

The changing face of dietary therapy for epilepsy

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Abstract Ketogenic diet is an established and effective non-pharmacologic treatment for drug-resistant epilepsy. Ketogenic diet represents the treatment of choice for GLUT-1 deficiency syndrome and pyruvate dehydrogenase complex deficiency. Infantile spasms, Dravet syndrome and myoclonic-astatic epilepsy are epilepsy syndromes for which ketogenic diet should be considered early in the therapeutic pathway. Recently, clinical indications for ketogenic diet have been increasing, as there is emerging evidence regarding safety and effectiveness. Specifically, ketogenic diet response has

been investigated in refractory status epilepticus and encephalopathy with status epilepticus during sleep. New targets in neuropharmacology, such as mitochondrial permeability transition, are being studied and might lead to using it effectively in other neurological diseases. But, inefficient connectivity and impaired ketogenic diet proposal limit ideal availability of this therapeutic option. Ketogenic diet in Italy is not yet considered as standard of care, not even as a therapeutic option for many child neurologists and epileptologists.

Conclusions: The aim of this review is to revisit ketogenic diet effectiveness and safety in order to highlight its importance in drug-resistant epilepsy and other neurological disorders.

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What is Known:

- Ketogenic diet efficacy is now described in large case series, with adequate diet compliance and side effects control.
- Ketogenic diet is far from being attempted as a first line therapy. Its availability varies worldwide.

What is New:

- New pharmacological targets such as mitochondrial permeability transition and new epileptic syndromes and etiologies responding to the diet such as refractory status epilepticus are being pointed out.
- Ketogenic diet can function at its best when used as a tailor-made therapy. Fine tuning is crucial.

Keywords Ketogenic diet · Drug-resistant epilepsy · GLUT1DS ketones · Modified Atkins diet · Dietary therapy

Abbreviations

AEDs	Antiepileptic drugs
CAU	Care as usual
DRE	Drug-resistant epilepsy
DS	Dravet syndrome

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ESES	Encephalopathy with status epilepticus during sleep
FE	Focal epilepsy
FIRES	Fever-induced refractory epileptic encephalopathy
GI	Gastrointestinal
GLUT1DS	GLUT-1 deficiency syndrome
HDL-C	HDL cholesterol
ILAE	International League Against Epilepsy
IS	Infantile spasms
KD	Ketogenic diet
LBD	Lafora body disease
LDL-C	LDL cholesterol
LGIT	Low glycemic index treatment
LKS	Landau-Kleffner syndrome
MAD	Modified Atkins diet
MAE	Myoclonic-astatic epilepsy
MCT	Medium-chain triglyceride diet
MD	Mitochondrial disorders
mPT	Mitochondrial permeability transition
PDCD	Pyruvate dehydrogenase complex deficiency
RSE	Refractory status epilepticus
SSP	Subacute sclerosing panencephalitis
TSC	Tuberous sclerosis complex
VNS	Vagal nerve stimulation
VPA	Valproic acid

Introduction

Current International League Against Epilepsy (ILAE) defines drug-resistant epilepsy (DRE) as ‘failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs (AEDs) schedules to achieve sustained seizure freedom’ [54]. The incidence of inadequate seizure control using standard drug therapy is still up to 30 % in paediatric epileptic population [34]. In those cases, non-pharmacological treatments such as epilepsy surgery, vagal nerve stimulation, immunoglobulin and behavioural and dietary therapies should be readily considered [53].

Ketogenic diet (KD) is composed of fat to protein ratio of 3:1 to 4:1 plus carbohydrates (in grammes). The concept of dietary therapy has been introduced at the beginning of the twentieth century, but it has been reconsidered only in the last two decades as a valuable option among alternative treatments of DRE, mainly in children [23]. The principal indications are GLUT-1 deficiency syndrome (GLUT1DS) and pyruvate dehydrogenase complex deficiency (PDCD) [46]. Infantile spasms, Dravet syndrome and myoclonic-astatic epilepsy are epilepsy syndromes for which KD should be considered early in the therapeutic pathway.

Major prejudices about its side effects, difficult compliance and doubts on efficacy have been overcome thanks to publication of large cases series [22, 57, 59, 69].

KD availability varies among different centres according to the level of expertise, experience and knowledge about it as a therapeutic option. Although the number of patients undergoing KD has increased, numbers remain low also because of lack of referrals and funding [60].

