RESEARCH

International Recommendations for the Management of Adults Treated With Ketogenic Diet Therapies

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Abstract

Objective

To evaluate current clinical practices and evidence-based literature to establish preliminary recommendations for the management of adults using ketogenic diet therapies (KDTs).

Methods

A 12-topic survey was distributed to international experts on KDTs in adults consisting of neurologists and dietitians at medical institutions providing KDTs to adults with epilepsy and other neurologic disorders. Panel survey responses were tabulated by the authors to determine the common and disparate practices between institutions and to compare these practices in adults with KDT recommendations in children and the medical literature. Recommendations are based on a combination of clinical evidence and expert opinion regarding management of KDTs.

Results

Surveys were obtained from 20 medical institutions with >2,000 adult patients treated with KDTs for epilepsy or other neurologic disorders. Common side effects reported are similar to those observed in children, and recommendations for management are comparable with important distinctions, which are emphasized. Institutions differ with regard to recommended biochemical assessment, screening, monitoring, and concern for long-term side effects, and further investigation is warranted to determine the optimal clinical management. Differences also exist between screening and monitoring practices among adult and pediatric providers.

Conclusions

KDTs may be safe and effective in treating adults with drug-resistant epilepsy, and there is emerging evidence supporting the use in other adult neurologic disorders and general medical conditions as well. Therefore, expert recommendations to guide optimal care are critical as well as further evidence-based investigation.

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Ketogenic diet therapies (KDTs) are high-fat, low-carbohydrate, adequate protein diets that induce fat metabolism and ketone body production. KDTs are effective in children with specific seizure types and epilepsy syndromes, which are often lifelong conditions, and require transition to adult providers for ongoing care. Within the last 2 decades, KDT use has increased in adult epilepsy management, with an emerging interest in neurologic disorders with no prior KDT use, such as dementia, Parkinson disease, and brain tumors.[1] KDT variants have also gained popularity for weight loss, type 2 diabetes, and exercise performance[2,3] among other non-neurologic conditions. Dedicated adult KDT centers remain scarce, leaving interested non-specialist clinicians with little or no evidence-based guidance to enable support for KDT treatment in their adult patients.[4–7]

This study synthesized results from a survey compiled from an international panel with experience treating adults with KDTs for epilepsy and other neurologic disorders about current clinical practice of KDTs for adults. The purpose was to identify common practices and compare these with more well-established pediatric practices and scientific evidence. We hypothesized that the application of KDTs at different medical institutions would vary but that common evidence-based practices were used and could be used to formulate a series of recommendations for use by neurologists, dietitians, nutritionists, general practitioners, and clinical researchers investigating use of KDTs in adults.

Methods

The lead authors (M.C.C. and S.W.) identified 20 medical institutions with expertise in treating adults with KDTs for epilepsy and other neurologic disorders and invited them to complete a 12-topic survey and contribute to the publication. Institutional representation consisted of 1 expert or expert pair (1 registered dietitian and/or neurologist), with practices established for >1 year treating >5 adults (patients aged 18 and older) with KDTs, although not exclusively in all instances (table 1). Participants were initially identified from attendees at the Fifth Global Symposium on Ketogenic Diet Therapies in 2016 who expressed interest in participating. The lead authors also attempted to contact the corresponding authors of articles published before 2017 in which the published document indicated that their research was conducted with adult participants. The topics included the distribution of institutions and patients treated, the types of KDTs used and criteria for individualized selection, how the therapies were initiated, monitored, supplemented and discontinued, contraindications, adverse effects and adherence. Surveys were distributed and returned by electronic mail and responses tabulated by topic in 2017–2018 (see supplemental file, links.lww.com/CPJ/A230). Authors from each institution summarized the survey findings and compared these with the current literature supporting or refuting the results when available and produced recommendations (Results and table 2). Responses to individual survey questions were presented as the percentage of agreeing respondents. For individual survey questions with incomplete responses, the percent agreement was determined with a denominator representing the number of responses that were provided. The lead authors combined submitted sections into a single document and removed redundancies, and the coauthors further revised the manuscript. All authors reviewed and revised a draft document and approved the final version for submission.

Standard Protocol Approvals, Registrations, and Patient Consents

Creation of this article did not involve experiments using human subjects, and there are no patient participants, recognizable persons in photographs, or videos included.

Data Availability

Any data not published within this article will be shared at the request of other investigators for purposes of replicating procedures and results.

Results

The international panel on adult KDTs included participants from 20 medical institutions (United States 9, United Kingdom 3, and 1 each in Canada, the Netherlands, Norway, Ireland, Italy, Australia, New Zealand, and India). The majority of the evidence supporting the panel recommendations was Class III and Class IV evidence. The highest class of evidence for each recommendation is included in the article when higher than Class IV and is otherwise based on panel consensus.

KDTs Used in Adults

Survey Results

An estimated 2,189 adults received evaluation for KDTs within the 20 centers at the time that the survey was completed (table 1). The mean number of patients seen at a single institution was 109 (median 90, SD ±92). The majority of patients began KDT as an adult, whereas 0%–42% transitioned from a pediatric ketogenic diet center to the adult clinic. The majority of institutions (60%) treated only adults with epilepsy, and the remainder treated adults with epilepsy and other neurologic disorders including brain tumors, headache disorders, Alzheimer disease, Parkinson disease, inclusion body myositis, Huntington disease, and normal pressure hydrocephalus. One center (Waikato Hospital) also treated adults with KDT for general medical conditions including non-neurologic malignancy and type 2 diabetes.

