms, biochemistry, lethargy, occurrence of kidney stones or other issues.

3.1.2. Reported outcomes

There was considerable variability in how outcomes were defined, the timing of assessments, and the measurement methods used. Only 4 studies used validated assessment tools including the Denver developmental screening test [50,58], the Chalfont Seizure Severity Scale [12], the Glasgow Coma Score and Modified Rankin Scale [69].

3.2. Efficacy of KDT with the ketogenic formulation – Seizure related outcomes

3.2.1. Seizure frequency

In total, 25 studies reported on seizure frequency outcomes. Studies of RSE, SRSE and FIRES are discussed separately later as a distinct group (see section 3.2.5). There was considerable variability in the reporting of seizure frequency outcomes and the criteria used to define seizure reduction. While some studies classified responders as individuals experiencing a $\geq$ 50 % reduction in seizures, others reported seizure freedom, a reduction of $>$ 90 %, or less frequently, a reduction of $>$ 75 %. Reported follow-up time points varied, with 1, 3, and 6 months being the most common, and a subset of studies (n = 5) extended follow-up to 12 months. Additionally, response rates were not consistently assessed relative to all subjects that started KDT (baseline cohort); instead, some studies reported the proportion of patients with a clinically relevant response relative to the number of patients still on KDT at each specific timepoint.

Fig. 2 and Supplementary Fig. S1 illustrate the proportion of subjects who achieved a $\geq$ 50 % reduction in seizures, along with, where available, the percentage of individuals experiencing $>$ 90 % seizure reduction or complete seizure freedom at 1, 3, 6, and 12 months following the initiation of a KD, with or without the ketogenic formulation studied in this review. Case reports were excluded from this analysis; however, the full dataset, including all extracted data, is available in Supplementary Table S1. To facilitate comparisons of seizure reduction outcomes, data at 1, 3, 6, and 12 months were recalculated relative to all subjects that started KDT (baseline, Fig. 2) and to the number of subjects still on KDT at each specific timepoint (retention, Supplementary Fig. S1).

Compared to baseline, the pooled average response rate in seizure control at 1, 3, 6, and 12 months of dietary management appears to be higher in individuals treated with KDT supplemented with the ketogenic formulation compared to those following KDT alone (61.2 vs. 30.2 %, 61.5 vs. 40.6 %, 66.1 vs. 52.3 %, and 44.5 vs. 23.4 %, respectively).

