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Conference review

The ketogenic diet: From molecular mechanisms to clinical effects☆

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Abstract

Recent years have witnessed an increased interest from pediatric neurologists, neuropediatricians, epileptologists and general neurologists in the use of the ketogenic diet (KD) for the management of refractory epilepsies, particularly in children and adolescents. This article summarizes current knowledge on various issues related to its use, as discussed at a recent international workshop. Aspects discussed in some detail include (i) the putative mechanisms responsible for the diet's anticonvulsant effects, based on results of biochemical and neurophysiological studies in experimental models; (ii) consensus and controversies on the modalities of initiation of the diet, and different protocols of implementation; (iii) indications and contraindications; (iv) efficacy data, also in relation to seizure type, syndromic form and patients age; (v) adverse effects; (vi) methodological aspects related to assessment of the diet's clinical effects, and perspectives for future research. Overall, the data reviewed indicate that considerable advances have been made in understanding the modes of action of the diet, its efficacy and tolerability profiles and its potential role in different types of epilepsy. Although clinical studies performed to date have important methodological limitations, including suboptimally characterized patients' populations and an uncontrolled design, a number of innovative, prospective randomized study protocols have been recently proposed and are being implemented. The results of these will hopefully provide much needed high-quality information to better define the role of the diet in the treatment algorithms in different epilepsy syndromes.

Keywords: Ketogenic diet; Epilepsy; Mechanisms of action; Efficacy; Safety; Review

☆ Summary of a Workshop held at the Institute of Neurology IRCCS C. Mondino Foundation, Pavia, Italy, 24 September 2005.

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1. Introduction

Recent years have witnessed an increased interest from pediatric neurologists, neuropediatricians, epileptologists and general neurologists in the use of the ketogenic diet (KD) for the management of refractory epilepsies. In parallel with this interest, a number of studies have been completed addressing a wide range of issues related to this diet, from its mechanisms of action in animal models to its efficacy and tolerability profiles in different populations of patients. In recognition of this, the Institute of Neurology IRCCS C. Mondino Foundation in Pavia, Italy, took the initiative of organizing, on 24 September 2005, an international workshop whose purposes were to (i) discuss the rationale for the use of the KD, and bridge basic science data with evidence from clinical experience; (ii) review critically and update current acquisitions on the use of the diet in the epilepsies; (iii) highlight controversies concerning indications and modes of application; (iv) identify areas and methodology for future research.

The workshop, which was attended by many leading experts from both sides of the Atlantic, provided a forum for constructive interaction between many disciplines which contribute to our knowledge in this area. The purpose of this manuscript is to summarize information that was presented at this workshop, as well as the main points that emerged from the associated discussions.

2. Dietary treatments for epilepsy: a historical perspective

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Individual seizures, as well as the repeated seizures associated with epilepsy are frightening to observers and may affect the quality of life of those affected. Throughout the millennia their etiology has been mysterious. Epilepsy, termed “The Sacred Disease” and “The Falling Sickness”, has been ascribed to many causes, including demonic possession (Tempkin, 1976). Even among the modern day Hmong tribes, seizures are ascribed to problems with the individual’s soul (Fadiman, 1997). The Hmong consider seizures as indication of possession of “a healing spirit” and consider the affected individual to have divine, shaministic abilities (Fadiman, 1997). This can result in an important example of cross-cultural misunderstanding. Seizures have also been ascribed to: “humors”, “toxins”, and infections (Lennox, 1960). Treatments have been empirical and have ranged from magic, to the ingestion of, or abstinence from certain foods and even of certain animal and human parts. Irritation and counter-irritation, trephination, prayer, and fasting have been prescribed. The removal of various organs and even death because of demonic possession has been used as treatment.

Bromide, the first useful antiepileptic drug (AED), was used in the 1850s for “hystero-epilepsy” and later used successfully in other forms of seizures. Phenobarbital introduced in 1917 and phenytoin in 1937 were but the first of what has become a plethora of new AEDs. Lack of understanding of the cause of seizures and epilepsy has, over time, seemed to be the mother of therapeutic intervention and invention. While we have learned much about the physiology of neuronal excitation and inhibition, even today we understand little about what causes most seizures or what triggers their occurrence. Our treatments, therefore, continue to remain largely empirical. The KD is only one of the more recent, empirically derived, effective therapies.

In the early 1920s, an osteopathic physician named Hugh Conklin “discovered” that epilepsy, “resulted from intoxication of the brain from substances coming from the intestine”, and devised a “cure” by fasting and having the patient imbibe only water for up to 20 days thus putting the intestine at rest (Freeman et al., 2002). At a time when there were few other effective treatments for seizures, the diet was documented to be effective. This was termed “The Water Treatment” for epilepsy. It was found that a calorie-restricted diet high in fats, with sufficient protein and limited carbohydrates could mimic the biochemical changes of this starvation and could preserve its beneficial effects on the seizures (Freeman et al., 2002). In modified form this has been became today’s KD. The beneficial effects of this dietary treatment were confirmed throughout the 1930s, and but then largely forgotten as first phenytoin and then other anticonvulsants became available. Medication was far easier to prescribe and take than the KD.

Interest in the KD was re-awakened during the early 1990s and since then multiple studies from many centres have concluded that the diet can be as effective or

even more effective in the management of children with difficult-to-control seizures than other currently available anticonvulsant medications (Freeman et al., 1998; Freeman and Vining, 1998). At Johns Hopkins, 150 consecutive children with multiple seizure types and having at least two seizures per day were started on the KD and followed up (Hemingway et al., 2001a; Mady et al., 2003). Slightly more than half of the children who had averaged >400 seizures per month at diet onset continued the diet for 1 year, and 27% of those children, had had a >90% decrease in their seizures. Three to 6 years later a similar percentage of this same group had continued, now off the diet, with few seizures, and many had decreased or eliminated their medications. There are no studies of AEDs documenting similarly good outcomes over comparable time periods.

The KD has been reported to be effective across a wide variety of ages, seizure types and severities (Mady et al., 2003; Kossoff et al., 2002a) as well as different etiologies (Kossoff et al., 2002a, 2005). It can be used in liquid form (Kossoff et al., 2004a,b), for bottle or tube feeding, and perhaps even in a modified form as the Atkins diet (Kossoff et al., 2003). The diet has few significant side effects and when properly supervised does not cause weight gain or substantial growth abnormalities (Vining et al., 2002) and has minimal effects on serum lipid profiles (Kwiterovich et al., 2003).

How the diet exerts its anticonvulsant effects is unknown, but is thought possibly to relate to serum levels of beta-hydroxy butyrate (Gilbert et al., 2000). Its mechanisms of action are the subject of considerable research, and of a recent book (Stafstrom and Rho, 2004). Perhaps understanding the mechanisms of action of the KD will lead to new approaches to treatment of the epilepsies.

3. The ketogenic diet: definitions and standard protocols

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The KD is a high-fat, low carbohydrate, normocaloric diet that mimicks the metabolic state of fasting. During a prolonged fast, body energy requirements are met by lipolysis and β-oxidation of fatty acids rather than by the breakdown of carbohydrates. Thus, the KD maintains an anabolic nutritional state in a metabolic situation of fasting. Any diet providing nutritional fat for the generation of ketones that serve as an alternative fuel to body tissues may be called "ketogenic". Ketones may produce an anticonvulsant effect, presumably due to changes in (a) cerebral energy metabolism; (b) cell properties decreasing excitability; (c) neurotransmitter function; (d) circulating factors acting as neuromodulators, and (e) brain extracellular milieu (Schwartzkroin, 1999).

For the treatment of intractable childhood epilepsy two types of KDs have thus far been developed. The diets differ in their composition of free fatty acids. The traditional long-chain triglyceride (LCT) diet is most commonly used (Swink et al., 1997; Lefevre and Aronson, 2000). A second type, the medium-chain triglyceride (MCT) diet is more ketogenic but less used as it often causes gastrointestinal side effects. An ongoing clinical trial at Great Ormond Street Hospital (London, UK) is currently comparing both ways of giving the diet. Finally, several infant formulas are now available in the USA and in Europe (Nordli et al., 2001; Klepper et al., 2002). Despite the worldwide use of the diet (Kossoff et al., 2005) (Fig. 1) and an increasing understanding of the underlying mechanisms, no international protocols have yet been developed. Age, groups, indications and contraindications, the initiation, ratio, and duration of the diet, as well as anticonvulsant co-medications are left to the treating physicians. Medical associations have been reluctant to promote the diet and the development of guidelines. As a result, both in the USA and in Europe centres follow individual protocols and the data obtained are difficult to evaluate. A substantial number of international clinical studies follow the Johns Hopkins Hospital protocol (http://www.neuro.jhmi.edu/Epilepsy/Peds/keto_diet.htm) (Swink et al., 1997). In German-speaking countries, a consensus on how to introduce and maintain the diet that closely follows the Hopkins protocol was introduced in 2003 (Klepper et al., 2004) (http://www.neuropaediatrie.com). Free KD software and a list of pediatric centres on the world wide web providing a KD program in the USA and worldwide is available on the website of the Packard Children's Hospital Stanford University Medical Center (http://www.stanford.edu/group/ketodiet/).

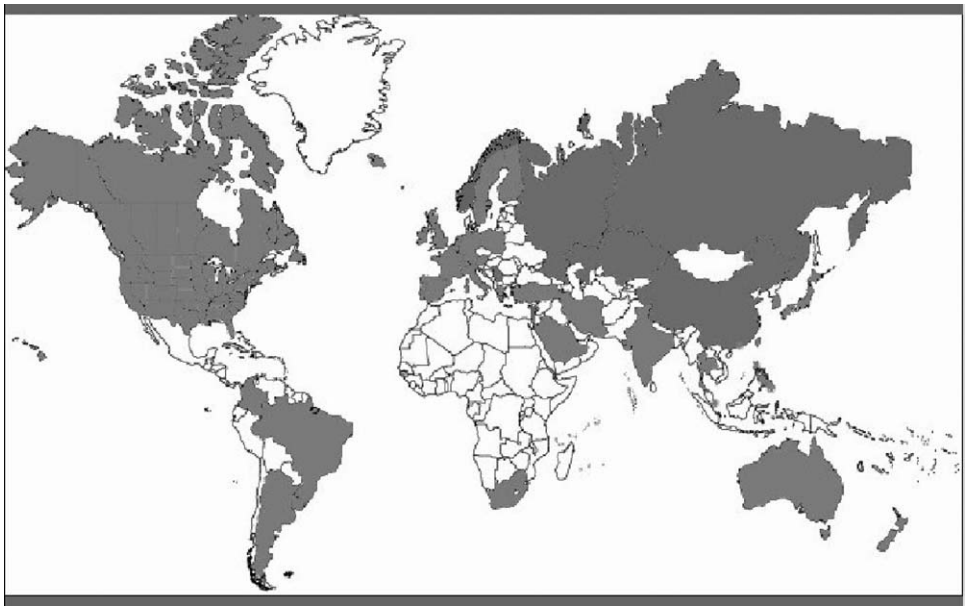
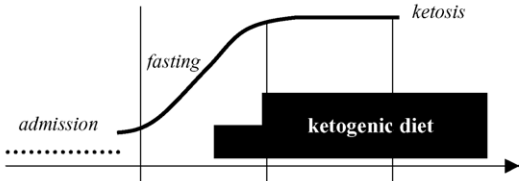


Fig. 1. Countries providing the ketogenic diet (highlighted in grey) as identified in a recent survey. Updated from Kossoff et al. (2005). Reproduced with permission from the author and from the publisher.

Indications for the KD are intractable childhood epilepsy, glucose transporter type 1 (GLUT1) deficiency syndrome, and pyruvate dehydrogenase complex deficiency. Before initiating a KD contraindications such as β-oxidation defects, liver or metabolic disease interfering with glucose or ketone homeostasis need to be excluded. A full history as well as a clinical and nutritional assessment is necessary. Finally, the compliance of patient and caretakers is essential. In the Johns Hopkins Hospital protocol and in the German consensus protocol patients are admitted to the hospital and ketosis is initiated by fasting. Reasons for hospitalisation are the difficulties of fasting in children and the potential hazards of prolonged fasting as an outpatient. Others have described benefits of the non-fasting KD compared with the initial fasting KD but prospective, randomized trials are not yet available to settle this controversial issue (Kim et al., 2004a; Wirrell et al., 2002). During fasting, basic laboratory parameters, in particular blood glucose and ketones in blood and urine need to be monitored closely, preferably at the bedside. Once ketosis is established the diet will be introduced starting with one-third of calories per meal. Calories are increased to two thirds of calories per meal after every 24 h and patients are discharged when the total amount of calories per meal is well tolerated. During admission patients, parents, and caretakers are educated about suitable food items, the calculation, and the preparation of ketogenic meals by the dietician. Multivitamins, minerals, and trace elements are supplemented. Follow-up demands regular outpatient admissions and easy access to the treating pediatrician and dietician. Side effects of the diet such as kidney stones and blood lipids need to be monitored (Kwiterovich et al., 2003; Ballaban-Gil et al., 1998). The time course of the introduction of a KD and essential investigations as outlined in the German consensus protocol is shown in Fig. 2.

Despite the resurgence of the diet several controversial issues about this treatment remain. KD protocols differ in the necessity of the initial fast as outlined above, the duration of the diet, fluid restriction, the use of MCT versus LCT fatty acids, and the need for carnitine supplements. Other issues such as the potential long-term adverse effects or the potential interactions of the diet with AEDs remain largely unanswered. Future progress in KD protocols will require an international expert panel to clarify definitions and develop standard protocols. Recommendations should be authorized by an international medical society to



investigations	evaluation	day -1	day 0-3	day 3-6	follow-up
ketones (urine)			6 - 8 h	•	•
ketones (blood)			6 - 8 h	•	•
blood gas analysis			6 - 8 h	•	•
Glucose	•		6 - 8 h	•	•
Lactate	•				
Ammonia	•				
carnitine profile	•				
organic acids (urine)	•				
body weight, height	•				•
Electrolytes, creatinine	•				•
liver parameters	•				•
blood lipids	•				•
abdominal ultrasound	•				•
EEG	•				•

Fig. 2. Algorithm of the introduction of the ketogenic diet as agreed by the consensus in German speaking countries (Klepper et al., 2004).

ensure quality control and to provide an interactive platform for physicians using the KD.

4. Implementation and monitoring: nutritional aspects

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4.1. Introduction

To obtain a level of ketosis adequate for seizure control, low amounts of carbohydrates and high amounts of fat are administered in a rigidly controlled ratio. The use of such an unbalanced diet in children requires particular attention in implementation and monitoring. The main nutritional problems that require careful monitoring arise from marginal or overt nutritional deficits (energy, proteins, minerals and vitamins) or from excess nutrients (lipids, saturated fat and cholesterol) which are peculiar to this diet.

4.2. Fasting versus non-fasting at initiation

Ketosis is usually induced with a short period of fasting (Freeman et al., 1996), followed by a gradual introduction of the high-fat diet. From a biochemical and physiological point of view, however, a period of fast is not *necessary* to induce and maintain a condition of metabolic ketosis. The key issue is whether fasting can be *useful* when initiating the diet in children with epilepsy. Advantages of fasting include a shorter time to onset of ketosis, improved screening conditions for identifying underlying metabolic disorders, and the need for a hospital admission period which allows to teach the family about the preparation of meals and the monitoring of ketosis (Katyal et al., 2000; Kossoff et al., 2005). On the other hand, disadvantages of fasting include psychological stress, the risk of hypoglycemia or dehydration, and the cost or inconveniency of hospitalisation and repeated blood tests. In a worldwide survey, fasting was found to be preferred in most countries, though it was shortened or eliminated by most physicians in Canada, UK, India, Sweden, The Netherlands and Korea (Kossoff and McGrogan, 2005). Unfortunately, only few groups that use the non-fasting

protocol have reported on their experience (Wirrell et al., 2002; Vaisleib et al., 2004; Kim et al., 2004a) and only one centre has compared the two protocols in their patients (Kim et al., 2004a). In the latter study, no significant difference was found in time to strong urinary ketosis between the two groups. As for early side-effects, moderate dehydration was less frequent in non-fasted subjects, but the incidence of hypoglycemia was not different between groups. Wirrell et al. (2002) reported that time to ketosis and diet efficacy in eight inpatients managed without fasting were similar to those described with fasting protocols. Groups using the non-fasting protocol have also compared inpatient versus outpatient initiation of the diet, and found no significant differences in seizure control between the two approaches (Vaisleib et al., 2004). More information from well-designed prospective studies, however, are needed to assess optimal non-fasting protocols and outpatient initiation of the diet. In any case, when the diet is initiated without hospitalisation, adequate facilities must be available to instruct families on meal preparation and monitoring techniques.

4.3. Providing adequate energy supply

It is extremely important to provide adequate energy intake to avoid protein (muscle mass) utilization as fuel. To this purpose, energy requirements of the child need to be determined by means of 3- or 7-day food diaries to estimate usual caloric intake, or by referral to the recommended dietary allowances (RDA) for healthy children of the same age range (Food and Nutrition Board, 2002). However, group estimates can give inaccurate results in individual subjects. In our protocol, we measure individual basal metabolic rate by indirect calorimetry before starting the diet and every 3 months, to adjust caloric needs. Gastrointestinal disturbances, poor appetite, food refusal, or intermittent fasting to restore adequate ketosis may determine a low energy intake and weight loss. We use a liquid formulated snack to compensate for poor caloric intake when needed.

4.4. Ensuring appropriate intake of proteins and amino acids

The maintenance of a constant ratio of fat to proteins + carbohydrates limits the amount of proteins which can be included in the diet, but it is generally possible to give 1 g protein per kg of body weight. This is slightly less than the RDA for infants (1.5 g/kg/day) and for children aged 1–3 years (1.1 g/kg/day), but it is adequate for older children. Proteins must be of high quality (i.e. rich in essential amino acids), which is usually the case because foods which are rich in animal proteins usually are also rich in fat.

A marginal intake of proteins, calories or other nutrients can affect growth. Two prospective (Vining et al., 2002; Liu et al., 2003) and several retrospective studies (Couch et al., 1999; Williams et al., 2002) have shown a decrease in growth percentiles and z scores in children on the KD. These children were subjected to caloric restriction at initiation of the diet with adjustments during the course of the treatment to match individual needs, and therefore no weight or height impairment was expected. In the latest study, a retrospective chart review by Peterson et al. (2005), children were given their usual caloric intake since the beginning of treatment. A decrease in height-for-age z scores was found at 6 and 12 months, which was significant only in subjects with high urinary ketosis (80–160 mg/dl). As a point of interest, subjects who stayed on the diet for 12 months tended to consume fewer kilocalories. At 6 months the weight change was predicted by kilocalories intake, but at 12 months it was not. Research is needed to identify factors that permit normal growth in some children but not in others. In clinical practice, all children on the KD should have their growth monitored by growth charts, and energy and protein levels should be adjusted to assist growth at a rate that allows seizure control to be maintained. Because measurement of body weight alone does not permit to assess changes in body protein content (muscle mass) induced by the diet, other estimates of body composition may be required (arm anthropometry, bioelectrical impedance analysis or dual X-ray absorptiometry). Biochemical tests (plasma proteins) may aid in identifying subclinical protein deficiency.