The panel agreed on definitions of 5 KDTs for the purpose of this article (table 3).[4,5,8–16] Nearly all institutions used 2 or more KDTs to treat 1 or more adults. Ninety percent used modified Atkins diet (MAD), and 84% used classic ketogenic diet (CKD), whereas 63% used modified ketogenic diet

(MKD) and/or low glycemic index treatment (LGIT). Fifty-eight percent used medium-chain triglyceride (MCT) oil in combination with another KDT to enhance ketone body production. Panel respondents identified the most important factors influencing the choice of KDT as follows: ease of diet application for the patient (100%), patient and/or caregiver preference, home setting, and mode of feeding (i.e., oral vs enteral feeding; 90% each).

Classification of Evidence

To date, there have been no clinical trials directly comparing safety, tolerability, feasibility, and/or efficacy of KDTs compared with one another exclusively in adults as defined.[17]

Recommendations

KDTs should be tailored to the needs of the individual, taking into consideration patient characteristics, underlying medical conditions, preference, support structure, autonomy, mode of feeding (nutritionally complete commercial formulas are available for use by tube-fed individuals), and ease of application. Therefore, all KDT strategies may be used to treat adults, the most common being MAD followed by CKD, then MKD and LGIT. MCT oil may be used with all forms of KDT. Randomized clinical trials directly comparing KDTs in adults are needed.

Selection of Adults With Seizure Disorders for KDTs

Survey Responses

There was a strong consensus among the panel about offering KDTs for the treatment of antiseizure drug (ASD)-resistant focal epilepsies (90%). The panel also recommended KDTs for adults with generalized epilepsies; 74% and 53% treated adults with juvenile myoclonic epilepsy and juvenile absence epilepsy, respectively. Most (74%) treated adults with Lennox-Gastaut syndrome (LGS) with KDTs and tube-fed adults (80%). A small portion (21%) reported starting KDTs as a first-line therapy. For adult patients with glucose transporter type 1 deficiency syndrome (G1DS), the panel agreed that the current standard of care is KDT.[18]

Evidence

KDTs have been shown to be particularly effective in children with specific disorders including tuberous sclerosis complex, LGS, Rett syndrome, G1DS,[18] genetic generalized epilepsies, polymicrogyria, and focal cortical dysplasia, which can all be lifelong diseases.[8] Pediatric guidelines[8] emphasize the importance of successful transitioning from pediatric to adult epilepsy diet centers.[19] Electroencephalography and brain MRI (when focal epilepsy is suspected) may improve characterization of epilepsy etiology before KDT initiation. These studies may reveal appropriate KDT candidates or patients who are more appropriate for epilepsy surgery.

Published randomized controlled trials of KDT use in adults with drug-resistant epilepsy are emerging[5,20,21] (Class II evidence). The degrees of response (0%–56%) vary substantially between reports and are influenced by poor adherence. Other factors such as ASD history, duration of seizure disorder, structural etiology, and reduction in serum concentrations of some ASDs[5] may also influence efficacy. However, studies indicate that adults with ASD-resistant focal epilepsy are more likely to respond to surgical evaluation than KDT when appropriate, given the higher anticipated rate of seizure freedom if performed[22,23] (Class III evidence). As in children, adults treated with KDTs frequently report benefits beyond fewer seizures such as reduced severity, a shorter postictal period, improved cognition, attention, sleep, and quality of life.[14]

Recommendations

KDTs are appropriate to offer to adults with seizure types and epilepsy syndromes for which these treatments are known to be effective in children including tuberous sclerosis complex, Rett syndrome, LGS, G1DS, genetic generalized epilepsies, and focal epilepsies due to underlying migrational disorders and resistant to ASDs. However, adults with ASD-resistant focal epilepsy should be offered surgical evaluation first, given the higher anticipated rate of seizure freedom via this route.[22,23]

Selection of Adults With Nonepilepsy Disorders for KDTs

Survey Results

One-third of the panel used KDTs in adults with brain tumors, 15% used KDTs to treat adults with migraine, 15% to treat adults with type II diabetes, and 15% used KDTs to treat adults for other nonepilepsy indications such as weight loss, Parkinson disease, metastatic (not primary) brain cancer, multiple sclerosis, and/or progressive supranuclear palsy.

Evidence

In the last decade, numerous KDT applications have been proposed for adults, particularly for obesity, type 2 diabetes, and related complications.[2] Positive results have emerged in other neurologic disorders including migraine comorbidity with obesity[24] and cluster headache.[25] Evidence shows that ketone bodies may be neuroprotective, increase mitochondrial biogenesis, and may have promising applications in neurodegenerative disorders such as Parkinson disease,[26] dementia,[27,28] and multiple sclerosis.[29] Finally, KDTs are also being explored in the treatment of adults with malignancy[30] (in particular malignant glioma[31]), amyotrophic lateral sclerosis,[32] stroke,[33] and psychiatric disorders.[34]

Recommendations

Adults with nonepilepsy neurologic and medical conditions interested in KDTs are encouraged to seek medical supervision and enrollment in ongoing clinical trials.

