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REVIEW

Current Perspectives On The Role Of The Ketogenic Diet In Epilepsy Management

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Abstract: Drug-refractory epilepsy is a commonly prevalent pediatric neurological illness of global significance. Ketogenic diet (KD) is a time-tested therapeutic modality for refractory epilepsy, which has reemerged as a robust alternative to anti-epileptic pharmacotherapy. There is a growing body of evidence which supports the anti-seizure efficacy, safety profile and feasibility of KD use in childhood epilepsy. In addition, this modality has been recognized to reduce anti-epileptic exposure, improve cognition and behavioral profile of patients as well as improve the quality-of-life of care-givers. Current indications of KD include refractory epilepsy syndromes, selected metabolic disorders (such as pyruvate dehydrogenase deficiency) and a host of varied neurological entities. KD research has broadened the knowledge-base about its mechanisms of action. Four types of KD are in vogue currently with varying nutritional constitution, palatability, administration protocols and comparable efficacy. KD initiation and maintenance are the result of concerted effort of a team of pediatric neurologist/epileptologist, nutritionist and patient's primary care-giver. Consensus is being formulated about various practical aspects of KD such as patient-selection, parental counseling, baseline work-up, dietary prescription, nutritional supplementation, concurrent anti-epileptic drug administration, follow-up and treatment-duration. Novel applications of KD include its use in neonatal epilepsy and super-refractory status epilepticus and tailor-made formulations such as cooking oil-based KD in predominantly rice-fed populations. Increasing body of clinical experience, improved nutritional designs and translational research are promoting KD as a major therapeutic modality. Currently, KD forms a core essence in the armamentarium against refractory epilepsy. In this review, we summarize the recent advances and current perspectives in the use of KD in refractory epilepsy.

Keywords: Modified Atkins Diet, low glycemic index diet, ketosis, intractable epilepsy, epileptic encephalopathies, ketogenic diet, epilepsy

Introduction

Epilepsy is a common neurological disorder encountered in pediatric practice, which accounts for nearly 1% of the global burden of disease across all ages.[1] Nearly 30% of all children with epilepsy display drug-refractoriness.[2] Management of children with drug-refractory epilepsy is a challenging proposition for health-care providers as well as primary caregivers. The adverse effects and often-unknown interactions between multiple drugs, frequent hospital visits, financial limitations and parental burnout are only few of the hurdles faced during the management of children with drug-refractory epilepsy. Epilepsy surgery is one of the the main treatment options for children and adults with refractory epilepsy. However, many children and adults with refractory epilepsy are not good surgical candidates. Also, epilepsy surgery is expensive, requires trained personnel and infrastructure, and hence is not easily available in many low resource settings.

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Ketogenic diet (KD) is being increasingly accepted worldwide as a practical, effective and safe management alternative in children and adults with refractory epilepsy who are not good surgical candidates. KD is a high fat, low carbohydrate diet, which has been used for the last several decades for the treatment of refractory epilepsy in children.[3] There has been a recent resurgence in its use. Now there are many less restrictive options available such as the Modified AtkinsDiet and the low glycemic index treatment. There is now emerging evidence of the use of KD and its variants in adults as well, and the use of KD in other non-epilepsy neurological conditions such as brain tumors, Alzheimer's disease, Amyotrophic Lateral Sclerosis, Parkinson's disease and autism. In this review, we discuss the current perspectives on the use of KD in children and adults with epilepsy.

Evidence Pertaining To The Use Of KD In Epilepsy

Preliminary evidence of efficacy of KD has been derived from uncontrolled studies of KD in drug-refractory epileptic children which revealed total seizure resolution in 16%, greater than 90% seizure-reduction in 32% and greater than 50% seizure reduction in 56%.[4] Neal et al conducted an RCT wherein children with drug-resistant epilepsy were randomized to receive KD either at enrolment (study arm) or after three months (control-arm) in addition to the ongoing anti-epileptic drugs.[5] on changes in the anti-epileptic drugs.[5] Children who received early KD (n=54) had significantly decreased seizure burden after four months than the controls (n=49) with a 38% decrease in seizures compared to 37% increase in seizures ($p< 0.0001$).[5]

Current evidence pertaining to the benefits of KD in epilepsy has evolved from prospective and retrospective case-series, anecdotal reports and consensus opinions of experts. The 2018 Cochrane Review summarizes data from eleven Randomized Controlled Trials (RCTs) pertaining to KD. This encompasses a total of seven hundred and seventy eight patients including seven hundred and twelve children and sixty six adults.[6] Maximum 'seizure freedom rate' and 'seizure reduction rate' seen with classical (4:1) KDwere 55% and 85% respectively noted three months after therapy initiation.[6] Other less restrictive variants of KD, such as MAD, displayed similar seizure-control efficacy as classical KD, but the authors noted a need for more robust studies.[6]

Indications Of KD

KD initiation requires careful consideration of many factors, as it is a long-term therapy requiring concerted effort of health-care providers, parents and patient cooperation. Therefore, indications for starting KD need to be well defined.