Ketogenic diet is an individualised treatment

More liberal versions of dietary therapy exist beyond the classical KD and medium-chain triglyceride diet (MCT): the modified Atkins diet (MAD) and low glycemic index treatment (LGIT) [30, 50, 71].

In the classical KD, the long-chain fats (90 %) compose the major percentage of daily caloric requirement and the remaining 10 % is from proteins and carbohydrates combined. Calories are initially reduced to 80–90 % of daily recommendations for age and then gradually increased according to the patient’s weight. Fluid supplementation is always recommended [46].

The MCT diet, described as more palatable, provides more ketones per calorie, allowing more carbohydrates and proteins inclusions and fewer calories from fats [35, 83].

The Atkins diet, classically used to reduce weight, allows the intake of fats and the restriction of carbohydrates. The MAD is ‘modified’ compared to Atkins diet as the ‘induction phase’ of diet limiting carbohydrates to the range of 15–20 g per day which is maintained indefinitely [44, 78]. This diet is probably the most suitable for adults, due to its use of household measures and unrestricted proteins [75].

In line with the established efficacy of KD in several specific conditions, the development of commercially available formulas provide a quick and complete fixed solution for administering KD. Also, they can be administered via feeding tube in neurologically impaired patients or in children younger than 12 months of age [33].

The consensus study group recommended the use of low-carbohydrate multivitamin and mineral supplements during the course of diet therapy. Oral citrates, antacids, carnitine and laxatives are optional supplements, and there is no evidence for empiric use [46].

Beyond the diet subtype, timing of diet administration, pharmacotherapy and efficacy based on the electroclinical and etiological diagnosis and patient’s tolerance have to be tailored on every patient. Aside from seizure reduction, neurobehavioral, cognitive [19, 29, 38, 64] and sleep improvement [13, 26] could influence the decision-making in the management and duration of the diet [76].

Ketogenic diet contraindications and limits

KD should be considered after two antiepileptic drug trials failure, with no age or gender specificity. Every patient must be screened for fatty acid transport and oxidation disorders for which KD is contraindicated (carnitine deficiency, beta-oxidation defects, pyruvate carboxylase deficiency and porphyria) [46]. Indeed, a patient with fat metabolism disorder may develop a severe alteration during fasting or KD setting.

There was no definitive consensus whether KD may be suitable also for patients with surgical resectable region, as partial seizures were considered less responsive to KD than generalised seizures [46]. But there is now evidence in literature on how KD could be a valuable additional non-invasive option even in patients with focal malformation of cortical development [15, 69].

‘Fine-tune’ of ketogenic diet

Great variability in the course, timing and response to KD exists. Although 3 months has always been considered the minimum time frame to define whether KD is effective [46], a diet implementation up to 6 months can be considered to ascertain either quantitative or qualitative response. Before achieving a stable positive or negative response to the diet, neurologists and dieticians often attempt to ‘fine-tune’ the KD and improve seizure control. Retrospective studies have tried to identify most frequent modifications and their influence, and a trend towards medication adjustments being more successful than dietary modifications has been outlined [76]. A recent study evaluated the impact of an intermitting fasting regimen on children having an incomplete response to KD, showing transient further seizure reduction [31].

Many children are on multiple medications at diet onset. Among the interventions that might potentiate KD efficacy, drug modifications are often done as a final option; in fact, specific indications on how to cope with anticonvulsant pharmacotherapy during KD are lacking. In a retrospective study, Kossoff et al. tried to assess whether medication reduction in the first month after starting KD had an advantage over a late taper [42]; all patients appeared to benefit equally and to well tolerate discontinuation even as early as the admission. Further accurate reporting of medication adjustments among patients on KD could guide physicians to better integrate anticonvulsant pharmacotherapy and KD in the future.

Several studies focused on the interaction between AED and KD. Despite valproic acid (VPA) in conjunction with KD was seen to be safe and well tolerated [61], latest publication showed that idiosyncratic interaction with high-fat dietary therapies can lead to apparent dietary treatment failure [34]. This could be explained by VPA selective inhibition of particular enzymes implicated in fatty acids beta-oxidation [79]. Lamotrigine significantly interferes with KD, reducing

ketosis achievement if used concomitantly [86]. Specifically, for the subgroup of GLUT1DS patients requiring an anticonvulsant beyond KD, some AEDs have been investigated for possible interactions with GLUT1DS such as barbiturates, diazepam, chloral hydrate and ethanol, which are inhibitors of GLUT1 function in vitro and might potentiate the effects of GLUT1-mediated glucose transport in patients with GLUT1DS. No inhibitory effects were observed for carbamazepine and phenytoin, indicating that these might be preferable in GLUT1DS [41].