4.5. Monitoring intake of carbohydrates

A low intake of carbohydrates is essential to maintain ketosis. Measuring urine ketones allows monitoring of adherence to the low carbohydrate intake. When possible, blood ketones, which have been shown to correlate better with seizure control, should be measured

Table 1
Nutritional monitoring protocol

Nutritional risk	Clinical effect	Monitoring method
Energy deficits	Weight loss; growth impairment	Anthropometry (weight, height, skinfold thickness); resting metabolic rate measurements
Protein deficits	Muscle mass loss, bone metabolism impairment	Arm muscle circumference; plasma proteins (albumin, pre-albumin, transferrin)
Lipid excess (saturated)	Atherosclerosis	Plasma lipids profile
Calcium deficits	Osteopenia and osteoporosis	Dual X-ray energy absorptiometry, bone metabolism markers
Selenium and potassium deficits	Cardiac complications	Whole blood or serum levels
Water-soluble vitamins deficits	Dermatitis, anemia, neurological symptoms, etc.	Plasma and urine levels, blood count

(Gilbert et al., 2000). The low content of starchy food and vegetables makes the KD extremely poor in fiber, which can cause constipation.

4.6. Optimizing intake of lipids

In a recent study of 141 children, the classic diet was found to cause a significant increase in atherogenic apoB-containing lipoproteins and a decrease in the anti-atherogenic HDL cholesterol after 6 months; significant but less marked changes persisted in those children who were followed up for 12 and 24 months (Kwiterovich et al., 2003). To reduce cardiovascular risk, the ratio of poly-unsaturated + mono-unsaturated fatty acids to saturated fatty acids needs to be increased in ketogenic meals, and blood lipid profile should be checked regularly.

4.7. Minerals and vitamins

Due to the limited food choice, the classic KD is also deficient in minerals and vitamins, and needs to be supplemented with sugar-free products. Inadequate calcium intake and limited sun exposure can impair bone mineralization in children already at risk of osteopenia and osteoporosis due to long-term AED therapy (Shet, 2004). Therefore, routine examinations of bone mineral density and/or bone enzymes are required.

4.8. Conclusions

Implementation and monitoring of the KD in children needs a dedicated team to assess basal nutritional status in order to improve caloric and nutrient prescription. Adequate supplementation is always needed. Careful monitoring of nutritional status during treatment is necessary to prevent malnutrition. The risk of malnutrition is particularly high in children with poor nutrition at baseline (Bertoli et al., 2002). Main nutritional risks and monitoring methods are summarized in Table 1.

5. Maximizing acceptability and compliance

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The composition of the KD is expressed by a ratio of fat to protein and carbohydrates weights equal to 4 (fat):1 (protein + carbohydrates); proteins are provided in order to meet but not to exceed the recommended amount of 1 g/kg of body weight, whereas total caloric intake is based on age-adjusted standards. This implies that 90% of dietary calories are derived from fat and no more than 2–3% are derived from carbohydrates. To maintain a stable ketosis, strict adherence to the dietary plan is required, and even small deviations in food preparation or the intake of small amounts of food outside the dietary plan may reduce blood ketones, causing a substantial reduction in the diet's efficacy (Casey et al., 1999; Carroll and Koenigsberger, 1998).

The potential short- and long-term side effects of the diet, together with the diet's harshness and unpalatability are the most important factors affecting adversely compliance and, consequently, clinical efficacy. Although large multicentre studies investigating specifically long-term compliance on the diet are lacking, a review of the literature indicates that less than one half of the patients remain on the diet for more than 1

year (Hemingway et al., 2001a; Freeman et al., 1998; Lightstone et al., 2001). Discontinuations are due to medical and non-medical reasons.

Our experience in a total of 32 children placed on the KD between September 1994 and August 2005 showed that 24 discontinued the diet after 1–33 months (18 within the first 12 months). Of these, 18 (75%) discontinued for medical reasons, specifically due to lack or loss of efficacy (16 patients) or adverse complications (3 patients, including 2 with severe metabolic acidosis and one with repeated probably diet-unrelated chest infections). Six children discontinued the diet for non-medical reasons; these included caregivers' issues and patients' unwillingness to continue on the diet. In fact, the diet's acceptance and compliance are strongly dependent on the collaboration of both the child and the parents. The preparation of meals can be burdensome for parents, who must pay great attention in choosing, weighing and cooking every dietary component. On the other hand, the direct involvement of parents in the management of their child's epilepsy often makes the diet more acceptable than expected. The poor palatability of some ketogenic meals is not a common cause of inadequate compliance, and it is almost never a cause for discontinuation. By contrast, ingestion of additional "forbidden foods" is one of the most common causes of an insufficient level of ketosis, and may be due to interference from a "sympathetic" relative or friend or the result of the child's own industry. The latter possibility is more frequent in older children and in children with mild cognitive impairment. To maximize acceptability, at our institution the nutritional and neurological teams have established a collaborative, highly interactive protocol (Table 2).

The recent introduction of nutritionally complete powdered formulas has provided an additional tool to improve compliance when suitable food is unavailable or cannot be conveniently administered, for example during illness. Regular monitoring of ketone bodies with urinary sticks or with capillary measurements

Table 2
Protocol for maximizing compliance with the ketogenic diet

	Operator
Before starting the diet	
Enrolment motivated patients/family	Neurologist
Detailed description to family and patients of both the role of the diet in the treatment of epilepsy (history, efficacy, side effects, etc.), palatability considerations, and need for strict adherence to meal preparation instructions	Neurologist, nutritionist
Dietary history. Seven-day diary with careful evaluation of patient's food habits and tastes in order personalize at best the dietary plan	Dietician
Clinical evaluation to identify possible chewing or swallowing impairment requiring special dietary strategies	Nutritionist
Compilation of a questionnaire concerning the acceptability of a selected list of ketogenic foods (lecithin, butter, high fat cream, olives, etc.)	Parents
Induction period (hospital)	
Training of parents to instruct them on how to choose, weigh, cook and serve ketogenic meals	Dietician
Continuous dietician's presence and assistance during intake of the first ketogenic meals	Dietician
Continuous neurologist's and nutritionist's monitoring and assistance during the period of hospital admission	Neurologist, nutritionist
After discharge from the hospital	
Daily phone contacts with dietician and nutritionist in the first 2 weeks	Nutritionist
Neurological and nutritional evaluation every 3 months	Nutritionist
24 h/day availability of nutritionist and dietician for any problem related to diet management	Neurologist, nutritionist, dietician
Dietary adjustments according to changing nutritional requirements, to changing taste and appetite, and to meet any other potential requirement	Nutritionist, dietician
Monitoring of ketones every day with urinary sticks	Parents
Delivery of a short manual containing the most important information required for maintenance of the diet. The manual is directed to all people involved in the management of the patient (including school teachers, educators, physiatrists, grandparents, etc.)	Nutritionist, dietician

with user-friendly instruments that determine simultaneously blood ketones and blood glucose, and the compilation of daily diary of seizures, are essential to the physician not only to assess compliance but also to evaluate the relationship between ketosis and seizure control.

A synergic collaboration between the patient's family and the epilepsy team is essential for a successful use of the diet. In contrast with using AEDs, managing epilepsy with the diet requires very active caregivers' involvement, and families are prone to balance their efforts to the extent of perceived results. If there is good efficacy, acceptance and compliance are greatly facilitated. In the long-term management of responders, we observed a reduced efficacy in 25% of patients and this was almost invariably associated with a reduced acceptance of the diet and with reduced plasma ketones. A reasonable hypothesis is that the reduction of compliance was the cause, and the decreased plasma ketones and loss of the diet's efficacy were the consequence. However, some kind of metabolic adaptation leading to reduced ketosis despite substantial compliance with the diet cannot be excluded. Reduced compliance is frequently a late consequence of the family's frustration when it becomes difficult or impossible to attain stable ketosis or effective seizures control.

6. How does the ketogenic diet work? A look into the mechanisms of action

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6.1. Introduction

One of the perplexing mysteries in the field of epilepsy is the question of how the KD works. This fundamental question is all the more compelling since the diet may yield considerable success when AEDs fail to adequately control seizure activity (Vining et al., 1998; Freeman et al., 1998). Ever since its introduction in the early 1920s, investigators have been curious about its effects on brain function, but few studies addressed mechanisms of the diet's action. Indeed, it was not until the mid-1990s that a resurgence in interest led to sustained research efforts into this non-medicinal therapy.

That dietary factors can influence brain function should not be surprising, and the concept of treating a chronic disorder such as epilepsy with nutritional approaches holds an intrinsic appeal. During the history of the diet's use, clinicians have attempted to modify its classic formulation to improve tolerability, and in the hopes of enhancing efficacy. Recent variations on this theme include the Atkins diet (Kossoff et al., 2003), the low glycemic-index diet (Pfeifer and Thiele, 2004), and diets supplemented or enriched in polysaturated fatty acids (PUFAs) (Schlanger et al., 2002; Fuehrlein et al., 2004). This interest has brought together investigators from diverse fields to focus on how systemic metabolic changes induced by a high-fat, low-carbohydrate diet – which results in prominent ketosis – can dampen neuronal excitability and/or hypersynchrony, the presumed end product(s) of the diet's action.

There have been numerous mechanistic hypotheses to explain the anticonvulsant activity of the KD. These include (1) changes in brain pH (e.g., acidosis which would favour neuronal inhibition through proton-sensitive ion channels) (Al-Mudallal et al., 1996); (2) changes in electrolyte and water balance (Millichap and Jones, 1964); (3) direct inhibitory actions of fatty acids (i.e., PUFAs) (Cunnane et al., 2002); (4) neurotransmitter alterations (Erecinska et al., 1996; Szot et al., 2001; Yudkoff et al., 2001a,b); and (5) changes in energy metabolism, reflected in part by ketone body production and metabolism (Appleton and DeVivo, 1974; Pan et al., 1999). Because of the striking ketosis associated with the diet, and the ease with which beta-hydroxybutyrate can be measured, much of the attention in this field has focused on the role of ketone bodies as mediators. However, little direct evidence in this regard has emerged to date (for a more extensive review, see Stafstrom and Rho, 2004).

6.2. Anticonvulsant effects of ketone bodies and actions on inhibitory neurotransmission

When fats are metabolized preferentially as the primary energy source, the liver produces ketone bodies (beta-hydroxybutyrate, acetoacetate and acetone). The prominent ketosis accompanying the diet

led Keith (1933) to consider whether ketone bodies were in fact anticonvulsant compounds. Seizures acutely induced by thujone (the active constituent of wormwood oil) in rabbits were blocked by pretreatment with acetoacetate (Keith, 1933), an observation that was recently confirmed in an audiogenic seizure susceptible mouse model (Rho et al., 2002). There have also been several historical reports of acetone possessing anticonvulsant effects (Helmholz and Keith, 1930; Keith, 1931; Jenney and Pfeiffer, 1958; Yamashita, 1976; Vodickova et al., 1995). The most extensive characterization of acetone's anticonvulsant properties was conducted by Likhodii et al. (2003), who demonstrated dose-dependent suppression of seizures by acetone administered intraperitoneally in four separate animal models of seizures and epilepsy: (1) the maximal electroshock (MES) test, which models human tonic–clonic seizures; (2) the subcutaneous pentylenetetrazole (PTZ) test, which models human typical absence seizures; (3) the amygdala kindling test, which models human complex partial seizures with secondary generalization; and (4) the AY-9944 test, which models chronic atypical absence seizures. Despite what appears to be broad-spectrum activity exhibited by acetone, the precise anticonvulsant mechanism(s), however, remain(s) unclear. Interestingly, epileptic patients who responded favourably to the diet were found to have elevations in brain acetone levels (with estimated concentrations upwards of 1 mM) as measured by magnetic resonance spectroscopy (Seymour et al., 1999). Curiously, there has been no clear demonstration of a direct anticonvulsant effect of the principal ketone body, beta-hydroxybutyrate (with either stereoisomer). While these in vivo studies are intriguing, at a cellular level, ketones do not appear to acutely influence synaptic transmission. Thio et al. (2000) utilized standard cellular electrophysiological techniques and found that millimolar concentrations of beta-hydroxybutyrate and acetoacetate did not affect: (1) excitatory post-synaptic potentials (EPSPs) and population spikes in CA1 pyramidal neurons after Schaffer collateral stimulation; (2) spontaneous epileptiform activity in the hippocampal–entorhinal cortex slice seizure model; and (3) whole-cell currents evoked by glutamate, kainate, and γ-aminobutyric acid (GABA) in hippocampal neurons.

Further mechanistic considerations focus on actions at the level of the mitochondrion, the organelle poised at the centre of molecular bioenergetics—responsible for cellular homeostasis but also the critical determinant of cell survival or death. As fatty acids comprise the bulk of the KD composition, and undergo beta-oxidation in mitochondria, it is presumed that this important metabolic shift alters the balance of important substrates and neurotransmitters, and at the same time, affects respiratory chain function with concomitant effects on mitochondrial respiration and control of oxidative stress, among other actions. Additionally, ketone bodies may be juxtaposed not simply as passive bystanders. Ketone bodies are generated by liver mitochondria as alternative substrates for fuel consumption (when the availability of glucose is low during fasting states), especially by the brain. However, recent evidence suggests that ketone bodies may also serve a teleological function in preserving brain function as neuroprotective agents (Kashiwaya et al., 2000; Tieu et al., 2003; Reger et al., 2004; Veech et al., 2001; Veech, 2004).

Yudkoff and colleagues have proposed that in the ketotic state, there are major shifts in brain amino acid handling, the most significant of which is the reduction of aspartate relative to glutamate, reflecting a shift in the equilibrium of the aspartate aminotransferase reaction (Yudkoff et al., 2001a, 2004a,b). This adaptation in the metabolism of the excitatory neurotransmitter glutamic acid (i.e., a decrease in the rate of glutamate transamination to aspartate) would be predicted to increase the rate of glutamate decarboxylation to GABA, the major inhibitory neurotransmitter, since more glutamate would be available for the synthesis of both GABA and glutamine (Erecinska et al., 1996; Yudkoff et al., 1996, 1997, 2001a,b, 2005). An increase in brain GABA levels would then be expected to dampen seizure activity (Fig. 3). Interestingly, in a variety of seizure models, the most consistent protection afforded by the KD was observed when seizures were evoked by the GABA receptor blockers picrotoxin, bicuculline and gamma-butyrolactone (Bough et al., 2003). Further, a recent animal study demonstrated that caloric restriction, resulting in mild ketosis, enhanced expression in the brain of both isoforms of glutamic acid decarboxylase (GAD65 and GAD67, the biosynthetic enzymes for GABA production), suggesting an increase in GABA levels (Cheng et al., 2004). However, while increased GAD expression might suggest enhanced GABA synthesis, the rela-

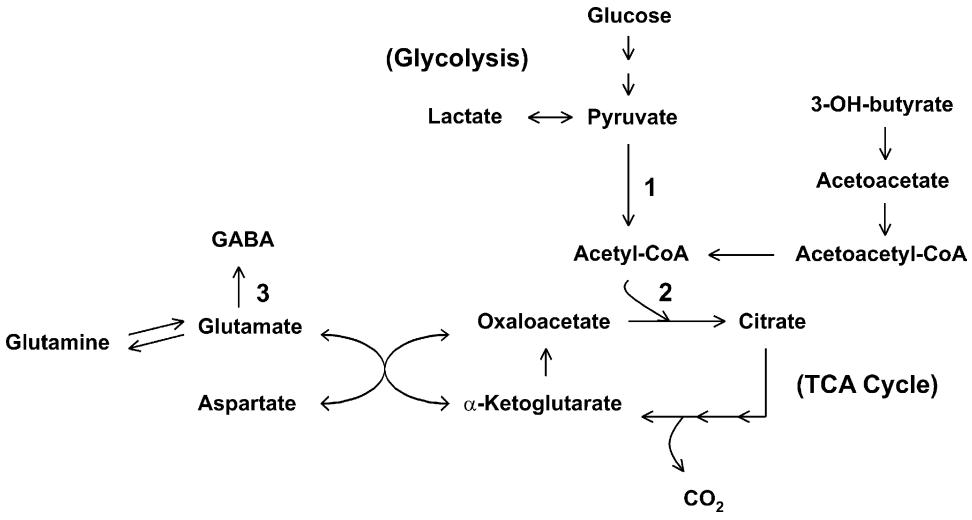

Fig. 3. Diagram illustrating the metabolic inter-relationships between brain metabolism of glutamate, ketone bodies and glucose. In ketosis, 3-OH-butyrate (beta-hydroxybutyrate) and acetoacetate contribute heavily to brain energy needs. A variable fraction of pyruvate (1) is ordinarily converted to acetyl-CoA via pyruvate dehydrogenase. In contrast, all ketone bodies generate acetyl-CoA which enters the tricarboxylic acid (TCA) cycle via the citrate synthetase pathway (2). This involves the consumption of oxaloacetate, which is necessary for the transamination of glutamate to aspartate. Oxaloacetate is then less available as a reactant of the aspartate aminotransferase pathway which couples the glutamate–aspartate interchange via transamination to the metabolism of glucose through the TCA cycle. Less glutamate is converted to aspartate and thus, more glutamate is available for synthesis of GABA (3) through glutamic acid decarboxylase (GAD). Adapted from Yudkoff et al. (2004c) with permission.

tionship between GAD expression and GABA levels is not entirely clear, and depends on numerous variables (Rimvall and Martin, 1992, 1994; Rimvall et al., 1993); increased GAD expression might actually reflect decreased GABA production. GAD expression is more accurately interpreted in the context of mRNA expression, GAD protein levels, GABA levels and turnover.

Clinically, few measures of excitatory or inhibitory neurotransmission have been reported in patients treated with the KD, or who became ketotic through other means. Dahlin et al. (2005) recently reported changes in several amino acids in the cerebrospinal fluid of patients on a KD, the most notable observation being that GABA levels were higher in responders than in nonresponders. Moreover, in very good responders (i.e., >90% seizure reduction), GABA levels were significantly higher at baseline as well as during the diet. On the other hand, CSF aspartate levels remained unchanged. The collective evidence from laboratory and clinical observations strongly suggests that the KD may enhance brain GABAergic inhibition, but not via the more established mechanism of post-synaptic $GABA_A$ receptor modulation shared by several anti-convulsant medications.