KD is generally preferred as a therapeutic modality in childhood epilepsy after the failure of multiple drugs in controlling seizures. There is a growing opinion among epileptologists that KD should be considered after the failure of two adequately chosen anti-epileptic drugs used in appropriate dosage.[7,8] It is preferred as the first line of therapy in deficiency of Glucose Transporter Type 1 and Pyruvate Dehydrogenase Deficiency.[7] Other indications of KD include refractory epilepsy syndromes such as Ohtahara Syndrome, West Syndrome, Lennox-Gastaut Syndrome, Dravet Syndrome, Epilepsy with myoclonic-atonic seizures and Tuberous Sclerosis Complex.[9] Multiple trials have demonstrated that KD is an effective treatment modality in children with Dravet Syndrome and hence it needs to be considered early in the course of therapy.[8,10–12] Caraballo et al performed a retrospective study of children with Dravet Syndrome where it was observed that ten out of thirteen children on KD had significant seizure reduction at twelve months of therapy initiation.[13] Dressler et al retrospectively studied the efficacy of KD in thirty-two children with Dravet Syndrome wherein they found that the efficacy of this modality was not significantly inferior to the gold standard anti-epileptic drug triple combination of stiripentol, clobazam and valproate and was significantly more effective than Levetiracetam alone.[14] The Italian consensus guidelines advocate early initiation of KD in the treatment of Dravet Syndrome.[8] KD has also been tried in variety of other conditions such as Febrile Infection Related Epilepsy Syndrome (FIRES), Angelman Syndrome, Rett Syndrome and tuberous sclerosis complex.[7]

Types Of KD In Current Practice

KD prescribed currently is of four main types (Table 1).

Classic KD

The classic KD is the conventionally prescribed KD, which has a ketogenic ratio of 4:1. "Ketogenic ratio" refers to the ratio of weight of fat to the combined weight of carbohydrates and proteins in a diet.[7,15] The primary challenges involved in prescribing classic KD account from its highly restrictive nature and the requirement of hospitalization at initiation that is practiced by most centers. Lower

Table 1 Composition Of Various Types Of Ketogenic Diet

Type Of KD	Percentage Of Total Calories Derived From Fat (%)	Percentage Of Total Calories Derived From Carbohydrate (%)	Percentage Of Total Calories Derived From Proteins (%)
Classic KD (4:1)	90	3	7
Modified Atkins Diet (MAD)	70	5	25
Medium Chain Triglyceride (MCT)-based KD	70	20	10
Low Glycemic Index (LGI)-based KD	45	27	28

Note: Adapted with permission from Wiley and Sons (W. Donald Shields, Eric H. W. Kossoff, Nonpharmacologic care for patients with Lennox-Gastaut syndrome: Ketogenic diets and vagus nerve stimulation, Epilepsia, John Wiley and Sons) Wiley Periodicals, Inc. © 2014 International League Against Epilepsy.[84]

ratios such as 2.5:1 have been used and shown to have equivalent efficacy and better tolerability.[7,16]

Medium-Chain Triglyceride (MCT) KD

This variant of KD was developed by Huttenlocher et al and is based on the provision of calories predominantly through MCT.[17] MCT-based KD, conceived in the 1950s, has more ketogenic potential than classic KD as MCT breaks down and gets absorbed rapidly, directly reaching the liver unlike long-chain triglycerides.[15] MCT-based KD is less restrictive and more palatable than classic KD as it allows for consumption of more carbohydrates and calories.[8,15,17,18] Neal EG et al compared classic KD with MCT-based KD in an RCT involving one hundred and forty-five children with intractable epilepsy, wherein both the dietary therapies were found to be comparable in their efficacy and tolerability.[5] Common adverse effects of MCT-based KD are abdominal discomfort and bloating sensation, which is responsible for discontinuation of therapy in majority of children.[9,19]

Modified Atkins Diet (MAD)

MAD, initially described in 2003, is a less restrictive KD where fat provides about 65% of the calories.[10,20] MAD initiation does not entail prior hospitalization, initial fasting or restriction of calories, fluids or proteins.[8,15] In this form of dietary therapy, children are encouraged to consume large amount of fats in the form of butter, ghee or cream with no active protein restriction.[15] In a randomized controlled trial conducted in India, the efficacy of MAD was evaluated in children with refractory epilepsy who were randomized to receive either MAD or no dietary therapy in addition to the ongoing medications for three months.[21] MAD was found to be effective and well tolerated.[21]

