

REVIEW

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Practical considerations of dietary therapies for epilepsy in adults



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Abstract

Despite the increasing number of anti-seizure medications becoming available, the proportion of patients with drug-resistant epilepsy remains unchanged. Dietary therapy for epilepsy is well-established practice in paediatric care, but relatively underutilised in adults. Recently, international recommendations have been published to guide the treatment of adults receiving dietary therapy for epilepsy.

This review focuses on the specific aspects of care unique to the management of adults receiving dietary therapy for epilepsy, including patient selection, diet composition, initiation, monitoring and cessation of dietary treatment. We emphasise the need for a multidisciplinary team approach with appropriately trained neurologists and dietitians to provide holistic care while the patients are receiving dietary therapy. Future research should focus on the optimal diet composition and meeting the psychosocial needs of adults with epilepsy to maximise efficacy and adherence to dietary treatment.

Keywords: Ketogenic diet, Epilepsy, Diet, Drug-resistant epilepsy, Nutrition

Background

Epilepsy is one of the most prevalent, serious neurological disorders, affecting approximately 50 million people worldwide. Epilepsy is associated with poorer health outcomes, including not only physical disability, but significant psychological and emotional burden leading to poor quality of life [1]. The underlying causes of epilepsy can be genetic, structural, metabolic, infectious, immune or in many cases the cause remains unknown [2].

For approximately 70% of people with epilepsy, seizures will be controlled with 1 or 2 anti-seizure medications [3]. Despite the growing number of anti-seizure medications that have become available over the past two decades, the proportion of people with drug-resistant epilepsy and uncontrolled seizures remains unchanged [4]. Non-drug treatment options for drug-resistant epilepsy may include surgery, neuromodulation and dietary therapy [5, 6].

Ketogenic diet therapy has been used for epilepsy treatment for over 100 years, traditionally in children. More recently, there have been an increasing number of trials investigating its efficacy in adults [7, 8]. In 2020, the first international recommendations for the management of adults treated with ketogenic diet therapies were published [9].

The classical ketogenic diet is a very low carbohydrate, high fat diet, which is difficult for children and adults to comply with [10]. Over time, there has been development in variations of the classical ketogenic diet, including the modified Atkin's, modified ketogenic, medium chain triglyceride and low glycaemic index diets (Table 1) [8]. These less restrictive diets have fuelled further interest in the use of dietary treatments in adults with drug-resistant epilepsy in the context of a multifaceted approach to attaining better seizure control.

Dietary management of epilepsy has a number of advantages over adding multiple anti-seizure medications in patients with drug resistant epilepsy and uncontrolled seizures. Unlike anti-seizure drugs, dietary therapies are not associated with neurotoxic adverse effects, idiosyncratic reactions, or pharmacokinetic interactions through hepatic enzyme induction. Dietary therapies may have

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additional benefits, such as weight management and patient empowerment for self-management of chronic diseases.

In this review, we focus on the practical aspects specific to the use of dietary therapies for epilepsy in adults in the outpatient setting. Use of dietary therapies for emergency inpatient indications (e.g. status epilepticus) has been discussed elsewhere [11].

Efficacy of dietary therapy for drug-resistant epilepsy in adults

There have been a small number of published randomised controlled and prospective, open-label studies investigating the efficacy and tolerability of dietary therapy for drug-resistant epilepsy in adults published to date [7, 12]. These studies vary in the dietary prescription used and duration of treatment. Response rate to dietary therapy, defined as $\geq 50\%$ reduction from baseline ranged between 21 and 86%, confounded by high drop-out rate and poor compliance with the dietary intervention. Adverse effects reported were rated as mild or moderate, namely weight loss, hyperlipaemia and gastrointestinal symptoms. The majority of adverse effects were transient and considered preventable or treatable, although they may have contributed to participant drop-out. The long-term effects on the development of cardiovascular disease require further investigation [13].