Contraindications and Potential Adverse Effects of KDTs in Adults

Survey Results

Only 11% of the panel considered a history of cardiovascular disease to be an absolute contraindication to KDTs, whereas

Table 1 Experience of the International Panel Treating Adults With Ketogenic Diet Therapies (KDTs)

Medical institution	Year adult treatment commenced	No. of adults treated	No. of adults on KDT that transitioned from the pediatric center (%)	No. of adults with epilepsy treated with KDT (%)
Dr. Janak Nathan's Sanjiv Clinic, Mumbai, India	1996	65	10 (15)	50 (77)
Academic Center for Epileptology, Kempenhaeghe and Maastricht University Medical Center, Heeze, The Netherlands	2005	68	7 (10)	68 (100)
The Charlie Foundation for Ketogenic Therapies, Santa Monica, CA	2006	100	36 (36)	28 (28)
University College London Hospitals NHS Foundation Trust, London, United Kingdom	2006	45	1 (2)	40 (89)
Mid-Atlantic Epilepsy and Sleep Center, Bethesda, MD	2007	100	9 (9)	72 (72)
Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Italy	2009	300	0 (0)	26 (9)
The Barberry, Birmingham, United Kingdom	2009	55	4 (7)	55 (100)
Johns Hopkins Hospital, Baltimore, MD	2010	330	21 (6)	330 (100)
Mater Group, South Brisbane, Australia	2010	53	2 (4)	53 (100)
National Center for Epilepsy, Oslo, Norway	2010	130	20 (15)	130 (100)
New York University School of Medicine, New York	2010	100	15 (15)	95 (95)
Matthew's Friends Clinics for Ketogenic Dietary Therapies, Lingfield, Surrey, United Kingdom	2011	110	1 (0.9)	40 (36)
Rush University Medical Center, IL	2012	300	5 (2)	300 (100)
University of Virginia, Charlottesville	2014	35	5 (14)	35 (100)
Mercy Health Hauenstein Neurosciences, Grand Rapids, MI	2014	80	7 (9)	80 (100)
UW Health, Madison, WI	2015	75	1 (1)	72 (96)
University of Toronto, Ontario, Canada	2015	100	25 (25)	100 (100)
St James' Hospital, Dublin, Ireland	2016	7	3 (42)	7 (100)
Waikato Hospital, Hamilton, New Zealand	2016	107	4 (4)	18 (17)
University of Denver, CO	2017	29	0 (0)	29 (100)
Total estimated adults treated with KDT		2,189		

Table 2 Summary of International Panel Recommendations for Ketogenic Diet Therapy (KDT) Management in Adults

KDTs should be tailored to the needs of the individual, considering patient preference, support structure, autonomy, mode of feeding, and ease of application. Therefore, all KDT strategies are recommended to consider, the most common being modified Atkins diet (MAD) followed by classic ketogenic diet (CKD), then modified ketogenic diet and low glycemic index treatment. Medium-chain triglyceride (MCT) oil can be used to supplement all forms of KDT.
KDTs are appropriate to offer adults with seizure types and epilepsy syndromes for which these treatments are known to be effective in children including tuberous sclerosis complex, Rett syndrome, Lennox-Gastaut syndrome, glucose transporter type 1 deficiency syndrome, genetic generalized epilepsies, and focal epilepsies due to underlying migrational disorders. However, adults with antiseizure drug-resistant focal epilepsy should be offered surgical evaluation first, given the higher anticipated rate of seizure freedom via this route.
Further evidence is needed to guide recommendations on KDT application in neurologic conditions beyond epilepsy such as headache, brain tumor, and dementia and general medical conditions including obesity and type 2 diabetes.
Certain metabolic disorders and porphyria are absolute contraindications to KDTs and typically present in childhood. Relative contraindications included osteopenia or osteoporosis, nephrolithiasis or history of nephrolithiasis, hyperlipidemia, and cardiovascular disease.
Preparation and training for KDTs must be individualized to provide the greatest likelihood of success. A variety of strategies can be used, most commonly including an individualized training with a dietitian and a physician, nurse, nurse practitioner, and/or dietitian. Group trainings are another option, and no randomized trials exist to determine which method is most effective. KDT initiation in adults is typically performed in an outpatient setting. Rapid or gradual initiation is based on center protocol or tailored to the individual.
Patients must be made aware of the possible side effects associated with the early weeks of KDT adaption such as fatigue, thirst, irritability, hunger, and altered bowel habits (particularly constipation) and provided with simple strategies on how to prevent or manage them.
All adults on oral food–based KDTs should be advised to increase their fluid consumption and take a multivitamin, mineral, and trace element supplement that meets recommended daily allowances. Additional vitamin D3 and calcium supplementation is of likely value to adults as well. Supplemental magnesium, carnitine, antiemetics, citrates, and antacids are recommended in symptomatic or at-risk patients.
Biochemical studies are recommended before the initiation of KDTs in adults. Metabolic screening may not be necessary for all adults pre-KDT, given that many contraindicated disorders present in infancy and early childhood. Regular outpatient follow-up and biochemical monitoring (complete blood count, comprehensive metabolic panel, fasting lipid profile, and vitamin D level) are important to identify and manage possible KDT complications. Serial bone mineral density scans beginning within 5 y of initiating KDT may be an additional consideration for adults with multiple associated risk factors.
Ketone monitoring (blood β-hydroxybutyrate or urine acetoacetate) is recommended during the early months of KDT as an objective measure of KDT adherence and biochemical response. However, diet adjustments should focus on optimizing the treatment response, minimizing side effects, and maximizing sustainability.
Initiating KDT with a simpler approach such as MAD and adjusting to include elements of CKD or MCT KD protocols where necessary to optimize the outcome may improve adherence; however, further investigation is warranted. Frequent support from a KDT team is important in the early stages to foster knowledge, skills, and confidence in adults managing their KDT.
A minimum of 3-mo KDT is recommended before any judgment of response is made. The time frame for KDT discontinuation is dependent on the underlying condition(s) being treated and response to treatment.