MAD has also been found useful in children with Lennox-Gastaut Syndrome.[22] Kim et al had found MAD to be of comparable efficacy as Classic KD in children with refractory epilepsy older than 2 years of age.[23] However, classic KD was significantly more effective in children younger than two years of age.[23]

The liberal nature of MAD and its ease of administration makes it a promising choice, especially for resource-limited settings as has been demonstrated through an Indian study of a simplified MAD which could be used by parents with low literacy levels.[24] In the West, the MAD has been used predominantly in adolescents and adults. However, it has been found useful even in infants and young children and is a more feasible option than KD in these populations in low resource settings.[25,26]

Low Glycemic Index (LGI) KD

LGI KD, pioneered by Pfeifer and Thiele in 2005, composed of 60% fats, 10%carbohydrates and 30% proteins.[27] This is a less restrictive form of dietary therapy where children are allowed to take carbohydrates with LGI such as strawberries and whole grain, whereas foodstuffs like potatoes and rice are prohibited.[27]

LGI-KD produces minimal ketosis compared to classic KD with equivalent anti-seizure efficacy. There are no head-to-head trials of LGIT versus other KDs in children with refractory epilepsy.[28] This variant of KD has been found to be particularly effective in controlling seizures in patients with Angelman Syndrome.[29,30,31] Sondhi et al, in their RCT, randomized one hundred and seventy children (1–15 years) with drug-refractory epilepsy to receive KD,

MAD or LGIT wherein they observed that MAD and LGIT were not non-inferior to KD though LGIT demonstrated >50% seizure reduction with a better safety profile.[29] Kim et al found MAD may have similar seizure control as classic KD in children with refractory epilepsy older than 2 years of age.[23]

Current Perspectives About The Mechanisms Of Action Of KD

The exact mechanism of action of KD is open to controversy and hence, a subject of active research. Current perspectives pertaining to the mechanism of action of KD have been summarized in Table 2. Glucose is the chief source of energy in humans during basal conditions. During fasting or starvation, ketone bodies (acetone, acetoacetate and Gamma hydroxybutyrate) are formed in the liver, which converts to acetyl coenzyme A that enters the citric acid cycle and gets oxidized in mitochondria to provide energy as an alternative to glucose.[32] The direct role of acetoacetate in seizure control has been demonstrated in animal models.[32] Ketone bodies may act through activation of various synergistic pathways that are still under evaluation. Different mechanisms that have been hypothesized include potassium channel activation leading to membrane hyperpolarization, positive feedback to GABAergic channels, negative feedback to Glutamatergic channels.[33] KD leads to elevated blood levels of polyunsaturated fatty acids (PUFAs) such as Docosahexaenoic acid, arachidonic acid and eicosapentaenoic acid. [33] As PUFAs are known to inhibit voltage-gated sodium channels and L-type calcium channels, it was presumed to be one of the possible mechanisms of action of KD in decreasing seizures.[33] This hypothesis was refuted by studies that failed to reveal any additional improvement with KD fortified with PUFA.[34,35] Notwithstanding the above, PUFAs are known to activate peroxisome proliferator-activated receptors (PPARs), which may have anti-seizure activity.[36]

Gut microbiome has gained popularity as one of the major players that may possibly have anti-epileptic properties. Studies in mice and humans have shown alteration of gut microbiota with KD, namely decrease in Actinobacterial load, which might be responsible for anti-seizure effects.[37–39] It has been demonstrated in mouse models that KD leads to increased gut population of *Akkermansia muciniphila* and *Parabacteroides merdae* which probably confer anti-seizure protection.[41] When these bacteria are transplanted into germ-free mice, they may induce seizure protection.[41] These bacteria have been found to decrease gamma-glutamylated ketogenic amino acids leading to neurotransmitter modulation, which has anti-seizure effects.[37–39]

Human studies have revealed that KD alters gut microbiome by varying degrees, notable being the selective increase in Bacteroides and decrease in Firmicutes and Actinobacteria in those individuals who have good seizure control.[37,39] As these changes have been noted in persons having good seizure

