Chapter 27
Ketogenic Diet and Epilepsy: The Role of Adenosine

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Abstract The ketogenic diet (KD) debuted in the 1920s as a metabolic treatment for epilepsy, based on the historical observation that fasting could prevent seizures. Similar to fasting, the high-fat, low-carbohydrate KD restricts glucose and favors oxidation of fatty acids, which in turn generates ketones for energy. Despite nearly a century of clinical use, proof of efficacy was only recently established, and little is known about how the KD works. The lure of a continually growing armamentarium of pharmacological options and the inherent challenges in implementing a dietary treatment versus a drug have combined to relegate the KD to a therapy of last resort. Indeed, better knowledge of how the KD exerts broad-spectrum clinical activity would be required to develop enhanced metabolism-based treatments, and perhaps even a "diet in a pill." Recent evidence strongly implicates adenosine as a mediator of KD action, as it is well known that adenosine is a fundamental link between metabolism and neuronal membrane excitability. Through a greater mechanistic understanding of how the KD—and adenosine in particular—works to dampen aberrant excitation in the brain, novel insights and molecular targets are bound to emerge. However, given the complexity of metabolic pathways in both normal and disease states, it will be important to determine specific cause-and-effect relationships. At present, given growing interest in metabolic dysfunction as a major pathophysiological substrate for a multiplicity of disease states, as well as urgent

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concerns regarding unbridled healthcare costs worldwide, we predict that research in the area of "translational metabolism" will gain further momentum. Here we highlight current research on mechanism(s) of KD action, with a focus on adenosine, and promote the concept that the KD is both an accessible and affordable therapy by describing an international case study of recent KD training and initial outcomes in the Republic of Georgia.

27.1 Introduction: Ketogenic Diet as a Metabolic Therapy

The ketogenic diet (KD) enjoys a long-standing track record as an effective treatment for epilepsy (Freeman et al. 1998, 2006, 2009; Vining et al. 1998; Neal et al. 2008, 2009). Historically, the observation that fasting, or a "water diet," could reduce seizure activity spurred the quest for a metabolism-based therapy that could mimic the biochemical and therapeutic effects of fasting, yet retain adequate caloric and nutritional intake (Wheless 2008). Accordingly, a KD was developed more than 90 years ago to treat seizures, and it has remained on the treatment landscape ever since. Its high-fat low-carbohydrate formulation restricts the amount of glucose available to generate adenosine triphosphate (ATP) through glycolysis; this fundamental metabolic shift favors fatty acid oxidation that then generates ketones as the predominant bioenergetic substrate (Bough and Rho 2007). Despite an early and broad understanding of the major biochemical changes induced by the KD, the critical mechanisms responsible for its anticonvulsant effects have been difficult to identify (Vamecq et al. 2005; Bough and Rho 2007; Maalouf et al. 2009; Masino and Rho 2012).

Notwithstanding the lack of mechanistic information, the KD has experienced periods of waxing and waning enthusiasm by clinicians and awareness by the public at large (Wheless 2008). Shortly after its initial implementation the KD fell out of favor, due primarily to the advent of newer antiepileptic drugs (AEDs) such as phenytoin which were easier to administer and were regarded as being equally efficacious (Wheless 2008). This pharmacological bias remained for many decades, despite the fact that a significant fraction of patients with epilepsy typically fail to respond to AEDs—with either traditional or newer agents (Mattson et al. 1985; Kwan and Brodie 2000). While not yet proven, there is a clinical impression that the KD may be more effective than drugs, especially since there can be impressive response rates in patients with medically-refractory epilepsy (Freeman et al. 2006; Kossoff and Rho 2009).

Numerous clinical reports note 50 % responder rates in at least half the children administered the KD, and approximately one-third achieve more than a 90 % reduction in their seizures, with 7–10 % becoming seizure free (Kossoff and Rho 2009; Payne et al. 2011). In further support of the KD's efficacy in the most challenging of cases, there is growing evidence that the KD treats refractory status epilepticus (Nabbout et al. 2010; Nam et al. 2011)—a devastating condition of unrelenting seizure activity that can ensue for days and weeks. While used most

Table 27.1 Comparison of energy distribution and fat:nonfat ratios of therapeutic ketogenic diets (KD), a modified (Mod) Atkins diet, and a regular diet

Energy distribution	Classic KD		Liberal KD		Mod Atkins	Regular[a]
Ratio (fat:nonfat)	4:1	3:1	2:1	1:1	1:1	0.2:1
Fat: kilocalories	90 %	87 %	80 %	70 %	64 %	30 %
Protein: kilocalories	10 %	13 %	20 %	30 %	30 %	15–25 %
Carbohydrate: kilocalories					6 %	45–55 %

[a] Dietary guidelines for Americans; US Department of Health & Human Services, 2011

often in children, the KD and related dietary formulations are also effective in adolescents and adults (Payne et al. 2011). A recent case report describes how initiation with a KD, and maintenance with a modified Atkins diet, was able to control medically and surgically refractory epilepsy in an adult in a neurocritical care unit (Cervenka et al. 2011).

Against this historically rich backdrop, there is a current resurgence in consideration of metabolism-based treatments. In addition to the traditional KD and its well-known medium-chain triglyceride (MCT) variation, there are also low-carbohydrate diets for weight loss (such as the Atkins and South Beach/low-glycemic index treatments) which have become increasingly popular as these related approaches are associated with more liberal and palatable foodstuffs (Kossoff et al. 2006; Muzykewicz et al. 2009). Importantly, the KD is now considered a truly international treatment for epilepsy, even in underdeveloped countries (Kossoff and McGrogan 2005; Kossoff et al. 2011).

Table 27.1 outlines the energy composition of several diets of varying stringencies—including a classic KD and a modified Atkins diet as compared to a "standard" diet. A KD is customized to the individual, and takes into account his or her energy and protein requirements prior to determining the carbohydrate and fat content of his or her diet (hence the ratio, defined by weight as fats to carbohydrate plus protein). For example, to provide sufficient protein for an inactive adult, a 1:1 ratio may be prescribed. To achieve the very high fat content of a KD, typical meals include a small serving of meat, fish, or protein and a small serving of vegetables. Butter, mayonnaise, vegetable or coconut oil, and heavy cream are incorporated based on preferences and in amounts required to satisfy the ratio of fat:(protein + carbohydrate) (Table 27.1).