Ketogenic diet suspension and transition

KD discontinuation timing and methods are tailored on every patient’s response. Among patients who had seizure control of more than 50 %, KD is typically discontinued after approximately 2 years, after weighting the risks and benefits.

Discontinuation is usually done gradually within 2 to 3 months by decreasing the ketogenic ratio and re-introducing carbohydrates. Despite the lack of evidence on the ideal weaning timing, a retrospective study demonstrated no significant increase in risk of seizure exacerbation with rapid KD discontinuation (less than 6 weeks). Patients who achieved a seizure reduction of 50–99 % and those who were on polytherapy had the highest risk overall [90]. Worsening of seizure frequency or severity is carefully monitored this time [35].

Martinez et al. analysed retrospectively the seizure control after discontinuation of KD in patients achieving seizure freedom and found that the presence of recent EEG epileptiform activity, abnormal MRI, lower initial seizure frequency and tuberous sclerosis complex significantly increase the likelihood of recurrence [63].

Children with GLUT1DS and PDCD may require longer KD treatment. With GLUT1DS patients, seizure control is nearly complete without significant side effects; therefore, the diet can be maintained up to 6–12 years [35]. No information is available about the maximum duration.

In patients undergoing KD for long periods, the transition from paediatric to adult specialist requires proper attention and endorsement. What should be understood is also whether adolescents with milder forms of GLUT1DS could safely discontinue the diet before adulthood. Multidisciplinary centres worldwide will be needed to provide adequate transition options [49].

Not only for GLUT1DS patients, further studies with longer follow-up will be required to describe efficacy, tolerability, duration of the treatment, as well as the prognosis after discontinuation, taking into account epileptic syndromes.

Side effects

Adverse effects may occur and should be monitored. However, most of the adverse effects such as metabolic abnormalities, gastrointestinal (GI) symptoms and nutritional deficiencies are preventable and proved to be treatable.

Immediate, short-term and long-term side effects have to be differentiated. Fasting is now considered optional, and many centres no longer fast children at diet initiation. Immediate side effects (hypoglycaemia, dehydration, acidosis and lethargy) are seen less commonly when a non-fasting approach is utilised [2]. The most common short-term side effects are GI symptoms (nausea, vomiting, diarrhoea and constipation) which may lead to poor compliance affecting the efficacy. High-fat diet prolongs gastric emptying causing disturbances, especially in patients with gastro-oesophageal reflux, which is a common characteristic in epileptic patients. Constipation might be consequential to a decreased intake of fibres and may be more severe in children with neurologic impairment leading to low mobilisation. Importantly, many children present GI disturbances before starting the diet, and exacerbations or reversal have been reported [36].

Dyslipidaemia is a common adverse effect. However, children undertaking KD can metabolise the higher fat and cholesterol provided by the KD over time. Many discordant data exist regarding lipid profile changes: some studies refer about modest HDL reduction, others about an ApoB increase and others report stable levels of both LDL and HDL cholesterol (LDL-C; HDL-C). Moreover, children receiving a formula-only KD did have lower total cholesterol than those on solid KD [6, 23, 36, 70]. A study on the effect of KD on vascular function found a gradual decrease in carotid distensibility and an increase in LDL-C, ApoB and triglycerides: LDL-C and LDL-C to HDL-C ratios were seen at 3 and 12 months, but these differences appeared to be reversible and not significant after 24 months of treatment [37].

Rare early-onset complications previously described are as follows: hypertriglyceridemia, transient hyperuricemia, hypercholesterolemia, infectious diseases, symptomatic hypoglycaemia, hypoproteinaemia, hypomagnesaemia, acute pancreatitis and persistent metabolic acidosis.

Long-term side effects including kidney stones, decreased linear growth, excessive weight loss, vitamin deficit and alterations in body composition could potentially occur with higher prevalence than short-term side effects.

Despite there are controversial data regarding body growth and bone density changes in patients treated with KD [3, 68, 82, 28], several reports showed poor linear growth, but the mechanism has not been clearly elucidated. GLUT1DS patients are the best candidates for studies with this aim, being their follow-up one of the longest. A recent case series on GLUT1DS adult patients treated with KD for more than

5 years demonstrated no major negative effects on body composition, bone mineral content and bone mineral density [4].