Table 2 Probable Anti-Seizure Mechanisms Of KD

Primary Physiological Change	Probable Hypothesized Mechanism Of Seizure Reduction
(a) Ketosis	(i) Hyperpolarization of neurons by Potassium channel activation
	(ii) Slow energy production (compared to pathway wherein energy is derived primarily from glucose) which leads to anti-seizure effects
	(iii) Potentiation of inhibitory neurotransmitters (eg, GABA)
	(iv) Augmented neuronal function through cellular
	(v) Chronic ketosis is postulated to stabilize and reduce synaptic hyperexcitability in order to conserve energy, thereby increasing seizure threshold
(b) Increased levels of Polyunsaturated Fatty Acids (PUFA)	(i) Activation of e peroxisome proliferator-activated receptors (PPARs)
	(ii) Hyperpolarization of neurons
(c) Alteration of gut microbiome	Possible role in increasing seizure threshold due to putative microorganisms (eg, Akkermansiamuciniphila and Parabacteroides) which has been noted in murine models as well as human studies of gut microbiome
(d) Alteration of proinflammatory and anti-inflammatory mediators	Reduced levels of Interleukin 1b and other proinflammatory cytokines in mice treated with KD supports the role of modulation of these inflammatory mediators in combating epilepsy

Note: Data from.[85–86]

control with KD, it has been hypothesized that KD may exert anti-seizure effects through modulation of gut microbiota.

Dysregulation of the mammalian target of rapamycin (mTOR) signaling pathway has been found to be one of the key regulators responsible for intractable epilepsy, especially in conditions such as Tuberous Sclerosis Complex (TSC) and cortical malformations.[40] It has been demonstrated through rat studies that KD inhibits mTOR pathway in healthy rats and prevents late mTOR activation after Kainic Acid induced status epilepticus.[40] Hence, mTOR pathway inhibition may be an important additional mechanism of action of KD.

Contraindications For KD

KD can be fatal for children with metabolic disorders that impair energy generation from lipids.[7] Hence, fatty acid oxidation disorders, primary carnitine deficiency, Carnitine Palmitoyl Transferase (CPT) deficiency Type I and Type II, Carnitine Translocase Deficiency, Pyruvate Carboxylase Deficiency and porphyria are absolute contraindications for initiation of KD.[7,8] Parental and patient non-compliance, lesional epilepsy amenable to surgical resection and use of propofol are relative contraindications for KD.[7] The contraindications for KD are summarized in Table 3.

Pre-Requisites To Be Fulfilled Before KD Initiation

Prescription of KD is a concerted decision which requires interaction between the treating pediatric neurologist/ epileptologist, nutritionist/dietary counselor and patient`s primary caregiver. The International Ketogenic Diet Study Group recommends structured counseling, meticulous nutritional assessment and certain mandatory laboratory investigations prior to initiation of KD.[7] The pre-requisites that need to be fulfilled prior to initiation of KD are noted below:

Table 3 Contraindications For Ketogenic Diet

Absolute Contraindications
Pyruvate carboxylase deficiency
Primary carnitine deficiency
Carnitine palmitoyltransferase I or II deficiency
Carnitinetranslocase deficiency
Medium chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency
Long chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency
Short chain acyl dehydrogenase deficiency
Medium chain acyl dehydrogenase deficiency
Long chain acyl dehydrogenase deficiency
Short chain acyl dehydrogenase deficiency
Porphyria
Relative contraindications
Non compliance
Propofol use
Definite surgical focus of epilepsy

Note: Data from.[7,8]

Parental Counseling Prior To Initiation Of KD

Various factors that are taken into account before considering KD include patient characteristics such as age, epilepsy syndrome, medications used, underlying metabolic illness (if any), financial issues, social issues and parental motivation. Multiple counseling sessions are held in order to educate the parents and to assess their readiness and competence to handle KD therapy. Group counseling, handouts, training videos and KD support groups have an immense role in the counseling process. In resource-limited settings with high prevalence of illiteracy, counseling needs to be tailored accordingly.[26] Counseling precedes the process of obtaining informed consent from parents prior to KD initiation.

Nutritional Assessment

Nutritionists constitute an integral part of any KD therapy center. The nutritionist assesses the dietary requirements of a prospective KD candidate and also looks into any food allergies, practicability and social issues before designing and advising a particular diet. Protocols may differ from center to center. Numerous diet calculators and mobile apps are available which aid in the process of obtaining individualized dietary calculation.