In many ways, the tremendous growth of KD centers worldwide, and scientific attention to this non-pharmacological treatment, would not have been possible without the sustained efforts of the Charlie Foundation to Cure Pediatric Epilepsy (http://www.charliefoundation.org; Santa Monica, California, USA), created by Jim and Nancy Abrahams, which brought substantial media attention to the benefits of the KD for epilepsy. For example, a 1997 made-for-television movie—"*First Do No Harm,*" starring Meryl Streep, documented the KD's "miraculous" effects on a young boy with catastrophic epilepsy which was unresponsive to numerous AEDs. Over the past decade and a half, the Charlie Foundation has been an invaluable resource for parents, patients, and professionals worldwide—and has been the

driving force for both clinical and scientific activity surrounding the KD. More recently, the organization Matthew's Friends (http://www.matthewsfriends.org), spearheaded by Emma Williams and based in the United Kingdom, has quickly evolved to represent another major international resource and a voice for advocacy and education. Perhaps the greatest testament to the remarkable scientific growth of the KD is the fact that compared to the 15 years prior to its renaissance in the mid 1990s, there has been a tenfold increase in citations indexed on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) over the subsequent 15 years. Part of this phenomenal growth is likely due to expanding interest in metabolism and its dysfunction relative to chronic diseases (WHO Special Issue 2004; Uauy et al. 2008).

27.2 Mechanisms Mobilized by Ketogenic Diet Therapy

Ultimately, to produce anticonvulsant effects, the KD must reduce neuronal activity and/or excitability. Accordingly, there has been intense interest in a detailed understanding of how the metabolic effects of a KD translate into reduced excitation and/or a hyperpolarized membrane potential, altered neurotransmitter release or receptor affinities, or myriad other mechanisms that would result in fewer seizures (Vamecq et al. 2005; Bough and Rho 2007; Masino and Rho 2012).

One cardinal feature is the profound metabolic shift induced by the KD. As noted earlier, the KD is high in fat and low in carbohydrates. The enhanced fatty acid oxidation and restricted carbohydrate content switch metabolism from the preferred ATP-generating pathway—i.e., glycolysis—to intermediary metabolism that results in increased production of ketone bodies, decreased glucose, and increased levels of circulating fatty acids (Kim do and Rho 2008). Proximal metabolic changes are shown in Fig. 27.1 and have been described in more detail elsewhere (Kim do and Rho 2008).

Regarding the collective mechanisms proposed as relevant or critical to KD therapy, there are a number of excellent reviews and the reader is referred to these sources for more comprehensive coverage (Bough and Rho 2007; Gasior et al. 2006; Kim do and Rho 2008; Maalouf et al. 2009; Rho and Stafstrom 2011; Masino and Rho 2012). As an overview, these postulated mechanisms include (1) acute and chronic biochemical changes observed with KD administration in vivo (e.g., increased ketone production, decreased serum glucose levels, a reduction in the generation of reactive oxygen species (ROS), increased fatty acid levels (perhaps importantly, polyunsaturated fatty acids [PUFAs] which possess membrane-stabilizing properties), increased bioenergetic reserves (consisting of increased levels of ATP and ADP), and a reduction in levels of adenosine kinase, the major adenosine-metabolizing enzyme) and (2) cellular mechanisms with potentially direct effects on neuronal excitability such as opening of ATP-sensitive potassium (K_{ATP}) channels that cause membrane hyperpolarization (Ma et al. 2007; Kawamura et al. 2010) and acetoacetate-mediated presynaptic release of excitatory neurotransmitters via an

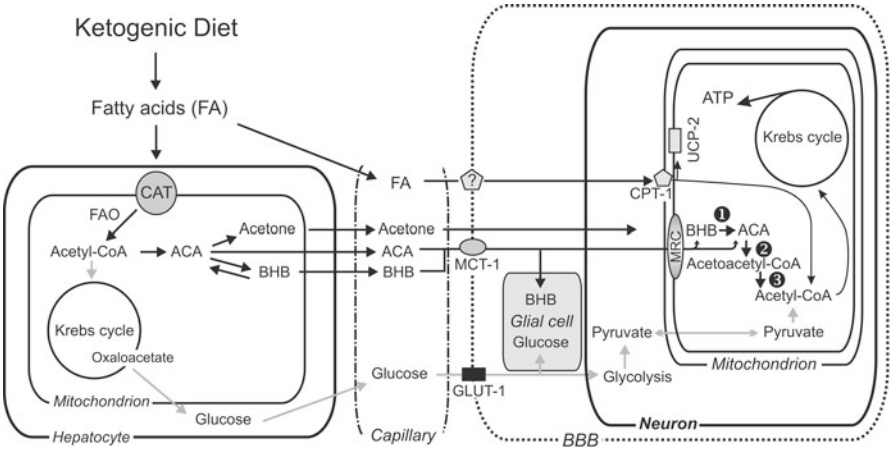

Fig. 27.1 Metabolic pathways involved in ketogenic diet (KD) treatment. In the liver (hepatocyte, *left*), fatty acids are ordinarily converted into acetyl-CoA which enters the tricarboxylic acid (TCA) cycle. When fatty acid levels exceed the metabolic capacity of the TCA cycle, acetyl-CoA is shunted to ketogenesis. Two acetyl-CoAs can combine through a thiolase enzyme to produce acetoacetyl-CoA, which is a precursor for the synthesis of acetoacetate (ACA) and β-hydroxybutyrate (BHB). Acetone, the other major ketone body, is produced primarily from spontaneous decarboxylation of ACA. These ketones are transported from the vascular lumen (capillary, *middle*) to the brain interstitial space, and to both glia and neurons. Within neurons (*right*), both ACA and BHB are transported directly into mitochondria, and ultimately converted to acetyl-CoA (through several enzymatic steps) which then enters the TCA cycle. Abbreviations: *CAT* carnitine-acylcarnitine translocase, *FAO* fatty acid oxidation, *ACA* acetoacetate, *BHB* β-hydroxybutyrate, *MCT-1* monocarboxylate transporter-1, *GLUT-1* glucose transporter-1, *BBB* blood–brain barrier, *CPT-1* carnitine palmitoyl transferase-1, *UCP* uncoupling protein, *ATP* adenosine triphosphate, (1) 3-hydroxybutyrate dehydrogenase, (2) succinyl-CoA:(CoA:3)3-oxoacid CoA transferase, (3) mitochondrial acetoacetyl-CoA thiolase. *MRC* mitochondrial respiratory complex. Reprinted with permission from Kim do Y, Rho JM, The ketogenic diet and epilepsy. Curr Opin Clin Nutr Metab Care 2008;11(2):113–120

interaction with vesicular glutamate transporters (VGLUTs) (Juge et al. 2010). A schematic summarizing these mechanisms is shown in Fig. 27.2, and mechanisms related to adenosine are discussed in more detail below.