The multidisciplinary dietary therapy team

Essential to the dietary therapy team are dietitians and neurologists with experience in the management of dietary therapies for epilepsy. The neurologist is responsible for overseeing the overall epilepsy management plan, including assessing suitability, monitoring and evaluation of dietary therapy. The dietitian formulates the nutrition prescription and provides nutrition education on implementing and maintaining dietary therapy. The dietitian closely monitors the patient's nutritional status and makes adjustments to the nutrition plan as required to minimise adverse effects associated with the diet. The addition of trained multidisciplinary healthcare professionals further supports the diet program. Epilepsy nurses may provide additional training on completion of seizure diaries, ketone testing and coordinate patient investigations. The inclusion of a pharmacist in the dietary therapy team is beneficial in reviewing and minimising carbohydrate content of medications and drug-diet interactions. Some patients may also benefit from psychological support to assist with the transition onto dietary therapy and maintain adherence.

A centre-based guideline for the model of care for the diet program should be in place. Aspects of the model of care to consider include referral and treatment pathways,

frequency and method of contact and frequency of pathology monitoring. Careful attention should be given to management of acute illness, hospital presentation, peri-operative and out-of-hours management [14]. Consultation with emergency, general medicine, surgery and intensive care unit departments may be required. In addition, adequate communication of dietary therapy plans should be provided to the patient's primary care physician and associated healthcare providers.

Dietary therapy most commonly is initiated in the outpatient setting; however the initiation protocol varies between centres [9]. Some centres have reported gradual introduction of the diet over days or weeks, whilst others report a more rapid transition depending on the individual patient's circumstances. Inpatient commencement of dietary therapy may be required in certain situations, where increased monitoring or complex, high intensity multidisciplinary support is required e.g. comorbid diabetes, oral feeding difficulties or gastrointestinal intolerance.

Patient selection

Generally speaking, dietary treatment can be considered for patients with drug-resistant epilepsy that is not amenable to epilepsy surgery. For patients diagnosed with glucose-transporter-1 or pyruvate dehydrogenase deficiency syndrome, dietary therapy is recommended as first-line treatment [15].

Patients should be evaluated for contraindications prior to commencing dietary therapy.

Fatty acid transport or oxidation disorders, disorders of carnitine metabolism and certain inherited errors of metabolism are absolute contraindications for dietary therapy [16]. The safety of dietary therapy for epilepsy during pregnancy and lactation is unknown. Data from animal studies of ketogenic diet exposure during pregnancy has shown harmful effects on maternal fertility and increased risk of ketoacidosis during lactation, as well as impaired foetal development [17, 18]. Careful risk and benefit assessment and appropriate counselling should be provided to females of child-bearing potential.

Relative contraindications may include the presence of metabolic comorbidities such as diabetes mellitus, liver or renal disease, malnutrition, food allergies or intolerance, history of kidney stones and cardiovascular disease. Increased monitoring or modifications to the dietary prescription may be required for patients with these conditions.

There are limited data on the safety and efficacy of dietary therapy in the older adults. This age group is particularly susceptible to cognitive adverse effects of anti-seizure medications, drug-drug interactions, and may not be suitable candidates for epilepsy surgery due to comorbidities. Therefore, dietary therapy may have