the majority (63%) considered it a relative contraindication and one-quarter did not consider it a contraindication. The majority (72%) of the panel did not consider osteopenia or osteoporosis to be a contraindication to initiating KDTs if an endocrinologist supervised the adult. Without endocrinology supervision, 47% considered these diagnoses to be a relative contraindication, and 18% considered them an absolute contraindication to starting KDTs. The majority of the panel (72%) considered nephrolithiasis or a history of nephrolithiasis to be a relative contraindication to KDTs, and 22% considered this an absolute contraindication. Renal failure was considered a relative or absolute contraindication for 45% and 40% of centers, respectively. The majority (84%) of panel respondents regarded acute pancreatitis as an absolute contraindication, and 74% considered prior history of pancreatitis as a relative contraindication. Liver failure was considered an absolute contraindication by most institutions (58%). The majority (65%) of the panel also considered baseline hyperlipidemia a relative though not absolute contraindication to KDTs, and the remainder did not consider it a contraindication. Forty-seven percent consider pregnancy to be an absolute contraindication and 42% a relative contraindication to starting KDTs. Over one-third (37%) of the panel considered anorexia to be an absolute contraindication to KDTs, and 58% considered it to be a relative contraindication.

Overall, the panel reported that the most common side effects encountered in adult patients on KDTs include (in descending order) constipation, weight loss, hyperlipidemia, leg cramps, menstrual irregularity (in women of childbearing age),[35,36] nausea, and vomiting. Side effects noted rarely or never within each institution included gallstones, orthostatic hypotension, osteopenia/osteoporosis, and nephrolithiasis.

Evidence

KDT is contradicted in adults with disorders of fatty acid transport and oxidation, organic acidurias, porphyria, and inborn errors of metabolism, which can lead to a catastrophic catabolic crisis in patients treated with KDT or fasted and are often identified in childhood.[8]

Relative contraindications based on known comorbid conditions in adults include familial hyperlipidemia, cardiac disease, osteopenia/osteoporosis, nephrolithiasis, cachexia,

Table 3 Ketogenic Diet Therapies (KDTs) Prescribed for Adults

KDT type	Prescription	Notes
Classic ketogenic diet (CKD)	Dietary assessment determines individual energy and protein requirements; the diet prescription is designed to deliver the required energy at a set ketogenic ratio of fat to carbohydrate and protein (e.g., 3:1 and 4:1); long-chain triglycerides (LCTs) are the predominant fat source; foods are weighed on a gram scale	The protein provision of higher ratio (>3:1) CKD may be inadequate for some adults; therefore, lower ratios may be used. Enteral feeds tend to be based on CKD
Medium chain triglyceride oil (MCT) ketogenic diet	Dietary assessment determines individual energy and protein requirements; designed to deliver 40%–60% of energy as MCT oil or emulsions; the remaining energy requirement is provided as protein (~15%), carbohydrate (~15%), and LCT fats (~20%); MCT is more ketogenic than LCT enabling a lower total fat intake and a slightly more liberal intake of carbohydrate and protein; foods are weighed/measured	MCT oil or MCT emulsion may be used as a fine-tuning option alongside any form of KDT if enhanced ketone production is desired
Modified Atkins diet (MAD)	Carbohydrate is restricted to 15–20 g (excluding dietary fiber) per day and measured using food labels and household measures, not weighing; fats are encouraged to satiety; protein remains unrestricted	Goal is to enable ketosis in the simplest manner by focusing primarily on carbohydrate restriction
Modified ketogenic diet	Dietary assessment determines individual energy requirements; carbohydrate provides around 5% energy (approximately 20–30 g excluding dietary fiber) and fat approximately 75%; carbohydrate intake is weighed/measured; fat intake is portion guided to ensure an adequate intake; a moderate, rather than unrestricted intake of protein foods is encouraged	This approach is a hybrid between the MAD and a CKD
Low glycemic index diet	Dietary assessment determines individual energy and protein requirements; carbohydrate provides around 10% energy (approx. 50–60 g including dietary fiber), protein approximately 30% and fat approximately 60%; carbohydrate is restricted to sources with a Glycemic Index of 50 or below; food portion guidance is based on household measures, not weighing	This approach focusses on glucose control rather than ketogenesis

pregnancy,[37] carnitine deficiency, and concomitant treatment with propofol[38] (in the setting of refractory status epilepticus)—with the caveat that systematic studies of side effects of chronic (≥2 years) KDT use in adults are scarce (table 4).