Baseline Investigations

Mandatory investigations that are obtained prior to initiation of KD include hemogram, liver and kidney function tests, serum electrolytes, serum vitamin D level complete lipid profile and serum acylcarnitine level.[7,8,33,42] Additional investigations are advised as warranted on individualized basis.[7]

KD Initiation: Basic Protocols

Traditionally, most centers hospitalized children prior to initiation of classic KD. Admission is utilized to counsel caretakers, perform thorough nutritional estimation, do baseline biochemical monitoring and assess for the initial adverse effects of KD. In the earlier protocols, children were made to

fast for 12 to 24 hrs prior to initiation of KD.[7] However, current consensus recommendations allow for a liberal approach and do not advocate fluid and carbohydrate restriction at initiation of KD.[7] Calories are progressively increased while maintaining the ratio of energy provided by fats and carbohydrates. The practice of calorie build-up in KD differs among centers. Conservative schools advocate gradual escalation of KD ratio from 1:1 to 4:1 by increasing relative quantity of fat in diet over few days. However, initiation of total fats on Day 1 may be equally efficacious and safe as per current evidence pertaining to KD in infants.[42] The current trend shows a shift towards domiciliary KD therapy in view of the inherent shortfalls of hospitalization. European consensus is in favor of admission of infants prior to KD initiation.[34,43] MAD and LGIT are usually initiated on outpatient basis. Primary caregivers are pivotal in the success of any dietary therapy and hence, these regimes are initiated after accessing the motivation, capability and interest of the primary-caregivers. They are initially called at close intervals till they gain confidence in sustaining the diet at home. MAD and LGIT are initiated without prior fasting or fluid restriction.

KD is usually tailor-made to a child depending on his age, food acceptance, socio-economic factors, parental convenience and experience of the center. There is a burgeoning growth of pre-fabricated, ready-to-eat KD formulations such as breakfast cereals and keto-snacks. These dietary options appear attractive but need to be validated by evidence and feasibility studies from an economic standpoint.

International KD Study Group recommendation advocates daily supplementation of multivitamin, calcium, vitamin D for children on KD.[7] There are mixed opinions about the supplementation of oral citrate to counteract kidney stone formation during KD therapy.[7,44]

Follow-Up Plan During KD Therapy

KD is a long-term therapy, which warrants regular follow-up. Follow-up protocols vary from center to center. At the initiation phase, daily follow-up may be required. Serum ketone (especially, beta hydroxyl butyrate) monitoring, though more accurate, may not be feasible as it is more expensive. An exclusive KD clinic with epileptologist/pediatric neurologist and nutritionist is a pre-requisite for KD therapy. Additional aids like videos, app-based platforms and patient helpline numbers may make the maintenance of therapy more practical. The frequency of follow-up is commonly monthly at the onset, which may be subsequently spaced out to about three-monthly follow-ups.[7] Infants may require prolonged close follow-up.[7]

At each clinic visit, special attention needs to be given to the frequency and pattern of seizures, difficulties faced in diet administration by parents, adverse effects and daily urinary ketone records. Parental concerns are addressed and diet is modified if required. Anti-seizure drugs are modified or continued as mandated. The child is examined in detail during every visit with special attention to anthropometry and signs of nutritional deficiency.

Laboratory tests that are obtained periodically include hemogram, liver and renal function tests, serum electrolytes, calcium, vitamin D level and lipid profile. These are advocated frequently at onset and less frequently subsequently. International KD study group recommends three-monthly investigations in the initial six months of KD therapy.[7] These include complete hemogram, liver function test, renal function test, serum calcium, magnesium, serum vitamin D level and fasting lipid profile.[7] Ultrasonographic screening for renal calculi, bone densitometry, electroencephalography (EEG) and serum carnitine level are performed at less frequent intervals.[7]

Adverse Effects Of KD

Various adverse effects of KD are as follows:

Gastrointestinal

Nearly 50% of the children started on KD have gastrointestinal adverse effects such as nausea, vomiting, diarrhea, pain abdomen, exacerbation of gastroesophageal reflux and constipation, especially during the initiation phase.[7,45]

Metabolic Abnormalities

Biochemical alterations that may be seen with KD include hypercholesterolemia, hypertriglyceridemia and depressed levels of low-density lipoprotein (LDL).[46] Lin et al had noted hypoglycemia in about one-fourth of children during the first week of therapy of KD initiation in a retrospective study of one hundred and fifty-eight children.[45]

Renal

As high as 3–7% of the children on KD therapy may develop renal calculi, the risk of which is reportedly decreased by co-administration of oral citrates.[47]

Growth

The impact of KD on growth is a subject of intense research, which has yielded mixed findings.[7,48] Decreased linear growth has been reported in children exposed to KD continuously for more than six months in six retrospective studies.[48–53]

On the contrary, Tagliabue et al studied eighteen children on KD prospectively for six months wherein they did not find any change in their weight or height.[54]

Cardiovascular

Speculations of detrimental cardiovascular outcomes in children on long-term KD have not been substantiated in studies on coronary intimal thickness.[55]