Table 1 Overview of dietary therapy for epilepsy prescription types

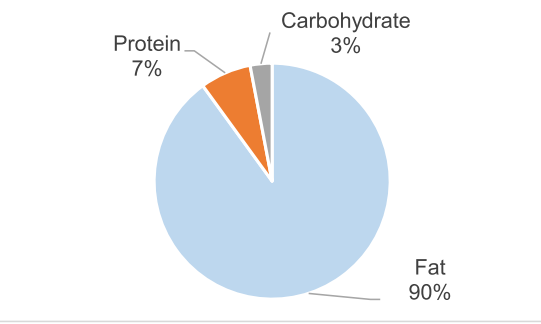
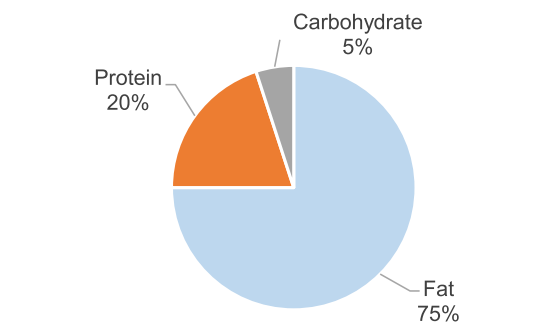
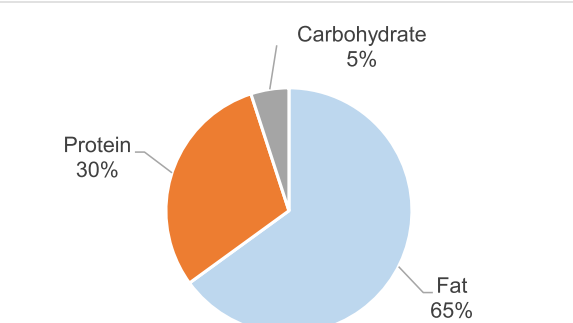
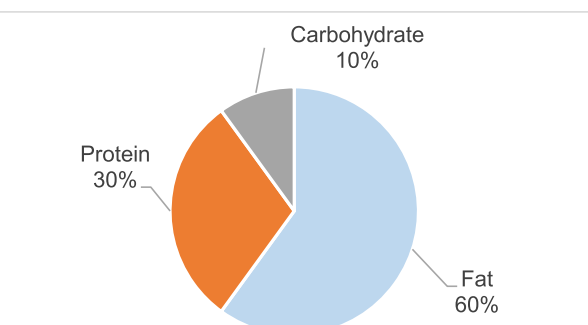
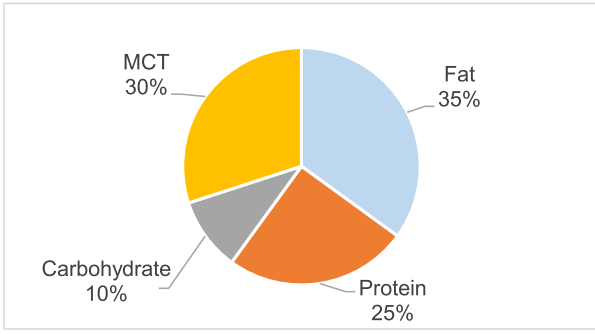
Diet type	Overview	Composition
Classical ketogenic diet	Prescribed as a fixed ratio of grams of fat:non-fat e.g. 4:1 or 3:1. All food and fluids must be weighed/measured and provided in the set ratio.	 <p>A pie chart representing the macronutrient composition of a classical ketogenic diet. The largest slice is light blue, representing Fat at 90%. A smaller orange slice represents Protein at 7%, and a very thin grey slice represents Carbohydrate at 3%.</p>
Modified ketogenic diet	Prescribed as a daily dietary macronutrient distribution. Uses household measures and smartphone applications for monitoring of dietary intake targets.	 <p>A pie chart representing the macronutrient composition of a modified ketogenic diet. The largest slice is light blue, representing Fat at 75%. An orange slice represents Protein at 20%, and a grey slice represents Carbohydrate at 5%.</p>
Modified Atkins® diet	Carbohydrate intake is limited to <30g per day. Liberal intake of protein, and fats are encouraged. Uses household measures and smartphone applications to monitor daily carbohydrate intake.	 <p>A pie chart representing the macronutrient composition of a modified Atkins diet. The largest slice is light blue, representing Fat at 65%. An orange slice represents Protein at 30%, and a grey slice represents Carbohydrate at 5%.</p>
Low Glycaemic Index Diet	Carbohydrate intake is limited to 50g per day with the glycaemic index of <50. Liberal intake of protein, and fats are encouraged. Uses household measures and smartphone applications to monitor daily carbohydrate intake	 <p>A pie chart representing the macronutrient composition of a low glycaemic index diet. The largest slice is light blue, representing Fat at 60%. An orange slice represents Protein at 30%, and a grey slice represents Carbohydrate at 10%.</p>

Table 1 Overview of dietary therapy for epilepsy prescription types (Continued)

Diet type	Overview	Composition
Medium Chain Triglyceride (MCT) supplements	Used in conjunction with other dietary therapy regimens to improve ketosis, treatment response and/or allow increased protein and/or carbohydrate provision. Provided at up to 30% of total caloric intake.	 <p>A pie chart illustrating the composition of the diet. The chart is divided into four segments: Fat (35%, light blue), Protein (25%, orange), MCT (30%, yellow), and Carbohydrate (10%, grey). Each segment is labeled with its component and percentage.</p>

advantages over other treatment options. However, highly restrictive diets in the older adults may increase the risk of the development of malnutrition and negatively affect quality of life [19]. Additionally, the risk of complications of cardiovascular disease also require consideration. Further research is needed to evaluate the risk versus benefit of dietary therapy for epilepsy in this patient population.