The breakdown of dietary fat is compromised in pancreatitis, and acute pancreatitis is considered a contraindication to KDT for that reason. One pediatric case report observed symptomatic cholelithiasis 12 months after the initiation of KDT for seizure control.[39]

Hypercholesterolemia occurs in approximately one-third of adults treated with KDT, possibly more so with CKD than with MAD[4,6,40,41] or other less strict variants, but may remit spontaneously with chronic (1 year) use, or after KDT discontinuation[6,8] (Class III evidence). Children treated chronically with KDT and adults treated with MAD for >1 year had no change in the carotid intima-media thickness, an indicator of cerebrovascular disease risk despite increases in potentially atherogenic small LDL particles.[40,42,43] However, an increase in arterial stiffness has been reported in children and young adults and correlated with serum cholesterol and triglyceride levels.[43]

There was 1 report of myocardial infarction in a patient with preexisting dyslipidemia on 4:1 CKD, 5 months after stopping.[36] Cardiac function in adults on KDT has not been systematically evaluated.

In children, chronic KDT use is associated with an increased rate of bone fractures, osteopenia, and osteoporosis.[44] However, there are little data on the prevalence of osteopenia or osteoporosis in KDT-treated adults. Adults may be at increased risk because of prolonged use of ASDs that can also cause bone loss.[45] In 1 study,[4] 11/139 adults had a bone density scan; 2 had newly diagnosed osteopenia or osteoporosis. However, a case series found no negative effects on bone mineral content or density in 3 adults with G1DS who had followed the diets for >5 years[46] (Class III evidence).

Table 4 Absolute and Relative Contraindications to Ketogenic Diet Therapies

Absolute contraindications
Carnitine deficiency (primary)[a]
Carnitine palmitoyltransferase I or II deficiency[a] (myopathic form may present in adolescence)
Carnitine translocase deficiency[a]
Mitochondrial fatty acid β-oxidation disorders[a]
Short-chain acyl dehydrogenase deficiency[a]
Medium-chain acyl dehydrogenase deficiency[a]
Long-chain acyl dehydrogenase deficiency[a]
Very-long-chain acyl dehydrogenase deficiency[a]
Medium-chain 3-hydroxyacyl-coenzyme A deficiency[a]
Long-chain 3-hydroxyacyl-coenzyme A deficiency[a]
Pyruvate carboxylase deficiency[a]
Pregnancy
Acute pancreatitis
Liver failure
Type 1 diabetes without endocrinology approval and/or supervision[a]
Porphyria
Relative contraindications
Epilepsy surgery candidate with a clear resectable lesion
History of pancreatitis
Cholecystectomy
Renal failure
Nephrolithiasis
Type 1 diabetes mellitus with endocrinology approval and/or supervision[a]
Type 2 diabetes mellitus without endocrinology approval and/or supervision
Osteopenia/osteoporosis without endocrinology approval or supervision
Hyperlipidemias
History of cardiovascular disease
History of cerebrovascular disease
History of anorexia
Severe gastroesophageal reflux
Inadequate social or care provider support
Poor adherence or difficulty maintaining adequate nutrition

[a] Symptoms typically present in childhood and adolescence.

Nephrolithiasis occurs in 2%–7% of KDT-treated children,[47] resulting from hypercalciuria. The risk of nephrolithiasis may be increased with the use of carbonic anhydrase inhibitors such as topiramate and zonisamide[48] (Class III evidence). Only 3 cases have been reported in adults.[6,7,49,50]

Animal studies of KDTs during pregnancy have reported variable outcomes ranging from beneficial effects on brain development to reduced brain volume, growth retardation, and alterations of organ growth.[51,52] There are 2 reported cases of human in utero exposure to KDT.[37] In 1 case, the infant was normal at 12 months, and in the other, the child was born with bilateral ear deformities of unknown significance.

Recommendations

Certain metabolic disorders and porphyria are absolute contraindications to KDTs and typically present in childhood (table 4). There was no consensus regarding avoiding KDTs in pregnancy, renal failure, or anorexia. Relative contraindications included osteopenia or osteoporosis, nephrolithiasis or history of nephrolithiasis, hyperlipidemia, and cardiovascular disease and may require referral to a specialist. Common side effects, which are typically mild, can often be managed with diet adjustments under the guidance of a dietitian or nutritionist and infrequently require medical intervention. Smaller meals, increased plant fiber intake, restriction of processed fat sources, exercise, and increased sodium and fluid intake can often prevent or alleviate common symptoms such as constipation.

Initiation of KDTs

Survey Results

The majority of the panel provided recipe ideas (85%), individualized training from a dietitian (75%), and preparatory guidance for meal planning (65%) before initiating a KDT. All 20 centers routinely initiated KDT in the outpatient setting, regardless of the KDT approach. However, 40% also reported initiating KDT during inpatient care for refractory or super-refractory status epilepticus. Pace of initiation varied between centers, with 40% reporting rapid initiation by changing all meals to the KDT prescription at the same time and 40% initiating the diet gradually by introducing KDT prescription over days or weeks. The remaining 20% determine the method of rapid vs gradual introduction based on the individual. Only 1 center indicated using a 24- to 48-hour fasting period before their rapid inpatient initiation method.