Hypoproteinaemia during KD is common; however, the underlying aetiologies have not been completely understood. Only one case of protein-losing enteropathy during the KD has been reported [66].

The impact of KD on arterial morphology, endothelial function and on cardiac diastolic function has also been evaluated in a cohort of epileptic children and young adults. In particular, arterial stiffness is increased before the increase of the intima media thickness, supporting that arterial stiffness is an early marker of vascular damage [14].

Prevention of nutrition-related side effects may be achieved through appropriate vitamins and minerals supplementation such as calcium, carnitine, selenium, zinc and vitamin D. Supplements should be carbohydrate-free. Until some years ago, there was a concrete risk of developing renal stones during KD; potassium citrate supplement, together with recommended fluid intake, is now often adopted as preventive agent [65].

Recently, the effects of a 12-week KD on inflammatory status, adipose tissue activity biomarkers, abdominal visceral and subcutaneous fat in children affected by GLUT1DS were evaluated. Results suggested that over a short period of time, KD does not affect inflammatory cytokines production and abdominal fat distribution [5]. Once again, more effective long-term studies are needed.

Old versus new ketogenic diet

The principal shortcoming in KD studies is the lack of a control group due to the fact that KD is traditionally reserved as the last treatment option after establishment of drug resistance. One double-blind study [24] and few randomised controlled trials have been published up to now [55, 69]. More specifically, Lambrecht et al. provided evidence that KD is effective compared to care as usual and Neal et al. studied the benefits of KD-treated group compared to no change in treatment in the control group, with the former seeing mean seizure frequency falling to 62 % and the latter seeing an increase to 137 % of seizure frequency compared to baseline. An example with direct comparison of a specific antiepileptic drug (ACTH) and KD in infantile spasms is present [45].

KD is the treatment of choice for two distinct disorders of brain metabolism: GLUT1DS and PDCD [3]. It is proved to be effective and safe as an early treatment for infantile spasms. A positive response has also been demonstrated in myoclonic-astatic epilepsy (Doose syndrome) [8], severe myoclonic epilepsy of infancy (Dravet syndrome) [7, 87], tuberous sclerosis complex [43] and Rett syndrome [76]. Moreover, a beneficial effect was seen in selected mitochondrial disorders, glycogenosis type V, Landau-Kleffner syndrome, Lafora body

disease [12] and subacute sclerosing panencephalitis [46]. Patients with focal, partial epilepsies appeared to have a reduced relative chance to obtain seizure freedom overall, especially if they have a localised lesion suitable for epilepsy surgery [56]. But, new reports in literature are describing good response to KD even in patients with focal malformation of cortical development [15, 69] (Table 1). Finally, refractory status epilepticus may become an indication [47].

As far as the international practise of KD is concerned, first and unique successful international consensus statement to identify shared attitudes in the clinical use of the KD dates to 2009, with 26 neurologists and dieticians from KD centres worldwide taking part in it [46].

Recently, a document outlining core requirements needed for a KD service has been published. This is to ensure the possibility of a broader network of KD and to make more accessible formulas and methods both for medical doctors and patients in new ketogenic diet (KD) centres in resource-limited regions of the world [52].

Old protocols have been revisited achieving optimal compliance and reduction of side effects up to zero. Fasting initiation is now considered optional; in selected patients, KD is now started without hospitalisation, and importantly, a normocaloric diet rather than hypocaloric diet has also been formulated.

Finally, challenging attempts to optimise KD use have been made in the direction of specific epileptic syndromes as epilepsy of infancy with migrating focal seizures and encephalopathy with status epilepticus during sleep (ESES). KD is also a well-tolerated treatment option for patients with ESES syndrome, with or without structural anomalies [10, 73].

