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REVIEW ARTICLE

ALSUntangled #63: ketogenic diets

RICHARD BEDLACK¹, PAUL E. BARKHAUS², BENJAMIN BARNES³, MORGAN BEAUCHAMP⁴, TULLIO BERTORINI⁵, MARK B. BROMBERG⁶, GREGORY T. CARTER⁷, VINAY CHAUDRY⁸, MERIT CUDKOWICZ⁹, CE JACKSON¹⁰, GLEB LEVITSKY¹¹, ISAAC LUND¹², CHRISTOPHER MCDERMOTT¹³ , STEVEN NOVELLA¹⁴, NATASHA OLBY¹⁵, LYLE OSTROW¹⁶, GARY L. PATTEE¹⁷, TERRY HEIMAN-PATTERSON¹⁸, DYLAN RATNER¹⁹, KRISTIANA SALMON²⁰, SUSAN STEVES²¹, MARK TERRELONGE²², PAUL WICKS²³  & ANNE-MARIE WILLS⁹

¹Neurology Department, Duke University, Durham, NC, United States, ²Neurology Department, Froedtert & the Medical College of Wisconsin, Kenosha, WI, United States, ³Neurology Department, Augusta University Medical College of Georgia, Augusta, GA, United States, ⁴North Carolina State University, Raleigh, NC, United States, ⁵Neurology Department, The University of Tennessee Health Science Center VolShop Memphis, Memphis, TN, United States, ⁶Neurology Department, University of Utah Health Hospitals and Clinics, Salt Lake City, UT, United States, ⁷St Lukes Rehabilitation Hospital, Physical Medicine and Rehabilitation, Chesterfield, MO, United States, ⁸Neurology Department, University of North Carolina School of Medicine Neuroscience Center, Chapel Hill, NC, United States, ⁹Neurology Department, Mass General Brigham Inc., Boston, MA, United States, ¹⁰Neurology Department, The University of Texas Health Science Center at San Antonio – Greehey Academic and Research Campus, San Antonio, TX, United States, ¹¹Real Health Clinic, Russian Federation, ¹²Green Hope High School, Cary, NC, United States, ¹³The University of Sheffield Institute for Translational Neuroscience, Sheffield, United Kingdom, ¹⁴Neurology Department, Yale University, New Haven, CT, United States, ¹⁵Neurology Department, North Carolina State University, Raleigh, NC, United States, ¹⁶Neurology Department, Johns Hopkins University, Baltimore, MD, United States, ¹⁷Neurology Department, University of Nebraska Medical Center College of Medicine, Omaha, NE, United States, ¹⁸Neurology Department, Temple University, Philadelphia, PA, United States, ¹⁹Longmeadow High School, Longmeadow, MA, United States, ²⁰Neurology Department, McGill Centre for Research in Neuroscience, Montreal, Canada, ²¹Nutrition Department, Duke University, Durham, NC, United States, ²²Neurology Department, University of California San Francisco, San Francisco, CA, United States ²³Independent, Lichfield, GB

Abstract

ALSUntangled reviews alternative and off label treatments with a goal of helping patients make more informed decisions about them. Here we review ketogenic diets. We shows that these have plausible mechanisms, including augmenting cellular energy balance and reducing excitotoxicity, neuroinflammation and oxidative stress. We review a mouse model study, anecdotal reports and trials in ALS and other diseases. We conclude that there is yet not enough data to recommend ketogenic diets for patients with ALS, especially in light of the many side effects these can have.

Keywords: *Ketone, ketogenic diet, alsuntangled, mitochondria, transgenic animals, therapy*

The ALSUntangled group

ALSUntangled reviews alternative and off-label treatments on behalf of people living with ALS (PALS). Here we review the use of ketogenic diets for which we have had 270 requests (1).

Overview

Ketogenic diets increase the formation of ketone bodies, chemicals that can be used as a source of energy by neurons in the brain (2). In general, ketogenic diets are high in fat, normal in protein,

Table 1. Comparison of ketogenic diets by the percentage of calories (from reference (2)).

	% Fat (LCT)	% Fat (MCT)	% Protein	% Carbohydrates
Classic Ketogenic diet	90	0	8.4	1.6
MCT diet	11	60	10	19
Atkins diet	60	0	35	5
Typical American diet	35	0	15	50

and low in carbohydrates (2). There are at least three different versions (Table 1), defined by the ratios of fat to protein + carbohydrate intake, and by the specific kind of fat (more typical long-chain triglycerides, LCTs, or more ketogenic medium-chain triglycerides, MCTs). Ketogenic diets have been effectively used as a treatment for drug-resistant epilepsy in children since the 1920s (2,3). Over the past two decades, these have been studied in neurodegenerative diseases including ALS (4,5). At least one Internet website currently advertises ketogenic diets as an ALS treatment (6).

Mechanistic plausibility

There are at least four mechanisms by which ketogenic diets could favorably impact ALS progression (reviewed in 7): improving brain energy production, decreasing excitotoxicity, reducing neuroinflammation, and ameliorating oxidative stress. Here we briefly summarize the evidence for these.