6.3. The role of PUFAs and modulation of mitochondrial uncoupling proteins (UCPs)

Ketone bodies are not the only substrates that increase during treatment with the KD. The diet is mostly comprised of fats, constituting ≥90% of the total calories by weight, and poly-unsaturated fatty acids (PUFAs) may represent a key fat constituent. Certain PUFAs are known to inhibit fast, voltage-dependent sodium channels (Xiao et al., 1995, 1998) and L-type calcium channels (Xiao et al., 1997). Such actions would be expected to dampen membrane excitability. More relevant, however, are reports that PUFAs may help reduce seizure activity (Yehuda et al., 1994; Voskuyl et al., 1998; Schlanger et al., 2002; Fuehrlein et al., 2004) and are elevated in patients treated with the diet (Fraser et al., 2003). Similar to the effects seen in cardiovascular disease models, it is

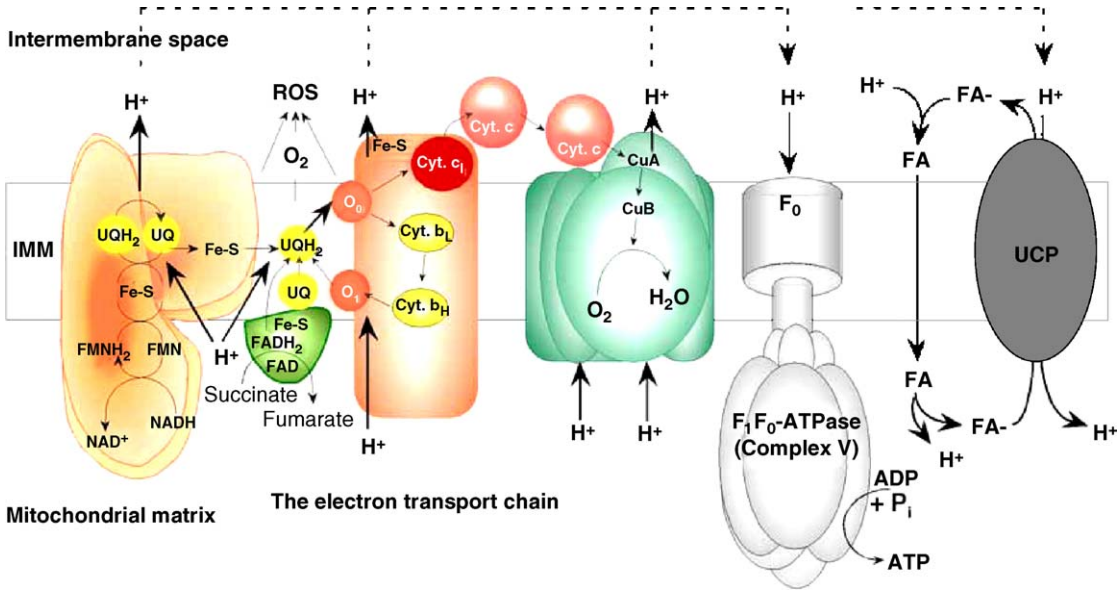

Fig. 4. Uncoupling action of an uncoupling protein (UCP). The electron transport chain builds up a proton gradient across the inner mitochondrial membrane (IMM) which provides the proton-motive force for ATP production (conversion of ADP to ATP through ATP synthase [Complex V]). The uncoupling proteins provide an alternative pathway for proton re-entry into the mitochondrial matrix, thereby generating heat instead of ATP. Two major hypotheses for how this occurs have been proposed: (1) the UCP transports protons directly; or (2) electroneutral, protonated fatty acids diffuse across the inner mitochondrial membrane and the proton is released in the matrix. The fatty acid anion is transported back to the intermembrane space by the UCP, and the cycle repeats. Adapted from Mattiasson and Sullivan (in press), with permission.

hypothesized that PUFAs possess anticonvulsant activity through modulation of voltage-gated ion channels (Vreugdenhil et al., 1996; Xiao and Li, 1999).

Fatty acids are also known to induce the activity of UCPs (see Fig. 4), several of which have been identified in the mammalian brain (Horvath et al., 2003; Mattson and Liu, 2003; Sullivan et al., 2003, 2004a; Krauss et al., 2005; Mattiasson and Sullivan, in press). Activation of mitochondrial UCPs results in a reduction of the proton gradient across the inner mitochondrial membrane, which dissipates heat and reduces ATP synthesis, calcium influx into the mitochondrial matrix, and reactive oxygen species (ROS) production (Horvath et al., 2003). Mitochondrial ROS production is intimately linked to the mitochondrial membrane potential ($\Delta\Psi$), and a high $\Delta\Psi$ promotes ROS production through increased electron shunting. UCPs dissipate $\Delta\Psi$ by increasing proton conductance, resulting in decreased ROS formation. Even a modest reduction of $\Delta\Psi$ can significantly reduce ROS production (Votyakova and Reynolds, 2001). The relevance of these observations to the KD's actions was recently illustrated by Sullivan et al. (2004b), who demonstrated that the diet increased mitochondrial UCP activity and decreased ROS formation in mouse hippocampus.

Reduction of calcium influx and ROS production are actions that are highly relevant to neuroprotection. However, how do such changes relate to an anticonvulsant effect? It is now well known that the dramatic metabolic and bioenergetic changes in the brain that accompany seizure activity can contribute to neuronal injury, in part through oxidative mechanisms (Liang et al., 2000; Frantseva et al., 2000; Ueda et al., 2002; Cock, 2002; Cock et al., 2002). Less appreciated is the notion that oxidative stress itself can provoke seizure activity. Increased mitochondrial free radical load, occurring through a variety of mechanisms, has been shown to produce seizure activity (Willmore et al., 1978; Patel, 2004) or enhance susceptibility to seizure provocation (Liang and Patel, 2004; Patel, 2004). Electrophysiological studies have also confirmed the seizure-provoking effects of oxidative stress. Exogenous H_2O_2 administration can mimic acute oxidative stress in vitro, and several studies have

shown that H_2O_2 exposure can induce neuronal hyperexcitability. In acute thalamo-cortical and hippocampal slices from rodents, H_2O_2 caused epileptiform activity both during infusion as well as after washout (Frantseva et al., 1998; Avshalumov and Rice, 2002).

Thus, there are emerging data that seizures may be precipitated by oxidative stress, and that a reduction in free radical formation may prevent seizure activity. While none of the clinically available anticonvulsant medications are believed to act principally through antioxidant mechanisms, the KD has been shown to reduce ROS formation (Sullivan et al., 2004b), through induction of several brain-specific mitochondrial UCPs. Additionally, in a preliminary study, Kim et al. (2004b) demonstrated that the ketone bodies beta-hydroxybutyrate and acetoacetate (in millimolar concentrations) prevented H_2O_2-induced hyperexcitability in acute neocortical brain slices and dissociated neurons, and that ketones were capable of significantly reducing ROS formation in isolated mitochondria. These observations suggest that the diet may protect against seizure activity (and may also be neuroprotective) through antioxidant mechanisms activated by fatty acids and ketones.

6.4. Actions mediated by the ATP-sensitive (K_{ATP}) and the two pore domain (K_{2P}) potassium channels

When one considers the pivotal role that mitochondria play in energy production, and asks how changes in energy metabolism might translate to alterations in neuronal membrane excitability, the involvement of ATP-sensitive potassium (K_{ATP}) channels must be strongly considered. K_{ATP} channels, first described in pancreatic beta cells, regulate insulin release by modulating the membrane potential. These channels are inhibited by high ATP/ADP ratios, and activated (resulting in hyperpolarization) when intracellular ATP levels are low.

K_{ATP} channels have been identified in neurons as well as glia in different brain areas, including hippocampus, hypothalamus, substantia nigra and dorsal vagus nerve. The highest expression of K_{ATP} channels is in the substantia nigra pars reticulata (SNPR) which, in addition to other well-known functions, is believed to be a subcortical modulator of seizure propagation (Iadarola and Gale, 1982; Depaulis et al., 1994). While experimental data linking the KD to K_{ATP} channels is not yet forthcoming, preliminary observations suggest that ketone bodies block repetitive firing of SNPR neurons through activation of K_{ATP} channels (G. Yellen, personal communication). It remains unclear, however, whether the biochemical changes induced by the diet actually favour or negate activation of K_{ATP} channels (Vamecq et al., 2005). Certainly, prior observations have suggested that the diet increases the level of bioenergetic substrates in the brain (De Vivo et al., 1978; Pan et al., 1999). Additionally, it is known that acute seizure activity is accompanied by increases in glucose metabolism (Chugani et al., 1994). These findings may suggest an inhibition, not activation, of K_{ATP} channels.

In addition to the plasmalemmal K_{ATP} channel, there exists a mitochondrial form, localized to the inner mitochondrial membrane, that is likely to be distinct in terms of molecular composition, pharmacologic regulation, and biological function(s) (Busija et al., 2004). While the specific role(s) of mitochondrial K_{ATP} (mitoK_{ATP}) channels has (have) yet to be elucidated, published data suggest that activation of these channels may reduce ROS formation (Ferranti et al., 2003), and by extension, potentially reduce neuronal excitability. While there remains some controversy regarding the effects of mitochondrial K_{ATP} channels on ROS production (Krenz et al., 2002; Xu et al., 2004), published reports may reflect tissue-specific and/or methodological differences. Interestingly, ROS has been reported to activate mitochondrial K_{ATP} channels (Avshalumov and Rice, 2003; Lebuffe et al., 2003), an action that may contribute to ischemic preconditioning (Gross and Peart, 2003).

In considering the multitude of molecular targets that are likely to be affected by the KD, Vamecq et al. (2005) have hypothesized that an alternative to the K_{ATP} channel is the K_{2P} (i.e., two pore domain) potassium channel. K_{2P} channels represent a diverse superfamily of channels that can regulate baseline membrane excitability (Franks and Honore, 2004). These channels may represent a more likely physiological link between metabolic activity and plasma membrane excitability since they can be modulated by changes in pH, osmolality, temperature, mechanical pressure, and are sensitively activated by certain PUFAs—all of these factors have been explored to one extent or another. On the other hand, while the link between PUFAs and K_{2P} channels is tantalizing, there is no evidence to date that the KD induces stable changes in pH or osmolality (De Vivo et al., 1978; Al-Mudallal et al., 1996).

6.5. Conclusions

Within the last decade, several putative molecular targets and novel insights have emerged. Not surprisingly, given all of the metabolic, physiological and hormonal changes induced by the KD, there is a multiplicity of relevant mediators involved and it is likely that no single mechanism, however well substantiated, will explain all of the diet's clinical effects. The complex mechanisms that are involved in seizure genesis and epileptogenicity, as well as the diverse treatment approaches taken clinically, strongly suggest that successful approaches, including the KD are likely based on fundamental mechanisms that are multiple, parallel and possibly synergistic.

7. Clinical evidence of efficacy: an overview from major trials

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7.1. Introduction

Despite 20 AEDs on the market, many of which have been introduced in the past decade, the incidence of pharmacological intractability has not been markedly reduced. Partly as a result of this, the KD is increasingly used in every continent (Kossoff et al., 2005). Many families of children with intractable epilepsy now ask about the KD at clinic visits, and the diet is no longer discouraged by physician (Hemingway et al., 2001b). What is, however, the evidence for its efficacy? In an era in medicine of increasing guidelines and practice parameters, many neurologists want straightforward recommendations based on evidence from randomized, controlled trials.

In 2000, an article written for the Blue Cross Blue Shield insurance company in the U.S. attempted to analyze all studies available at the time (Lefevre and Aronson, 2000). In this article, 11 studies were identified; 9 of which were retrospective from Johns Hopkins. Only two were prospective (Vining et al., 1998; Freeman et al., 1998), one was multicentre (Vining et al., 1998). Although none were controlled, the authors of this review felt that the diet demonstrated a "significant reduction in seizure frequency" and that "it is unlikely that this degree of benefit can result from a placebo response and/or spontaneous remission". In all studies combined, 16% were seizure-free, 32% greater than 90% improved, and 56% with a 50% or higher response.

Three years later, with more data available, the Cochrane Library performed their own review of the literature from 1966 to 2003 (Levy and Cooper, 2003). In this review, utilizing more stringent criteria, they were less convinced about the diet's efficacy. Their stated objective was to find randomized, controlled studies to prove the diet's efficacy. None were found. They concluded "there is no reliable evidence from randomized controlled trials to support the use of KDs for people with epilepsy". However, the reviewers still classified the diet as a "possible option" because "a small number of observational studies lend some support for a beneficial effect."

With this confusing data, how does the diet fit into a physician's treatment algorithm? In 2001, *Epilepsy and Behavior* published "The Expert Consensus Guidelines", in which 100 adult and pediatric epileptologists reviewed clinical case scenarios and provided their treatment options in order of preference (Karceski, 2001). Among this group, the diet did not fare well. For idiopathic generalized epilepsy, the diet ranked in 15th position in a list of possible therapies; 74% of the physicians considered it an appropriate choice, but only as third-line therapy. Even in symptomatic generalized epilepsies (e.g., Lennox Gastaut syndrome), the diet ranked no higher than 9th to 11th place.

7.2. Evidence from retrospective studies

Information on studies with over 20 patients is presented in Table 1. All studies generally describe multiple and varied seizure types, most commonly Lennox Gastaut syndrome and other generalized epilepsy syndromes typically with difficult-to-control seizures. One of the earliest retrospective studies was by Dr. Peterman from the Mayo Clinic in Rochester, Minnesota in 1925 (Peterman, 1925). He reported on a "new dietary treatment" in 17 children aged 1–15 years. Amazingly, 10 (60%) were seizure-free, and 4 (23%) were >90% improved. Relatively few papers followed and the diet became less popular with the introduction of phenytoin and other AEDs. Hopkins and Lynch (1970) reported the treatment of 34 patients with a 3:1 ratio KD. Only

three (8.8%) were seizure-free, but 71% had either "much" or "moderate" improvement.

In 1986, the modern era of KD studies began with Sill's report (Sills et al., 1986) of 50 patients treated with an MCT diet. Of these, 44% had a >50% improvement in seizures, and 8 (16%) were seizure-free. Interestingly, 86% of the children with absence epilepsy and 50% of those with myoclonic–astatic epilepsy had a >50% improvement.

Kinsman et al. (1992) reviewed 58 children from Johns Hopkins Hospital; 67% had a >50% improvement, with 29% having a "near complete" response. Almost two thirds were able to reduce medications and more than one-third were reportedly more alert and interactive. Due to the interest elicited by this publication, many other studies at Johns Hopkins Hospital, including four important prospective studies in the past decade, were subsequently completed (see below).

Two studies in infants have been recently published. One reported that 54% of 32 infants had a >50% response (19% seizure-free); in this population, the diet was remarkably well tolerated and ketosis was attained easily (Nordli et al., 2001). A retrospective review of 23 children specifically with intractable infantile spasms found that 6 (46%) of the 13 remaining on the diet at 12 months had a >90% spasm reduction (Kossoff et al., 2002a). Age less than 1 year and trials of two or fewer AEDs correlated with higher likelihood of improvement.

A retrospective study from Johns Hopkins Hospital and the University of Texas at Houston reported on 45 adolescents aged 12–19 years who had faced many years of epilepsy (Mady et al., 2003). Despite the concerns that the diet might be too restrictive for an adolescent population, seizure improvement and tolerability were remarkably similar to those in more typical school-age children.

The KD's use worldwide has blossomed since the late 1990s, with many retrospective studies continuing to report high response rates (Table 1) (Hassan et al., 1999; Vaisleib et al., 2004; Kankirawatana et al., 2001; Coppola et al., 2002; François et al., 2003; Kim et al., 2004a; Klepper et al., 2004).

7.3. Prospective uncontrolled studies

In the first modern prospective study, Schwartz et al. (1989) reported that, of 63 patients given one of three diets including the classic, MCT, and a modification, 81% showed a >50% response (Table 1). The classic diet had the highest efficacy and was the best tolerated. In 1998, two prospective studies from Johns Hopkins were published. The first (Vining et al., 1998) was a multicentre (seven hospitals) study of 51 children aged 1–8 years with intractable epilepsy, who had a mean of 230 seizures per month and had failed an average of seven AEDs. At 6 months, 53% had a >50% response, 6 (12%) were seizure-free and 73% remained on the diet. The second prospective study from Johns Hopkins was a single-centre study of 150 consecutive children aged 1–16 years with more than two seizures per week that had failed at least two AEDs and were followed-up for 1 year (Freeman et al., 1998). At baseline, children had a mean of 410 seizures per month and a history of exposure to 6.2 AEDs. In this group, 71% were able to remain on the diet, and 51% had a >50% improvement, 32% with a >90% reduction at 6 months. In general, those who discontinued the diet before 1 year did so due to inefficacy rather than restrictiveness. No specific seizure type preferentially improved, but age older than 8 years at diet initiation was slightly less likely to show an improvement. In comparing outcome on the diet to many new add-on medications, the authors considered the diet as potentially more effective.

A small study on a modified low-carbohydrate (Atkins) diet in six children and adults published in 2003 reported that four patients had a >50% response, correlating with level of ketosis (Kossoff et al., 2003). A follow-up prospective study assessed 20 children with intractable epilepsy for 6 months, initially with 10 g of carbohydrate per day (Kossoff et al., in press). Nearly two thirds of the patients had a significant seizure reduction, a similar to the traditional KD. The diet was very well tolerated with no significant weight loss nor cases of kidney stones. Interestingly, the presence of large urinary ketosis appeared to be less important than commonly reported for the KD. Further studies in both children and adults with this novel ketogenic therapy are underway.