New targets: ketogenic diet as a therapeutic option for refractory status epilepticus

Standard treatments for status epilepticus include intravenous antiepileptic medications and coma-inducing agents. Unfortunately, a significant subset of patients does not

Table 1 Comparison of “Old” and “New” ketogenic treatment approach

	Old	New
Qualified patients	Drug-resistant epilepsy Paediatric population	GLUT1DS [38]; PDCD [46]; MAE [8]; DS [87]; TSC [43]; RS [76]; MD; Glycogenosis type V; LKS; LBD [12]; SSP [46]; FE; encephalitis; FIRES [48]; glioma [67]; neurodegenerative diseases [81] Also adolescent and adults [62, 80]
Initiation	Mandatory hospitalisation 12–48 h fasting Fluid restriction	Outpatient and Inpatient initiation [56, 84] Fasting is optional [3, 39, 89] Increased fluid intake [46]
Diet type	Classic 4:1 KD	Different ratios of classic KD (4:1 3:1 2:1) MCT–MAD–LGIT
Daily caloric requirement	Limited (strict hypocaloric)	Adjusted for age, weight and activity [84]
AEDs management	No guidelines available	No guidelines available Suggested tailor-made management [76]
Follow-up	Urine ketones monitoring	Blood ketones monitoring [85]
Predictors of efficacy	Any predictor of efficacy available	Recent studies on EEG and clinical response [58, 88]
Neuropsychological/behavioural response	Potential [58]	Evaluated [9, 21]
Side effects (SE)	Addressing the side effects late Fasting SE (ie., hypoglycaemia, lethargy, dehydration) Rare long-term SE (early discontinuation)	Prevention rather than correction (introduction of supplements*) [25, 65] No fasting SE Long-term SE (discordance and lack of strong data) [4, 68]
Compliance rate	Poor	Improved [35]
Discontinuation	At least 2 weeks	At least 3 months [51]
Transition	No programme available	Programme available but not yet implemented [49, 51]

GLUT1DS GLUT1 deficiency syndrome, *PDCD* pyruvate dehydrogenase complex deficiency, *MAE* myoclonic-astatic epilepsy, *DS* Dravet syndrome, *TSC* tuberous sclerosis complex, *RS* Rett syndrome, *MD* mitochondrial disorders, *LKS* Landau-Kleffner syndrome, *LBD* Lafora body disease, *SSP* subacute sclerosing panencephalitis, *FE* focal epilepsy, *FIRES* fever-induced refractory epileptic encephalopathy

*Potassium citrate, calcium, carnitine, selenium, zinc, vitamin D

respond to conventional therapies. The largest study of KD for refractory status epilepticus (RSE) is by Nabbout et al., who retrospectively examined the use of KD for RSE secondary to fever-induced refractory epileptic encephalopathy (FIRES). The KD was started using various formulas via nasogastric tubes, and glucose was removed from both medications and intravenous fluids. Within a mean of 2.8 days, all but one of the eight children developed ketonuria and, remarkably, seven of these eight children rapidly responded to KD [47].

Data until now (more than 30 patients) suggest that the KD is a reasonable and safe option for treatment of RSE with immunomediated causes (encephalitis and FIRES) [48]. Early consideration of KD in the management of RSE seems safe and well tolerated, with no demonstrated interactions with antibiotics or AEDs, and a possible anti-inflammatory action has been suggested [26].

Moreover, a report of two paediatric patients with refractory myoclonic status epilepticus showed improvement in seizure control with KD for a minimum follow-up of at least 6 months [11].

Cases of severe RSE have also been proposed to be responsive to KD. However, more prospective, randomised controlled trials studies are needed to conclusively evaluate its efficacy and eventually determine the optimal protocol for KD initiation.

New targets of neuropharmacology

The concept that KD may be neuroprotective brought to a broader coverage of its use in epilepsy but might also have an implication in neurodegenerative or metabolic derangement [74, 81]. An experimental study on a rodent model of epilepsy has been utilised—the KCNA1-null mutant mouse—and ketone bodies effects on mitochondrial permeability transition (mPT) were tested. Data revealed that the first direct link between mPT and seizure control provides a potential mechanism for the KD action through the cyclophilin D subunit of the mPT complex. Given that mPT is increasingly being implicated in diverse neurological disorders, these results suggest that metabolic substrates might represent a worthy paradigm for therapeutic development [40].

The potential the anti-inflammatory action of KD is acquiring more relevance. Data suggest that exploiting cellular mechanisms associated with ketone-based metabolism offers new therapeutic opportunities for controlling pain and peripheral inflammation [20].

A potential anti-seizure role of dietary protein or individual amino acids in the KD has been hypothesised. Hartman et al. study raises the possibility that D-leucine may represent a new class of anti-seizure agents [32].

Lastly, neuroactive peptides could play a role in modulating epileptic activity. Des-acyl ghrelin, which is increased in catabolic states, had an anticonvulsant activity in status

epilepticus animal model. A des-acyl ghrelin analogue, EP-80,317, was also effective in preventing seizure induction by pilocarpine when preventively administered in rats [27].