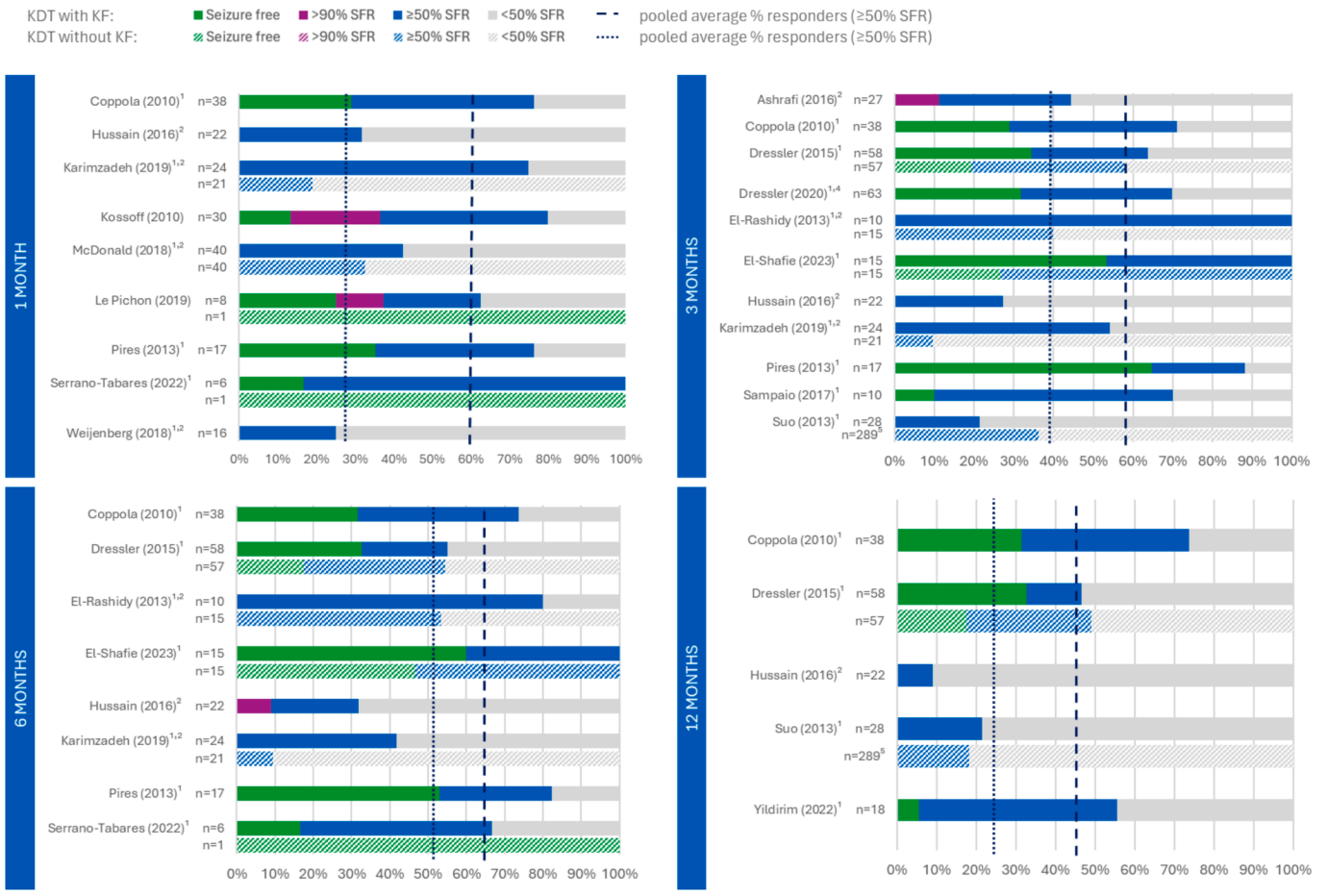

Fig. 2. Percentage of patients on ketogenic diet therapy (KDT) with or without the ketogenic formulation (KF) under investigation (KetoCal) achieving ≥ 50 % seizure frequency (SFR) reduction, >90 % SFR, or complete seizure freedom at 1, 3, 6, and 12 months, compared to baseline. [1] > 90 % SFR not reported; [2]seizure freedom not reported; [4]control group not included as not possible to separate results for subjects exclusively receiving breastmilk (BM) from those receiving BM + KF; [5]two control groups combined (meal planner + Qitong). Vertical dashed lines represent pooled average % responders (≥50 % SFR), which was calculated based on the total N subjects at baseline/specific timepoints and the total N subjects with ≥ 50 % SFR reported across papers (cohort studies) included in the figures.

Studies incorporating control groups often reported slightly better response, with a greater proportion of patients achieving a clinically significant reduction in seizures (≥50 %) [9,42,64] or attaining complete seizure freedom [36,38].

3.2.2. *Seizure severity and burden*

Only three studies specifically reported on seizure severity and or burden (Table 1). Griffen et al. [70] found that although seizure frequency remained similar between adult patients on KDT alone (control period) compared to when supplementing KDT with the ketogenic formulation in a 2.5:1 ratio (intervention period), individuals with the worst seizure intensity and burden experienced improvements in both measures when using the ketogenic formulation. Similarly, El-Rashidy et al. [12] evaluated 25 paediatric patients on either 4:1 CKD liquid diet (n = 10) or the Modified Atkins Diet (MAD) (n = 15). After 3 and 6 months on diet, 100 % of the ketogenic formulation (CKD) group experienced decreased seizure severity versus 93.3 % in the MAD group (3-month Chalfont severity score decreased by 31.95 ± 18.7 (CKD group) versus mean decrease of 16.03 ± 7.06 in the MAD group).

In a similar design, El-Shafie et al. [46] assessed CKD versus MAD in 40 children with DRE and reported a statistically significant 100 % reduction in seizure severity after 3 and 6 months in both groups, with no significant differences between diet groups. Additionally, after six months, all patients experienced shorter seizures and a faster return to normal post-seizure onset.

3.2.3. *Time to ketosis and improved seizure control*

Few studies assessed the time required to achieve ketosis and observe the therapeutic benefits of a ketogenic diet. Among those that have, reported timelines varied, likely due to differences in diet composition, population characteristics, and study protocol. Weijenberg et al. [65] reported stable ketosis (≥2.5 mmol/L blood beta-hydroxybutyrate for 2 days) within 1–20 days (mean 7 days) and seizure reduction within 7–28 days. Kossoff et al. [51] and Sampaio et al. [59] reported that ketosis was reached within several days to two weeks in paediatric patients following either a MAD with the ketogenic formulation or a CKD (50–100 % ketogenic formulation) respectively. In adults, McDonald et al. [72] observed a median time of 4–4.5 days to achieve ketosis in both MAD and MAD with the ketogenic formulation groups. Dressler et al. [45] reported beta-hydroxybutyrate levels reaching ≥ 2 mmol/L within 41 h for infants fed with the ketogenic formulation alone and within 47 h in those receiving a combination of breast milk and the ketogenic formulation with no significant difference between groups. El-Shafie et al., [46] focussed solely on the time to seizure improvement, reporting benefits within 10–14 days, depending on diet type. In a study of 45 children treated with CKD alone or CKD with the ketogenic formulation, 8 of 19 participants in the CKD-only (without the ketogenic formulation) group did not produce ketones. In contrast, all children in the CKD plus ketogenic formulation group successfully achieved ketosis. Notably, patients in the CKD-only group struggled to consume home-made ketogenic foods [50].

3.2.4. Antiseizure medication use

Eleven studies (excluding (S)RSE/FIRES studies) examined the number of antiseizure medications (ASMs) trialled before or at the time of KDT initiation with the ketogenic formulation, with the number of ASMs ranging from zero to twelve [38,43,45,46,52,54,55,58,60,64,66]. Seven studies assessed changes in ASM use following KD initiation. Of these, six reported a reduction in the number of ASMs, ranging from one to eight [43,45,46,52,54,64]. In the study by Le Pichon et al., [52], 50 % of infants managed with KDT with the ketogenic formulation were completely weaned from ASMs, and one patient (12.5 %) went from a total of 3 to 1 ASM. In contrast, one patient's ASM did not change and in two patients one ASM was added. Pires et al., [58] reported addition of one to two ASMs when seizure freedom was not achieved within one month.