Evidence

During an initial clinical evaluation with the treating physician and dietitian for KDT, patient expectations regarding diet effects on seizure control, neurologic symptoms, glucose control (in diabetes), weight, and cognition are typically discussed.[6,7,53] Providers solicit information regarding degree of family or other social support (particularly cohabitants) and relevant psychosocial challenges such as personality traits, autonomy, motivation, alcohol and illicit substance intake, vocation, income, and cultural/religious preferences before starting KDT and address needs that are identified. If a move directly to a formal KDT does not appeal, a slower approach, sequentially lowering carbohydrate intake and increasing fat intake using

Table 5 Monitoring While KDT is Being Introduced and Adjusted to Optimize Effect

Daily	
Symptoms	A log of seizures and/or other symptoms pertinent to the individual
Ketosis	Use of blood ketone (β-hydroxybutyrate) or urine ketone (acetoacetate) monitoring, once or twice daily until symptoms improve or consistent levels are achieved, after which frequency can be reduced
Glucose	May be used instead of or alongside blood ketone monitoring when concerns are raised regarding hypoglycemia and in patients with diabetes
Food intake	A record of food and drink consumed, based on the KDT protocol used; MAD requires carbohydrate tracking, whereas modified ketogenic diet requires some tracking of added fats too
Weekly	
Weight	A record of weight on digital scales; ideally same time of day once a week
Other	
Fluid intake bowel function	A record of fluid intake and/or bowel function may be relevant to some adults

Abbreviations: KDT = ketogenic diet therapy; MAD = modified Atkins diet.

recipes from low-carbohydrate, higher-fat lifestyle books and recipe websites recommended by the treating team (to ensure that sources are reputable), may be considered.

A pre-KDT nutritional assessment generally evaluates height, weight, energy and nutrient intake, food preferences, food restrictions, and practical aspects relating to existing food patterns. These data provide the basis for the individualized KDT prescription.

During the practical diet training session, the patient and family are taught to identify carbohydrate, fat, and protein sources and provided with appropriate education and advice on how to measure these as required by their KDT prescription. Provision of simple individualized meal plans and recipe ideas can assist enormously with the introduction and initiation phase. Guidance is provided on managing meals outside the home and creating menus on a restricted budget when needed.[4,14,15,54]

Recommendations

Preparation and training for KDTs must be individualized to provide the greatest likelihood of success. A variety of strategies can be used, most commonly including an individualized training with a dietitian and a physician, nurse, nurse practitioner, and/or dietitian. Group trainings are another option, and no randomized trials exist to determine which method is most effective. KDT initiation is typically performed in an outpatient setting. Rapid or gradual initiation is based on center protocol or tailored to the individual. No randomized trials directly compare feasibility, tolerability, safety, and efficacy of these strategies in adults, and further investigation is warranted.

KDT Supplementation

Survey Results

Ninety percent of the panel recommend multivitamin and mineral supplementation on starting KDT, with 10% either not recommending any or only recommending supplementation if a deficiency is identified. Sixty-five percent of the centers recommend calcium supplementation on initiation of KDT, whereas the remaining 35% of centers supplement only if clinically indicated. Similarly, 45% supplement with vitamin D3 on KDT initiation, with the remaining 55% only supplementing if a deficiency is identified. By contrast, magnesium supplements were only recommended by 15% unless a deficiency was present. The majority (90%) of adult centers do not routinely prescribe carnitine unless levels are low or adults become symptomatic with fatigue, irritability, hypoglycemia, and/or confusion.

The recommendation for added salt to foods was limited to symptom management (in patients who became hypotensive due to reduced sodium intake), which was agreed on among 83% of centers. Adequate (30–35 mL/kg/d) fluid intake was recommended on starting the diet among 67% of the centers within the panel, whereas one-quarter would implement this recommendation in response to hypercalciuria and the increased risk of kidney stones or constipation. Specific advice on how to manage constipation by increased fiber and fluid intake, laxatives, and/or stool softeners was provided when starting adult patients on KDT only when bowel dysfunction was identified by 90% of respondents. Within the panel, 75% recommended antiemetics, and 70% recommended antacids only if gastrointestinal symptoms persisted.

Evidence

All KDT approaches restrict the intake of carbohydrate-containing foods, and the CKD also limits protein intake. Therefore, regular food sources of essential micronutrients such as fruits, vegetables, grains, cow's milk, meat, and fish become more limited. As long-term ASD use may compromise bone health[45] (Class III evidence), adequate calcium, vitamin D3, and magnesium intake is of particular importance to those adults using KDT alongside enzyme-inducing ASDs.

Comparable to pediatric recommendations, carnitine monitoring and supplementation remains controversial with limited evidence of carnitine deficiency developing in patients following KDT long term[55] (Class III evidence). Supplementation with citrates reduces the incidence of nephrolithiasis to 0.9% by the process of urine alkalinization[47,56] in children on a CKD and therefore may be used in adults prescribed a CKD as well and less often for modified KD variants.

Gastrointestinal symptoms such as nausea, indigestion, and reflux have been reported during the initiation phase; however, a gradual introduction of ketogenic meals into the diet may help minimize these symptoms.

Recommendations

All adults on oral food–based KDTs should be advised to increase their fluid consumption and take a multivitamin, mineral, and trace element supplement that meets recommended daily allowances. Additional vitamin D3 and calcium supplementation is of likely value to adults as well. Supplemental magnesium, carnitine, antiemetics, citrates, and antacids are recommended in symptomatic or at-risk patients.