Now that a plateau has been reached in terms of clinical understanding of KD application, clarification of neuronal and molecular mechanisms of its effects is crucial.

New targets: ketogenic diet and cancer

The reason why KD could be used with cancer derives from the evidence that cancer cells, unlike normal cells, are unable to use ketone bodies because of their altered oxidative phosphorylation [77]. This potential of KD has been investigated mainly in animal models of brain tumours. For example, the growth of malignant astrocytoma and glioblastoma xenografts in mice was inhibited significantly by a calorie-restricted KD, which also had significantly enhanced the antitumour effect of radiation therapy in glioma patients [1]. A recent publication by Schwartz et al. reported the experience of two glioma patients undergoing an energy-restricted KD that resulted effective in controlling the progression of some gliomas and had no major side effects. Finally, neuroblastoma showed up as a potential target of KD adjuvant therapy [67].

Compliance and ketogenic diet economics

Compliance is crucial in validating KD therapy and involves patients, families and caregivers. Meals preparation can be burdensome for parents and caregivers and requires great attention. Moreover, KD-positive effects may appear slowly and not satisfactorily. That is why compliance should be continuously assessed during follow-up, in order to be sure that KD efficacy can be properly evaluated. In the specific set of GLUT1DS patients, where KD is exclusively efficacious, compliance has proved to be much better than in other conditions for which KD is indicated [16].

Sometimes, in order to ameliorate compliance, KD ratios can be lowered by implementation of carbohydrates. At present, its palatability is somehow improving and more KD-based formula, although expensive, are readily available.

A recent study has evaluated KD cost-effectiveness compared with care as usual (CAU) in patients with intractable epilepsy; despite seizure reduction, KD showed to have an unfavourable cost per QALY ratio [18]. A previous study showed that compared to vagal nerve stimulation (VNS), which constitutes a valid non-pharmacologic alternative for intractable epilepsy, KD is more effective and less costly, after 12 months [17]. Indeed, when coping with intractable