27.3 Ketogenic Diet and Adenosine

Against this pleiotropic backdrop, and the many parallel and potentially synergistic pathways toward a reduction in membrane hyperexcitability, the question arises as to where adenosine fits in. Adenosine is in a unique position to translate KD-induced changes in metabolism into altered neuronal activity, and may be a critical mechanism for mediating the protective effects of the KD in epilepsy (and perhaps other neurological disorders). Similar to the KD, adenosine has been shown to be

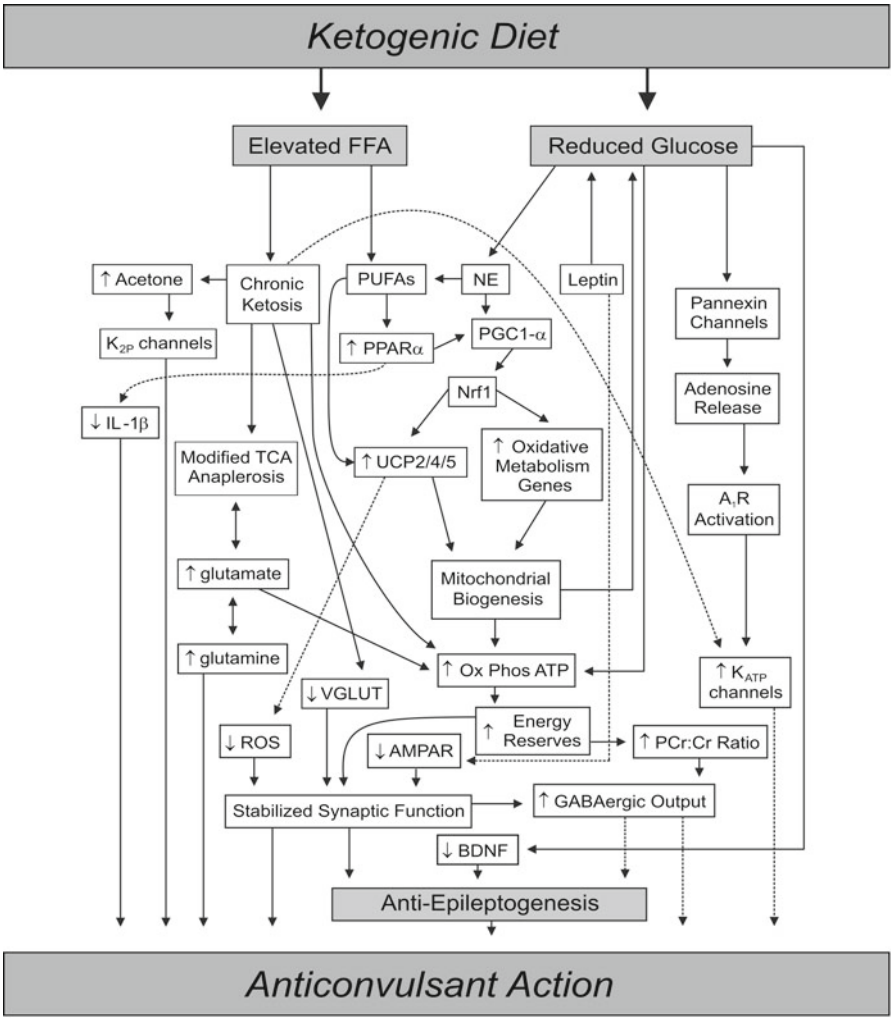

Fig. 27.2 Hypothetical pathways leading to the anticonvulsant effects of the ketogenic diet (KD). A KD elevates free fatty acids (FFAs) and reduces glucose (*top*), and each of these consequences mobilizes a host of mechanisms which could lead to anticonvulsant actions (*bottom*). Mechanisms related to adenosine are shown on the *right*. Elevated FFAs lead to chronic ketosis and increased concentrations of polyunsaturated fatty acids (PUFAs) in the brain. Chronic ketosis is anticipated to lead to increased levels of acetone; this might activate K_{2P} channels to hyperpolarize neurons and limit neuronal excitability. Chronic ketosis is also anticipated to modify the tricarboxylic acid (TCA) cycle, as would the presence of anaplerotic substrates such as triheptanoin. This would increase glutamate and, subsequently, GABA (γ-aminobutyric acid) synthesis in brain. Among several direct inhibitory actions, PUFAs boost the activity of brain-specific uncoupling proteins (UCPs). This is expected to limit reactive oxygen species (ROS) generation, neuronal dysfunction, and resultant neurodegeneration. Acting via the nuclear transcription factor peroxisome proliferator-activated receptor-α (PPARα) and its co-activator peroxisome proliferator-activated receptor γ co-activator-1 (PGC-1α), PUFAs would induce the expression of UCPs and coordinately up-regulate several dozen genes related to oxidative energy metabolism. PPARα expression is inversely correlated

effective in controlling seizures (likely via actions at the adenosine A_1 receptor (A_1R) subtype) (Dunwiddie 1999; Boison et al. 2011). However, systemic side effects, rapid metabolism and promiscuity with other adenosine receptor subtypes, and signaling mechanisms have hampered efforts over the past two decades to develop adenosine-based therapies for epilepsy. This scenario—in part fueled by linking adenosine to the KD—is now changing, and there is growing interest in reevaluating purinergic neurotransmission in epilepsy (Boison 2008; Masino and Geiger 2008; Masino et al. 2011a, b).

With respect to the relationship between metabolic changes and adenosine, diverse lines of evidence suggest that both the KD and ketones enhance brain energy metabolism. De Vivo and colleagues (1978) were the first to demonstrate that a KD increased ATP levels (and indeed all major measures of cellular bioenergetic reserves), and subsequent studies have generally confirmed these observations (Nakazawa et al. 1983; Bough et al. 2006; Nylen et al. 2009; Kim do et al. 2010).

In addition to increased levels of bioenergetic substrates, investigators have also shown that the KD increases mitochondrial numbers and profiles (Bough et al. 2006; Nylen et al. 2009), and preferentially up-regulates genes involved in

Fig. 27.2 (continued) with interleukin-1β (IL-1β) cytokine expression; given the role of IL-1β in hyperexcitability and seizure generation, diminished expression of IL-1β cytokines during KD treatment could lead to improved seizure control. Ultimately, PUFAs would stimulate mitochondrial biogenesis. Mitochondrial biogenesis is predicted to increase adenosine triphosphate (ATP) production capacity and enhance energy reserves, leading to stabilized synaptic function and improved seizure control. In particular, an elevated phosphocreatine:creatine (PCr:Cr) energy-reserve ratio is predicted to enhance GABAergic output, perhaps in conjunction with the ketosis-induced elevated GABA production, leading to diminished hyperexcitability. Reduced glucose coupled with elevated free fatty acids is proposed to reduce glycolytic flux during KD, which would further be feedback inhibited by high concentrations of citrate and ATP produced during KD treatment. This would activate metabolic ATP-sensitive potassium (K_{ATP}) channels. Ketones may also directly activate K_{ATP} channels. Reduced glucose alone, under conditions of adequate or enhanced energy levels, activates pannexins on CA3 pyramidal neurons, releasing ATP into the extracellular space; ATP is converted via ectonucleotidases to adenosine which subsequently activates adenosine receptors (A_1R). A_1R activation is also coupled to K_{ATP} channels. Ultimately, opening of K_{ATP} channels would hyperpolarize neurons and diminish neuronal excitability to contribute to the anticonvulsant (and perhaps neuroprotective actions of the KD). Increased leptin, seen with KD treatment, can reduce glucose levels and inhibit α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated synaptic excitation. Reduced glucose is also expected to down-regulate brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB, a tyrosine kinase) signaling in brain. As activation of TrkB pathways by BDNF has been shown to promote hyperexcitability and kindling, these potential KD-induced effects would be expected to limit the symptom (seizures) as well as epileptogenesis. Boxed variables depict findings described from KD studies; *up* or *down arrows* indicate the direction of the relationship between variables as a result of KD treatment. *Dashed lines* are used to clarify linkages and are not meant to suggest either magnitude or relative importance compared to *solid lines*. Published previously as Fig: 78-4, p. 1015 from 'Mechanisms of Ketogenic Diet Action' by Susan A. Masino and Jong M. Rho in "Jaspers Basic: Mechanisms of the Epilepsies, 4E" edited by Noebels, J, Avoli M, Rogawski MA, Olsen RW, and Delgado-Escueta AV (2012). By permission of Oxford University Press, Inc

mitochondrial metabolism (Noh et al. 2004; Bough et al. 2006). Typically, such effects have been observed after maintenance on a KD for 2–4 weeks, but in published reports to date, a detailed time course for these effects has not been established. The biochemical, ultrastructural, and gene profiling from microarray expression studies all comport with animal research and clinical observations to indicate that in most cases, the anticonvulsant effects of the KD may take two or more weeks to develop (Freeman et al. 2006; Bough and Rho 2007; Kossoff and Rho 2009).

The compelling evidence that the KD increases ATP levels places the mechanistic spotlight squarely on adenosine. ATP is dephosphorylated rapidly to adenosine (via action of ectonucleotidases), and any increase in extracellular ATP will ultimately result in greater activation of adenosine receptors (Dunwiddie et al. 1997; Cunha et al. 1998; Dunwiddie 1999; Masino et al. 2002). There is direct evidence that the adenosine produced via dephosphorylation of ATP acts on inhibitory A_1Rs, which would lead to an anticonvulsant effect (Dunwiddie et al. 1997; Cunha et al. 1998; Masino et al. 2002). This fundamental link between metabolism and neuronal activity is discussed in an expanded fashion in an initial review postulating the potential mechanistic role of adenosine in KD therapy (Masino and Geiger 2008).

27.4 Evidence Linking the Ketogenic Diet to Adenosine

Two primary lines of evidence have bolstered support for adenosine's role in mediating the anticonvulsant effects of the KD. These include (1) an in vitro model of the KD—in particular, mirroring two essential features, namely, reduced glucose and normal or elevated ATP levels (Kawamura et al. 2010); and (2) assessment of electrographic seizure activity in cohorts of transgenic mice exhibiting spontaneous seizures, with and without KD treatment (Masino et al. 2011a, b). While these complementary studies have begun to address basic mechanisms of KD action, there are many questions that remain unanswered.

Kawamura and colleagues employed cellular electrophysiological techniques to address the question of whether a reduction in glucose (along with adequate or increased ATP levels) would result in membrane hyperpolarization, a *sine qua non* of anticonvulsant activity (Kawamura et al. 2010). This study was designed with the assumption that clinically, seizure control relates weakly to blood ketone levels, but perhaps more consistently with blood glucose (Freeman et al. 2006). Certainly, earlier studies have supported the concept that calorie restriction (with or without KD treatment) exerts anticonvulsant (and potentially anti-epileptogenic) effects (Todorova et al. 2000; Greene et al. 2001), and that reduced glucose may be more important than increased ketosis (Greene et al. 2003), but perhaps not in brain extracellular fluid (Samala et al. 2011). In animal models, the relationship between blood glucose levels and seizure frequency is not consistent (Mantis et al. 2004; Hartman et al. 2010), but the underlying idea behind reduced glucose is that cellular energy is compromised and as such, neurons are simply unable to reach high levels of repetitive firing required to sustain seizure activity. This concept, however, is in striking contrast

Table 27.2 Predicted and observed effects of the ketogenic diet in mice with adenosine-based electrographic seizures

Mouse model	A_1R expression	Predicted change in seizure frequency	Observed change in seizure frequency	Glucose-induced change in seizure frequency
Wild type: (C57BL/6)	Unaltered	N/A (no seizures)	N/A	No change
Transgenic: *Adk-tg*	Unaltered	Robust suppression	88 % decrease ($p<0.001$)	Reversed to 85 % of baseline ($p<0.001$)
Transgenic: $A_1R^{+/-}$	50 % normal	Partial suppression	53 % decrease ($p<0.001$)	Reversed to 89 % of baseline ($p<0.001$)
Transgenic: $A_1R^{-/-}$	No receptors	No suppression	4 % decrease (N.S.)	No change (N.S.)

Abbreviations: *Adk-tg* adenosine kinase overexpressing transgenic mice, $A_1R^{+/-}$ adenosine receptor subtype 1 heterozygous mutant, $A_1R^{-/-}$ adenosine receptor subtype 1 homozygous (null) mutant, *N.S.* not significant. From Masino et al. (2011b)

to several lines of evidence demonstrating increased, not decreased, bioenergetics (DeVivo et al. 1978; Bough et al. 2006; Nylen et al. 2009; Kim do et al. 2010).

The combination of increased intracellular ATP and decreased extracellular glucose revealed a novel adenosine-mediated autocrine mechanism in hippocampal CA3 neurons (Kawamura et al. 2010). The CA3 subfield of the hippocampus was chosen because it is a highly seizure-prone area. In short, Kawamura and colleagues found that ATP—released directly into the extracellular space through pannexin-1 channels and dephosphorylated to adenosine—led to activation of A_1Rs, which under these conditions hyperpolarized the membrane potential via coupling to the opening of K_{ATP} channels (Kawamura et al. 2010). This autocrine inhibition in CA3 did not require any direct exposure to ketones; rather, a combination of reduced glucose and sufficient or increased ATP was all that appeared necessary for this effect.

The second major line of evidence invoking adenosine in KD action emerged from experiments involving transgenic mice exhibiting spontaneous electrographic seizures due to deficient adenosine signaling (Masino et al. 2011a, b). After feeding a KD for 3–4 weeks, Masino and colleagues found that the diet reduced seizures by 90 % in mice overexpressing adenosine kinase (and hence deficient in extracellular adenosine) but with intact A_1Rs. In contrast, a KD was only partially effective in reducing electrographic seizures in mice with a partial complement of A_1Rs and was completely ineffective in mice lacking A_1Rs altogether (see Table 27.2). Similar to clinical reports, where anticonvulsant effects reverse rapidly with glucose infusion (Huttenlocher 1976), a systemic injection of glucose restored seizures in mice that experienced a KD-induced reduction in seizures. Further supporting the role of adenosine in KD action, adenosine kinase was down-regulated in normal mouse brain after 3–4 weeks of KD feeding, and levels of this enzyme were increased in tissue obtained from human patients with epilepsy, consistent with a deficiency in adenosine signaling (Masino et al. 2011a, b). Taken together, these data indicate that the anticonvulsant effects of the KD may be in part due to increased adenosine acting at inhibitory A_1Rs, and perhaps further augmented by deficiencies in adenosine

kinase activity. At present, whether the KD induces changes in A_1R expression or affinity, or alters other aspects of the regulation of adenosine, is unknown. It is clear, however, that the relationship between the KD and adenosine signaling must be explored in other clinically relevant seizure models. Finally, it would be of great interest to determine whether augmentation of adenosine signaling might influence epileptogenesis, as there are reports suggesting a disease-modifying effect of the KD (Gasior et al. 2006; Maalouf et al. 2009; Stafstrom and Rho 2012).

27.5 Current Recommendations and Emerging Applications of Ketogenic Diet Therapy

The KD demonstrates an overall success rate equivalent to or perhaps superior to available AEDs (Kossoff and Rho 2009). However, with the exception of a few tertiary epilepsy centers (and a select few epileptic conditions), the KD has been relegated to the status of therapeutic last resort. It is becoming increasingly clear that this practice should be reevaluated (Nordli 2009). The most recent and comprehensive set of recommendations for implementation of the KD was published in 2009 as an international consensus statement commissioned by the Charlie Foundation (Kossoff et al. 2009b). This document addresses the following clinical management considerations: patient selection, pretreatment counseling and evaluation, specific dietary therapy selection (indications and contraindications), short-term and long-term implementation, supplementation with vitamins and minerals, follow-up visits and management, adverse event monitoring, concomitant use of AEDs, and eventual KD discontinuation. The consensus recommendations were made on the basis of best available evidence, considered areas of agreement and controversy, and touched upon unanswered questions and future research opportunities.

Based on anecdotal clinical observations wherein patients maintain a seizure-free state even after discontinuation of the KD (Hemingway et al. 2001; Marsh et al. 2006; Freeman et al. 2006), and a rapidly expanding experimental literature attesting to the neuroprotective effects of such high-fat, low-carbohydrate diets (both in vivo and in vitro) (Gasior et al. 2006), the notion that the KD may be effective for other neurological disorders arose—particularly those conditions associated with neurodegeneration (Maalouf et al. 2009; Stafstrom and Rho 2012). To date, dietary and metabolic therapies have been attempted in either experimental models or patients for the following conditions other than epilepsy: headache, neurotrauma, Alzheimer disease, Parkinson disease, sleep disorders, brain cancer, autism, and pain (Stafstrom and Rho 2012). The general impetus for using various diets to treat—or at least ameliorate symptoms of—these disorders stems from both a lack of effectiveness of pharmacological therapies and the intrinsic appeal of implementing a more "natural" treatment.

Whether adenosine is critically involved in the neuroprotective effects of the KD against any or all of these conditions remains to be determined. Certainly, there is existing evidence that adenosine acting at A_1Rs can produce neuroprotective actions

(Dunwiddie and Masino 2001; Masino and Geiger 2008; Tozaki-Saitoh et al. 2011; Gomes et al. 2011). Additionally, chronic adenosine exposure may lead to diverse epigenetic effects on DNA/RNA methylation (Skinner et al. 1986; Boison et al. 2002; Boison 2011). Adenosine and homocysteine are formed from S-adenosylhomocysteine, which is produced from S-adenosylmethionine via the action of methyltransferases. Thus, altered adenosine would influence the S-adenosylmethionine cycle. Adenosine's role in methylation reactions has long been recognized (Henderson 1979), and dysregulated adenosine metabolism (putatively increased due to a genetic loss of adenosine kinase) has been shown to inhibit DNA transmethylation. Specifically, a lack of adenosine kinase resulted in decreased adenine nucleotides and increased S-adenosylhomocysteine (a potent inhibitor of transmethylation reactions) in the liver (Boison et al. 2002). Yet these aspects of adenosine metabolism and regulation have not been the focus of adenosine-based therapeutics in recent decades—the goals of drug discovery have been primarily to influence adenosine receptor signaling. It may be time to revisit the potential biochemical and epigenetic roles of adenosine in determining cellular homeostasis and dysfunction in health and disease, respectively (Boison et al. 2011). Clearly epigenetic changes have enormous potential for disease-modifying effects, and further studies are necessary to clarify the long-term consequences of both the KD and adenosine on epigenetic nucleic acid modifications.

27.6 Use of the Ketogenic Diet in a Developing Country

Although the KD originated in the 1920s in the United States, variations on this metabolism-based therapy have been established in numerous academic and non-academic centers in over three dozen countries worldwide (Kossoff and McGrogan 2005; Kossoff et al. 2011), and there are anecdotal reports of several centers exploring uses of the KD outside of epilepsy, including brain cancer (A. Evangeliou, personal communication; T. Seyfried, personal communication). One of the authors (B.Z.-K.) has provided hands-on training to clinical staff at dozens of regional and international medical centers. In developing countries, these training workshops have been sponsored by The Charlie Foundation and/or provided free of charge in exchange for travel and accommodations. Because of the necessary coordination among neurologists, dietitians, and hospital staff, preparation for such visits often takes an entire year or more. KD meals are planned using local food supplies and sources, cultural preferences, and practices.

Box 27.1 highlights KD training and outcomes in the Republic of Georgia, a former member of the Soviet Union. The Republic of Georgia suffered from economic crisis and civil unrest since the collapse of the Soviet Union, and the healthcare system which had provided complete services for all citizens dissolved under the new democracy and is still struggling to recover. Healthcare is no longer free, with serious implications for patient care. Whereas in the United States prior laboratory studies rule out disorders in fatty acid metabolism and evaluate blood chemistries,

Box 27.1 Recent Training and Initial Outcomes: Republic of Georgia

In 2006, based on his work with pediatric epilepsy, Dr. Gia Milekshevelli, a neurologist working in the capital city Tbilisi, Republic of Georgia, received the Bernard D'Sousa International Fellowship Award. Dr. Milekshevelli's award included an all-expense, 2-week training at the Children's Hospital at Scottish Rite in Atlanta, Georgia (USA). Dr. Milekshevelli learned about the treatments available in the United States for pediatric epilepsy which included medication therapy, surgery, and the ketogenic diet. With limited access to antiseizure medications in Republic of Georgia, he knew dietary treatment was a feasible alternative.

With support from the Charlie Foundation, KD training was arranged in 2007. Dr. Milekshevelli's daughter, a medical student, served as an interpreter for two neurologists and pharmacist during the training and diet initiation in several patients by the author (B.Z.-K.). Families brought everything needed to the hospital to start the diet over 3 days, including food, dishes, utensils, soap, bedding, towels, etc., as well as ice and coolers to store their food.

One adult and two pediatric patients diagnosed with medication-resistant epilepsy of unknown etiology were identified as candidates for the KD (no EEG equipment was available to assist with further classification). All had severe developmental and cognitive delays. None had received special education and physical or speech therapy, nor did they have assistive devices such as special feeding utensils or wheelchairs. Their constant care was provided by their families. A KD was calculated for each patient and translated into Georgian for the family. The pharmacist reviewed and minimized the carbohydrate content of each patient's medications; she also provided the vitamin and mineral supplements.

A 4:1 KD ratio (90 % fat) was used for the children and a 1:1 ratio (70 % fat) was used for the adult. A rapid initiation method involved one ketogenic meal the first day, two the second day, and three the third day. Between meals each received a ketogenic beverage to provide the goal of calories for each patient. Within 3 days, all of the patients were producing strong urine ketones. The families ensured that every bit of food and drop of beverage was consumed, and worked together to prepare meals and share food and ideas to make the diet palatable for their children.

Case 1: Patient MR was 20 months of age. Her seizures started at 2 months of age and were described as "polymorphic" (characterized by two or more seizure types). She was trialed on an antiseizure medication that cost her family an entire month's salary. Her seizures did not improve, and the family discontinued it after 2 months. At the first meeting she lay flaccid in her mother's

(continued)

Box 27.1 (continued)

arms for the entire hour. Because she had such poor head control, she was spoon-fed thickened ketogenic drinks between meals. She was very weak and feeding her took hours each day.

Three weeks after starting the diet she was holding her head erect on her own and her mother reported that she was cooing for the first time. Her seizures declined dramatically over the next several months and she eventually became seizure free. She has been off of the diet for over a year and now, 4 years later, she remains seizure and medication free.

Case 2: Patient SK was 3 years old. He had generalized tonic-clonic seizures, had been trialed on all seven medications available at the time in Republic of Georgia, and was diagnosed with medication-resistant epilepsy. He appeared to be at an infant level physically and cognitively. He could sit by himself if positioned appropriately, but could not crawl or pull himself up.
SK had many seizures during the hospitalization for diet initiation. He had a history of constipation and, unfortunately, the KD did not help—constipation is a common side effect. He remained on the diet for 3 months.

Case 3: Patient AH was a 34-year-old lean, physically fit man. He had generalized seizures, and was diagnosed with medication-resistant epilepsy. He had the cognitive function of a child and could only speak in brief phrases.
AH had a prolonged seizure during the second day of diet initiation. However, he recovered without rescue medication. Over the 4 days of diet initiation his language skills improved markedly and he began speaking in full sentences. He remained on this very liberal KD for a year. Although he continued to have generalized tonic-clonic seizure every few months, his family was satisfied with the improvement in cognition, especially his verbal skills. When the medication Keppra became available in Georgia, he was started on this and discontinued the diet.

To date, Dr. Milekshevelli remains in contact with the author (B.Z-K.) and has placed a total of 12 patients on the diet: seven (58 %) have experienced significant improvement in seizure control, including three (25 %) who are seizure free. Although a small cohort, these statistics are impressive. Dr. Milekshevelli continues to advance his treatment of people with epilepsy, and has invited experts from Europe to visit him and review and offer advice on his most challenging patients. In 2009 he received certification in analyzing EEG data and he now has an EEG machine. Most recently, Dr. Milekshevelli trained his colleague, a neurologist in Bulgaria, on KD therapy and continues to mentor him.

(continued)

Box 27.1 (continued)

Ketogenic diet team members in the Republic of Georgia: Left to right; three mothers, author (B-.Z.K.), and Dr. Gia Milekshevelli

One of the mothers in the Republic of Georgia preparing her child's diet

these tests may be unavailable or unreliable in some countries; close monitoring with in-patient diet initiation is recommended under these circumstances.

Results in multiple countries have replicated published efficacy with pharmacoresistant epilepsy as well as success when drugs are not available or not economically viable. Western diets contain approximately 50 % of energy as carbohydrate. KDs limit carbohydrate-rich foods to less than 10 % of energy, and protein is consumed in moderate amounts—much lower than the typical Western diet. Fat is the KD's main source of energy and the least expensive food group when compared in terms of energy density to carbohydrate (i.e., bread, cereal, grains, and fruit) and protein-rich foods (i.e., meat and cheese). In the Republic of Georgia, success with a small cohort of patients yielded promising results—25 % became seizure free—underscoring that a dietary approach is accessible and affordable in countries with limited resources. In India, picture books and simple measuring devices allow successful application of the KD available to patients who cannot read (J. Nathan, personal communication). The KetoCalculator program (https://www.ketocalculator.com) is written in English and uses the metric system for diet calculations; this tool has been used successfully to help administer the KD in many countries.

27.7 Summary and Conclusions

Even though the KD demonstrates an overall success rate equivalent or potentially superior to available AEDs, aside from a few treatment centers it has been consistently relegated as a therapy of last resort for epilepsy. However, there is growing recognition that the KD should be considered in the treatment algorithm at a much earlier stage, and perhaps for a multiplicity of other neurological disorders (Nordli 2009; Stafstrom and Rho 2012) with specific predictions related to its effects on adenosine (Masino et al. 2009). Certainly, it is now well appreciated that the KD and its variants constitute both an affordable and accessible metabolic therapy. At a scientific level, the positive bioenergetic approach represented by the KD may be a general paradigm for restoring brain homeostasis, and is less likely to produce treatment resistance and significant untoward side effects (Boison et al. 2011). As the KD approaches its 100th anniversary (i.e., 2021), a critical reflection of its fascinating saga and its late maturation as a valid clinical and scientific entity places the KD on an exciting platform for further advances during the next century, especially as the leading metabolism-based treatment for a variety of neurological disorders.

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References

Boison D (2008) The adenosine kinase hypothesis of epileptogenesis. Prog Neurobiol 84(3):249–262

Boison D (2011) Adenosine: a novel regulator of DNA methylation in epilepsy. Presented as part of "The "Methylation Hypothesis:" Does Epigenetic Chromalin Modification Play a Role in Epileptogenesis?", organized by I. Blumcke, American Epilepsy Society 65th annual meeting, 2011, IW.8. Baltimore, MD

Boison D, Scheurer L, Zumsteg V, Rülicke T, Litynski P, Fowler B, Brandner S, Mohler H (2002) Neonatal hepatic steatosis by disruption of the adenosine kinase gene. Proc Natl Acad Sci USA 99(10):6985–6990

Boison D, Masino SA, Geiger JD (2011) Homeostatic bioenergetic network regulation—a novel concept to avoid pharmacoresistance in epilepsy. Expert Opin Drug Discov 6(7):713–724

Bough KJ, Wetherington J, Hassel B, Pare JF, Gawryluk JW, Greene JG, Shaw R, Geiger JD, Dingledine RJ (2006) Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. Ann Neurol 60:223–235

Bough KJ, Rho JM (2007) Anticonvulsant mechanisms of the ketogenic diet. Epilepsia 48(1):43–58

Cervenka MC, Hartman AL, Venkatesan A, Geocadin RG, Kossoff EH (2011) The ketogenic diet for medically and surgically refractory status epilepticus in the neurocritical care unit. Neurocrit Care 15(3):519–524

Cunha RA, Sebastião AM, Ribeiro JA (1998) Inhibition by ATP of hippocampal synaptic transmission requires localized extracellular catabolism by ecto-nucleotidases into adenosine and channeling to adenosine A1 receptors. J Neurosci 18(6):1987–1995

DeVivo DC, Leckie MP, Ferrendelli JS, McDougal DB Jr (1978) Chronic ketosis and cerebral metabolism. Ann Neurol 3(4):331–337

Dunwiddie TV (1999) Adenosine and suppression of seizures. Adv Neurol 79:1001–1010

Dunwiddie TV, Masino SA (2001) The role and regulation of adenosine in the central nervous system. Annu Rev Neurosci 24:31–55

Dunwiddie TV, Diao L, Proctor WR (1997) Adenine nucleotides undergo rapid, quantitative conversion to adenosine in the extracellular space in rat hippocampus. J Neurosci 17(20):7673–7682

Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM (1998) The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics 102(6):1358–1363

Freeman J, Veggiotti P, Lanzi G, Tagliabue A, Perucca E, Institute of Neurology IRCCS C. Mondino Foundation (2006) The ketogenic diet: from molecular mechanisms to clinical effects. Epilepsy Res 68(2):145–180

Freeman JM, Vining EP, Kossoff EH, Pyzik PL, Ye X, Goodman SN (2009) A blinded, crossover study of the efficacy of the ketogenic diet. Epilepsia 50(2):322–325

Gasior M, Rogawski MA, Hartman AL (2006) Neuroprotective and disease-modifying effects of the ketogenic diet. Behav Pharmacol 17(5–6):431–439

Gomes CV, Kaster MP, Tomé AR, Agostinho PM, Cunha RA (2011) Adenosine receptors and brain diseases: neuroprotection and neurodegeneration. Biochim Biophys Acta 1808(5):1380–1399

Greene AE, Todorova MT, McGowan R, Seyfried TN (2001) Caloric restriction inhibits seizure susceptibility in epileptic EL mice by reducing blood glucose. Epilepsia 42(11):1371–1378

Greene AE, Todorova MT, Seyfried TN (2003) Perspectives on the metabolic management of epilepsy through dietary reduction of glucose and elevation of ketone bodies. J Neurochem 86(3):529–537

Hartman AL, Zheng X, Bergbower E, Kennedy M, Hardwick JM (2010) Seizure tests distinguish intermittent fasting from the ketogenic diet. Epilepsia 51(8):1395–1402

Hemingway C, Freeman JM, Pillas DJ, Pyzik PL (2001) The ketogenic diet: a 3- to 6-year follow-up of 150 children enrolled prospectively. Pediatrics 108(4):898–905

Henderson JF (1979) Regulation of adenosine metabolism. In: Baer HP, Drummond GI (eds) Physiological and regulatory function of adenosine and adenine nucletides. Raven, New York, pp 315–322

Huttenlocher PR (1976) Ketonemia and seizures: metabolic and anticonvulsant effects of two ketogenic diets in childhood epilepsy. Pediatr Res 10(5):536–540

Juge N, Gray JA, Omote H, Miyaji T, Inoue T, Hara C, Uneyama H, Edwards RH, Nicoll RA, Moriyama Y (2010) Metabolic control of vesicular glutamate transport and release. Neuron 68(1):99–112

Kawamura M Jr, Ruskin DN, Masino SA (2010) Metabolic autocrine regulation of neurons involves cooperation among pannexin hemichannels, adenosine receptors, and KATP channels. J Neurosci 30(11):3886–3895

Kim do Y, Rho JM (2008) The ketogenic diet and epilepsy. Curr Opin Clin Nutr Metab Care 11(2):113–120

Kim do Y, Vallejo J, Rho JM (2010) Ketones prevent synaptic dysfunction induced by mitochondrial respiratory complex inhibitors. J Neurochem 114(1):130–141

Kossoff EH, McGrogan JR (2005) Worldwide use of the ketogenic diet. Epilepsia 46(2):280–289

Kossoff EH, Rho JM (2009) Ketogenic diets: evidence for short- and long-term efficacy. Neurotherapeutics 6(2):406–414

Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP (2006) A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. Epilepsia 47(2):421–424

Kossoff EH, Zupec-Kania BA, Rho JM (2009a) Ketogenic diets: an update for child neurologists. J Child Neurol 24(8):979–988

Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina-Bergqvist AG, Blackford R, Buchhalter JR, Caraballo RH, Helen Cross J, Dahlin MG, Donner EJ, Klepper J, Jehle RS, Kim HD, Christiana Liu YM, Nation J, Nordli DR Jr, Pfeifer HH, Rho JM, Stafstrom CE, Thiele EA, Turner Z, Wirrell EC, Wheless JW, Veggiotti P, Vining EP, Charlie Foundation, Practice Committee of the Child Neurology Society, Practice Committee of the Child Neurology Society, International Ketogenic Diet Study Group (2009b) Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia 50(2):304–317

Kossoff EH, Caraballo RH, du Toit T, Kim HD, Mackay MT, Nathan JK, Philip SG (2011) Dietary therapies: a worldwide phenomenon. Epilepsy Res [Epub Aug 17]

Kwan P, Brodie MJ (2000) Early identification of refractory epilepsy. N Engl J Med 342(5):314–319

Ma W, Berg J, Yellen G (2007) Ketogenic diet metabolites reduce firing in central neurons by opening K_{ATP} channels. J Neurosci 27(14):3618–3625

Maalouf M, Rho JM, Mattson MP (2009) The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Res Rev 59(2):293–315

Mantis JG, Centeno NA, Todorova MT, McGowan R, Seyfried TN (2004) Management of multifactorial idiopathic epilepsy in EL mice with caloric restriction and the ketogenic diet: role of glucose and ketone bodies. Nutr Metab (Lond) 1(1):11

Marsh EB, Freeman JM, Kossoff EH, Vining EP, Rubenstein JE, Pyzik PL, Hemingway C (2006) The outcome of children with intractable seizures: a 3- to 6-year follow-up of 67 children who remained on the ketogenic diet less than one year. Epilepsia 47(2):425–430

Masino SA, Geiger JD (2008) Are purines mediators of the anticonvulsant/neuroprotective effects of ketogenic diets? Trends Neurosci 31(6):273–278

Masino SA, Rho JM (2012) Mechanisms of ketogenic diet action. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV (eds) Jasper's basic mechanisms of the epilepsies, 4th edn. Oxford University Press, New York, pp 1001–1022

Masino SA, Diao L, Illes P, Zahniser NR, Larson GA, Johansson B, Fredholm BB, Dunwiddie TV (2002) Modulation of hippocampal glutamatergic transmission by ATP is dependent on adenosine A1 receptors. J Pharmacol Exp Ther 303(1):356–363

Masino SA, Kawamura M, Wasser CD, Pomeroy LT, Ruskin DN (2009) Adenosine, ketogenic diet and epilepsy: the emerging therapeutic relationship between metabolism and brain activity. Curr Neuropharmacol 7(3):257–268

Masino SA, Li T, Theofilas P, Sandau US, Ruskin DN, Fredholm BB, Geiger JD, Aronica E, Boison D (2011a) A ketogenic diet suppresses seizures in mice through adenosine A1R receptors. J Clin Invest 121(7):2679–2683

Masino SA, Kawamura M Jr, Ruskin DN, Geiger JD, Boison D (2011b) Purines and neuronal excitability: links to the ketogenic diet. Epilepsy Res [Epub Aug 29]

Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, Williamson PD, Treiman DM, McNamara JO, McCutchen CB et al (1985) Comparison of carbamazepine,

phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl J Med 313(3):145–151
Muzykewicz DA, Lyczkowski DA, Memon N, Conant KD, Pfeifer HH, Thiele EA (2009) Efficacy, safety, and tolerability of the low glycemic index treatment in pediatric epilepsy. Epilepsia 50(5):1118–1126
Nabbout R, Mazzuca M, Hubert P, Peudennier S, Allaire C, Flurin V, Aberastury M, Silva W, Dulac O (2010) Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). Epilepsia 51(10):2033–2037
Nakazawa M, Kodama S, Matsuo T (1983) Effects of ketogenic diet on electroconvulsive threshold and brain contents of adenosine nucleotides. Brain Dev 5(4):375–380
Nam SH, Lee BL, Lee CG, Yu HJ, Joo EY, Lee J, Lee M (2011) The role of ketogenic diet in the treatment of refractory status epilepticus. Epilepsia 52(11):e181–e184
Nathan JK, Purandare AS, Parekh ZB, Manohar HV (2009) Ketogenic diet in Indian children with uncontrolled epilepsy. Indian Pediatr 46(8):669–673
Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross JH (2008) The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 7(6):500–506
Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross JH (2009) A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia 50(5):1109–1117
Noh HS, Lee HP, Kim DW, Kang SS, Cho GJ, Rho JM, Choi WS (2004) A cDNA microarray analysis of gene expression profiles in rat hippocampus following a ketogenic diet. Brain Res Mol Brain Res 129(1–2):80–87
Nordli DR Jr (2009) The ketogenic diet, four score and seven years later. Nat Clin Pract Neurol 5(1):12–13
Nylen K, Velazquez JL, Sayed V, Gibson KM, Burnham WM, Snead OC 3rd (2009) The effects of a ketogenic diet on ATP concentrations and the number of hippocampal mitochondria in Aldh5a1(-/-) mice. Biochim Biophys Acta 1790(3):208–212
Payne NE, Cross JH, Sander JW, Sisodiya SM (2011) The ketogenic and related diets in adolescents and adults—a review. Epilepsia 52(11):1941–1948
Rho JM, Stafstrom CE (2011) The ketogenic diet: what has science taught us? Epilepsy Res [Epub Aug 29]
Samala R, Klein J, Borges K (2011) The ketogenic diet changes metabolite levels in hippocampal extracellular fluid. Neurochem Int 58(1):5–8
Skinner MA, Ho HJ, Chan VL (1986) Inhibition of methylation of DNA and tRNA by adenosine in an adenosine-sensitive mutant of the baby hamster kidney cell line. Arch Biochem Biophys 246(2):725–732
Stafstrom CE, Rho JM (2012) The ketogenic diet as a treatment paradigm for diverse neurological disorders. Front Pharmacol 3:59
Todorova MT, Tandon P, Madore RA, Stafstrom CE, Seyfried TN (2000) The ketogenic diet inhibits epileptogenesis in EL mice: a genetic model for idiopathic epilepsy. Epilepsia 41(8):933–940
Tozaki-Saitoh H, Tsuda M, Inoue K (2011) Role of purinergic receptors in CNS function and neuroprotection. Adv Pharmacol 61:495–528
Uauy R, Kain J, Mericq V, Rojas J, Corvalán C (2008) Nutrition, child growth, and chronic disease prevention. Ann Med 40(1):11–20
Vamecq J, Vallée L, Lesage F, Gressens P, Stables JP (2005) Antiepileptic popular ketogenic diet: emerging twists in an ancient story. Prog Neurobiol 75(1):1–28
Vining EP, Freeman JM, Ballaban-Gil K, Camfield CS, Camfield PR, Holmes GL, Shinnar S, Shuman R, Trevathan E, Wheless JW (1998) A multicenter study of the efficacy of the ketogenic diet. Arch Neurol 55(11):1433–1437
Wheless JW (2008) History of the ketogenic diet. Epilepsia 49(Suppl 8):3–5
World Health Organization (WHO) (2004) Special issue on diet, nutrition and prevention of chronic diseases. Public Health Nutr 7(1A):Suppl 1001