Prolonged QT interval and cardiomyopathy have been reported as an adverse effect of prolonged KD therapy with poorly understood causative mechanisms, relative selenium deficiency being one of them.[59] Long-term adverse effects of KD have not been adequately studied.[7]

Skeletal

Osteoporosis and vitamin D deficiency may be observed in children on KD, especially when these children are on multiple anti-seizure medications.[50,60]

Rare Adverse Effects

Rare adverse effects of long-term KD exposure include pancreatitis and transaminitis especially with concurrent valproate use, which may be exacerbated by viral illnesses.[7]

Table 4 Adverse Effects Reported With KD

Gastrointestinal	Abdominal Pain
	Emesis
	Constipation
	Pancreatitis
	Hepatitis (with concurrent valproic acid use)
Renal	Renal Calculi
Metabolic	Hypertriglyceridemia
	Hypercholestorelemia
	Elevated levels of Low density Lipoproteins (LDLs)
Cardiac	Thickening of coronary intima and media is known in long term KD use. (However, risk of coronary artery disease with KD use is not proven till date)
	Cardiomyopathy
	Prolongation of QT interval
Growth	Deceleration of height velocity
Skeletal	Osteoporosis

Note: Data from.[7,35,36,45–48,55,60]

The common adverse effects of KD have been depicted in Table 4. Patel et al observed that children on long-term KD had normalization of height, weight and serum cholesterol after a median period of six years of discontinuation of therapy.[61] This may be indicative of the fact that there is resolution of adverse effects after discontinuation of KD.

Antiepileptic Drugs And KD

It is recommended that anti-epileptic drug formulations should be converted from liquid to tablet form in children on KD, in order to restrict additional carbohydrate intake. Studies do not support dose modification of anti-epileptic drugs or serum drug level monitoring in children on KD.[7] KD and Valproic acid both have the propensity to cause secondary carnitine deficiency and hence, when both agents are used concurrently, periodic serum carnitine assay is recommended.[7] Administration of KD to a child on carbonic anhydrase inhibitors such as topiramate, zonisamide or acetazolamide may increase the chance of development of metabolic acidosis. Hence, periodic serum bicarbonate level monitoring of these children is warranted, especially at the initiation of therapy.[62] Risk of urolithiasis multiplies with chronic administration of zonisamide and KD concurrently, whereas the same has not been demonstrated with concurrent use of topiramate and KD.[63] This warrants periodic screening ultrasound of kidney and bladder. It is recommended to taper antiepileptic drugs after about one month of initiation of KD.[7] Gradual tapering is advised, especially when benzodiazepines or phenobarbitone is used.[7]

Steroids And KD

Ville D et al conducted a pilot study on the role of combined therapy of KD and oral steroids in forty-two children with corticosteroid-resistant or dependent epileptic encephalopathy.[64] All children attained desirable level of urinary ketosis and fourteen children had good seizure control for six months.[64] KD helped in withdrawal of steroids in all the responders.[64] The study proved the potentially beneficial role of combined therapy of KD and corticosteroids in epileptic encephalopathies.

Discontinuation Of KD

Discontinuation of KD is individualized. International KD Study Group recommends atrial of three months after initiation of KD in order to evaluate its efficacy.[7] It is discontinued if there is initial worsening of seizures.[68] Though there is no cut-off for the maximum period of KD use, two years are accepted as a fairly appropriate

duration of KD use in children who have a reduction of seizures by more than 50%.[68] It is also recommended that an informed decision of KD discontinuation should be taken based on risk–benefit ratio analysis.[7] Prolonged KD therapy is indicated in Glucose Transporter Type I (GLUT 1) Deficiency till adulthood.[65] On the other hand, short duration of KD for 6 months has been found to be effective in West Syndrome.[66]

Classic KD is conventionally tapered over four to six weeks prior to discontinuation. 4:1 KD is modified by gradual addition of regular foods containing carbohydrates. During this process, 4:1 KD is reinitiated anytime if there is a significant increase of seizure burden. Increased seizure frequency to the tune of 14% has been reported with KD stoppage.[67]

In situations where KD does not show marked benefit, rapid taper is tolerated. Studies have revealed that children with structural brain lesions, tuberous sclerosis and persistently abnormal electroencephalographs are at greater risk of seizure recurrence after stoppage of KD.[69,70] Approximately 80% of the children with refractory epilepsy do not have recurrence after stoppage of KD.[6]