3.2.5. (S)RSE and FIRES

Sixteen studies, comprising 11 paediatric and five adult cohorts, assessed the efficacy of KDT in the management of RSE, SRSE, or FIRES. All studies utilised the ketogenic formulation studied, either administered enterally or in combination with parenteral nutrition. A summary of key findings is presented in Table 2. Responders were generally defined as patients who experienced an interruption of status epilepticus following KD initiation. The definition of "time to ketosis" varied across studies, with some describing it as the initial detection of ketosis, while others considered it the point at which ketone levels reached a clinically significant or therapeutic threshold. Patients were in status epilepticus for a considerable duration before KD initiation, ranging from 1 to 101 days (mean 18.7). Following KD initiation, the time to status resolution varied between 1 and 21 days (mean 6.6). Nine studies reported on ASM use both prior to KD initiation as well as at time of hospital discharge. The number of ASMs prior to KD initiation ranged from one to nine. At the time of discharge, number of ASMs reduced for most patients to between one and six.

Overall, the KD was generally well tolerated in patients with (S)RSE/FIRES, with reported adverse effects consistent with those typically observed in critical care settings, including acidosis, hypoglycaemia, hyperketosis, weight loss, lipid derangements, and gastrointestinal symptoms.

3.3. Efficacy of KDT with the ketogenic formulation – Non-seizure related outcomes

3.3.1. Quality of life and functional outcomes

Few studies (8/41) assessed the impact of KDT on quality of life and cognitive functioning, yet every study assessed at least one seizure related outcome. El-Shafie et al. [46] compared CKD + the ketogenic formulation versus the MAD and found that after six months, 46.7 % of children in the CKD group and 66.7 % in the MAD group demonstrated improved attention, as reported by parents. Similarly, Sampaio et al. [59], using a regimen of two portions of the ketogenic formulation and two KD meals daily, observed that 8 out of 10 children experienced enhanced attention and activity levels, also reported by parents. Karimzadeh et al. [50] assessed the cognitive function in children with moderate to severe developmental disorders using the Denver developmental screening test and noted improvements in the ketogenic formulation group (30–50 % requirements from the ketogenic formulation) after six months, although the extent and method of assessment were unclear. Notably, two patients experienced cognitive decline, but again little detail was shared. Pires et al. [58] also employed the Denver screening and found that 47 % of infants (8/17) showed psychomotor improvement after one month on KDT, as reported by parents or neurologists, despite only three infants achieving seizure freedom. In a case series [61], two children were treated with CKD using the ketogenic formulation for FIRES and while neither child regained their normative pre-FIRES cognitive levels, both returned to school with only mild cognitive impairments—an outcome the authors deemed more favourable than typically observed in the literature, likely due to KD's role in optimizing seizure control both acutely and long-term. Lastly, Le Pichon et al. [52] explored the feasibility of incorporating breast milk into a KD alongside the ketogenic formulation in nine infants and found that parents of all but one reported an improvement in quality of life.

In adults, only two studies have examined non-seizure outcomes. Cervenka et al. [69] assessed Glasgow Coma Scale (GCS) scores in 15 patients with SRSE pre-KD and at hospital discharge. Of these, five patients did not survive; however, among the 10 survivors, nine (60 %) regained their pre-SRSE baseline GCS. Finally, Griffen et al. [70] found no significant differences in reported health-related quality of life parameters between children and adults treated with either KD alone or KD supplemented with the ketogenic formulation in a 2.5:1 ratio.

3.4. Ketogenic diet therapy outcomes

3.4.1. Compliance and retention

Studies examining compliance (also referred to as adherence in some studies) and retention among patients using KDT as a management option for epilepsy have reported varying outcomes depending on the dietary approach and supplementation with FSMPs. McDonald et al. [72] compared adherence among 80 participants following MAD. Of these, 40 received 237 mL (1 carton) of the ketogenic formulation in a 4:1 ratio in the first month (intervention group) while the remaining 40 did not start the ketogenic formulation until the second month (control group). More than half of the patients in both groups (51.5 % in the control group and 62.9 % in the treatment group) maintained compliance to the KD at six. Moreover, patients who received the ketogenic formulation in the first month were significantly more likely to continue the MAD beyond the initial two-month study period. The median diet duration was 25 months (range: 7–49 months) in the intervention arm compared to 20 months (range: 9–30 months) in the control arm. Similarly, the 2.5:1 ketogenic formulation was well tolerated among 19 participants who completed a 28-day control period on KDT without the ketogenic formulation, followed by a 28-day intervention period with a daily intake of $\geq$ 200 mL of the 2.5:1 ketogenic formulation [70]. A majority (63 %) of participants agreed or strongly agreed that the addition of the 2.5:1 ketogenic formulation facilitated adherence to their prescribed KDT. Notably, five participants with baseline adherence below 50 % during the control period demonstrated a significant increase in adherence during the intervention (from 31 % to 64 %).

Retention rates also varied across studies but appeared higher in those managed with KD plus the ketogenic formulation studied. Karimzadeh et al. [50] found that retention rates in the group receiving CKD plus the ketogenic formulation were consistently higher than those in the CKD-only group at 1, 3, and 6 months (75 % vs. 19 %, 54.2 % vs. 9.5 %, and 41.7 % vs. 9.5 %, respectively). Similarly, McDonald et al. [72] found that retention rates were higher among patients who received the ketogenic formulation in the first month compared to those who started it in the second month. Retention rates were 77.5 % vs. 62.5 % at one month, 67.5 % vs. 55 % at two months, and 47.5 % vs. 30 % at three months.