A summary of outcome data in prospective studies including at least 20 patients is given in Table 3. Overall, results show some disparity between countries, with 6-month efficacy rates ranging from 27% of patients with a 50% seizure reduction in Italy (Coppola

Table 3
A summary of retrospective and prospective efficacy studies of the ketogenic diet including over 20 patients and published since 1970 (not including abstract presentations)

Reference	No. of patients	Age range (years)	>90% improvement rate at 6 months	>50% improvement rate at 6 months
Hopkins and Lynch (1970)	34	1–13		71
Sills et al. (1986)	50	2–15	24	44
Schwartz et al. (1989)[a]	59	<5–54	41	81
Kinsman et al. (1992)	58	0.2–7	29	67
Vining et al. (1998)[a]	51	1–9	29	53
Freeman et al. (1998)[a]	150	1–16	32	51
Hassan et al. (1999)	52	2–9		67
Kankirawatana et al. (2001)[a]	35	0.2–13	75	
Nordli et al. (2001)	32	0.5–1.5		55
Kossoff et al. (2002a)	23	0.5–2	39	72
Coppola et al. (2002)[a]	56	1–23		27
François et al. (2003)	29	0.3–12.5		41
Mady et al. (2003)	45	12–19	29	50
Kim et al. (2004a)	124	2–7	53 (3 months)	76 (3 months)
Klepper et al. (2004)	111	0.1–18	17	31
Vaisleib et al. (2004)	54	2–14		65

[a] Prospective studies.

et al., 2002) to 75% of patients with a >90% reduction in Thailand (Kankirawatana et al., 2001).

7.4. Prospective randomized studies

Four randomized studies are being completed in the USA and UK. In a study from Johns Hopkins, 20 children with intractable Lennox Gastaut syndrome were admitted, fasted, slowly advanced onto the KD over 3 days and randomized to either receive an additional daily solution containing saccharin or glucose. After 1 week, they were crossed to the opposite arm before discharged to home. The study, currently being analyzed, was the first to prove that the KD could be studied in a double-blinded, randomized, placebo-controlled manner. Dr. Helen Cross at Great Ormond Street Hospital in London is completing a prospective randomized study comparing the classical KD with an MCT oil diet, with a control period of 4–16 weeks incorporated for each individual patient. Dr. Christina Bergqvist at the Children's Hospital of Philadelphia is currently analyzing a third randomized study of the value of a fasting compared to a gradual initiation of the diet. A fourth study by our group is examining the Atkins diet in children, randomized to either 10 or 20 g of carbohydrate per day, with a crossover period after 3 months for each patient.

7.5. Conclusions

The efficacy of the KD was initially assessed mostly in small, single-centre, retrospective studies. In recent years, reports of the diet's efficacy worldwide have continued to show that approximately half of patients will have half their seizures, and about one-third in total will have one-tenth their baseline number of seizures. Prospective studies have confirmed these data, and four randomized studies are in the process of completion. Although clearly a need exists for further prospective studies, the quality of evidence for the diet's efficacy is improving over time.

8. Seizures type and epilepsy syndrome as predictors of response

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8.1. Introduction

Few studies have investigated clinical outcome after starting the KD in well-defined epileptic syndromes.

Moreover, there are no randomized trials comparing the diet with placebo or with AEDs, and most of the large scale studies conducted to date only reported results after short term treatment. For these reasons, defining the comparative efficacy of the KD in relation to specific syndromes or seizure types is no easy task. In this report, this aspect will be addressed by reviewing briefly data from the literature and by presenting our personal experience.

8.2. Literature data

With respect to response to the diet in relation to seizures type, several studies have reported particularly favourable outcomes in children with myoclonic seizures (Wheless and Sankar, 2003); these data, however, refer to observations in large series of patients with drug resistant epilepsies, and there are no published studies that document the comparative efficacy of the diet in different types of myoclonic epilepsies. A study by Maydell et al. (2001) did not find any significant difference in the diet's efficacy when patients with partial seizures were compared with those with generalized seizures.

Studies relating response to specific epilepsy syndromes are even fewer. Efficacy of the KD in Lennox Gastaut syndrome has been reported (Wheless, 2004; Mckay et al., 2005), but diagnostic electro-clinical criteria do not appear to have been always fulfilled in these studies. Freeman and Vining (1999) have described a significant reduction in seizure frequency (>50%) after 5 days of the introduction of the diet in all of the 17 Lennox Gastaut patients with atonic or myoclonic seizures included in their study.

Recently, Nordli et al. (2001) and Kossoff et al. (2002a) reported a beneficial effect of the diet against infantile spasms in patients with West syndrome of different etiologies unresponsive to conventional AEDs. However, efficacy rates in relation to specific etiologies, or specific EEG patterns, were not specified. Than et al. (2005) also reported favourable results in patients with infantile spasms, and did not exclude the possibility of a good outcome even in patients with structural brain abnormalities. In the latter report, the presence of complex partial seizures was regarded as a predictor of an unfavourable response to the KD.

A recent study by Caraballo et al. (2005) reported on the effectiveness of the KD in the treatment of severe myoclonic epilepsy of infancy (Dravet syndrome). In this report, 20 patients meeting the diagnostic criteria for the syndrome were enrolled; 10 of the 13 children who remained on the diet for a duration of follow-up of 1–4 years had a significant reduction of seizures. These results are of particular interest because of the homogeneity of the cohort and the long-term follow-up.

8.3. Our experience

We took part in an Italian multicentre study that assessed 56 children, adolescents and young adults with refractory epilepsy; and we also reported separately our personal experience in a total of 36 patients (including 16 who had taken part in the multicentre study) (Coppola et al., 2002; Bertoli et al., 2005). In these studies, which included patients with partial and generalized symptomatic epilepsies, myoclonic–astatic epilepsy, Lennox Gastaut syndrome and others epileptic encephalopaties, we did not identify a statistically significant relationship between outcomes on the diet and either seizure type or epilepsy syndrome. Subsequent evaluation of our experience, however, have led us to hypothesize a good response of the diet can be especially observed in patients with diffuse migrational disorders. During the years between 1994 and 2004 we treated seven patients (mean age 8.2 years, range 2.8–16.1) showing diffuse migrational disorders; four of them experienced, at 9 months since the introduction of the diet, a decrease in seizure frequency between 50% and 90%. Than et al. (2005) have also suggested that these patients may respond particularly well to the diet. A biological basis for putatively better responses in patients with severe migrational disorders may be found in the observation that the cerebral structure of these patients bears some resemblance to the foetal brain's structure. There is evidence that, as in suckling rats, the more immature the cerebral cortex is, the more it uses ketone bodies instead of glucose as an energetic substrate (Crino and Chou, 2000; Morris, 2005); accordingly, it is possible that patients with diffuse cortical malformations could utilize more efficiently ketone bodies in their cerebral metabolism. While it is acknowledged that surgical intervention, whenever possible, remains the treatment of choice in drug refractory epilepsy caused by focal cortical dysplasia, some patients

may benefit from the diet, at least before surgery is applied.

It has been suggested that patients with Lafora body disease may also respond favourably to the diet (Minassian, 2001). Given the pathophysiology of this disorder, it is reasonable to hypothesize that the diet, by promoting the brain utilization of ketones instead of glucose, might reduce glycogen synthesis and possibly decrease polyglucosan accumulation and slow down the progression of the disease. In a pilot study (Cardinali et al, submitted for publication) we assessed the effects of the diet in five patients with Lafora body disease (average age at our first observation: 13.2 ± 3.2 years), in order to determine the feasibility of its long-term term use in adolescents with this condition, and its potential impact on clinical outcome. The diet was well tolerated in all five patients for a period of 28.4 ± 8.8 months, but the illness showed a progressive deterioration, with worsening of the myoclonus, appearance of new seizure types, and increased frequency of generalized tonic–clonic seizures. Moreover, four of the five patients showed a significant decline in cognitive functions, with special reference to memory, long lasting attention and performance abilities. These findings seem to argue against a protective role of the diet on the progression of the disorder, but further studies are necessary before definite conclusions can be drawn. Moreover, our patients were started on the diet years after the clinical onset of the disease, when Lafora bodies accumulation and neuronal degeneration had already become established. Observations in a knockout mouse model of the disease suggest that whatever treatment is applied, it should be started as early as possible, because already developed pathological changes do not appear to reversible (Ganesh et al., 2002). This raises the possibility of exploring the potential value of the KD in genetically diagnosed, pre-symptomatic siblings of Lafora disease patients.

8.4. Conclusions

There is inadequate information on how short- and long-term outcome on the KD relates to the type of the epileptic disorder and/or ictal semiology. Prospective studies with large and homogeneous cohorts of patients with well-defined electro-clinical features are needed to address this issue, which has obvious practical implications for the selection of the best candidates for treatment.

9. Is there a role for the ketogenic diet beyond childhood?

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In one of the earliest publications (Peterman, 1924) reporting significant benefits from ketosis, patients treated with the diet ranged from 3.5 to 35 years, although no information was provided as to the influence of age on outcome. In subsequent years, the diet was increasingly used for adults; the largest series reported to date, published in 1930 (Barborka, 1930) included 100 patients aged 16–51 years. Only 27 were aged 30 or above, and 38 were under age 20 and could be more appropriately classified as adolescents. Ketosis typically occurred, but interestingly several patients had improved seizure control without persistent ketosis. Overall, 56% had a >50% response and 12% were seizure-free, outcomes remarkably similar to those reported for children in the next 80 years. Interestingly, the authors commented that "there seems to be no question but that the patient who can be afforded the best opportunity for treatment is the child or young adult . . . whereas older patients . . . are the least likely to be benefited" (Barborka, 1930). Although not systematically monitored, cholesterol increased in several patients; amenorrhea occurred in 12 (21%) of the 56 women treated, an occurrence also seen in a recent study of adolescents (Mady et al., 2003). For nearly 70 years, thereafter, the KD was used only sporadically for adults in some centres. In a 1989 study comparing the MCT oil diet to the classical KD, Schwartz et al. (1989) described 4 adults out of 63 patients. None of the 4 adults had any significant improvement.

In 1999, a retrospective assessment of the KD in 11 adults (9 women, age 19–45 years, baseline seizure frequency 2–30 per month) was reported from the Jefferson centre in Philadelphia (Sirven et al., 1999). All were treated with a typical calorie and fluid restricted 4:1 ratio diet after a 24–72 h fast. At 8 months, 6 (55%) had a >50% seizure reduction and 3 (27%) had a >90% improvement, similar to most studies of children. Only two patients were unable to achieve

and maintain ketosis; all patients reported constipation and all women described menstrual irregularities. Cholesterol increased over 6 months from a baseline of 208 to 291 mg/dl and triglycerides were only slightly increased from 190 to 203 mg/dl. A follow-up study from the same group with 15 additional patients (total 26) was presented at the 2003 meeting of the American Epilepsy Society in poster form (Nei et al., 2003). Similarly to the previous study, 54% had a >50% response, and the authors were able to differentiate outcome based on seizure type. They indicated that the 12 patients with symptomatic generalized epilepsy had the best outcome, with 73% having a >50% response, compared with only 27% of the 11 adults with partial epilepsy. Improvement, when it occurred, tended to be in the initial 2 weeks of the diet. Diet duration was relatively short, only 7 months on average. Only 11% continued the KD for 2 years, and all of these patients had symptomatic generalized epilepsy. Weight loss was also described, with a mean decrease of 6.7 kg. Further information about these two studies are detailed in a textbook chapter on adults and the KD (Sperling and Nei, 2004).

In 2001, a retrospective study of 45 highly motivated adolescents with intractable epilepsy (age 12–19 years) was reported (Mady et al., 2003). Six months after diet initiation, 28/45 (62%) remained on the diet, with 6/28 (21%) having 50–90% seizure reduction and 8/28 (29%) having >90%. These results were similar to those observed in younger children (Vining et al., 1998; Freeman et al., 1998). Patients with multiple seizure types (generalized epilepsy) did best, similar to the adult study from the Jefferson centre (Nei et al., 2003). The restrictions of the diet did not appear to be a major problem, with only 22% discontinuing the diet primarily for this reason. Weight loss (60%) and menstrual dysfunction (45% of females) were the most common side effects.

A small case series of the benefits of a modified Atkins diet (providing more protein and no fluid or calorie restriction) was reported in 2003, with three out of six patients being older than 18 years of age (Kossoff et al., 2003). An 18-year-old female had a 90% improvement in seizures almost immediately, with large urinary ketosis, and was maintained on the diet for 20 months without side effects. In contrast, a 42-year-old man and 52-year-old man had less success. The younger man maintained moderate ketosis for 3 months but had no measurable seizure reduction. The older patient was unable to create ketones because he was given carbohydrates in his chronic care facility, and discontinued the diet after 8 months. Encouraged by the above results, we have started a study of adults aged 18 and over using a modified Atkins diet; carbohydrates are limited to initially 15 g per day and medications are left unchanged for the first month. Daily multivitamin and calcium supplementation is provided, and frequent serum and urine laboratory monitoring is performed. In approximately 10 patients to date, results are mixed and continue to be correlated with level of ketosis.

In conclusion, studies of the use of the KD for adolescents and adults are still in their "infancy" despite over 80 years of clinical use for children. Efficacy appears to be similar to published studies of children. Further prospective studies, including perhaps a less restrictive modified Atkins diet, are warranted. Side effects such as weight loss, dysmenorrhea, constipation, and dyslipidemia will need monitoring in any future studies.

10. Discussion summary—implementation procedures and efficacy data

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Q. By current standards of evidence-based medicine, the quality of the studies conducted with the KD leaves much to be desired. We have no adequately controlled trials that demonstrate efficacy, and most reports did not characterize adequately patients in terms of seizure type and epilepsy syndrome. How can these concerns be addressed?

A. Everyone acknowledged that we need prospective studies of better quality. While the nature of the KD makes blinding difficult, recent developments summarized in Dr. Kossoff's presentation show that randomized studies are now being initiated, and that even double-blind protocols (e.g., by administering glucose versus saccharin in addition to the diet, with the monitoring of ketosis by an external investigator) can be practically and ethically feasible, at least over lim-

ited assessment periods. While limitations of current evidence are acknowledged, Dr. Freeman and other presenters remarked that the time course and magnitude of improvement is hardly compatible with a placebo response or with the natural history of the seizure disorder. It is hard to question the diet's efficacy when children with a long standing history of frequent daily seizures improve dramatically during the fasting period and remain persistently improved for months and years thereafter. Outcome data in terms of sustained seizure freedom observed with the KD appear to be greater than those reported for "historical controls" included in AED trials. Nevertheless, it is a fact that overall the quality of the efficacy data is not satisfactory, and that it is important in future studies to use prospective controlled designs, and to include patients with better defined epilepsy syndromes.

Q. There seems to be controversy about what implementation procedure is best. We have been presented with different initiation protocols, controversial data on the need for hospital admission, even different types of diets.

A. We do not have adequate data to answer these issues. Again, randomized comparative studies are needed to determine the value of fasting, fluid restriction, and other initiation procedures, to determine how much ketosis is needed for seizure control, and whether the level of ketosis should to be adjusted in relation to specific patients' characteristics. On the issue of hospital admission, most participants considered it advantageous to ensure adequate involvement and training of family members. Hospital admission also ensures better adjustment of dietary needs, and prompt recognition and treatment of potential early adverse effects, for example in children with a previously unrecognized metabolic defect. There was some discussion on the pros and cons of alternative diets, such as the Atkins diet. The prevailing view was that the classical diet is the best documented in terms of efficacy data. The Atkins diet has some attractiveness in terms of acceptability, particularly in adolescents and adults, and it might be offered when compliance with the classical diet is anticipated to be problematic. However, failure to respond to the Atkins diet should not be regarded as an indication that the classical diet will not work in that patient.

Q. Dr. Tagliabue described a rather comprehensive set of investigations to monitor the effects of the diet. Should these be all part of our routine monitoring procedures?

A. Dr. Tagliabue clarified that some of the investigations, for example some anthropometric and metabolic measurements, are conducted in her centre as part of a research protocol, and should not be regarded as necessary in a routine setting. Some tests, such as bone mass determinations and abdominal ultrasound, may only be required on a case-by-case basis, for example when nutritional status and liver enzymes justify concerns with bone mineralization loss, or when the finding of blood in urine raises suspicions about possible renal stones. It appeared from the discussion that laboratory monitoring at some European centres tends to be more intensive than in North America. In any case, there was agreement that the need for testing for nutritional deficiencies can be minimized by providing patients with appropriate supplementation of vitamins and minerals.

Q. How can we best monitor ketosis, by determinations in blood or by simply checking urine ketones?

A. Dr. Kossoff commented that one study did suggest an improved outcome with monitoring blood ketones (Gilbert et al., 2000). Overall, however, he felt that there is still insufficient evidence to conclude that blood testing ensures an improved outcome compared with simply monitoring urinary ketones. He also felt that devices for monitoring blood ketones are less than optimal at the current state of technology.

Q. What do we do when blood biochemistry shows abnormalities, particularly high levels of triglycerides and cholesterol?

A. There was consensus that dyslipidemias are rarely a cause for discontinuing the diet. Changes in blood lipids can usually be managed by dietary adjustments, e.g. by altering the caloric intake and/or modifying the ratio of unsaturated to saturated fat. On further investigation, some cases of problematic dyslipidemias often turn out to reflect co-morbid conditions, such as familial hypertriglyceridemia.

Q. If a child does well on the KD, how long should the diet be continued? On the other hand, if the diet does not appear to work, how long should we go on before we give it up?

A. There was agreement that duration of treatment should be determined on a case-by-case basis. In GLUT1 deficiency syndrome and in pyruvate dehydrogenase (E1) deficiency syndrome, the diet usually needs to be continued for several years. In epilepsies that responded well to the KD, discontinuation of the diet may be considered after about 2 years. In non-responders, a trial of about 3 months will usually be sufficient to conclude that diet is not going to help.

11. Adverse effects and contraindications

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11.1. Introduction

Before starting the KD, clinicians need to be aware of the type of epilepsy, the characteristics of the patients, the type of potential adverse effects, and the diet's medical contraindications (Kossoff, 2004; Kang et al., 2005).

11.2. Adverse effects

Most side effects of the diet are mild and do not significantly affect the acceptability of the treatment in the majority of patients (Hemingway et al., 2001a; Coppola et al., 2002). In general, tolerability is poorer in young patients with refractory epilepsy and mental retardation than in other populations.

Table 4
Early onset adverse effects of the ketogenic diet

Gastrointestinal effects (nausea, vomiting, loss of appetite, constipation)
Dehydration
Sepsis
Cardiomyopathy
Hepatitis
Pancreatitis
Biochemical disturbances (hypoglycemia, hypertriglyceridemia, hyperuricemia, hypertransaminemia, hypercholesterolemia, hypoproteinemia, hypomagnesemia, hyponatremia, metabolic acidosis)

Table 5
Long-term or late-onset adverse effects of the ketogenic diet

Growth retardation
Hepatic failure
Constipation
Exacerbation of gastro-esophageal reflux
Mineral deficiencies
Vitamin deficiencies
Urolithiasis
Osteopenia
Cardiomyopathy
Prolonged QT interval
Optic neuropathy
Basal ganglia injury
Anemia
Biochemical disturbances (hypocarnitinemia, dyslipidemias, elevated very long chain fatty acids)

Most of the early onset adverse effects of the diet (Table 4) are transient and can be carefully managed with conservative strategies. These include gastrointestinal disturbances such as nausea, loss of appetite, refusal to drink, and vomiting, usually associated with gastritis and fat intolerance. Another disturbance is constipation that can be caused by a decrease in ingestion of food and fibers; laxatives or enemas can successfully control it.