Energy production. Impairments in brain energy production and metabolism are believed to play key roles in ALS pathophysiology (4,8). Ketogenic diets and the ketone bodies they generate have been shown to improve markers of brain mitochondrial energy production in multiple animal models of different diseases (4,8–11) including ALS (12). Previous trials targeting mitochondrial dysfunction in people with ALS have failed to show benefits (13,14), but newer agents that accomplish this in different ways are currently in trials (NCT04414345, NCT04098406).

Excitotoxicity. Excitotoxicity from excessive amounts of glutamate has long been implicated in ALS pathophysiology (15,16). Riluzole, a drug that prolongs survival in people with ALS, acts in part by reducing glutamate release (17). Other drugs that reduce glutamate-mediated excitotoxicity have failed to produce benefits in PALS (reviewed in 18). Ketone bodies can also reduce glutamate release (19). Ketogenic diets reduce brain glutamate levels in some (20) but not all animal studies (9).

Neuroinflammation. Inflammation occurs in the brains and spinal cords of people with ALS and is believed to play a role in driving disease progression (21,22). Many clinical trials are currently testing products that reduce neuroinflammation (for

example, NCT04057898, NCT04579666, NCT04499963, NCT04297683, NCT04436510). Ketone bodies can inhibit caspase-1 activation and block the release of pro-inflammatory chemicals called cytokines, and ketogenic diets can reduce biomarkers of neuroinflammation and improve clinical measurements in animal models of different diseases (23).

Oxidative stress. Oxidative stress has long been implicated in ALS pathophysiology (24). One anti-oxidant called edaravone slowed progression in a trial of people living with ALS (25). Many other antioxidants have not shown such a benefit (26). Ketogenic diets can boost the production of endogenous antioxidants and reduce some markers of oxidative stress in animal models (27,28).

Based on the ability of ketogenic diets to favorably alter biomarkers of brain energy production, inflammation, and oxidative stress, and to reduce brain glutamate levels in animals, we assign a Table of Evidence (TOE) “Mechanisms “grade of B (Table 2). Full descriptions of our TOE and what the different grades mean can be found in reference 29.

Pre-Clinical

We found one study of a ketogenic diet in the G93A mutant SOD1 mouse model of ALS (12). Animals treated with this diet (caloric composition, fat 60%, carbohydrate 20%, protein 20%) had delayed loss of motor function, better-preserved body weight, and more motor neurons in their spinal cord at autopsy compared to animals fed a standard diet (fat 10%, carbohydrate 70%, protein 20%). Blood ketones were >3.5 times higher in the ketogenic diet-fed animals compared to controls. In addition, in vitro experiments showed the neuroprotective effect of the principal ketone body, D- β -3 hydroxybutyrate (DBH), on mitochondrial ATP generation and neuroprotection. This study is flawed due to the very small sample size and lack of randomization. This has never been independently replicated. Based on this positive, flawed published study, we assign a TOE “Pre-Clinical” grade of C (Table 2).

Of interest, a different pre-clinical study administered a medium-chain triglyceride (which was metabolized into ketone bodies) into the G93A mutant SOD1 mouse model of ALS (30). This also resulted in delayed motor function and better

Table 2. Table of evidence for ketogenic diets.

	Grade	Explanation
Mechanism	B	In animals, ketogenic diets can favorably alter biomarkers of brain energy production, inflammation, and oxidative stress, and reduce brain glutamate levels
Pre-clinical	C	One flawed study in an ALS mouse model suggests benefits on motor function, weight, and motor neuron counts
Cases	D	2 PALS on PatientsLikeMe reported “moderate” effectiveness but we did not have records to validate their diagnoses or improvements
Trials	U	We found only one completed trial of a ketogenic diet for ALS; the single enrolled patient had stable ALSFRS-R over 28 weeks, but the lack of a control group precludes interpretation
Risks	D	Most patients on ketogenic diets experience side effects and these can be severe

preserved spinal cord motor neuron counts. Unfortunately, most of the drug studies done in this mouse model of ALS have not translated into benefits for PALS (31).

Cases

In the PatientsLikeMe Community, seven PALS reported using ketogenic diets and four provided detailed treatment evaluations (32). Two reported “moderate” effectiveness, and two “can’t tell.” No more details are available on these patients. We were unable to validate their diagnoses or treatment reports. One neurologist on the ALSUntangled team (GL) had a patient with confirmed bulbar onset ALS try a ketogenic diet; this did not slow their progression and was complicated by rhabdomyolysis (33). We found no other PALS who reported trying ketogenic diets for their ALS. Based upon the two cases with unconfirmed subjective benefits, we assign a TOE “Cases” grade of D (Table 2).