Selection of types of dietary therapy

Over the past two decades, there have been a number of variations of the classical ketogenic diet to make these more feasible in adults, including the modified ketogenic, modified Atkin's, low glycaemic index and medium chain triglyceride diets used in epilepsy treatment (Table 1). To date, no head-to-head evaluation trials comparing the different dietary regimens in adults has been conducted. A more pragmatic approach may be taken in the clinical setting, evaluating the patients' baseline nutrition knowledge, level of commitment to dietary therapy and lifestyle factors when deciding on the appropriate dietary therapy. In addition, patients may transition from one diet regimen to another. For example, when first commencing on dietary therapy, a less restrictive option such as the low glycaemic index diet may first be instituted, then subsequently the patient may transition to a modified ketogenic diet. Similarly, if a patient has had a good response to the modified ketogenic diet, but was experiencing adverse effects, such as gastrointestinal intolerance, unintentional weight loss or maintaining adherence, a trial of transition to a less restrictive diet option may be considered.

Diet initiation

At the initial consultation, the dietitian in consultation with the neurologist will evaluate a patient's suitability for dietary therapy, recommend an appropriate diet prescription and request appropriate investigations (see Table 2). On commencement of dietary therapy for

epilepsy, consideration should be made on the expected duration of dietary treatment for assessment of efficacy. In general, the patient should aim to maintain their recommended diet for a minimum of 3 months to assess tolerability and efficacy.

The dietitian should provide nutrition education and counselling and advise on nutrition, vitamin and mineral supplementation, in particular b-group vitamins, calcium, vitamin D and selenium [20]. Carnitine is essential in the metabolism of fatty acids and valproic acid. Patients receiving valproic acid concurrently with a high fat diet are at higher risk of carnitine deficiency. Carnitine deficiency may in turn result in ineffective metabolism of valproic acid and fatty acids and may lead to cardiomyopathy, elevated ammonia and hyperlipidaemia. Prophylactic oral levocarnitine supplementation should be given to prevent deficiency commencing at a minimum of 10 mg/kg/day. Levocarnitine dosage can be increased to a maximum dose of 3000 mg per day if there is suspected or confirmed deficiency, elevated blood lipids and/or elevated ammonia levels [21, 22]. Patients receiving carbonic anhydrase inhibitors such as zonisamide and topiramate, may be at higher risk of kidney stones and should be monitored appropriately. Treatment of metabolic acidosis with potassium citrate may prevent the formation of kidney stones [23].

Monitoring of dietary therapy

At each follow-up visit the dietary prescription, tolerability, treatment efficacy and side-effects should be evaluated and the results of the monitoring investigations reviewed (see Table 2). Decisions to change dietary prescription and management of adverse effects should be made in collaboration with the patient, dietitian and neurologist.

The most common reported adverse effects for adults receiving dietary therapy have been gastrointestinal disturbance, including constipation, diarrhoea, nausea and vomiting [7, 9]. Constipation can be initially managed

Table 2 Recommended monitoring investigations for adults while receiving dietary therapy for epilepsy [9]

Investigation	Parameter	Frequency
Nutrition assessment	Mandatory Height Weight Dietary intake Side effects	Baseline Each clinic visit
Pathology	Mandatory Urea and electrolytes Liver function tests Full blood examination Blood urea nitrogen Fasting lipid profile Fasting glucose	Baseline Every 3–6 months
	Mandatory Carnitine (if on valproate) Vitamins & mineral levels: vitamin D, vitamin B12, folate, iron studies, zinc, Selenium	Baseline Every 6–12 months
	As clinically indicated Ammonia Plasma amino acids Serum beta-hydroxy-butyrate HbA1c Drug levels Blood ketone levels Blood glucose levels	As required
Other investigations	Urinalysis Urine organic acids Urine creatine calcium ratio Urine ketone levels	As required
	Electroencephalogram Electrocardiogram Lumbar puncture Radiological imaging Renal tract ultrasound Bone density testing	As required

with dietary manipulation, ensuring adequate fibre and fluid intake. Laxatives may be required if constipation persists. Smaller and more frequent meals and snacks may assist with management of nausea, vomiting and diarrhoea. If fat malabsorption is suspected, introduction of medium chain triglycerides may be beneficial. Dyslipidaemia may occur initially when commencing dietary therapy for epilepsy, however in the majority of cases the levels return to baseline by 12 months. Persistent hyperlipidaemia can be managed by increasing the ratio of mono- and poly-unsaturated fats, in particular omega-3 fatty acids and reducing saturated fats in the diet [16].