Dehydration is one of the most common complications that occur early after initiation of the diet (Wheless, 2001; Kang et al., 2004). It can be prevented by avoiding a fasting period and/or by encouraging oral or intravenous intake of fluids without dextrose (Wheless, 2001). Potentially serious complications include sepsis, cardiomyopathy, lipoid aspiration pneumonia, hepatitis and acute pancreatitis. Sometimes these complications may be related to concomitant use of some AEDs, especially valproic acid (VPA). Fatal fulminating sepsis in sporadic cases has been attributed to pre-existing metabolic disease (Kang et al., 2004). Overall, serious complications may lead to discontinuation of the diet in 6–12% of patients.

The list of early onset biochemical disturbances comprises hypoglycemia, hypertriglyceridemia (which may lead to pancreatitis), hypercholesterolemia, transient hyperuricemia, increased liver transaminases (especially in patients receiving VPA), hypoproteinemia, hypomagnesemia, hyponatremia and metabolic acidosis (Galvan et al., 2001; Wheless, 2001; Kang et al., 2004; Coppola et al., 2002; Vining, 1999; Freeman et al., 2000).

Long-term or late-onset adverse effects (Table 5) include growth retardation (mainly related to protein deficiency), hepatic failure, vitamin and mineral deficiencies, immune disturbances (impaired neutrophile function, related to imbalanced diet and protein restriction) and cardiomiopathy, which may also be seen in the early phases of treatment (Vining, 1999; Coppola et al., 2002; Wheless, 2001; Galvan et al., 2001; Furth et al., 2000; Vining et al., 2002). Another late-onset complication is nephrolithiasis, which may result from chronic acidosis, dehydration, and fat malabsorption, and may be more common in patients receiving carbonic anhydrase inhibitors such as topiramate (TPM) and/or zonisamide (ZNS). Osteopenia may be caused by nutritional deficiencies, reduced sunlight exposure, immobilisation and underlying AEDs.

Late-onset biochemical disturbances include secondary hypocarnitinemia, iron deficiency anemia, vitamin and mineral deficiencies, increased uric acid production, low serum bicarbonate levels, persistent hyponatremia, sustained metabolic acidosis, and dyslipidemias (Vining, 1999; Kossoff, 2004; Furth et al., 2000).

Physicians should be aware of the above complications, so that they can be carefully monitored and successfully prevented and treated as appropriate. The risk of side effects, in any case, should be carefully weighed against the potential benefits of the diet, which may include better seizure control and the possibility of reducing AEDs, which may result in improved attention and vigilance, improved behaviour, normalization of the circadian wake–sleep cycle, and decreased hyperkinesia and impulsivity (Nordli et al., 2001; Kang et al., 2005; Coppola et al., 2002).

11.3. Contraindications

Medical contraindications of the KD include several inborn errors of metabolism such as defects in fat and ketone metabolism, porphyria and some mitochondrial disorders (Wheless, 2001; François et al., 2003; Galvan et al., 2001).

If a child has an unrecognized inborn error of metabolism, serious complications may occur during the initial fasting period (Wheless, 2001; Galvan et al., 2001). Relevant inborn errors of metabolism where the diet can be hazardous include carnitine deficiencies, either primary (carnitine palmitoyltransferase I and II and carnitine translocase) or secondary. Fatty acid defects are absolute contraindications to the diet, and this is especially true for medium chain acyl-CoA dehydrogenase deficiency (MCAD). Other defects in fat metabolism that can exacerbate ketotic hypoglycemia are long-chain acyl-CoA dehydrogenase deficiency (LCHAD), short chain acyl-CoA dehydrogenase deficiency (SCHAD) and mitochondrial and ketone metabolism defects (Wheless, 2001; Kang et al., 2005). The KD should never be used in children with pyruvate carboxylase deficiency, in whom its administration may have fatal consequences.

The diagnosis of inborn errors of metabolism is often difficult. Patients can present with refractory epilepsy and non-specific symptoms that can be attributed to seizures or drugs. In some of these cases, the epilepsy may be secondary to inborn errors of metabolism, a possibility which should be considered always and particularly in children with associated developmental delay of unknown aetiology, hypotonia, exercise intolerance, cyclic vomiting, fatigability, hepatomegaly, cardiomyopathy, pigmentary retinitis, hypoacusia, metabolic acidosis, hypoglycemia or unexpected ketonuria. In other cases of intractable epilepsy, the MRI findings, funduscopy, and nerve conduction velocity may give useful clues to diagnosis. In such cases, and especially before introducing the KD, it is essential to conduct a careful clinical evaluation and a biochemical screening (plasma, urine and, in some cases, CSF) to exclude the possibility of an inborn error of metabolism which can be worsened by the diet (Galvan et al., 2001; Moreno-Villares et al., 2001; Kossoff, 2004).

On the other hand, in some other inborn errors of metabolism or mitochondriopathies where altered mitochondrial function leads to glycolysis dysfunction, the KD may be beneficial because it provides an important alternative energy source capable of crossing the blood–brain barrier and maintaining cerebral energy metabolism (Cuellar and Molinero, 2003; Levy and Cooper, 2003; Kang et al., 2004). These conditions include glucose transport defects, some pyruvate dehydrogenase deficiencies, phosphofructokinase deficiency and some mithocondrial cytopathies due to Complex I deficiency presenting with hypoketotic hypoglycemia.

Some patients have immunologic defects which may worsen with the diet, and in these cases previ-

ous screening for immunologic disorders is required (Kang et al., 2005; Freeman et al., 2000; François et al., 2003; Wheless, 2001).

Particular caution should be exercised when using the diet in patients treated with VPA, TPM, ZNS and acetazolamide, even though use of these drugs is not considered a formal contraindication to the diet (Galvan et al., 2001; Coppola et al., 2002; Kang et al., 2005).

Finally, the diet is not a viable option whenever adequate compliance with implementation and monitoring procedures is not expected.

12. Potential interactions between the ketogenic diet and drugs

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12.1. Introduction

Patients started on the KD often continue to receive AED treatment, and there is also a possibility of other medications being administered for concomitant or intercurrent conditions. Therefore, the possibility of interactions between the diet and drugs needs to be considered.

12.2. Interactions between the diet and AEDs

Potential interactions between the diet and AEDs have been little investigated. There are reports of increased sedation in phenobarbital-treated children after starting the diet, and it has been stated that phenobarbital dosage may need to be reduced, often by about 30%, particularly in children with high serum phenobarbital levels at baseline (Kossoff and Vining, 2004). No particular underlying antiepileptic medication has been found to increase or reduce the probability of a favourable response to the diet. Therefore, as far as efficacy is concerned, the preferred underlying AED should be the one which has been (or is expected to be) most effective in the individual patient. Special concerns, however, exist when the KD is combined with AEDs which may produce adverse effects similar to those associated with the diet. Important examples of such effects include metabolic acidosis, acute pancreatitis, hepatitis, urolithiasis, and cardiomiopathy.

Both the diet and carbonic anhydrase inhibiting AEDs such as topiramate, zonisamide and acetazolamide may cause metabolic acidosis, and there is a higher risk of acidosis when the diet is co-administered with these agents. Takeoka et al. (2002) found a <20% decrease in bicarbonate levels in 9 out of 14 TPM-treated children, which was mostly seen at the time of diet induction. It was suggested that bicarbonate levels be monitored carefully when the diet is co-administered with TPM and that bicarbonate supplements be given if the patient becomes symptomatic.

Acute pancreatitis is a rare but often fatal complication (Stewart et al., 2001); it can be caused by hypertriglyceridemia (Toskes, 1990), and may be precipitated by valproic acid (Chapman et al., 2001). If pancreatitis occurs after initiating the diet, discontinuation of the diet and adequate supportive treatment are required for a successful recovery. Kang et al. (2004) reported one patient who developed pancreatitis early in the course of the KD; the patient had been treated with valproic acid for 2 years before starting the diet, and recovered only after abandoning the diet. According to De Vivo et al. (1998) and Ballaban-Gil et al. (1998), hepatitis can be caused by impairment of fatty acid oxidation or carnitine deficiency, especially in patients in whom the diet is combined with valproic acid. Kang et al. (2004), however, found no statistically significant association between hepatitis and the use of valproic acid in their patients managed with the KD. All 10 patients with hepatitis from their series had AST and ALT values of less than 200 mg/dl and continued on the diet.

Urolithiasis is another possible complication of the diet (Furth et al., 2000; Kielb et al., 2000), and may be facilitated by carbonic anhydrase inhibitors, such as topiramate and zonisamide. The four patients reported by Kang et al. (2004) with calcium oxalate stones were receiving topiramate in addition to the diet. Kossoff et al. (2002b), however, were unable to confirm that the combined use of carbonic anhydrase inhibitors and the KD increases the risk of kidney stones. They recom-

mended that all patients treated with this combination be given increased hydration and that urine alkalinization be considered for children with previous renal abnormalities, a family history of urolithiasis, hematuria, or elevated urine calcium-to-creatinine ratios. If renal stones are found, they suggested discontinuation of the carbonic anhydrase inhibitor.

Cardiomyopathy is a potentially fatal complication of the diet, which may manifest as bradycardia, diminished QRS voltage and prolonged QT intervals (Best et al., 2000). It has been reported to correlate with selenium deficiency (Bergqvist et al., 2003), low serum bicarbonate, elevated serum beta-hydroxybutyrate and carnitine deficiency (De Vivo et al., 1998; Kang et al., 2004), though some authors did not find evidence of hypocarnitinemia on the diet (Freeman et al., 2000; Coppola et al., in press). As valproic acid may also reduce carnitine levels, there may be a potential for an interaction leading to an increased risk for this side effect. Most authors, however, agree that carnitine supplementation should be reserved only to hypocarnitinemic patients manifesting clinical symptoms such as generalized weakness, excessive fatigue, decreased muscle force or mild cardiomegaly (De Vivo et al., 1998).

To reduce the risk of adverse interactions with the diet, physicians may consider reducing the AED load during use of the diet. Some authors advice not to modify AED therapy for many months until efficacy and adverse effects of the diet have been evaluated fully; however, early reduction of some AEDs, such as benzodiazepines and phenobarbitone, may be necessary to minimize side effects, such as excessive drowsiness and generalized hypotonia (Vining, 1997). Others, however, advocate early AED reduction (Freeman et al., 1998). Recently, Kossoff et al. (2004) evaluated the impact of early versus late AED reduction after initiation of the diet. Six months after the diet was initiated, AED reduction was possible in 53 of the 81 (65%) children included in the study. Of these 53 children, 30 (57%) underwent early AED tapering in less than a month. In the early taper group, 17% experienced a transient seizure increase during AED reduction, but all these children had >50% seizure decrease after 3 months. The authors concluded that early reduction of AEDs is safe, but it offers no specific advantage in comparison to late tapering.

12.3. The ketogenic diet and general anesthesia

The KD is not incompatible with induction of general anesthesia. The first experiences with general anesthesia in patients on the diet dates back to Hinton et al. (1982), who described changes in metabolic variables, consisting of mild metabolic acidosis and slight decreases in pH, in three patients undergoing simple inhalation anesthesia for minor surgery. More recently, Valencia et al. (2002) reported their experiences in nine children aged 1–6 years who underwent general anesthesia for surgical procedures, some requiring more than one procedure. At the time of anesthesia, these children were receiving the diet for a mean period of 21 months (range 2–60 months) and continued on it until the "nothing by mouth" preparation period, which lasted 12 h. The diet was restarted post-operatively on case-by-case criteria; initially, children were administered carbohydrate-free fluids and were then placed on the diet. In 9 out of 24 procedures, general anesthesia lasted $\geq$3 h, and in one patient >11.5 h. Blood glucose remained unchanged even during prolonged procedures; this may relate to the experimental observation that the ketotic state produced by the diet may offer protection from insulin-induced hypoglycemia (Johnson and Weiner, 1978). There was, however, a trend for metabolic acidosis to develop during the course of long procedures, where a mild reduction occurred in both pH and bicarbonates. In a few cases, patients were administered bicarbonates intravenously. No patient experienced peri- or post-operative complications; in the five children on TPM, there was an increase in acidosis. Most commonly used anesthetics were nitric oxide, hysoflurane, sevoflurane, and thiopental sodium; in three cases, propofol was administered uneventfully. Propofol, however, may by itself cause severe complications such as metabolic acidosis, lipemia, rabdomyolisis, and myocardial failure (Hanna and Ramundo, 1998; Wolf et al., 2001; Baumeister et al., 2004). In one case, propofol was fatal in a 10-year-old boy on the KD treated for refractory status epilepticus (Baumeister et al., 2004). Propofol may derange fatty acid oxidation by impairing the entry of long-chain esterified acylcarnitine into the mitochondria, thus leading to a deficiency of the mitochondrial respiratory chain at the 11-complex level. For this reason, Baumeister et al. (2004) state that propofol should not be used in children for long lasting anesthesia, especially those on the KD.

12.4. Interactions with carbohydrate-containing medications

Some medications contain carbohydrates in their formulation, potentially altering the ratio of fats to carbohydrates and proteins in the diet regimen. If this is overlooked, ketosis can be inhibited with potential loss of seizure control. Care providers and parents should be alerted about the carbohydrates in some medications, including not only glucose content, but also the content of reduced carbohydrates such as glycerin. Lists of carbohydrate content of the most frequently used medications have been published (Lebel et al., 2001; McGhee and Katyal, 2001).

13. Clinical trials of ketogenic products: methodological aspects

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13.1. Introduction

The increasing use of the KD has led to greater demand for specialist nutritional products that can be administered safely and easily to patients. These products must be adequately assessed for safety and efficacy, thereby ensuring the confidence of health professionals and consumers alike. The challenge is to ensure that the data collected provides a high level of evidence, which can pose an interesting challenge in trials involving a dietary product. Recent experience with the KetoCal clinical trial program has highlighted some of the methodological problems that may be encountered in this area.

The KD may be achieved from regular foods. For some, however, using regular foods is not an option, for example those who are tube fed. For others, regular foods alone may not provide the specific nutritional requirements or variety needed, for example a high MCT content or full vitamin, mineral and trace element requirements. Further, the KD is inadequate in most micronutrients if not supplemented (Liu et al., 2003). There is a real need for specialised nutritional products. Whilst such products can help to achieve dietary adequacy, they also serve another important function. Simply, specialised nutritional products can make the diet easier to achieve for both prescribers and carers, more palatable for the patient and ultimately provide more choice for all.

KetoCal was developed in response to requests from clinicians and dietitians looking for a nutritionally complete tube feed suitable for administration of the KD. The product is presented as a powdered formula designed to mimic the classical diet in a ratio of 4:1 and provides a convenient alternative to mixing a modular ketogenic liquid feed. As the product is nutritionally complete, the time demand for calculation of the diet is also minimized. When the product was developed in 2001, there was already an emerging consensus on the efficacy of the KD in refractory epilepsy (Lefevre and Aronson, 2000); therefore, the initial goal for the trial program was simple—to show that the product was capable of mimicking the KD in terms of attaining and maintaining ketosis and *not* to show that the diet itself is efficacious in attaining seizure control. Data from two pilot case series were collected to test product acceptability and efficacy in achieving ketosis before initiating a multicentre trial. Some of the difficulties in obtaining quality data in KD trials became apparent early in the trial program, while others became clear only during the development of the multicentre trial.

13.2. Patient numbers and patient access

In Europe, the population of children and adolescents with active epilepsy is approximately 0.9 million (Forsgren et al., 2005), and those with refractory epilepsy are estimated to be less than 30% of this number. Further, not all children with refractory epilepsy are considered appropriate for treatment with the diet, either for social and/or medical reasons. Numbers diminish further when the target population of a KD study is fully defined. For the initial case series, the aim was to recruit children aged 1–16 years of age with refractory epilepsy who were tube fed. While these criteria alone limited the available patient pool, the greatest concern was ensuring access to the suitable patients. Although historically the KD has been offered as a treatment option at limited centres, and sometimes to limited patient numbers within individual centres, the increasing demand, funding and resources now available has allowed the diet to be offered routinely to a greater number of patients. To maximize access,

recruitment took place at multiple centres across multiple countries.

13.3. Inclusion and exclusion criteria

While achieving adequate recruitment is a problem common to many clinical trials, other challenges are more specific to trials of nutritional products. For example, as in the case of KetoCal, products are often designed for a specific age range, thereby limiting patient numbers. In addition, the quantity of product consumed can be critical. It was of great importance in the case series to ensure that sufficient product be consumed daily to allow outcome measures to be attributed to the product rather than other oral intake. For example, although KetoCal can be used as a milk-shake style meal replacement/emergency regime, patients using this mode of intake could not be guaranteed to consume sufficient product daily. Moreover, it is not ethical to encourage those who can eat regular meals to consume the majority of their energy requirements from a liquid supplement. Thus, the target population became children who were tube fed, to ensure a minimum of 80% of prescribed energy requirements were derived from the product. To document this, participants /careers completed daily intake records.

13.4. Study design

The study design adopted for the KetoCal multicentre trial incorporates a prospective baseline for data comparison. In this study, tube fed children with refractory epilepsy are to be given KetoCal for a minimum of 6 months. The baseline is established by following children for a 2-month period during which time they continue to receive their standard feed alongside any underlying AEDs (Fig. 5). During the run-in, baseline data on growth and seizure frequency are recorded, to be used as a comparison to data collected during the intervention phase.

Dr. Helen Cross at Great Ormond Street (GOS) Hospital in London has developed an interesting alternative methodological approach, which allows incorporation of a randomized control group (Fig. 6). At the screening visit, patients are randomized to the MCT or classical diet, and then they are further randomized to commence the diet after either a 4-week, or a 16-week period. This 12-week difference allows one group to continue standard treatment while the other receives the ketogenic, thereby effectively incorporating a parallel-group control. Such a study design begins to address the criticism concerning the lack of published data on the efficacy of the diet using a control group (Lefevre and Aronson, 2000; Thiele, 2003; Levy and Cooper, 2003).

13.5. Data collection methods

When numerous sites are involved in a clinical trial, it is essential that data collection be consistent between the centres. During the design of the protocol for the KetoCal multicentre trial, the methods for the assessment of mental development, cognitive changes and quality of life generated much debate. In fact, assessment methods of these parameters vary significantly between countries (Levy and Cooper, 2003). The obvious difficulty arising here is the lack of consistency when it comes to data collation. It is recommended that all studies in this area use validated scales, thus allowing for comparative data analysis.