However, Dressler et al. [44] found no significant difference in retention rates between groups, regardless of whether patients initiated KDT with the ketogenic formulation or with solid foods alone (100 % at 3 months, 57.4% at 6 months and 53 % at 12 months). This difference may be explained by the younger age of participants in Dressler's study (mean age: 2.86 $\pm$ 3.1 years), compared to the adult population in McDonald et al.'s study. Notably, 50 % of Dressler's cohort was under 1.5 years old.

3.4.2. Convenience and palatability

Several studies have evaluated the palatability, tolerability, and ease of use of the ketogenic formulations under investigation. Kossoff et al. [51] conducted a study involving 30 paediatric participants who were initiated on a MAD supplemented with a portion (400 kcal) of the

Table 2
Outcomes in RSE, SRSE and FIRES.

Author Year Reference Condition	**#subjects Gender Nutrition**	**Age at SE start** mean (range) years	**Duration SE before KD** mean (range) days	**Time to ketosis** mean (range) days *method*	**Time to SE resolution after KD start** mean (range) days	**Responder rate** n (%)	**#ASMs prior to KD initiation** mean (range)	**#ASMs at hospital discharge** mean (range)	**Adverse events** n (%)	**Deceased** n (%)	**Continued KD ≥ 3 months** n (%)
Appavu 2016 [36] SRSE	9 KF (4F, 5 M)	9.22 (2–16)	21.89 (1–45)	4.63 (0–8) (n = 8/9) *urine*	7.75 (1–19)	9 (100)	3 (1–6)	3.5 (3–5)	8 (88.9) none 1 (11.1) acidosis, hypophosphatemia, hypokalaemia	1 (11.1)	4 (57.1)*
	1 first TPN/IL (M)	3.5	7	13 *urine*	9	1 (100)	3	3	1 (100) none	0 (0)	1 (100)
Breu 2021 [39] SRSE	3 KF (1F, 2 M)	1 (0–3)	2.33 (1–4)	3.58 (1–7) *serum*	2.67 (1–5)	3 (100)	2.67 (0–4)	*not reported*	1 (33.3) flatulence & constipation 1 (33.3) diarrhoea 1 (33.3) dehydration 1 (33.3) high ketosis	2 (66.7)	*not clearly reported*
	2 KF and IV combined (1F, 1 M)	6.68 (1–12)	5 (1–9)	6.65 (1–18) *serum*	8 (1–15)	2 (100)	4.5 (4–5)	*not reported*	2 (100) hypertriglyceridemia 1 (50) hyperlipidaemia 1 (50) hypercholesterinaemia, pancreatitis, catecholamines, hepatopathy	1 (50)	*not clearly reported*
	2 first IV then KF (1F, 1 M)	5.93 (1–10)	25 (8–42)	3.58 (1–7) *serum*	15 (n = 1)	1 (50)	3 (2–4)	*not reported*	1 (50) weight loss, paralytic ileus 1 (50) reduced drinking, diarrhoea	0 (0)	*not clearly reported*
	1 IV (F)	0	9	1 *serum*	1	1 (100)	0	*not reported*	1 (100) dystrophia, constipation	1 (100)	*not clearly reported*
Byler 2013 [40] FIRES	1 KF (M)	5	22	*not reported*	*not clearly reported*	1 (100)	5	3	no hypoglycaemia, hypoxia, sepsis or other reported side effects	0 (0)	1 (100)
Caraballo 2014 [41] RSE	10 KF (4F, 6 M)	5 (2–9)	*not reported*	3 (2–4) *urine*	*not reported*	7 (70)	*not reported*	*not reported*	6 (60) none 1 (10) vomiting 1 (10) hypoglycaemia 2 (20) pancreatitis	0 (0)	7 (70)
Caraballo 2015 [42] RSE	2 KF (2 M)	3.33 (1.42–1.92)	21 *n = 1 not reported*	*not reported*	within 3–7	2 (100)	4.5 (4–5)	1.5 (1–2)	*not reported*	0 (0)	2 (100)
Cervenka 2011 [68] RSE	1 KF (M)	49	58	11 *urine*	*not clearly reported*	1 (100)	10	*not reported*	no hypoglycaemia, acidosis or other reported side effects	0 (0)	1 (100)
Cervenka 2017 [69] SRSE	15 KF (10F, 5 M)	46.67 (20–79)	12.67 (2–39)	3.5 (0–16) *serum/ urine*	5 (0–10)	11 (73.3)	8.13 (5–12)	*not reported*	5 (33.3) none 3 (20) acidosis 2 (13.3) hyperlipidaemia 2 (13.3) constipation 2 (13.3) hypoglycaemia 1 (6.7) hyponatremia 1 (6.7) weight loss	5 (33.3)	3 (20)
Farias-Moeller 2017 [47]	7 KF (5F, 2 M)	5.71 (2–8)	18.86 (7–41)	4.6 (2–13) *urine*	*not reported*	4 (66.67)**	median 4 (IQR 3–4; all subjects)	median 3 (n = 6/KF subjects)	7 (100) none	1 (14.3)	5 (71.4)
SRSE	1 first IV, then KF (M)	5	10 to IV, 39 to KF	5 after IV, 8 after KF *urine*	*not reported*	1 (100)			1 (100) hypertriglyceridemia & pancreatitis with IV, none with enteral	0 (0)	1 (100)
	1 IV (F)	5	16	4 *urine*	*not reported*	1 (100)		*not reported*	1 (100) hypertriglyceridemia	0 (0)	0 (0)
	1 KF (F)	16	18	*not reported*	*not reported*	*unclear*	3	*not reported*	1 (100) falling plasma protein	0 (0)	0 (0)
Fung 2015 [48] SRSE	3 KD, no FSMP (1F, 2 M)	10 (6–16)	16.67 (12–21)	*not reported*	*not reported*	*unclear*	4.33 (4–5)	*not reported*	1 (33.3) none but struggled with compliance	0 (0)	0 (0)