Monitoring on KDTs

Survey Results

At baseline, >50% of the panel obtain the following biochemical studies: complete blood count (CBC), comprehensive metabolic panel (CMP), fasting lipid profile, 25-hydroxy vitamin D, total and free carnitine, ASD levels (when relevant), and ketones (urine and/or blood). Half of those surveyed also check zinc. Less than half check 1 or more of vitamin B12, vitamin E, copper, selenium, and vitamin A. The majority of those surveyed do not check 1-month labs (outside of ketone monitoring) unless there are special circumstances. For example, patients on certain medications (e.g., oxcarbazepine, carbamazepine, and some used for hypertension and diabetes) may warrant earlier lab monitoring for electrolyte disturbances after starting KDT.

There was great variation in which follow-up labs were checked and at what intervals. At 3-month follow-up, at least half of those surveyed check a CBC, CMP, fasting lipid profile, vitamin D level, and ketones. At 6 months, the same are checked, but less than half recheck vitamin D at this time point. At 1 year, the same labs are checked plus carnitine. For pediatric patients, selenium is a standard follow-up recommendation, and zinc and copper are considered optional.[8] Most centers indicated that some labs were checked more often if indicated. After 1 year, most centers check labs less often, typically at 6-month or 1-year intervals. Half of the panel obtain bone mineral density scans within the first 5 years of initiating KDT.

Evidence

As recommended for children, adults on KDTs are typically evaluated at regular intervals in an outpatient clinic by a medical practitioner and dietitian, familiar with KDT management. Time intervals for full clinical review are generally 3, 6, 12 months and then annually or as indicated. In the interim, regular telephone and/or email communication between the patient and their team can enable discussion of the home monitoring data (table 5) and prompt diet adjustments.

Baseline or pre-KDT biochemical studies screen for any preexisting abnormalities or contraindications and establish a reference for comparing follow-up laboratory studies while on KDT. In addition to labs routinely obtained by the panel, urine calcium, urine creatinine, and a urine pregnancy test (for premenopausal women)[4,49] may be considered. The main difference between biochemical monitoring for adults and children is that serum acylcarnitine profile, urine organic acids, and serum amino acids are typically not obtained in adults unless there is a strong clinical suspicion of an underlying metabolic disorder.[8]

An increasing number of adults initiate diet changes before accessing clinical evaluation and pre-KDT lab tests. It is important to know the duration of diet change when interpreting lab results. For example, elevated pre-KDT lipids may require individualized treatment or monitoring. However, elevated lipids 3 months after starting KDT are common, typically returning to baseline within 1 year, and can simply be monitored unless they remain elevated[41] (Class III evidence).

Pediatric guidelines do not recommend bone mineral density testing (dual-energy X-ray absorptiometry scan) pre-KDT but consider testing optional in follow-up. However, adults have cumulative risk factors for compromised bone health such as chronic enzyme-inducing ASD exposure, immobility, hormonal fluctuations, menopause, vitamin D deficiency, and prior fractures.

Recommendations

Biochemical studies are recommended before the initiation of KDTs in adults. Metabolic screening may not be necessary for all adults pre-KDT, given that many contraindicated disorders present in infancy and early childhood. Regular outpatient follow-up and biochemical monitoring (CBC, CMP, fasting lipid profile, and vitamin D level) are important to identify and manage possible KDT complications. Serial bone mineral density scans beginning within 5 years of initiating KDT may be an additional consideration for adults with multiple associated risk factors.

Monitoring Ketones on KDTs

Survey Results

Three primary methods of ketone measurement are used including capillary testing of blood β-hydroxybutyrate (βHB), urine testing of acetoacetate (AA), and breath testing of acetone concentrations. Eighty-five percent of the panel use urine AA measurement, and 60% use blood βHB values to monitor diet adherence, with 55% recommending a combination of the 2. Only 1 center reported using breath ketones. Blood βHB monitoring most accurately reflects ketone metabolism and seizure reduction[57]; however, urine AA and breath testing are less invasive. There was no consensus regarding optimal frequency of measurements (ranging from twice daily to clinic visits only).

Evidence

The primary goal of KDT is symptom management rather than level of ketosis per se. If symptoms are optimally

managed at a low level of ketosis (<1 mmol/L serum βHB, <40 mg/dL AA), there is no need to manipulate the KDT to pursue higher ketone levels. When relying on urine AA as a biomarker of adherence long term, it is important to take into consideration the hypothesized process of ketoadaptation,[3] which may lead to reduced urinary excretion.

Recommendations

Ketone monitoring (blood βHB or urine AA) is recommended during the early months of KDT as an objective indication of KDT adherence and biochemical response. However, diet adjustments should focus on optimizing the treatment response, minimizing side effects, and maximizing sustainability.

Adherence With KDTs

Survey Results

Seventy percent of the panel indicated that the main issue influencing adult adherence was an inadequate response to KDT, with 50% reporting difficulties coping with the carbohydrate restriction. Other adherence issues considered relevant (by fewer than 50% of the panel) were conflict with established food preferences, time demands, limited meal variety, increased costs, and difficulty maintaining KDT during social occasions.[12,21,58]

Evidence

A meta-analysis found that CKD and MAD compliance in adults was about 45% combined; however, compliance for MAD was higher (56%) than CKD or MKD (38%; $p = 0.006$).[59] Adherence in adults who are dependent on caregivers to facilitate enteral or oral feeding is expected to be similar to that found in the pediatric population, although this has not been studied systematically.