13.6. Conclusions

All clinical studies pose unique methodological challenges, and those involving nutritional products for

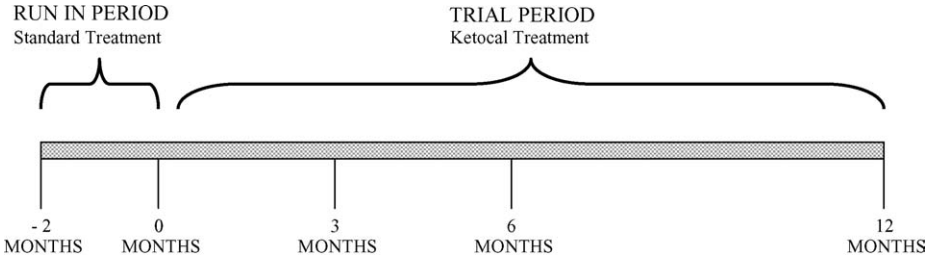

Fig. 5. Schematic diagram of the KetoCal multicentre trial.

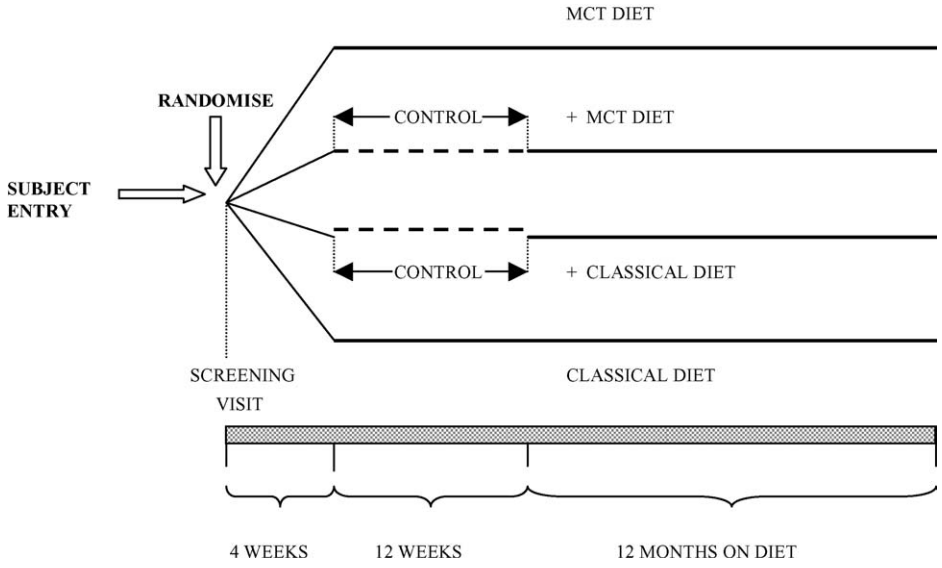

Fig. 6. Schematic diagram of the Great Ormond Street (GOS) Ketogenic Diet Trial.

the KD are no exception. Specific challenges concern patient numbers and access, product consumption, certain data assessment methods and controlling the study. The emphasis of future study designs needs to shift towards addressing some of the criticisms of the current data, specifically randomizing and controlling, in order to provide the best quality data possible. Adopting validated methods allowing for comparative data analysis will assist further.

14. The role of the ketogenic diet in the modern treatment of epilepsy

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14.1. Introduction

The precise role of the KD in the modern treatment of epilepsy is difficult to determine because of the absence of comparative studies. No studies have systematically examined the KD versus medications in specific epilepsy syndromes. Older work with the diet examined its response in relation to seizure types, not epilepsy syndromes, and never in head-to-head comparisons with other treatments. For the most part, treatment was not randomized, prospective, or blinded in these reports. Only recently have investigators begun to examine the response of selected epilepsy syndromes to treatment with AEDs, but such studies are just beginning and none has compared AEDs to the KD. Considering these substantial limitations, only experiential comments can be made concerning the role of the KD, supplemented where possible by appropriate references.

14.2. Primary therapy

The KD is first-line therapy for seizures occurring in association with GLUT1 deficiency syndrome and pyruvate dehydrogenase (E1) deficiency (Wexler et al., 1997; Wang et al., 2005; Klepper et al., 2002). In both conditions, the diet provides effective seizure control while providing essential fuel for brain metabolic activity. Ketone bodies can be utilized to provide the missing fuel which cannot be provided by glucose. In the case of GLUT1 deficiency syndrome this is because of the inability of glucose to adequately enter the brain. In the case of pyruvate dehydrogenase deficiency, the difficulty lies in the inability to metabolize pyruvate so that the substrate cannot enter the Kreb cycle. In both cases, ketones can be used as alternative fuel to power

brain energy needs. In this manner, the diet is not only an anticonvulsant treatment, but it also treats the other non-epileptic manifestations of these diseases. In addition, Wexler et al. (1997) reported increased longevity and improved mental development in patients with E1 deficiency who had earlier initiation of the diet or greater carbohydrate restriction. It has also been shown that the diet is effective in the treatment of GLUT1 deficiency syndrome, although even early treatment may not eliminate neurological disabilities (Wang et al., 2005; Klepper et al., 2002).

14.3. Secondary treatment

The KD may be considered as an alternate treatment, usually after the failure of valproic acid, for generalized epilepsies, particularly those with myoclonic seizures including early myoclonic epilepsy, early infantile epileptic encephalopathy, and myoclonic-absence epilepsy. Given the effectiveness of the diet in the treatment of myoclonic epilepsies, it could be considered as first line treatment for patients with those very severe epileptogenic encephalopathies that are notoriously difficult to control with medications, including the Lennox Gastaut syndrome. Recently, Fejerman and colleagues (Fejerman et al., 2005) reported on the effectiveness of the KD in the treatment of severe myoclonic epilepsy of infancy (Dravet syndrome). The diet is also useful in myoclonic–astatic epilepsy (personal observations, in preparation for publication). Since most parents prefer the convenience of a medication, it is unusual to try the KD before at least one or two AEDs have failed, but given the lack of efficacy of drugs and some of the advantages of the KD this policy should be re-examined in each individual case. Indeed, a retrospective review of patients treated at Johns Hopkins showed that the diet can indeed be used as first line treatment in epilepsies that are not yet intractable (Rubenstein et al., 2005).

The KD can also be beneficial in infants with West syndrome (Kossoff et al., 2002a). In our series of infants treated with the diet, those with infantile spasms did slightly better than those infants presenting with other types of seizures (Nordli et al., 2001).

14.4. Tertiary treatment

The diet can be used for a wide variety of seizure types and epilepsy syndromes. However, our group uses it very rarely in patients with symptomatic localization-related epilepsies. A recent publication showed that patients with complex partial seizures as the predominant seizure type fared less well than patients with other forms of seizure types (Than et al., 2005).

14.5. Contraindications

As important as understanding when the diet may be used to good advantage is knowledge of when to avoid the diet. The KD is absolutely contraindicated in children with pyruvate carboxylase deficiency, where administration of the diet may be lethal. We have never used the diet in patients with fatty acid oxidation disorders or organic acidurias like 3-hydroxy-methyl glutaryl Co-A lyase deficiency. Although we used to avoid the diet in certain respiratory chain abnormalities, recently a group from South Korea showed that the diet can be used successfully in some patients with respiratory chain abnormalities (Chul Kang et al., 2005).

15. Unsolved questions and priorities for future research

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Even though many advances in understanding the effects of the KD have been made recently, most of the clinical data remain to be confirmed by prospective controlled trials.

The diet is traditionally considered a therapy of last resort, but recent data suggest that it could be valuable in new-onset epilepsy. These data raise the question about the appropriate place of the diet in the treatment schedule: which patients, when to start, how to start and for how long to maintain the diet.

One of the challenges in future research will be to identify predictive factors of good, immediate, complete, and sustained *response*. Today, few predictive data are available (Than et al., 2005). It seems that the diet could be more effective when introduced early in the course of epilepsy, and in patients with high seizure activity. But should it be maintained for years or would just a few weeks offer optimal benefit?

In our experience, the diet seems to work particularly well in epilepsies that have experienced recent worsening. However, this needs to be confirmed and explained. The optimal duration of the diet is also a major issue. There is growing evidence that the metabolic tolerability may become a problem after 2–3 years on the diet. This contrasts with the fact that even when there has been an apparent major benefit, there is rarely relapse when stopping the diet. This would support the notion that at times the diet is maintained for too long. May be there is a sizeable number of patients who do not really benefit from the diet for more than a few weeks, and in whom the diet could be given with major benefit only for a few weeks. All this needs to be investigated prospectively and requires a multicentre collaboration.

The optimal *methods of initiating the diet* need to be clarified since outpatient protocols without fluid restriction are claimed to give the same results as the inpatient protocols (Vaisleib et al., 2004).

In the field of biochemical research, the mechanisms of action of the diet still remain to be identified. The relationship between ketosis and seizure control remains unclear. Indeed, in spite of the fact that ketosis is believed to be necessary for clinical efficacy, the correlation between the anticonvulsant action of the diet and the level of ketosis is not clearly established. Potentially useful insights may come from measurement of the levels of ketone bodies, their metabolites, neurotransmitters in the CSF of patients during chronic ketosis (Yudkoff et al., 2004a,b).

16. Discussion summary—risks to benefit ratio, indications and conclusions

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Q. The list of adverse events given in Dr. Campistol's presentation is quite long, but some of these events are anecdotal. Which adverse effects should we especially concerned with?

A. This issue was extensively addressed by Dr. Freeman. He remarked that, for some anecdotal adverse events observed during treatment with the diet, a cause-effect relationship has not been established. Clearly, neither the diet, nor any other therapy is free of side effects. The physician and the patient or family must weigh the risks, side effects, and consequences of the diet against the risks, consequences and side effects of the alternative therapies. The diet is certainly not all natural or holistic, but neither are medications. What are the risks of the diet and what are the consequences of those risks? Those were summarized by Dr. Freeman as follows:

- The diet works equally well in most forms of epilepsy in most patients, and has few complications.
- Most side effects are indeed mild, do not affect acceptability and rarely lead to diet discontinuation. It is well tolerated by younger and retarded patients. However, there is evidence for its usefulness in adolescents and adults as well.
- Dehydration due to decreased intake during the initiation of the diet occurs, but is easily managed, and may not be considered a side effect. Fasting has its own specific benefits, and it is still recommended routinely at John's Hopkins.
- Sepsis is not a side effect of the diet. Cardiomyopathy has been reported but its relation to the diet is unclear. One patient at John's Hopkins had a cardiomyopathy prior to the diet, did well on the diet, but was taken off the diet when the condition recurred and died 9 months later, off the diet. Was the cardiomyopathy related to the diet? Probably not.
- Lipoid aspiration occurs when aspirating individuals are fed lipids. Gastroesophageal reflux and a risk of aspiration may be regarded as relative contraindications to the KD. Hepatitis and pancreatitis, on the other hand, occur in patients on AEDs and are not prevented by the KD; pancreatitis may occur with hypertriglyceridemia.
- The incidence of "serious complications" depends on the definition of "serious" but is very rare on the diet.
- Biochemical "disturbances" have indeed been reported. Asymptomatic hypoglycemia is frequent during diet initiation. A persistent asymptomatic blood sugar of less than 80 mg/dl is a common consequence of a diet low in carbohydrate and high in fat, but is it a side effect? Some centres believe that

keeping glucose in the "low" range is therapeutic in and of itself.
- Growth retardation is mild in younger children on the KD for prolonged period of time and catches up after the diet is stopped.
- Slightly elevated lipids are also common, but their long-term consequences are unclear, and their levels after diet discontinuation have not been studied. Marked elevations are uncommon and may be managed with diet adjustments without having to stop the diet.
- Nephrolithiasis is common (6%) and needs to be closely followed and managed. However, nephrolithiasis is virtually never a reason for remove a child from the diet.

In summary, there are consequences to every action and inaction that we, as physicians, undertake. There are consequences to every AED we choose, but also consequences to not choosing a medication. There are clearly consequences to the KD, most of them beneficial—a decrease in seizures, a decrease in medications, an increasing clarity to intellect, as medications are decreased. There are also side effects to the diet, most of them mild. It is important when counseling parents prior to beginning the diet to be specific as to the incidences of side effects, especially when rare. Providing a list of all of the bad things that occur rarely to these children who are already handicapped by seizures, with or without the additional handicaps of motor or mental impairment, some with underlying and unknown diseases, without putting the side effects into context and without noting their frequency or their consequences does a disservice to the population we are trying to serve.

Q. How much should we be concerned about potential risks of starting the diet in patients who are on valproic acid, zonisamide and topiramate?

A. There was consensus that use of these AEDs is not an absolute contraindication to the diet. However, there was no agreement on whether these patients are at special risk for adverse effects. Dr. Freeman and Dr. Kossoff felt that the safety record of the KD in patients on valproic acid, zonisamide and topiramate is substantially similar to that seen in patients on other AEDs. Although pancreatic and/or hepatic toxicity has been reported occasionally in children treated with the diet together with valproic acid, these disorders also occur in patients taking valproic acid alone (or the diet alone), and the evidence pointing to valproic acid as a potential risk factor is only circumstantial. Dr. Campistol, however, mentioned that in his practice he preferred, as a measure of caution and whenever possible, to avoid starting the diet in children on high dosages of valproic acid. As for other potential side effects, Dr. Nordli remarked that, in his experience, use of the KD together with carbonic anhydrase inhibitors such as topiramate and zonisamide increases the risks for nephrolithiasis and, possibly, metabolic acidosis. Dr. Kossoff, however, disagreed.

Q. It is clear that some of the benefits of the KD result from a reduction in AED load. How long should we wait before tapering down medications, and how many patients can have their AEDs discontinued completely?

A. Dr. Kossoff reported that the practice at Johns Hopkins is usually to reduce barbiturates and benzodiazepines shortly after starting the diet. In general, however, medications begin to be reduced after a child has been on the diet for about 3 months. However, there are no adequate studies to guide the optimal policy with respect to reduction of AED therapy. In his centre, about one third of children stabilized on the KD have completed successful tapering, and are no longer taking any AED.

Q. While we understand that we have no good data from formal studies, it would be useful to hear the faculty's opinion about what types of epilepsies are likely to show the best response based on their experience.

A. Dr Nordli commented that, in his experience, children with cryptogenic and symptomatic generalized epilepsies tend to respond more favourably than those with focal epilepsies, though he acknowledged that preliminary reports in children with diffuse migration disorders are promising. Epilepsy syndromes that he felt may respond well to the diet include severe myoclonic epilepsy of infancy (Dravet syndrome), myoclonic–astatic epilepsy, West syndrome, Lennox Gastaut syndrome, early myoclonic epilepsy, and early infantile epilepsy encephalopathy. There are also promising reports in Rett's syndrome, and in children with autism. On the other hand, intractable absence seizures generally do not do well on the diet. There was general consensus on Dr. Nordli's comments. How-

ever, it was equally agreed that we lack good predictors of outcome on the KD, and that prospective studies in homogeneous cohorts with specific epilepsy syndromes are needed. Everyone expressed the wish that the workshop, together with the present report, could act as catalyst towards establishing networks of interested physicians and developing collaborative protocols to address the many gaps in knowledge that still remain.

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References

Al-Mudallal, A.S., LaManna, J.C., Lust, W.D., Harik, S.I., 1996. Diet-induced ketosis does not cause cerebral acidosis. Epilepsia 37, 258–261.

Appleton, D.B., DeVivo, D.C., 1974. An animal model of the ketogenic diet. Epilepsia 15, 211–227.

Avshalumov, M.V., Rice, M.E., 2002. NMDA receptor activation mediates hydrogen peroxide-induced pathophysiology in rat hippocampal slices. J. Neurophysiol. 87, 2896–2903.

Avshalumov, M.V., Rice, M.E., 2003. Activation of ATP-sensitive K+ (K(ATP)) channels by H_2O_2 underlies glutamate-dependent inhibition of striatal dopamine release. Proc. Natl. Acad. Sci. U.S.A. 100, 11729–11734.

Ballaban-Gil, K., Callahan, C., O'Dell, C., Pappo, M., Moshe, S., Shinnar, S., 1998. Complications of the ketogenic diet. Epilepsia 39, 744–748.

Barborka, C.J., 1930. Epilepsy in adults: results of treatment by ketogenic diet in one hundred cases. Arch. Neurol. 6, 904–914.

Baumeister, F.A., Oberhoffer, R., Liebhaber, G.M., Kunkel, J., Eberhardt, J., Holthausen, H., Peters, J., 2004. Fatal propofol infusion syndrome in association with ketogenic diet. Neuropediatrics 35, 250–252.

Bergqvist, A.G., Chee, C.M., Lutchka, L., Rychik, J., Stallings, V.A., 2003. Selenium deficiency associated with cardiomyopathy: a complication of the ketogenic diet. Epilepsia 44, 618–620.

Bertoli, S., Striuli, L., Testolin, G., Cardinali, S., Veggiotti, P., Salvatori, G.C., Tagliabue, A., 2002. Nutritional status and bone mineral mass in children treated with ketogenic diet. Recent. Prog. Med. 93, 671–675.

Bertoli, S., Cardinali, S., Veggiotti, P., Tagliabue, A., 2005. Nutritional and pharmacological management of childhood epilepsy: ketogenic diets and common AEDs. Curr. Med. Chem. Immunol. Endocrinol. Metab. Agents 5, 113–123.

Best, T.H., Franz, D.N., Gilbert, D.L., Nelson, D.P., Epstein, M.R., 2000. Cardiac complications in pediatric patients on the ketogenic diet. Neurology 54, 2328–2330.

Bough, K.J., Gudi, K., Han, F.T., Rathod, A.H., Eagles, D.A., 2003. An anticonvulsant profile of the ketogenic diet in the rat. Epilepsy Res. 50, 313–325.

Busija, D.W., Lacza, Z., Rajapakse, N., Shimizu, K., Kis, B., Bari, F., Domoki, F., Horiguchi, T., 2004. Targeting mitochondrial ATP-sensitive potassium channels—a novel approach to neuroprotection. Brain Res. Rev. 46, 282–294.

Caraballo, R., Cersosimo, R., Sakr, D., Cresta, A., Escobal, N., Fejerman, N., 2005. Ketogenic diet in patients with Dravet syndrome. Epilepsia 46, 1539–1544.

Cardinali, S., Canafoglia, L., Bertoli, S., Franceschetti, S., Lanzi, G., Tagliabue, A., Veggiotti, P. A pilot study of a ketogenic diet in patients with Lafora body disease. Epilepsy Res., submitted for publication.