(*continued on next page*)

Table 2 (*continued*)

Author Year Reference Condition	**#subjects Gender Nutrition**	**Age at SE start** mean (range) years	**Duration SE before KD** mean (range) days	**Time to ketosis** mean (range) days *method*	**Time to SE resolution after KD start** mean (range) days	**Responder rate** n (%)	**#ASMs prior to KD initiation** mean (range)	**#ASMs at hospital discharge** mean (range)	**Adverse events** n (%)	**Deceased** n (%)	**Continued KD ≥ 3 months** n (%)
Kaul 2022 [71] SRSE	12 KF (7F, 5 M) *n = 3 combined w/ IV amino acids* *n = 2 combined w/ IV lipids*	median 58 (23–74)	11.08 (4–29)	*not reported*	9.1 (2–21)	10 (83.3)	5 (4–8)	not reported	1 (33.3) increase in breakthrough seizures 1 (33.3) vomiting, suspected sepsis 7 (58.3) none2 (16.7) hypertriglyceridemia2 (16.7) diarrhoea 1 (8.3) vomiting 1 (8.3) hypoglycaemia1 (8.3) tongue swelling	4 (33.3)	*not clearly reported*
Nabbout 2010 [56] FIRES	4 KF (2F, 2 M)	7.13 (6–8)	26.25 (8–55)	2.5 (2–4) *urine*	4.8 (4–6)	4 (100)	4.5 (3–6)	*not reported*	*not reported*	0 (0)	4 (100)
	5 KD*** (3F, 2 M; 2-3yrs)	5.75 (4–7)	21 (4–50)	3 (3) (n = 4/5) *urine*	4.67 (4–5)	3 (60)	4.2 (3–6)	*not reported*	*not reported*	1 (20)	2 (40)
Noviawaty 2020 [73] SRSE	1 KF (M)	38	49	5 *urine + serum*	7	1 (100)	7	6	*not reported*	0 (0)	1 (100)
Singh 2015 [61] FIRES	2 KF (1F, 1 M)	8.5 (7–10)	8 (3–13)	8.5 (2–17) *serum*	2 (n = 1, N = 1 unclear)	2 (100)	7	2.5 (2–3)	*not reported*	0 (0)	2 (100)
Sort 2013 [62] RSE	3 KF (1F, 2 M; 3-11yrs)	8 (3–11)	20.67 (6–48)	8 (1–17) *method not reported*	7 (1–13)	2 (66.67)	8.33 (7–9)	3 (n = 2)	1 (33.3) weight loss, hypertriglyceridemia	1 (33.3)	0 (0)
Strzelczyk 2013 [74] SRSE	1 first IV then KF (F)	14	16	3.5 *urine*	*not clearly reported*	1 (100)	7	5	*not reported*	0 (0)	*not clearly reported*
Wusthoff 2010 [75] SE	2 KF (1F, 29yrs; 1 M, 34yrs)	31.5 (29–34)	60.5 (20–101)	9 (8–10) *serum*	5 (4–6)	2 (100)	7.5 (7–8)	3.5 (3–4)	*not reported*	0 (0)	1 (50) n = 1 unclear

ASM; antiseizure medication, F; female, FIRES; febrile infection related epilepsy syndrome, FSMP; food for special medical purposes, IL; intralipid, IV; intravenous, KD; ketogenic diet, KF; ketogenic formulation (KetoCal), M; male, RSE; refractory status epilepticus, SE; status epilepticus, SRSE; super refractory status epilepticus, TPN; total parenteral nutrition

*N = 2 lost to follow up.

**N = 1 no EEG data available.

***N = 5 standard KD locally made with "home-made ingredients" prior to availability the ketogenic formulation under investigation.

ketogenic formulation for one month. Following this period, the ketogenic formulation supplement was discontinued to evaluate its impact. The inclusion of the ketogenic formulation resulted in a significant increase in total daily fat intake, yielding a macronutrient ratio of 1.8:1 compared to the 1:1 ratio observed with MAD alone. The supplement was well tolerated and palatable for the majority of participants (n = 26), with only four children refusing to consume it as a shake but incorporating it into foods instead. Notably, 47 % of participants opted to resume the ketogenic formulation supplementation upon study completion, suggesting its perceived effectiveness, convenience, and palatability. Ashrafi et al. [37] reported that 59 % of children and parents found the diet palatable and tolerable when a 4:1 powdered version of the ketogenic formulation was used to supplement home cooked foods. Similarly, Sampaio et al. [59] found that most patients accepted and tolerated the ketogenic formulation well (4:1 ketogenic formulation given twice daily to supplement oral diet), with only one child (10 %) disliking its taste. Parents and clinicians both highlighted the formulation's ease of use and its role in facilitating KD initiation and adherence.