Recommendations

Major barriers to diet adherence include difficulty with carbohydrate restriction and an inadequate response to treatment. Beginning with a less restrictive KDT approach such as MAD and adjusting to include elements of MKD or MCT KD protocols where necessary to optimize the outcome may improve adherence[21,59] (Class II evidence), and further investigation is warranted. Frequent support from a KDT team and appropriate practical resources are important in the early stages to foster knowledge, skills, and confidence in adults managing their KDT.

Discontinuation of KDTs

Survey Results

Because of the lack of evidence, no consensus protocol exists for the discontinuation of KDTs; 75% of centers encourage adults to remain on KDT for at least 3 months before considering discontinuation.[8] Sixty percent of centers taper the adult diet over 1–8 weeks, 25% take 3 months or longer, and 15% discontinue immediately. The relapse rates after discontinuation of KDT seem to be increased in patients with focal seizures or symptomatic etiology.[60] Further adult studies are needed to establish safe and effective processes of discontinuing KDT.

Evidence

In pediatric practice, positive responders typically remain on KDT for 2 years before considering weaning.[8] This is based on common practice of weaning ASDs in children who become seizure free[61] and the potential complications of long-term restrictive diets.[58] In adults, ASDs may also be weaned after 2 years of seizure freedom based on clinical circumstance. However, because the majority require lifelong epilepsy treatment or use KDT for nonepilepsy conditions, there is no recommended time limit for remaining on KDT. The discontinuation process is individualized and may last several weeks or months. The literature suggests withdrawing KDT slowly in those who have followed it chronically or had a dramatic response.[61]

Recommendations

KDT in adults is not time limited. However, a minimum of 3 months KDT is recommended before any judgment of response is made. The time frame for KDT discontinuation is dependent on the underlying condition(s) being treated and response to treatment. Further evidence is needed to guide recommendations on KDT application in neurologic conditions beyond epilepsy such as headache, brain tumor, and dementia and general medical conditions including obesity and type 2 diabetes.

Discussion

Despite its use as an effective antiseizure therapy since the 1920s, KDT remains novel within adult neurology across much of the world. This document represents an international effort to relate current clinical practice of KDT use in adults, drawing on the experience of 20 centers in 10 countries and a review of current literature. With a relatively mild side effect profile and the potential to reduce seizures in nearly 60% of adults with drug-resistant epilepsy,[20] the panel recommends incorporating these treatments into the repertoire of available options. New evidence is emerging that KDT may also improve quality of life[14] and reduce symptoms in other neurologic and general medical conditions (Class III evidence).[26–30,32–34,62] However, adherence is a major limitation for adults on KDT, and risks of long-term side effects remain largely unknown, so close monitoring and management are essential.

Current KDT practice in adults is broadly similar to practice in children, where extensive clinical experience and published guidance already exists.[8] However, the panel highlighted several considerations unique to adults. These included incorporating liberal KDT approaches in adults to enhance practicality and adherence.[21] In common with practice in children, KDT is individually tailored to meet the nutritional requirements and practical circumstances of each adult. When using CKD, such as in enteral feeding, lower ratios

(<3:1) are recommended to ensure that protein requirements for adults are met.

Although absolute metabolic contraindications and cautions relating to feeding difficulties, gastrointestinal dysfunction, and digestion remain the same for both children and adults, the panel highlighted a range of common adult conditions such as hyperlipidemia, heart disease, diabetes, low bone density, and pregnancy that bring additional consideration, caution, and monitoring to KDT use.

The panel recommended pre-KDT biochemical studies to screen for preexisting abnormalities and to establish a reference for comparing follow-up results after 3, 6, and 12 months and then annually or as required. Metabolic studies such as urine organic acid and serum amino acid levels are typically not obtained in adults unless there is a strong clinical suspicion for an underlying metabolic disorder. Updated genetic evaluation may also be considered in adults with intellectual disability and epilepsy of unknown etiology. Serial bone mineral density scans may be obtained every 5 years.

All panel members routinely initiated KDT in the outpatient setting for the majority of adult cases compared with the relative frequent (80%) inpatient initiation in pediatric patients.[8] However, the pace of diet initiation varied by center and individual requirements.

The majority of the panel use KDT for the management of seizure disorders only. Although interest in the use of KDT in the management of other conditions such as Parkinson disease, Alzheimer disease, migraine, brain tumors, multiple sclerosis, and many others is increasing in the preclinical research and public domains, additional clinical evidence is required before KDT use can justifiably expand further.

There are several important limitations to this study. The lead authors identified coauthors in part based on prior participation in international ketogenic diet symposia and those that published articles pertaining to KDTs for adults before the survey was distributed. Studies discussed in the article included those published after the survey was conducted, and therefore, the authors and articles of more recent literature may have been unintentionally excluded. The majority of the contributors were known to the lead authors, resulting in a potential for bias.

A final consideration is that it is challenging to perform a truly double-blinded randomized clinical trial comparing a diet with another type of intervention, and therefore, the majority of the evidence supporting the panel recommendations is considered Class III and Class IV. This highlights the need for expert recommendations to better inform practitioners attempting to incorporate KDTs into their treatment algorithms for epilepsy and other diseases. The study identifies gaps in knowledge that warrant further investigation.

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Appendix *(continued)*

Name	Location	Contribution
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