Carroll, J., Koenigsberger, D., 1998. The ketogenic diet: a practical guide for caregivers. J. Am. Diet. Assoc. 98, 316–321.

Casey, J.C., McGrogan, J., Pillas, D., Pyzik, P., Freeman, J., Vining, E.P., 1999. The implementation and maintenance of the ketogenic diet in children. J. Neurosci. Nurs. 31, 294–302.

Chapman, S.A., Wacksman, G.P., Patterson, B.D., 2001. Pancreatitis associated with valproic acid: a review of the literature. Pharmacotherapy 21, 1549–1560.

Cheng, C.M., Hicks, K., Wang, J., Eagles, D.A., Bondy, C.A., 2004. Caloric restriction augments brain glutamic acid decarboxylase-65 and -67 expression. J. Neurosci. Res. 77, 270–276.

Chugani, H.T., Rintahaka, P.J., Shewmon, D.A., 1994. Ictal patterns of cerebral glucose utilization in children with epilepsy. Epilepsia 5, 813–822.

Chul Kang, H., Joo Kim, Y., Wook Kim, D., Dong Kim, H., 2005. Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. Epilepsia 46, 272–279.

Cock, H.R., 2002. The role of mitochondria and oxidative stress in neuronal damage after brief and prolonged seizures. Prog. Brain Res. 135, 187–196.

Cock, H.R., Tong, X., Hargreaves, I.P., Heales, S.J.R., Clark, J.B., Patsalos, P.N., Thom, M., Groves, M., Schapira, A.H.V., Shorvon, S.D., Walker, M.C., 2002. Mitochondrial dysfunction associated with neuronal death following status epilepticus in rat. Epilepsy Res. 48, 157–168.

Coppola, G., Veggiotti, P., Cusmai, R., Bertoli, S., Cardinali, S., Dionisi-Vici, C., Elia, M., Lispi, M.L., Sarnelli, C., Tagliabue, A., Toraldo, C., Pascotto, A., 2002. The ketogenic diet in children, adolescents and young adults with refractory epilepsy: an Italian multicentric experience. Epilepsy Res. 48, 221–227.

Coppola, G., Epifanio, G., Auricchio, G., Federico, R.R., Resicato, G., Pascotto, A., in press. Plasma free carnitine in epilepsy children, adolescents and young adults treated with old and new antiepileptic drugs with or without ketogenic diet. Brain Dev.

Couch, S.C., Schwarzman, F., Carroll, J., Koenigsberger, D., Nordli, D.R., Deckelbaum, R.J., DeFelice, A.R., 1999. Growth and nutritional outcomes of children treated with the ketogenic diet. J. Am. Diet. Assoc. 99, 1573–1575.

Crino, P.B., Chou, K., 2000. Epilepsy and cortical dysplasias. Curr. Treat. Options Neurol. 2, 543–552.

Cuellar, R., Molinero, M., 2003. The treatment of children with difficult to control epilepsy. Rev. Neurol. 37, 371–375.

Cunnane, S.C., Musa, K., Ryan, M.A., Whiting, S., Fraser, D.D., 2002. Potential role of polyunsaturates in seizure protection achieved with the ketogenic diet. Prostaglandins Leukotr. Essent. Fatty Acids 67, 131–135.

Dahlin, M., Elfving, A., Ungerstedt, U., Amark, P., 2005. The ketogenic diet influences the levels of excitatory and inhibitory amin acids in the CSF of children with refractory epilepsy. Epilepsy Res. 64, 115–125.

De Vivo, D.C., Leckie, M.P., Ferrendelli, J.S., McDougal Jr., D.B., 1978. Chronic ketosis and cerebral metabolism. Ann. Neurol. 3, 331–337.

De Vivo, D.C., Bohan, T.P., Coulter, D.L., Dreifuss, F.E., Greenwood, R.S., Nordli Jr., D.R., Shields, W.D., Stafstrom, C.E., Tein, I., 1998. L-Carnitine supplementation in childhood epilepsy: current perspectives. Epilepsia 39, 1216–1225.

Depaulis, A., Vergnes, M., Marescaux, C., 1994. Endogenous control of epilepsy: the nigral inhibitory system. Prog. Neurobiol. 42, 33–52.

Erecinska, M., Nelson, D., Daikhin, Y., Yudkoff, M., 1996. Regulation of GABA level in rat brain synaptosomes: fluxes through enzymes of the GABA shunt and effects of glutamate, calcium, and ketone bodies. J. Neurochem. 67, 2325–2334.

Fadiman, A., 1997. The Spirit Catches You and You Fall Down. Farrar, Strauss, Giroux, New York, p. 21.

Fejerman, N., Caraballo, R., Cersosimo, R., 2005. Ketogenic diet in patients with Dravet syndrome and myoclonic epilepsies in infancy and early childhood. Adv. Neurol. 95, 299–305.

Ferranti, R., da Silva, M.M., Kowaltowski, A.J., 2003. Mitochondrial ATP-sensitive K^+ channel opening decreases reactive oxygen species generation. FEBS Lett. 536, 51–55.

Food and Nutrition Board, Institute of Medicine, 2002. Dietary References Intakes for Energy, Carbohydrate, Fiber, Fats, Fatty Acids, Cholesterol, Proteins and Amino Acids. National Academy Press, Washington, DC.

Forsgren, L., Beghi, E., Oun, A., Sillanpaa, M., 2005. The epidemiology of epilepsy in Europe—a systematic review. Eur. J. Neurol. 12, 245–253.

François, L.L., Manel, V., Rousselle, C., David, M., 2003. Ketogenic regime as anti-epileptic treatment: its use in 29 epileptic children. Arch. Pediatr. 10, 300–306 (in French).

Franks, N.P., Honore, E., 2004. The TREK K2P channels and their role in general anaesthesia and neuroprotection. Trends Pharmacol. Sci. 25, 601–608.

Frantseva, M.V., Perez Velazquez, J.L., Carlen, P.L., 1998. Changes in membrane and synaptic properties of thalamocortical circuitry caused by hydrogen peroxide. J. Neurophysiol. 80, 1317–1326.

Frantseva, M.V., Perez Velazquez, J.L., Tsoraklidis, G., Mendonca, A.J., Adamchik, Y., Mills, L.R., Carlen, P.L., Burnham, M.W., 2000. Oxidative stress is involved in seizure-induced neurodegeneration in the kindling model of epilepsy. Neuroscience 97, 431–435.

Fraser, D.D., Whiting, S., Andrew, R.D., Macdonald, E.A., Musa-Veloso, K., Cunnane, S.C., 2003. Elevated polyunsaturated fatty acids in blood serum obtained from children on the ketogenic diet. Neurology 60, 1026–1029.

Freeman, J.M., Vining, E.P., 1998. Ketogenic diet: a time-tested, effective, and safe method for treatment of intractable childhood epilepsy. Epilepsia 39, 450–451.

Freeman, J., Vining, E., 1999. Seizures decrease rapidly after fasting: preliminary studies of the ketogenic diet. Arch. Pediatr. Adolesc. Med. 153, 946–949.

Freeman, J.M., Kelly, M.T., Freeman, J.B., 1996. The Epilepsy Diet Treatment (An Introduction to The Ketogenic Diet), 2nd ed. Demos Vermande, New York, NY.

Freeman, J.M., Vining, E.P.G., Pillas, D.J., Pyzik, P.L., Casey, J.C., Kelly, M.T., LCSW, 1998. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics 102, 1358–1363.

Freeman, J.M., Kelly, M.T., Freeman, J.B., 2000. The Ketogenic Diet, 3rd ed. Demos Medical Publishers, New York.

Freeman, J.M., Kelly, M.T., Freeman, J.B., 2002. The Ketogenic Diet: A Treatment for Epilepsy, 3rd ed. Demos Medical Publishers, New York.

Fuehrlein, B.S., Rutenberg, M.S., Silver, J.N., Warren, M.W., Theriaque, D.W., Duncan, G.E., Stacpoole, P.W., Brantly, M.L., 2004. Differential metabolic effects of saturated versus polyunsaturated fats in ketogenic diets. J. Clin. Endocrinol. Metab. 89, 1641–1645.

Furth, S.L., Casey, J.C., Pyzik, P.L., Neu, A.M., Docimo, S.G., Vining, E.P., Freeman, J.M., Fivush, B.A., 2000. Risk factors for urolithiasis in children on the ketogenic diet. Pediatr. Nephrol. 15, 125–128.

Galvan, M., Arellano, M., Sans, A., Sanmarti, F.X., Gomez, L., Vernet, A., Campistol, J., 2001. Dieta cetógena: una alternativa valida en epilepsias refractarias? Rev. Neurol. 33, 1–5 (in Spanish).

Ganesh, S., Delgado-Escueta, A.V., Sakamoto, T., Avila, M.R., Machado-Salas, J., Hoshii, Y., Akagi, T., Gomi, H., Suzuki, T., Amano, K., Agarwala, K.L., Hasegawa, Y., Bai, D.S., Ishihara, T., Hashikawa, T., Itohara, S., Cornford, E.M., Niki, H., Yamakawa, K., 2002. Targeted disruption of the Epm2a gene causes formation of Lafora bodies, neurodegeneration, ataxia, myoclonus epilepsy and impaired behavioral response in mice. Hum. Mol. Genet. 11, 1251–1262.

Gilbert, D.L., Pyzic, P.L., Freeman, J.M., 2000. The ketogenic diet: seizure control correlates better with serum beta-hydroxibutyrate than with urine ketones. J. Child Neurol. 15, 787–790.

Gross, G.J., Peart, J.N., 2003. KATP channels and myocardial preconditioning: an update. Am. J. Physiol. Heart Circ. Physiol. 285, H921–H930.

Hanna, J.P., Ramundo, M.L., 1998. Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. Neurology 50, 301–303.

Hassan, A.M., Keene, D.L., Whiting, S.E., Jacob, P.J., Champagne, J.R., Humphreys, P., 1999. Ketogenic diet in the treatment of refractory epilepsy in childhood. Pediatr. Neurol. 21, 548–552.

Helmholz, H.F., Keith, H.M., 1930. Eight years' experience with the ketogenic diet in the treatment of epilepsy. JAMA 95, 707–709.

Hemingway, C., Freeman, J.M., Pillas, D.J., Pyzik, P.L., 2001a. The ketogenic diet: a 3–6 years follow-up of 150 children prospectively enrolled. Pediatrics 108, 898–905.

Hemingway, C., Pyzik, P.L., Freeman, J.M., 2001b. Changing physician attitudes toward the ketogenic diet: a parent-centered

approach to physician education about a medication alternative. Epilepsy Behav. 2, 574–578.
Hinton, W., Schwartz, R.H., Loach, A.B., 1982. Diet induced ketosis in epilepsy and anaesthesia. Metabolic changes in three patients on a ketogenic diet. Anaesthesia 37, 39–42.
Hopkins, I.J., Lynch, B.C., 1970. Use of ketogenic diet in epilepsy in childhood. Aust. Paediatr. J. 6, 25–29.
Horvath, T.L., Diano, S., Barnstable, C., 2003. Mitochondrial uncoupling protein 2 in the central nervous system: neuromodulator and neuroprotector. Biochem. Pharmacol. 65, 1917–1921.
Iadarola, M.J., Gale, K., 1982. Substantia nigra: site of anticonvulsant activity mediated by gamma-aminobutyric acid. Science 218, 1237–1240.
Jenney, E.H., Pfeiffer, C.C., 1958. The convulsant effect of hydrazides and the antidotal effect of anticonvulsants and metabolites. J. Pharmacol. Exp. Ther. 122, 110–123.
Johnson, W.A., Weiner, M.W., 1978. Protective effects of ketogenic diets on signs of hypoglicemia. Diabetes 27, 1087–1091.
Kang, H.C., da Chung, E., Kim, D.W., Kim, H.D., 2004. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia 45, 1116–1123.
Kang, H.C., Kim, Y.J., Kim, D.W., Kim, H.D., 2005. Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. Epilepsia 46, 272–279.
Kankirawatana, P., Jirapinyo, P., Kankirawatana, S., Wongarn, R., Thamanasiri, N., 2001. Ketogenic diet: an alternative treatment for refractory epilepsy in children. J. Med. Assoc. Thai. 84, 1027–1032.
Karceski, S. (Ed.), 2001. The expert consensus guideline series: treatment of epilepsy. Epilepsy Behav. 2, A1–A50.
Kashiwaya, Y., Takeshima, T., Mori, N., Nakashima, K., Clarke, K., Veech, R.L., 2000. D-Beta-hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. Proc. Natl. Acad. Sci. U.S.A. 97, 5440–5444.
Katyal, N.G., Koehler, A.N., McGhee, B., Foley, C.M., Crumrine, P.K., 2000. The ketogenic diet in refractory epilepsy: the experience of Children's Hospital of Pittsburgh. Clin. Pediatr. 39, 153–159.
Keith, H.M., 1931. The effect of various factors on experimentally produced convulsions. Am. J. Dis. Child 41, 532–543.
Keith, H.M., 1933. Factors influencing experimentally produced convulsions. Arch. Neurol. Psych. 29, 148–154.
Kielb, S., Koo, H.P., Bloom, D.A., Faerber, G.J., 2000. Nephrolithiasis associated with the ketogenic diet. J. Urol. 164, 464–466.
Kim, D.W., Kang, H.C., Park, J.C., Kim, H.D., 2004a. Benefits of the nonfasting ketogenic diet compared with the initial fasting ketogenic diet. Pediatrics 114, 1627–1630.
Kim, D.Y., van Brederode, H., Sullivan, P.G., Spain, W.J., Rho, J.M., 2004b. Ketone bodies protect neocortical neurons against acute oxidative stress. Epilepsia 45 (Suppl. 7), 199.
Kinsman, S.L., Vining, E.P., Quaskey, S.A., Mellits, D., Freeman, J.M., 1992. Efficacy of the ketogenic diet for intractable seizure disorders: review of 58 cases. Epilepsia 33, 1132–1136.
Klepper, J., Leiendecker, B., Bredahl, R., Athanassopoulos, S., Heinen, F., Gertsen, E., Florcken, A., Metz, A., Voit, T., 2002. Introduction of a ketogenic diet in young infants. J. Inherit. Metab. Dis. 25, 449–460.
Klepper, J., Leiendecker, B., Riemann, E., Baumeister, F.A., 2003. The ketogenic diet in German-speaking countries: update. Klin. Padiatr. 216, 277–285 (in German).
Kossoff, E.H., 2004. More fat and fewer seizures: dietary therapies for epilepsy. Lancet Neurol. 3, 415–420.
Kossoff, E.H., McGrogan, J.R., 2005. Worldwide use of the ketogenic diet. Epilepsia 46, 280–289.
Kossoff, E.H., Vining, E.P.G., 2004. The ketogenic diet. In: Shorvon, S.D., Perucca, E., Fish, D.R., Dodson, E.W. (Eds.), The Treatment of Epilepsy. Blackwell Science, Oxford, pp. 262–268.
Kossoff, E.H., Pyzik, P.L., McGrogan, J.R., Vining, E.P., Freeman, J.M., 2002a. Efficacy of the ketogenic diet for infantile spasms. Pediatrics 109, 780–783.
Kossoff, E.H., Pyzik, P.L., Furth, S.L., Hladky, H.D., Freeman, J.M., Vining, E.P., 2002b. Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. Epilepsia 43, 1168–1171.
Kossoff, E.H., Krauss, G.L., McGrogan, J.R., Freeman, J.M., 2003. Efficacy of the Atkins diet as therapy for intractable epilepsy. Neurology 61, 1789–1791.
Kossoff, E.H., McGrogan, J.R., Freeman, J.M., 2004a. Benefits of an all-liquid ketogenic diet. Epilepsia 45, 1163.
Kossoff, E.H., Pyzik, P.L., McGrogan, J.R., Rubenstein, J.E., 2004b. The impact of early versus late anticonvulsant reduction after ketogenic diet initiation. Epilepsy Behav. 5, 499–502.
Kossoff, E.H., Thiele, E.A., Pfeifer, H.H., McGrogan, J.R., Freeman, J.M., 2005. Tuberous sclerosis complex and the ketogenic diet. Epilepsia 46, 1684–1686.
Kossoff, E.H., McGrogan, J.R., Bluml, R.M., Pillas, D.J., Rubenstein, J.E., Vining, E.P., in press. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. Epilepsia.
Krauss, S., Zhgn, C.-Y., Lowell, B.B., 2005. The mitochondrial uncoupling-protein homologues. Nat. Rev. Mol. Cell. Biol. 6, 248–261.
Krenz, M., Oldenburg, O., Wimpee, H., Cohen, M.V., Garlid, K.D., Critz, S.D., Downey, J.M., Benoit, J.N., 2002. Opening of ATP-sensitive potassium channels causes generation of free radicals in vascular smooth muscle cells. Basic Res. Cardiol. 97, 365–373.
Kwiterovich Jr., P.O., Vining, E.P., Pyzik, P., Skolasky Jr., R., Freeman, J.M., 2003. Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. JAMA 290, 912–920.
Lebel, D., Morin, C., Laberge, M., Achim, N., Carmant, L., 2001. The carbohydrate and caloric content of concomitant medications for children with epilepsy on the ketogenic diet. Can. J. Neurol. Sci. 28, 322–340.
Lebuffe, G., Schumacker, P.T., Shao, Z.H., Anderson, T., Iwase, H., Vanden Hoek, T.L., 2003. ROS and NO trigger early preconditioning: relationship to mitochondrial KATP channel. Am. J. Physiol. Heart Circ. Physiol. 284, H299–H308.
Lefevre, F., Aronson, A., 2000. Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. Pediatrics 105, E46.
Lennox, W.G., 1960. Epilepsy and Related Disorders. Little and Brown, Boston.
Levy, R., Cooper, P., 2003. Ketogenic diet for epilepsy. Cochrane Database Syst. Rev., 3, CD001903.

Liang, L.P., Ho, Y.S., Patel, M., 2000. Mitochondrial superoxide production in kainate-induced hippocampal damage. Neuroscience 10, 563–570.

Liang, L.P., Patel, M., 2004. Mitochondrial oxidative stress and increased seizure susceptibility in Sod2(−/+) mice. Free Radic. Biol. Med. 36, 542–554.

Lightstone, L., Shinnar, S., Callahan, C.M., O'Dell, C., Moshe, S.L., Ballaban-Gil, K.R., 2001. Reasons for failure of the ketogenic diet. Neurosci. Nurs. 33, 292–295.

Likhodii, S.S., Serbanescu, I., Cortez, M.A., Murphy, P., Snead III, O.C., Burnham, W.M., 2003. Anticonvulsant properties of acetone, a brain ketone elevated by the ketogenic diet. Ann. Neurol. 54, 219–226.