KD In Special Circumstances

KD In Infants

Neonatal onset epilepsy is a challenging entity wherein multiple drugs may not guarantee seizure freedom. KD use is controversial in neonatal age group in view of the unique physiology of infants and the recommendation of exclusive breast-feeding in this age group. The largest study of KD in infancy was performed by Le Pichon et al between 2005 and 2016 wherein nine infants with drug-resistant epilepsy between 1 and 13 months of age were treated with KD.[71] All the infants were continued on breast-feed for at least one month after initiation of dietary therapy. All of them achieved significant ketosis with four having significant seizure freedom and none having side effects.[70] The above study reinforced the role of KD as a safe, effective and practical management modality in breastfeeding infants with drug-refractory epilepsy. An international expert consensus pertaining to KD in infancy reinforces the various aspects of this therapy.[43]

KD In Resource-Limited Settings

MAD may be a more practical option for resource-limited settings compared to classic KD as it can be initiated as a domiciliary therapy with readily available home-based diets and less restrictive regimes. In an open-label randomized controlled study from India, the efficacy of a simplified Modified Atkins Diet (MAD) regime was evaluated in children with refractory epilepsy whose parents had poor literacy.[24]

In the study, forty-one children with refractory epilepsy (study group) were administered MAD for three months along with anti-epileptic drugs, while the control group comprising forty children received anti-epileptic drugs alone.[24] The study group had significantly higher number of children with more than 50% seizure reduction and minimal adverse effects, thus underscoring the efficacy, feasibility and tolerability of MAD in resource-limited settings.[24] The International League Against Epilepsy (ILAE) Task Force on Dietary Therapy have recommended certain practical steps for KD in resource-limited settings after due consideration of the unique challenges in such settings.[71] Core recommendations of the Task Force included short-term training of manpower in KD therapy, mandatory multivitamin and trace element (including selenium) supplementation and baseline investigation guidelines.[71]

KD In FIRES And SRSE

Management of Super-Refractory Status Epilepticus (SRSE) is a therapeutic challenge. KD has been reported to be effective in controlling seizures in the PICU.[72,73]

Appavu B et al performed a retrospective study to evaluate the efficacy of KD in pediatric SRSE.[73] Ten children (ages between two to sixteen years) with SRSE secondary to varying etiologies were identified among whom four had generalized and rest had focal status epilepticus.[73] KD was initiated after a median duration of eighteen days. Nine children had cessation of SRSE within seven days of start of KD indicating the efficacy of KD for treating pediatric SRSE.[51]

Arya et al studied the efficacy of KD in pediatric convulsive Refractory Status Epilepticus (RSE) in children recruited through any of the eleven institutions participating in the Pediatric Status Epilepticus Research Group (pSERG) between January 2011 to December 2016.[74] Fourteen children were administered KD, eleven of whom received it via enteral route.[74] Electroencephalographic resolution of seizure was achieved within one week of starting KD in ten children while eleven children could be weaned off from intravenous anti-epileptic infusions within two weeks of initiation of KD.[74] Adverse effects noted in three patients included gastroparesis and elevated triglyceride levels.[74]

KD In Adults

KD is gaining popularity as an effective therapeutic modality in adults with epilepsy.[75] Many epileptic adolescents who have benefitted with KD have transitioned to adulthood who continue to prefer using KD.[76] In addition, individuals with adult-onset epilepsy with drug-refractory seizures are increasingly turning towards KD in view of its better adverse effect profile. A meta-analysis of pooled data from twelve studies on the use of different types of KD in adults with drug-refractory epilepsy revealed that the efficacy of KD ranges from 13% to 70% in adults.[76] Compliance is a major challenge in adults with studies showing an adherence rate of 45%.[76] KD has proven to be effective in the management of SRSE in adults. In a recent multicentric phase I/II clinical trial, Classic KD was used in fifteen adults with SRSE, eleven of whom attained seizure resolution over a median period of five days.[77]

KD Administration In Children On Gastrostomy Tube Feeds

Children with refractory epilepsy and feeding issues mandating gastrostomy tube feeding may be administered KD through a gastrostomy tube effectively as portrayed through a case series of twelve children with static encephalopathy and intractable epilepsy on gastrostomy feeding.[56,57]

Socioeconomic Aspects Pertaining To KD Therapy

Any chronic medical management modality may impose various crucial repercussions on the socioeconomic aspects of the patients, their family members and society as a whole. Some of these salient aspects pertaining to KD have been highlighted through recent studies, as mentioned below.

Financial Implications Of KD

Financial viability is one of the key determinants of chronic therapy. Wijnen et al compared twenty-six children with intractable epilepsy receiving KD with twenty-two receiving other therapies in a study with sixteen-month follow-up wherein it was seen that KD leads to better seizure control with no significant difference in the Quality Adjusted Life Years (QALY) and cost-effectiveness per QALY of the two groups.[57] Awaiting further studies on this aspect, KD may be accepted as a financially viable option for the management of refractory epilepsy in children.