McDonald et al. [72] compared MAD with a MAD supplemented with the ketogenic formulation (4:1 ratio). Participants rated the taste, texture, and tolerance of MAD with a median score of 8 (out of 10) and convenience with a score of just 6–7. In contrast, convenience and tolerability of the MAD supplemented with the ketogenic formulation scored a median of 9, however the taste score was lower (median score of 6) than with MAD alone. More recently, Griffen et al. [70] reported that 89 % of participants found the ketogenic formulation (2.5:1 ratio) easy to use, and 94 % found it manageable to consume the recommended volume (≥200 ml) and integrate it into their daily routine.

3.5. Adverse effect outcomes

3.5.1. Gastrointestinal tolerance

Gastrointestinal (GI) tolerance of KDT was reported in 27 studies, including seven case reports, while the other papers did not consider or report tolerance as an outcome (see Table 1). The most frequently reported GI symptoms associated with KDT included constipation, vomiting, and diarrhoea, though these were generally not distinguished between those following KD alone, those using the ketogenic formulation studied, or those combining KD with other formulations. Other GI-related symptoms were less commonly reported, including reflux, dysphagia, and abdominal pain or bloating.

Notably, Griffen et al. [70] was the only study to assess the severity of GI symptoms—categorized as none, mild, moderate, or severe—during both a control period of KDT and an intervention period involving KDT plus the ketogenic formulation in a 2.5:1 ratio. No significant differences in individual GI symptoms or the severity of pooled symptoms were observed between the intervention and control periods. Dietitians reported that patients tolerated the intervention feed as expected (ITT: 92 %) and most patients (ITT: 85 %) confirmed they tolerated it well, either by self-report or through their parent or carer. In two studies [12,50], GI tolerance was cited as a reason for discontinuing KDT, whereas in another two [58,60] no significant GI intolerance was reported as a reason for stopping or modifying the diet. Additionally, Sampaio et al. [59] found that patients experienced no major GI side effects or tolerance issues.

3.5.2. Anthropometry

The majority of studies reporting on anthropometry or growth outcomes reported no significant changes to weight [37,38,46,65] or no significant differences between intervention and control [45,70]. Yildirim et al. [67] observed a significant increase in weight and height in infants and young children following a CKD or MAD with the ketogenic formulation for a period of 12 months, but annual growth of those on the CKD fell behind compared to their age. Merino-Hernandez et al. [54] reported suboptimal weight gain in one infant taking the ketogenic formulation.

3.5.3. Biochemistry

As you would expect, many studies included biochemistry outcomes such as lipid panels and blood glucose measurements to monitor typical side effects of KDT, such as hypoglycaemia, acidosis, hyperlipidaemia, hypertriglyceridemia and hypercholesterolemia. No significant differences in incidence of these adverse events were reported between groups following a KD with or without the ketogenic formulation [12,44,55].

4. Discussion

This review explored the safety, acceptability, palatability and efficacy of KetoCal (hereafter referred to as ketogenic formulation) in managing DRE in both children and adults. To our knowledge, this is the first comprehensive review to examine the specific role of a ketogenic formulation in supplementing and facilitating the implementation of KDT. Our findings highlight the benefits of the ketogenic formulation studied in enhancing dietary adherence, improving convenience, and increasing the palatability of KDT, ultimately supporting KDT compliance and its therapeutic potential for individuals with DRE. In addition, several included reports suggest additional benefits of KDT plus the ketogenic formulation versus KDT alone on seizure frequency reduction and seizure severity.

KDT is a well-established intervention for DRE, with clinical evidence supporting its efficacy for over a century [7,76,77]. Since its commercial introduction in 1998, the studied ketogenic formulation has been utilized in 72 studies investigating the efficacy of KDT. This review included 41 studies in which outcomes relevant to the ketogenic formulation users were extractable. Substantial heterogeneity was observed across studies in terms of outcome definitions, assessment timing, and measurement methodologies, with few studies employing validated assessment tools; limitations previously identified in the literature [78].

Reported response rates (proportion of DRE patients reporting a ≥ 50 % SFR) varied somewhat across studies, which may be due to the heterogeneous study samples and differences in epilepsy syndromes studied. However, individuals treated with KDT supplemented with the ketogenic formulation demonstrated a numerically higher pooled average response rate in seizure control at 1, 3, 6, and 12 months of management compared to those following KDT alone. In addition, compared to control groups following KD without use of the ketogenic formulation, a greater proportion of patients were reported to achieve ≥ 50 % SFR [12,50,72] or seizure freedom [44,46].

Moreover, pooled average reported response rates to KD with the ketogenic formulation (~61 % at 1 and 3 months, ~66 % at 6 months and ~ 45 % at 12 months follow-up) in studies included in this review are somewhat higher compared to those of KD alone reported in published RCTs. For example, In an RCT, Neal et al. [76] initiated 73 patients on a CKD and 72 patients on a MCT KD. Compared to baseline they reported that 24.7/29.2 % (CKD/MCT), 24.7/19.4 %, and 17.8/22.2 % experienced a ≥ 50 % SFR at 3, 6 and 12 months, respectively. In addition, Lambrechts et al. [15] reported that 34.6 % and 50 % of their cohort of 26 DRE patients had a ≥ 50 % SFR at 1 and 3 months after introduction of a KD.

These findings suggest that the addition of the studied ketogenic formulation may enhance the efficacy of KDT in managing DRE, which could partly be the result of the increased convenience, palatability and compliance to KDT. No serious adverse events or deaths were attributed to the ketogenic diet with or without the ketogenic formulation, reinforcing the general safety of KDT.