Similar to anti-seizure medications, treatment efficacy of dietary therapy for epilepsy is usually defined as > 50% reduction in seizure frequency from baseline [24]. However, individualised assessment of treatment efficacy should also be considered. Examples of this may include reduction in hospital admissions, reduction in convulsive seizures, reduction in drug burden, shorter duration, intensity or recovery period of seizures, improvement in mood and/or improvement in cardiovascular disease risk factors.

Concurrent reduction in anti-seizure medications and liberalisation of dietary prescription should be avoided. If relevant, advice on the implication of medication and diet changes on driving restrictions should be provided in accordance with the local driving guidelines.

Duration of dietary therapy

With the exception of patients with glucose-transporter-1-deficiency syndrome and pyruvate dehydrogenase deficiency, where dietary treatment is lifelong, it is common in paediatric practice to discontinue diet after 2 years [16]. In adult patients, who are seizure-free, it may be acceptable to consider the same two-year period for diet weaning. However, in adults who have responded to dietary therapy, but continue to have seizures and diet is well tolerated without adverse effects, it may be reasonable to continue diet long-term.

Discontinuation of dietary therapy

A weaning schedule should be prepared in consultation with the patient, dietitian and neurologist. The weaning schedule includes a gradual reintroduction of carbohydrate and reduction of fats the diet. Rapid reintroduction

of carbohydrate may result in breakthrough seizures. There is high variability in diet weaning protocols between centres, from immediate cessation to gradual reduction over greater than 3 months [9]. The diet prescription, treatment duration, efficacy, patient adherence and adverse effects are all factors that influence the down titration schedule. In patients where dietary therapy has been ineffective, of short duration (i.e., less than 6 months) and/or presence of serious adverse effects, transition to a regular diet may occur more rapidly. In contrast, diet weaning may occur more gradually in patients with improved seizure control or on a longer duration (i.e., more than 1 year) of dietary therapy.

Provision of dietary therapy

Dietary therapy is a well-established treatment in paediatric epilepsy, however the practice has not been widely translated into adult care. In a recent international survey of neurology care providers only 17% of respondents stated dietary therapy for epilepsy was a “very” or “extremely” accepted treatment in adults compared to 84% in children [25]. Adult neurologists and dietitians may lack adequate exposure and training in dietary therapy for epilepsy, leading to reduced use. Internationally, there are few dedicated adult dietary therapy for epilepsy services [9, 26]. It is particularly problematic for children transitioning from paediatric to adult care when an appropriate adult dietary service is not available. In this situation, adults may have to remain under paediatric services or cease dietary therapy. Moreover, there may be a reluctance to offer dietary therapy to adolescents due to inability to continue care into adulthood.

Despite there being similarities in the way dietary therapy is provided to children and adults with epilepsy, the high attrition rate in adult trials may be of concern to adult neurologists when recommending dietary therapy [7]. Development of dietary regimens, specific to the nutritional needs of adults including dietary advice tailored to the individual's preferences may be beneficial to improve the acceptance of dietary therapy. In addition, frequent access to a specialist dietitian, up-to-date resources, adequate health insurance coverage, food subsidies and patient peer support may also aid in improving dietary therapy adherence for adults.

Conclusion

Diet is an underutilised treatment for adults with drug resistant epilepsy. Inclusion of dietary therapy for epilepsy curriculum should be included as part of training for adult neurologists and dietitians providing epilepsy care. In addition, an expansion of the current level is needed to ensure adults with epilepsy have sufficient access to specialist dietary therapy services. Future research should aim to address the specific nutrition and

psychosocial needs of adults for maintaining dietary therapy for epilepsy.

Abbreviation

MCT: Medium Chain Triglyceride

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NK conceptualised the manuscript idea and drafted the initial manuscript; J-PN, PK and TOB revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

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Consent for publication

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Competing interests

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