Effect Of KD On Quality Of Life (QoL)

Implementation of KD is challenging. Right from the acceptance of this modality to procurement of the essential tools such as a weighing scale and glucometer, to the daily preparation and adhering to a dietary regime requires strict family support and motivation. These intangible stressors and gains reflected through seizure control and reduction of anti-epileptic drugs may ultimately decide the perceived quality of life of the immediate family members. Poelzer et al conducted a systematic review of literature from 2007 to 2014 pertaining to children on various forms of KD to evaluate the effect of KD on the QoL of their immediate family members.[58] It emerged that no study directly addressed the issue of QoL.[58] Surrogate markers like poor adherence to KD and high dropout rates may be indicative of poor QoL.[58] Therefore, improvement of QoL may be ensured by pre-counseling and regular interaction between parents and health-care providers.[58] It is also a case in point that studies need to fathom the effect of KD on the QoL of patients as well as their family members.

Effect Of KD On The Cognitive And Behavioral Profiles Of Children With Epilepsy

KD has been known for having positive cognitive and behavioral effects in children with epilepsy. This effect seems independent of seizure control and reduction in anti-epileptic drugs. Ijff et al compared the effects of KD on the cognition and behavior of twenty-eight children with refractory epilepsy treated with KD to that of twenty-two others who were treated with drugs during the first four months of therapy.[78] Objective assessments proved that children in KD group had statistically significant improvement of cognition and behavior vis-à-vis the non-KD group, which was attributed to an independent effect of KD and not secondary to seizure-control itself.[78]

KD And Risk Of Sudden Unexpected Death In Epilepsy

Refractory epilepsy is a proven risk factor for Sudden Unexpected Death in Epilepsy (SUDEP).[79] Kcna1-null mutant mouse model which lacks the potassium channel Kv1.1 alpha is studied frequently as it is at a high risk for SUDEP due to its physiological variables.[80] Simeone KA et al carried out a proof of concept trial wherein they demonstrated the efficacy of KD in prolonging the life of

Kcna1-null mice by 47%, thereby demonstrating that KD is likely to diminish rates of SUDEP and prolong life expectancy.[80]

New Frontiers In Dietary Therapy

Triheptanoin is a synthetic edible oil which is composed of a seven-carbon compound called heptanoic acid.[81] It is used as an anaplerotic agent that replenishes the Intermediary metabolites of Tricarboxylic acid pathway.[81] There are reports of triheptanoin being successfully used as for refractory seizure control in numerous mouse models of epilepsy and as a neuroprotectant in Huntington's chorea and Glucose Transporter Type I deficiency.[81] Its efficacy as an add-on trial for seizures has been highlighted in a pilot trial of twelve children with refractory epilepsy.[82]

Triheptanoin therapy is well tolerated except for gastrointestinal adverse effects.[82] Poor palatability of KD owing to its extremely high fat content is a major reason for its discontinuation, which has prompted studies of alternative dietary therapies in epilepsy. The anti-seizure efficacy of a non-ketogenic diet comprising carbohydrates with low glycemic index, medium-chain fatty acids, PUFA with a high ratio of branched chain amino acids to aromatic amino acids was tried by Dallérac et al on the chronic kainate mouse model of epilepsy.[83] They demonstrated good seizure and the study provided proof of concept that a non-ketogenic regimen may have effective seizure control.[83]

Conclusion

KD is rapidly gaining its pride of place as an effective management modality in management of drug-refractory epilepsy and certain metabolic disorders. There is a growing body of research pertaining to previously little known aspects about the mechanism of action of KD. RCTs have provided irrefutable evidence supporting the efficacy of KD in seizure control. Various other beneficial effects of KD such as improvement of cognitive and behavioral aspects of children and quality of life of parents are additional bonuses of KD. Early administration of KD is advocated in certain conditions such as Dravet Syndrome and GLUT-1 transporter deficiency. Besides classic KD, MAD, MCT-based KD and LGIT KD have been increasingly used in clinical practice. It is being increasingly used in adolescents and adults. Clinical and translational research may further the body of evidence pertaining to the use of KD in refractory epilepsy, thereby opening the doors to better management of this common neurological disorder. In view of the therapeutic efficacy, safety and economic feasibility, KD is likely to emerge as a popular therapy in resource-constrained as well as developed societies worldwide.

Author Contributions

JNG: Literature review and initial draft manuscript preparation, final approval of the version to be published.

SS: Literature review, critical review of manuscript for important intellectual content and final approval of the version to be published.

Both authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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