Formulation-based KDs have long been recognized for their potential benefits in KDT, particularly in improving management efficacy, patient compliance, and long-term retention. Early evidence by Kossoff et al. [32] demonstrated that among tube-fed individuals, 59 % experienced a > 90 % SFR, nearly twice the average response rate observed in broader KD populations. This improved efficacy is likely due to increased stability of intake via tube feeds compared to oral diets. Furthermore, in a

cohort study of 109 infants and young children (aged ≤ 3 years), those receiving a ketogenic formulation—either exclusively or in combination with solid foods—were more likely to continue the KD. Recognizing these advantages, the International Ketogenic Diet Consensus Recommendations designated exclusively formula-fed infants and children as having an absolute indication for KDT [9]. McDonald et al. [72] suggest that supplementing MAD with a ketogenic formulation may serve as an effective strategy to enhance compliance in adults with DRE, thereby improving compliance to KDT. Our findings suggest that compliance and thus retention tend to be higher in infants and young children than in adults. Early nutritional support, such as supplementation with the ketogenic formulation under investigation in this review, may contribute to long-term adherence. However, several factors may influence compliance, including patient age, mode of feeding (oral vs. enteral), and the level of support provided to both patients and caregivers by the ketogenic therapy team.

Interestingly, some studies [41] have reported sustained compliance to KD and the studied ketogenic formulation, even when seizure frequency reduction did not meet the commonly targeted threshold of ≥ 50 %. This observation suggests that patients and their caregivers may perceive additional benefits beyond seizure control, such as reductions in seizure severity or overall burden, as highlighted by Griffen et al. [70]. Furthermore, improvements in quality of life or other clinical outcomes may also contribute to continued compliance, underscoring the multifaceted impact of KDT and the ketogenic formulation beyond seizure frequency alone.

The convenience and palatability of the ketogenic formulation are also likely to contribute to improved compliance and retention to KDT. Palatability and especially convenience/ease of use was generally rated highly by patients and parents/caregivers [37,59,70,72]. In a comparison of the MAD with and without the ketogenic formulation supplementation, McDonald et al. [72] found that while the taste of the supplemented diet received a slightly lower median score (6) compared to MAD alone, convenience and tolerability were rated higher (median score of 9). More recently, Griffen et al. [70] reported that 89 % of participants found the ketogenic formulation easy to use, and 94 % were able to integrate the prescribed volume into their daily routine. These findings collectively suggest that specialised KD formulations such as the ketogenic formulation under investigation here may play a critical role in optimising compliance to KDT by enhancing tolerability, convenience and ease of integration into daily life. Finally, if the ketogenic formulation is available as an FSMP, it could make KDT more affordable for families, thereby increasing access to an effective management option for patients with DRE.

Parents and caregivers often report significant improvements in their children's overall quality of life and other non-seizure outcomes when managed with KDT [24,25]. However, the assessment and understanding of these benefits remain limited in the existing literature [78]. Notably, within this review, only Le Pichon [52] and Griffen [70] considered quality of life and health-related quality of life, respectively. Additionally, Cervenka [69] assessed GCS as an indicator of cognitive function. While findings suggest that KD supplemented with the ketogenic formulation, may support cognitive and functional improvements, the quality of outcome assessment was often poor, relying primarily on subjective caregiver reporting. Future research should therefore use standardised, validated assessment tools to more clearly define the full impact of KDT on quality of life. However, measuring functional and quality of life outcomes in this population—often comprising children and adults with complex care needs—remains particularly challenging. Existing quality of life measures can fail to fully capture the small, yet meaningful improvements, and may emphasise limitations rather than abilities [24]. Anecdotally, caregivers have highlighted that such tools fail to reflect the day-to-day functional changes they consider most valuable.

In light of this, there is increasing recognition of the need for outcome measures that better reflect meaningful benefits for patients with DRE and their families. Recent initiatives include the development and validation of The Seizure Related Impairment Assessment Scale (SERIAS), an instrument that assesses seizure burden alongside treatment-related side effects [79] and a proxy-reported outcome measure is under development, tailored for children with DRE treated with KDT, focusing on quality of life and social functioning (in preparation). These tools may provide more sensitive and relevant metrics for evaluating the full spectrum of benefits beyond seizure reduction.

Participants had trialled between zero and twelve antiseizure medications (ASMs) before initiating the KD, exceeding the recommended two to three ASMs prior to considering KDT [9]. This suggests that KDT continues to be introduced late in the epilepsy management pathway. Additionally, adjustments to ASM dosage or number were reported in only seven studies. Parents and caregivers are often highly motivated to reduce ASM use due to concerns about adverse effects for their children [25], highlighting the need for greater consideration of ASM use in future research.

RSE is a severe neurological condition in which seizures persist despite first- and second-line management options. In many cases, it progresses to SRSE, where seizures continue for ≥ 24 h despite anaesthetic therapy or recur upon withdrawal. FIRES predominantly affects previously healthy children and young adults following a mild febrile illness, often leading to RSE or SRSE [80]. These conditions are devastating, frequently resulting in long-term cognitive impairment, significant morbidity, and mortality. The use of KDT in these critical scenarios is gaining traction [81]. In intensive care settings, KDT can be initiated rapidly using ketogenic formulations or ketogenic PN, facilitating metabolic adaptation even in critically ill patients. KDT has shown promise as an effective adjunctive management option with many patients achieving resolution of status epilepticus (Table 2). Despite its efficacy in managing status epilepticus, it is often introduced late in the course of management (ranging from 1 to 110 days; Table 2), prompting consideration of whether earlier implementation could lead to better outcomes.