Trials

We found one previous trial of a ketogenic diet in PALS (NCT01016522). This study started in 2009 and was terminated in 2015 due to low enrollment (34). The only enrolled patient tolerated a diet of KetoCal 4:1 enteral formula (80% fat 17% protein 3% carbohydrates) administered via PEG for 28 weeks. No serious adverse events occurred. Non-serious adverse events included transient nausea, stomach pain, dizziness, diarrhea, muscle spasms, increased sweating, and tremor. After an initial 5 kg weight loss, his weight stabilized. His ALSFRS-R, Forced vital capacity, and McGill Quality of Life scores was stable throughout the trial. His Iowa Fatigue Scale score

improved indicating a lessening of fatigue. Without a control group, these efficacy outcomes cannot be interpreted. Therefore, we assign a TOE “Trials” grade of U (Table 2).

Of interest, there has been a randomized, double-blind, 6-month-long trial comparing a high-fat hypercaloric diet ($n=8$ patients) to a high-carbohydrate hypercaloric diet ($n=6$ patients) and an isocaloric diet ($n=6$ patients). Patients on the high-fat hypercaloric diet experienced more adverse events including weight loss than those in the other groups. Patients on the high-carbohydrate hypercaloric diet had the fewest adverse events including deaths and were least likely to drop out of the study early (35).

Risks and costs

Most patients on ketogenic diets in previous trials across different indications (ex. 36–42) report adverse events. These commonly include nausea, diarrhea, stomach pain, dehydration, flu-like symptoms, bad breath, pancreatitis, electrolyte disturbances, decreased bone density, and kidney stones. Weight loss often occurs on ketogenic diets (41); unfortunately, weight loss may be especially problematic for PALS because it is correlated with accelerated progression (43). Serious adverse events can occur in up to 10% of patients in trials of ketogenic diets and can include severe hypoproteinemia, hemolytic anemia, renal tubular acidosis, marked increase in transaminases (40). Rhabdomyolysis (33) and fatal cardiac arrhythmias (44) have been reported. Based on these reports, we assign a TOE “Risks” grade of D. It is important to again note that there are very few reports of any kind documenting the safety and tolerability of ketogenic diets in people with ALS; there could be different side effects in this population.

The cost of ketogenic diets can be comparable to a regular diet (45). However, some experts suggest hospitalization during initiation (46) and regular consultation with a nutritionist on these diets to maintain compliance and minimize side effects (47). It is estimated that 40 h of telephone follow-up each year may be necessary for patients on ketogenic diets (48). Because of the low carbohydrate allowance, the recommended daily allowance of several vitamins and minerals is difficult to meet; supplementation of B, C and D vitamins, and calcium, magnesium, zinc, iron, copper, and selenium may be necessary (49). All this will add to the cost.

Conclusion

Ketogenic diets have plausible mechanisms for treating ALS. One flawed preclinical study and two PatientsLikeMe participants reported benefits; these were not independently verified. Two other

PatientsLikeMe participants and one patient under the care of an ALSUntangled investigator did not show benefits. A trial of a ketogenic diet was only able to enroll a single patient and their experience cannot be interpreted due to the lack of any control group. We hope to see another trial of a ketogenic diet in people with ALS. Until then, given the frequent side effects, we do not advise such diets for the treatment of ALS.

Declaration of interest

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ORCID

Christopher McDermott  <http://orcid.org/0000-0002-1269-9053>

Paul Wicks  <http://orcid.org/0000-0002-2293-9284>

References

1. ALSUntangled. Available at: <https://www.alsuntangled.com/future-reviews/>. Accessed July 23, 2021.
2. Wikipedia. Available at: https://en.wikipedia.org/wiki/Ketogenic_diet. Accessed August 6, 2021.
3. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database Syst Rev*. 2020;2020:CD001903.
4. Gano L, Patel M, Jong R. Ketogenic diets, mitochondria, and neurological diseases. *J Lipid Res*. 2014;55:2211–28.
5. Paganoni S, Wills A. High-fat and ketogenic diets in amyotrophic lateral sclerosis. *J Child Neurol*. 2013;28:989–92.
6. Dr. David Perlmutter. Available at: <https://www.drperlmutter.com/use-ketogenic-diet-treating-als/>. Accessed August 6, 2021.
7. Veyrat-Durebex C, Reynier P, Procaccio V, Hergesheimer R, Corcia P, Andress C, et al. How can a ketogenic diet improve motor function? *Front Mol Neurosci*. 2018;11:15.
8. Vandoorne T, De Bock K, Van Den Bosch L. Energy metabolism in ALS: an underappreciated opportunity? *Acta Neuropathol*. 2018;135:489–509.
9. Bough K, Wetherington J, Hassel B, Pare J, Gawryluk J, Green J, et al. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. *Ann Neurol*. 2006;60:223–5.
10. Nylen K, Perez Velazquez J, Sayed V, Gibson K, Burnham W, Snead O. The effects of a ketogenic diet on ATP concentrations and the number of hippocampal

- mitochondria in *Aldh5a1(-/-)* mice. *Biochim Biophys Acta*. 2009;1790:208–12.
11. Masino S, