



# Ketogenic Dietary Therapy Controversies for Its Second Century

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## Abstract

As the ketogenic diet approaches 100 years of continuous use, we reflect on its successes and consider new avenues of research for the next century. One controversial question is regarding whether ketogenic dietary therapies could be successful first-line treatments for epilepsy. Second, is it possible to mimic the mechanisms of action of ketogenic dietary therapy with a drug (eg, a tablet formulation)? A third controversy worthy of future study involves its expanded usage in adults with refractory epilepsy and its role in treating women of childbearing age. Finally, as flexible, alternative diets have recently become widely available, is it feasible and safe to have families and patients start ketogenic dietary therapy successfully on their own with limited medical supervision?

## Keywords

ketogenic, diet, fasting, ketosis, epilepsy

## Introduction

It is perhaps the ultimate comeback story in the modern era for the treatment of epilepsy. One hundred years ago, Dr Russell Wilder at the Mayo Clinic in Rochester, Minnesota, theorized that a low-carbohydrate, high-fat diet could mimic the beneficial effects of fasting, which had been recognized as helpful in suppressing seizures for over a decade.<sup>1</sup> He was partially correct—the “ketogenic” diet, as he named it, did reduce seizures, but as recent research has demonstrated, its effects are vastly different from fasting mechanistically.<sup>2,3</sup> For the next 20 to 30 years, the classic ketogenic diet was one of the most popular epilepsy treatments for children and adults with few options other than phenobarbital and bromides available. The period from 1940 to 1980 saw a gradual, steady decline in ketogenic diet use, likely due to a combination of new antiseizure drugs such as phenytoin, carbamazepine, and valproate, but also an abrupt drop-off in published clinical research for unclear reasons. The ketogenic diet was relegated to status as a treatment of last resort, only used for children with the most refractory epilepsy syndromes at a handful of pediatric epilepsy centers.

The comeback started in 1994 with the creation of the Charlie Foundation patient support group ([www.charliefoundation.org](http://www.charliefoundation.org)), which helped fund and stimulate multicenter clinical trials, the first edition of a ketogenic diet guidebook,<sup>4</sup> media attention, and regional new ketogenic diet center trainings. Today, as we near the 100-year anniversary from 1921, ketogenic dietary therapy has returned to the mainstream of epilepsy care. Most pediatric (and gradually more adult) epilepsy centers offer ketogenic dietary therapies, and randomized controlled trials to date have demonstrated efficacy,<sup>5-9</sup> several expert consensus statements have been published to guide care,<sup>10-12</sup> and biannual international ketogenic diet scientific conferences, the seventh of which will be held later this year in Brighton, United Kingdom. Finally, innovative strategies for modifying the classic ketogenic diet have recently emerged such as the medium chain triglyceride oil diet, the modified Atkins diet, and the low glycemic index treatment, to address issues of compliance and ease of initiation.

What does the future hold for the upcoming second century of ketogenic dietary therapy? It has been demonstrated as effective in all ages, with evidence documenting epilepsy





**Table 1.** Seizure Disorders and Epilepsy Syndromes (Listed Alphabetically) in Which Ketogenic Dietary Therapy Has Been Consistently Reported as  $\geq 70\%$  With  $>50\%$  Seizure Reduction.<sup>10</sup>

Angelman syndrome
Complex I mitochondrial disorders
Dravet syndrome
Epilepsy with myoclonic-atic seizures (Doose syndrome)
Glucose transporter protein 1 (Glut-1) deficiency syndrome
Febrile infection-related epilepsy syndrome (FIRES)
Formula-fed (solely) children or infants
Infantile spasms
Ohtahara syndrome
Pyruvate dehydrogenase deficiency
Super-refractory status epilepticus
Tuberous sclerosis complex

etiologies with perhaps ideal use (Table 1),<sup>10</sup> and adverse effects are now being screened for, identified, and even prevented. However, there are still some very important questions that hopefully will be answered by the next generation of researchers in the years to come. In this review, 4 of the more controversial questions are posed to stimulate discussion and identify future research directions in ketogenic dietary therapies.

1. Could ketogenic dietary therapy be used as a first-line treatment?

One of the most common questions currently asked by neurologists as well as patients and their families is “If ketogenic dietary therapy works so well, why do we have to wait until after we try 2 or more antiseizure drugs to use it?” Practically, to justify early use, one would have to be able to identify one of several epilepsy conditions shown to be highly responsive to ketogenic dietary therapy within a few months; however, most of the “indications” for ketogenic dietary therapy (Table 1) take longer time periods to diagnose.<sup>10</sup> Some of these conditions do have limited published evidence for early or first-line ketogenic dietary therapy use, primarily for infantile spasms, epilepsy with myoclonic-atic seizures (Doose syndrome), and glucose transporter type 1 (Glut1) deficiency syndrome.<sup>13-15</sup> Genetic testing, especially for SLC2A1 mutations for Glut1 deficiency, may in the future identify patients responsive to ketogenic dietary therapy earlier than ever before, perhaps even before seizures begin.

What about the vast majority of patients with idiopathic epilepsy or other known causes? Patients with focal epilepsy, idiopathic generalized epilepsies (eg, absence and juvenile myoclonic epilepsy), and even with structural malformations have been reported to benefit from ketogenic dietary therapies.<sup>10</sup> In both adults and children, ketogenic dietary therapy has been used as “monotherapy” replacing antiseizure drugs, but this is not the norm.<sup>16,17</sup> Implementing outpatient, nonfasting ketogenic diet starts or alternative diets (eg, modified Atkins diet, low glycemic index treatment) is an attractive way for these patients and families to start ketogenic dietary therapy

quickly without a hospital admission (and required insurance approval).<sup>10</sup> Immediate, simple initiation removes a possible barrier to first-line use when compared to the relative ease of starting an antiseizure drug in clinic. There is more on this in the final question of this review, but the ketogenic diet community should consider expanding the scope of rigorous and systematic analyses to pave the way for future randomized trials comparing ketogenic dietary therapy to an antiseizure drug for new-onset epilepsies.

2. Can ketogenic dietary therapy ever be replicated in a pill?

The ultimate “holy grail” question for basic scientists investigating the mechanisms of action of ketogenic dietary therapy and for the pharmaceutical industry concerns whether or not researchers could create a tablet (or solution) that replicates the effects of this dietary change.<sup>18</sup> If this were possible, then the lifestyle modification of ketogenic dietary therapy would be no longer necessary. Patients with epilepsy would never have to restrict their foods at home nor face stigma in school or at social occasions. As studies investigate novel uses for ketogenic dietary therapy in conditions other than epilepsy (eg, cancer, autism, dementia, migraine), having a tablet as the intervention versus a dietary change might certainly help with trial enrolment and compliance.

Unfortunately, but perhaps predictably, ketogenic dietary therapy has been shown in the past few decades to have multiple distinct mechanisms of action.<sup>19</sup> As a result, no single compound mimicking all of its effects has been discovered or created. However, several innovative researchers have identified new compounds which do appear to do part of what ketogenic dietary therapy can accomplish. These include triheptanoin,<sup>20</sup> 2-deoxyglucose,<sup>21</sup> decanoate,<sup>10</sup> ketone salts, and esters.<sup>22</sup> Recent studies have also demonstrated that alterations in the gut microbiota that occur during use of ketogenic dietary therapy may also lead to elevated GABA/glutamate levels and improved seizure control in a mouse model.<sup>23</sup>

As these new compounds are developed and tested in clinical trials, will they prove to be substitutes for ketogenic dietary therapy or perhaps more appropriately as supplements for a patient already on this treatment? If a patient on ketogenic dietary therapy is doing well, but not completely seizure-free, would they benefit from the addition of one of these compounds to act synergistically with? Would a patient struggling with diet compliance be more motivated and successful with the addition of one of these therapies? One thing is certain, pharmaceutical companies are currently very interested in ketogenic dietary therapy not as an alternative to their drugs, but as a potential new “metabolic” class of drugs worthy of investigation.

3. What is the role in treating women of childbearing age with ketogenic diet therapies?

One of the fastest growing populations of patients starting ketogenic dietary therapy today are adults with epilepsy. A

PubMed search revealed that 42 peer-reviewed manuscripts have been published on the treatment of epilepsy or status epilepticus in humans, containing “adult(s)” and “ketogenic diet(s)” or “modified Atkins” or “low glycemic index” in the title. Among these, 35 (83%) have been published in the last decade and over half in the last 5 years alone. Studies have demonstrated relatively equivalent efficacy for seizure control between adults and children, which despite no data to the contrary, had been typically dismissed by most neurologists.<sup>9,24</sup> Adults with juvenile myoclonic epilepsy and super-refractory status epilepticus may do particularly well.<sup>25,26</sup> Epilepsy centers worldwide are starting to offer dietary therapy for adults, and an expert consensus guideline is in preparation (personal communication, Dr Mackenzie Cervenka).

Among the adults starting ketogenic dietary therapy, women of childbearing age are of particular interest to the ketogenic diet community, especially recognizing the lack of demonstrated safe antiseizure drugs due to known teratogenicity.<sup>27</sup> To date, there has been only one publication documenting pregnancy outcomes of 2 women on ketogenic dietary therapy.<sup>28</sup> With the growing interest in ketogenic dietary therapy beyond epilepsy (for other neurologic disorders, cancer, obesity, and diabetes specifically),<sup>29</sup> hopefully we will learn more about the potential risks to a fetus as more women are treated, but for now it is not clear. Information from a large multicenter pregnancy registry similar to those designed to track teratogenicity prevalence with antiseizure drugs and/or prospective trial (if approved by an institutional review board) would help tremendously to clarify the risks but will take many years to complete and analyze. Additional information about potential negative effects of ketogenic dietary therapy on bone density and menstrual cycles<sup>30,31</sup> is also of paramount importance to adult women and needs to be further explored.

#### 4. Can ketogenic dietary therapy be started by a patient or family on their own?

Nearly every article, chapter, review, or book written about ketogenic dietary therapy for epilepsy will state in the first paragraph that these therapeutic diets are medical treatments that should never be started without medical supervision. However, with the current surge in ketogenic dietary therapy popularity beyond epilepsy, widespread Internet resources, recipe books, and even computer programs for calculating ketogenic ratios and meal plans, most ketogenic diet centers like ours are seeing a dramatic rise in “self-guided” ketogenic diet therapies.<sup>32</sup> Of course these patients require guidance and advice to keep them medically safe and free of adverse effects. Just as with artisanal cannabidiol products and other nonprescription “alternative” products, side effects do exist. Many of these patients and families express surprise that vitamins and calcium are required and routine laboratory studies are recommended.<sup>10</sup>

However, a number of these self-starting patients have been anecdotally successful in inducing ketosis and also reducing seizures. In fact, the concept behind the modified Atkins diet as a ketogenic dietary treatment began with a mother who read

a paperback Atkins book and started on her own in 2001 and is one of the original published cases.<sup>33,34</sup> A pilot study of an e-mail-based initiation protocol for adults with epilepsy proved surprisingly feasible, although with overall results slightly lower than starting adults in the outpatient clinic setting.<sup>35</sup>

This simplified, patient-initiated approach provides advantages during the expansion of use of ketogenic dietary therapy. Developing countries with limited resources, and at times no dietitian support, could still use alternative diets in this way.<sup>36</sup> A consensus guideline was created specifically for this potential usage.<sup>37</sup> Patients and families might consider a home-based alternative diet as a “test” of feasibility and effectiveness, then choose not to start ketogenic dietary therapy if neither prove to be the case. Although disappointing perhaps, a negative trial might avoid the time and expense of an unnecessary hospital admission or ketogenic clinic visit. The emergence of telemedicine may also allow for a more structured home-based approach. Finally, centers with long waitlists for appointments to start ketogenic dietary therapy may be unconsciously creating a barrier to increased use. Studies challenging the anecdotal claim that ketogenic dietary therapy must be done under direct supervision are warranted, but in the meantime, patients and families who choose to start on their own should be supported and assisted to achieve the best possible outcomes if possible.

## Conclusions

Ketogenic dietary therapies for epilepsy, proposed as a treatment 100 years ago, have reemerged from dormancy in the past several decades and gained worldwide acceptance. Studies have resolved questions regarding efficacy, patient populations with specific seizure disorder and epilepsy syndrome types that would benefit most, overall adverse effect profile and management, and even incorporated flexibility in initiation and maintenance. Many important questions remain to be studied, and this review highlights just four of these controversial issues. Hopefully, further investigation will address these research topics and stimulate further hypotheses to be explored in the next century of use and beyond.

## Declaration of Conflicting Interests

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