Liu, Y.M., Williams, S., Basualdo-Hammond, C., Stephens, D., Curtis, R., 2003. A prospective study: growth and nutritional status of children treated with the ketogenic diet. J. Am. Diet. Assoc. 103, 707–712.

Mady, M.A., Kossoff, E.H., Mc Gregor, A.L., Wheless, J.W., Pyzik, P.L., Freeman, J.M., 2003. The ketogenic diet: adolescents can do it, too. Epilepsia 44, 847–851.

Mattiasson, G., Sullivan, P.G., in press The emerging roles of UCP2 in health, disease and therapeutics. Antioxidants Redox Signaling.

Mattson, M.P., Liu, D., 2003. Mitochondrial potassium channels and uncoupling proteins in synaptic plasticity and neuronal cell death. Biochem. Biophys. Res. Commun. 304, 539–549.

Maydell, B.V., Wyllie, E., Akhtar, N., Kotagal, P., Powasky, K., Cook, K., Weinstock, A., Rothner, A.D., 2001. Efficacy of ketogenic diet in focal versus generalized seizures. Pediatr. Neurol. 25, 208–212.

McGhee, B., Katyal, N., 2001. Avoid unnecessary drug-related carbohydrates for patients consuming the ketogenic diet. J. Am. Diet. Assoc. 101, 87–101.

Mckay, M., Bicknell-Royle, Nation, J., Humphey, M., Harvey, S., 2005. The ketogenic diet in refractory childood epilepsy. J. Paediatr. Child Health 41, 353–357.

Millichap, J.G., Jones, J.D., 1964. Acid–base, electrolyte, and amino acid metabolism in children with petit mal. Etiologic significance and modifications by anticonvulsant drugs and the ketogenic diet. Epilepsia 90, 239–255.

Minassian, B.A., 2001. Lafora's disease: towards a clinical, pathologic, and molecular synthesis. Pediatr. Neurol. 25, 21–29.

Moreno-Villares, Oliveros-Leal, L., Simon-Heras, R., Mateos-Beato, F., 2001. La vuelta a la dieta cetógena: qué papel desempeña en el tratamiento de las convulsiones infantiles refractarias? Rev. Neurol. 32, 1115–1119.

Morris, A.A., 2005. Cerebral ketone body metabolism. J. Inherit. Metab. Dis. 28, 109–121.

Nei, M., Sperling, M.R., Liporace, J.D., Sirven, J.I., 2003. Ketogenic diet in adults: response by epilepsy type. Epilepsia 44 (Suppl. 9), 282.

Nordli Jr., D.R., Kuroda, M.M., Carroll, J., Koenigsberger, D.Y., Hirsch, L.J., Bruner, H.J., Seidel, W.T., De Vivo, D.C., 2001. Experience with the ketogenic diet in infants. Pediatrics 108, 129–133.

Pan, J.W., Bebin, E.M., Chu, W.J., Hetherington, H.P., 1999. Ketosis and epilepsy: 31P spectroscopic imaging at 4.1 T. Epilepsia 40, 703–707.

Patel, M., 1951-1962. Mitochondrial dysfunction and oxidative stress: cause and consequence of epileptic seizures. Free Radic. Biol. Med. 37.

Peterman, M.G., 1924. The ketogenic diet in the treatment of epilepsy: a preliminary report. Am. J. Dis. Child 28, 28–33.

Peterman, M.G., 1979. Ketogenic diet in epilepsy. JAMA 84.

Peterson, S.J., Tangney, C.C., Pimentel-Zablah, E.M., Hjelmgren, B., Booth, G., Berry-Kravis, E., 2005. Changes in growth and seizure reduction in children on the ketogenic diet as a treatment for intractable epilepsy. J. Am. Diet. Assoc. 105, 718–725.

Pfeifer, H.H., Thiele, E.A., 2004. Low glycemic index diet as an alternative to the ketogenic diet in the treatment of intractable epilepsy in childhood. Epilepsia 45 (Suppl. 7), 184.

Reger, M.A., Henderson, S.T., Hale, C., Cholerton, B., Baker, L.D., Watson, G.S., Hyde, K., Chapman, D., Craft, S., 2004. Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. Neurobiol. Aging 25, 311–314.

Rho, J.M., Anderson, G.D., Donevan, S.D., White, H.S., 2002. Acetoacetate, acetone, and dibenzylamine (a contaminant in L-(+)-beta-hydroxybutyrate) exhibit direct anticonvulsant actions in vivo. Epilepsia 43, 358–361.

Rimvall, K., Martin, D.L., 1992. Increased intracellular g-aminobutyric acid selectively lowers the level of the larger of two glutamate decarboxylase proteins in cultured GABAergic neurons from rat cerebral cortex. J. Neurochem. 58, 158–166.

Rimvall, K., Sheikh, S.N., Martin, D.L., 1993. Effects of increased gamma-aminobutyric acid levels on GAD67 protein and mRNA levels in rat cerebral cortex. J. Neurochem. 60, 714–720.

Rimvall, K., Martin, D.L., 1994. The level of GAD67 protein is highly sensitive to small increases in intraneuronal gamma-aminobutyric acid levels. J. Neurochem. 62, 1375–1381.

Rubenstein, J.E., Kossoff, E.H., Pyzik, P.L., Vining, E.P., McGrogan, J.R., Freeman, J.M., 2005. Experience in the use of the ketogenic diet as early therapy. J. Child Neurol. 20, 31–34.

Schlanger, S., Shinitzky, M., Yam, D., 2002. Diet enriched with omega-3 fatty acids alleviates convulsion symptoms in epilepsy patients. Epilepsia 43, 103–104.

Schwartz, R.H., Eaton, J., Bower, B.D., Aynsley-Green, A., 1989. Ketogenic diets in the treatment of epilepsy: short-term clinical effects. Dev. Med. Child Neurol. 31, 145–151.

Schwartzkroin, P.A., 1999. Mechanisms underlying the anti-epileptic efficacy of the ketogenic diet. Epilepsy Res. 37, 171–180.

Seymour, K.J., Bluml, S., Sutherling, J., Sutherling, W., Ross, B.D., 1999. Identification of cerebral acetone by 1H-MRS in patients with epilepsy controlled by ketogenic diet. MAGMA 8 (1), 33–42.

Shet, R.D., 2004. Metabolic concerns associated with antiepileptic medications. Neurology 63 (Suppl. 4), S24–S29.

Sills, M.A., Forsythe, W.I., Haidukewych, D., MacDonald, A., Robinson, M., 1986. The medium chain triglyceride diet and intractable epilepsy. Arch. Dis. Child 61, 1168–1172.

Sirven, J., Whedon, B., Caplan, D., Liporace, J., Glosser, D., O'Dwyer, J., Sperling, M., 1999. The ketogenic diet for intractable epilepsy in adults: preliminary results. Epilepsia 40, 1721–1726.

Sperling, M.R., Nei, M., 2004. The ketogenic diet in adults. In: Stafstrom, C., Rho, J. (Eds.), Epilepsy and the Ketogenic Diet. Humana Press, Totowa, NJ.

Stafstrom, C.E., Rho, J.M., 2004. Epilepsy and the Ketogenic Diet. Humana Press, Totowa, NJ.

Stewart, W.A., Gordon, K., Camfield, P., 2001. Acute pancreatitis causing death in a child on the ketogenic diet. J. Child Neurol. 16, 682.

Sullivan, P.G., Dube, C., Dorenbos, K.D., Steward, O., Baram, T.Z., 2003. Mitochondrial uncoupling protein-2 protects the immature brain from excitotoxic neuronal death. Ann. Neurol. 53, 711–717.

Sullivan, P.G., Spring, J.E., Hal, E.D., Scheff, S.W., 2004a. Mitochondrial uncoupling as a therapeutic target following neuronal injury. J. Bioenerg. Biomembr. 36, 353–356.

Sullivan, P.G., Rippy, N., Dorenbos, K., Concepcion, R., Agarwal, A., Rho, J.M., 2004b. The ketogenic diet increases mitochondrial uncoupling protein levels and activity in mouse hippocampus. Ann. Neurol. 55, 576–580.

Swink, T.D., Vining, E.P., Freeman, J.M., Freeman, J.M., 1997. The ketogenic diet. Adv. Pediatr. 44, 297–329.

Szot, P., Weinshenker, D., Rho, J.M., Storey, T.W., Schwartzkroin, P.A., 2001. Norepinephrine is required for the anticonvulsant effect of the ketogenic diet. Brain Res. Dev. Brain Res. 129, 211–214.

Takeoka, M., Riviello Jr., J.J., Pfeifer, H., Thiele, E.A., 2002. Concomitant treatment with topiramate and ketogenic diet in pediatric epilepsy. Epilepsia 43, 1072–1075.

Tempkin, O., 1976. The Falling Sickness, 2nd ed. Johns Hopkins University Press.

Than, K.D., Kossoff, E.H., Rubenstein, J.E., Pyzik, P.L., McGrogan, J.R., Vining, E.P., 2005. Can you predict an immediate, complete, and sustained response to the ketogenic diet? Epilepsia 46, 580–582.

Thiele, E., 2003. Assessing the efficacy of antiepileptic treatments: the ketogenic diet. Epilepsia 44 (Suppl. 7), 26–29.

Thio, L.L., Wong, M., Yamada, K.A., 2000. Ketone bodies do not directly alter excitatory or inhibitory hippocampal synaptic transmission. Neurology 54, 325–331.

Tieu, K., Perier, C., Caspersen, C., Teismann, P., Wu, D.C., Yan, S.D., Naini, A., Vila, M., Jackson-Lewis, V., Ramasamy, R., Przedborski, S., 2003. D-Beta-hydroxybutyrate rescues mitochondrial respiration and mitigates features of Parkinson disease. J. Clin. Invest. 112, 892–901.

Toskes, P.P., 1990. Hyperlipidemic pancreatitis. Gastroenterol. Clin. N. Am. 19, 783–791.

Valencia, I., Pfeifer, H., Thiele, E.A., 2002. General anesthesia and the ketogenic diet: clinical experience in nine patients. Epilepsia 43, 525–529.

Ueda, Y., Yokoyama, H., Nakajima, A., Tokumaru, J., Doi, T., Mitsuyama, Y., 2002. Glutamate excess and free radical formation during and following kainic acid-induced status epilepticus. Exp. Brain Res. 147, 219–226.

Vaisleib, I.I., Buchhalter, J.R., Zupanc, M.L., 2004. Ketogenic diet: outpatient initiation, without fluid or caloric restriction. Pediatr. Neurol. 31, 198–202.

Vamecq, J., Vallee, L., Lesage, F., Gressens, P., Stables, J.P., 2005. Antiepileptic popular ketogenic diet: emerging twists in an ancient story. Prog. Neurobiol. 75, 1–28.

Veech, R.L., Chance, B., Kashiwaya, Y., Lardy, H.A., Cahill Jr., G.F., 2001. Ketone bodies, potential therapeutic uses. IUBMB Life 51, 241–247.

Veech, R.L., 2004. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. Prostaglandins Leukotr. Essent. Fatty Acids 70, 309–319.

Vining, E.P.G., Freeman, J.M., Ballaban-Gil, K., Camfield, C.S., Camfield, P.R., Holmes, G.L., Shinnar, S., Shuman, R., Trevathan, E., Wheless, J.W., 1998. A multicenter study of the efficacy of the ketogenic diet. Arch. Neurol. 55, 1433–1437.

Vining, E.P.G., 1997. Ketogenic diet. In: Engel Jr., T.A., Pedley (Eds.), Epilepsy: A Comprehensive Textbook. Lippincott-Raven, Philadelphia, pp. 1339–1344.

Vining, E.P.G., 1999. Clinical efficacy of the ketogenic diet. Epilepsy Res. 37, 181–190.

Vining, E.P.G., Pyzik, P., McGrogan, J., Hladky, H., Anand, A., Kriegler, S., Freeman, J.M., 2002. Growth of children on the ketogenic diet. Dev. Med. Child Neurol. 44, 796–802.

Vodickova, L., Frantik, Vodickova, A., 1995. Neutrotropic effects and blood levels of solvents at combined exposures: binary mixtures of toluene, *o*-xylene and acetone in rats and mice. Cent. Eur. J. Public Health 3, 57–64.

Voskuyl, R.A., Vreugdenhil, M., Kang, J.X., Leaf, A., 1998. Anticonvulsant effect of polyunsaturated fatty acids in rats, using the cortical stimulation model. Eur. J. Pharmacol. 341, 145–152.

Votyakova, T.V., Reynolds, I.J., 2001. DeltaPsi(m)-dependent and -independent production of reactive oxygen species by rat brain mitochondria. J. Neurochem. 79, 266–277.

Vreugdenhil, M., Bruehl, C., Voskuyl, R.A., Kang, J.X., Leaf, A., Wadman, W.J., 1996. Polyunsaturated fatty acids modulate sodium and calcium currents in CA1 neurons. Proc. Natl. Acad. Sci. U.S.A. 93, 12559–12563.

Wang, D., Pascual, J.M., Yang, H., Engelstad, K., Jhung, S., Sun, R.P., De Vivo, D.C., 2005. Glut-1 deficiency syndrome: clinical, genetic, and therapeutic aspects. Ann. Neurol. 57, 111–118.

Wexler, I.D., Hemalatha, S.G., McConnell, J., Buist, N.R., Dahl, H.H., Berry, S.A., Cederbaum, S.D., Patel, M.S., Kerr, D.S., 1997. Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets. Studies in patients with identical mutations. Neurology 49, 1655–1661.

Wheless, J., 2001. The ketogenic diet: an effective medical therapy with side effects. J. Child Neurol. 16, 633–635.

Wheless, J., 2004. Nonpharmacological treatment of the catastrofic epilepsy of childhood. Epilepsia 45 (Suppl. 5), 17–22.

Wheless, J., Sankar, R., 2003. Treatment strategies for myoclonic seizures and epilepsy syndromes with myoclonic seizures. Epilepsia 44 (Suppl. 11), 27–37.

Williams, S., Basualdo-Hammond, C., Curtis, R., Schuller, R., 2002. Growth retardation in children with epilepsy on the ketogenic diet (A retrospective chart review). J. Am. Diet. Assoc. 102, 405–407.

Willmore, L.J., Sypert, G.W., Munson, J.V., Hurd, R.W., 1978. Chronic focal epileptiform discharges induced by injec-

tion of iron into rat and cat cortex. Science. 200, 1501–1503.

Wirrell, E.C., Darwish, H.Z., Williams-Dyjur, C., Blackman, M., Lange, V., 2002. Is a fast necessary when initiating the ketogenic diet? J. Child Neurol. 17, 179–182.

Wolf, A., Weir, P., Segar, P., Stone, J., Shield, J., 2001. Impaired fatty acid oxidation in propofol infusion syndrome. Lancet 357, 606–607.

Xiao, Y.F., Li, X., 1999. Polyunsaturated fatty acids modify mouse hippocampal neuronal excitability during excitotoxic or convulsant stimuli. Brain Res. 846, 112–121.

Xiao, Y.F., Kang, J.X., Morgan, J.P., Leaf, A., 1995. Blocking effects of polyunsaturated fatty acids on Na+ channels of neonatal rat ventricular myocytes. Proc. Natl. Acad. Sci. U.S.A. 92, 11000–11004.

Xiao, Y.F., Gomez, A.M., Morgan, J.P., Lederer, W.J., Leaf, A., 1997. Suppression of voltage-gated L-type Ca^{2+} currents by polyunsaturated fatty acids in adult and neonatal rat cardiac myocytes. Proc. Natl. Acad. Sci. U.S.A. 94, 4182–4187.

Xiao, Y.F., Wright, S.N., Wang, G.K., Morgan, J.P., Leaf, A., 1998. Fatty acids suppress voltage-gated Na^{+} currents in HEK293t cells transfected with the alpha-subunit of the human cardiac Na^{+} channel. Proc. Natl. Acad. Sci. U.S.A. 95, 2680–2685.

Xu, Z., Ji, X., Boysen, P.G., 2004. Exogenous nitric oxide generates ROS and induces cardioprotection: involvement of PKG, mitochondrial KATP channels, and ERK. Am. J. Physiol. Heart Circ. Physiol. 286 (4), H1433–H1440.

Yamashita, J., 1976. Convulsive seizure induced by intracerebral injection of semicarbazide (an anti-vitamin B6) in the mouse. J. Nutr. Sci. Vitaminol. (Tokyo) 22, 1–6.

Yehuda, S., Carasso, R.L., Mostofsky, D.I., 1994. Essential fatty acid preparation (SR-3) raises the seizure threshold in rats. Eur. J. Pharmacol. 254, 193–198.

Yudkoff, M., Daikhin, Y., Nelson, D., Nissim, I., Erecinska, M., 1996. Neuronal metabolism of branched-chain amin acids. Flux through the aminotransferase pathway in synaptosomes. J. Neurochem. 66, 2136–2145.

Yudkoff, M., Daikhin, Y., Nissim, I., Grunstein, R., Nissim, I., 1997. Effects of ketone bodies on astrocyte amino acid metabolism. J. Neurochem. 69, 682–692.

Yudkoff, M., Daikhin, Y., Nissim, I., Lazarow, A., Nissim, I., 2001a. Brain amino acid metabolism and ketosis. J. Neurosci. Res. 66, 272–281.

Yudkoff, M., Daikhin, Y., Nissim, I., Lazarow, A., Nissim, I., 2001b. Ketogenic diet, amino acid metabolism, and seizure control. J. Neurosci. Res. 66, 931–940.

Yudkoff, M., Daikhin, Y., Nissim, I., Lazarow, A., Nissim, I., 2004a. Ketogenic diet, brain glutamate metabolism and seizure control. Prostaglandins Leukotr. Essent. Fatty Acids 70, 277–285.

Yudkoff, M., Daikhin, Y., Nissim, I., Nissin, I., 2004b. The ketogenic diet, interactions with brain amino acid handling. In: Staftrom, C.E., Rho, J.M. (Eds.), Epilepsy and the Ketogenic Diet. Humana Press, Totowa, NJ, pp. 181–191.

Yudkoff, M., Daikhin, Y., Nissim, I., Lazarow, A., Nissim, I., 2004c. Ketogenic diet, amino acid metabolism and seizure control. Prostaglandin Leukotr. Essent. Fatty Acids 70, 277–285.

Yudkoff, M., Daikhin, Y., Nissim, I., Horyn, O., Lazarow, A., Luhovyy, B., Wehrli, S., Nissim, I., 2005. Response of brain amino acid metabolism to ketosis. Neurochem. Int. 47, 119–128.