Across five studies examining adults with SRSE treated with KDT, an unexpectedly high proportion of patients continued an oral KD beyond the acute phase of ICU admission (2/2 [73]; 1/1 [68]; 6/11 [69]; and 1/8 [71]). Notably, these individuals not only recovered from a critical condition but also had to adapt to a complex dietary regimen while managing co-existing comorbidities—an adjustment that is likely to be both challenging and unexpected. However, patient perspectives and experiences regarding the longer-term continuation of KDT following ICU discharge remain largely unexplored. Further investigation into these factors could provide critical insights into adherence, tolerability, and potential therapeutic benefits, thereby informing clinical practice and enhancing patient-centred care.

Vitamin and mineral deficiencies are a recognised risk associated with KDT due to its restrictive nature [82–84]. To mitigate this risk, KDT protocols typically include comprehensive vitamin and mineral supplementation [9]. The ketogenic formulation under investigation is nutritionally complete, providing a broad spectrum of essential micronutrients alongside a ketogenic macronutrient composition, making it a valuable adjunct in KDT management. While none of the studies in this review specifically evaluated the adequacy of vitamin and mineral intake in individuals following KDT, it is plausible to suggest that the inclusion of the ketogenic formulation as a supplement may enhance overall micronutrient sufficiency. Further research is warranted to assess its effectiveness in preventing deficiencies and optimising nutritional status in this population.

GI tolerance is often not reported separately for the ketogenic formulation group; however, the findings of this review align with existing literature, which identifies constipation, vomiting and diarrhoea as common issues associated with KDT [6,7]. To help mitigate GI symptoms, liquid variants of the ketogenic formulation have been developed that incorporate a unique multi-fibre blend while maintaining the same low carbohydrate high fat macronutrient profile. This

multi-fibre blend has demonstrated improved tolerance compared to single-fibre supplements [85]. Notably, a study by Griffen et al. [70] found a significant increase in the number of patients reporting an absence of GI symptoms after introducing a multi-fibre LQ version of the ketogenic formulation studied. In addition, McDonald et al. [72] reported a trend for fewer cases of constipation in those managed with MAD plus a multi-fibre version of the ketogenic formulation compared to those managed with MAD alone.

5. Strengths and limitations

This is the first comprehensive synthesis of evidence on the use of a specific ketogenic formulation (KetoCal) in DRE. Strengths of the review include the use of systematic search strategies, blinded screening with agreement between independent reviewers, piloting of the data extraction tool and partial double data extraction to enhance reliability. However, some limitations should be noted. We did not perform a formal quality appraisal or risk of bias assessment of the included studies, which may affect the rigour of findings. The scope of the review was limited to a single ketogenic formulation. While this focused approach may limit generalisability, it enabled a more detailed exploration of the evidence specific to this formulation and its use, recognising that formulations vary widely. Moreover, the formulation studied was the only one available for a long time; other ketogenic formulations were introduced only in the late 2010 s and early 2020 s, and there is limited literature on their use to date. The review was funded by the manufacturer of the ketogenic formulation studied, which may introduce potential bias despite deliberate efforts to maintain objectivity. To mitigate this risk the author team included experienced ketogenic dietitians and medical review of the manuscript was undertaken by an expert in the field. As is typical for scoping reviews, we do not offer clinical recommendations but instead highlight gaps in the literature and inconsistencies in reporting the use of ketogenic formulations. Addressing these issues in future research could enhance the quality and comparability of studies in this field.

6. Conclusions and future work

This review highlights the integral role of KetoCal, a specialised ketogenic formulation, in enhancing compliance, convenience, and palatability of KDT for children and adults with DRE. Additionally, this ketogenic formulation plays a vital role in facilitating KDT administration in intensive care settings, particularly for managing (S)RSE. While the formulation offers nutritional benefits, including micronutrient sufficiency when used as a sole source of nutrition, its direct impact on seizure reduction remains variable, although several reports suggest additional benefits of KD plus the ketogenic formulation versus KD alone on SFR and seizure severity. Future research should focus on improving consistency in outcome reporting, particularly by incorporating assessments of non-seizure outcomes, which are highly relevant to parents. Additionally, few studies have documented the actual volume of the ketogenic formulation consumed or the proportion of nutritional requirements it fulfils, making this an important area for future comparisons. As the use of KDT in intensive care settings continues to rise, exploring patient perspectives and experiences regarding long-term adherence to KDT post-ICU discharge remains crucial.

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CRediT authorship contribution statement

Jennifer H. Carroll: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Zoe Simpson:** Writing – review & editing. **Laura Healy:** Writing – review & editing. **Clare Szwec:** Writing – review & editing. **Denise Leonne Hofman:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization.

Declaration of competing interest

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Appendix 1. PubMed search strategy

refractory [tiab] OR intractable [tiab] OR resistant [tiab]

AND

KetoCal OR formula OR feed
Filters: from 1998/1/1—–2024/11/29
Filters:

- Publication date: from 1998/1/1—–2024/11/29
- Article type: Case Reports, Classical Article, Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Dataset, Equivalence Trial, Evaluation Study, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Validation Study
- Species: Human

Search returned 280 records.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2025.110683.

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