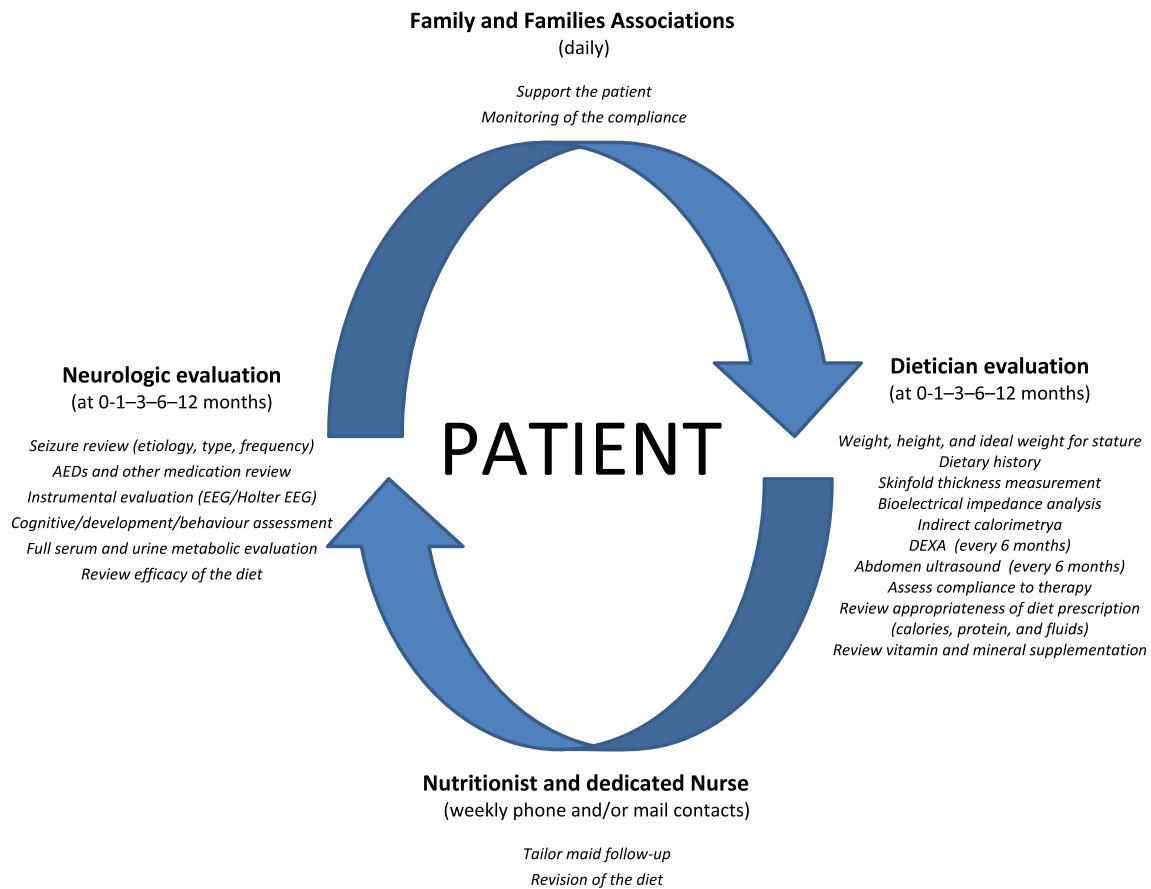


Fig. 1 A proposed multidisciplinary approach for tailor-made Ketogenic Diet for drug-resistant epilepsy

epilepsy, both KD and VNS compared to CAU resulted to be more effective but also more expensive.

Ketogenic diet in European countries versus the world

As to our experience in Italy, KD is still underutilised and does not stand as a properly known alternative for many child neurologists and epileptologists. This could influence data availability about the effective response to KD. Even if there are no data yet showing a positive correlation to early implementation of KD, we know that epilepsy refractoriness and encephalopathies are likely to become more severe if not properly managed.

It could be extremely beneficial to have a European consensus, in addition to the international consensus [46], and national protocols [87], in order to better deal with the local needs and to reinforce a multidisciplinary approach (Fig. 1) to KD, not to be easily found.

And along with a more consolidated multidisciplinary approach, family associations on KD are to be greatly encouraged as they represent an important factor providing social support and awareness. It would therefore be

advisable to set a European net of medical centres promoting KD and social support.

Conclusions

Inefficient connectivity and big differences in KD management and proposal worldwide are still a considerable obstacle.

Moreover, large regions of the world do not have widespread availability of KD (e.g., Caribbean, Central America, Africa, Eastern Europe and Southeast Asia regions). The reason for that is likely to be found in poor and heterogeneous availability of KD teams, dietetic and formula supplements and even appropriate food [52].

It is very crucial to stay focused on the importance of KD as a valid alternative treatment for DRE and, more in general, on the correct management of intractable epilepsy. Adequate non-pharmacologic choices should be prospected earlier in the therapeutic pathway, in order to change or arrest disease course. There should be then more awareness about the sanitary costs due to frequent hospitalizations, expensive drugs and highly specialised multidisciplinary medical teams.

Even social and affective consequences are to be kept in mind when deciding for a therapeutic intervention in DRE.

Also, although no prospective studies of developmental or behavioural outcomes have been performed so far, anecdotal evidence and parental reports have indicated that children treated with KD show increased alertness and better cognitive functioning, as well as improved behaviour [25, 29, 72, 21]. Maybe, focusing only on seizure control may not express the full range of KD potential.

More precise tuning and understanding of KD should be continuously searched in order to give more information and expectancy to families.

Current research on KD mechanism of action could show new insights in re-evaluating cerebral metabolism and in applying KD also to neurologic conditions other than epilepsy and thus exploring new populations.

And future perspectives, both for epilepsy and cancer application of KD, might be the use of novel metabolomics and proteomic technologies, still unexplored with patients undergoing KD.

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Compliance with ethical standards All the Authors have read and approved the submission of the manuscript, in which the material has not been published and is not being considered for publication elsewhere in whole or in part in any language. All the authors meet the appropriate authorship criteria; nobody who qualifies for authorship has been omitted from the list. Authors' contribution and funding sources have been properly acknowledged, and the authors approved the acknowledgement of their contribution. All the authors have full access to all of the data that support the publication.

I confirm that my manuscript complies with the ethical rules applicable for this journal.

Conflict of interest The authors declare that they do not have any conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

I confirm that the manuscript does not report any data collected from humans or animals and does not involve human participants and reporting health related outcomes.

I confirm that I have read journal's guidance on competing interests and I confirm that none of the authors have any competing interests in the manuscript.

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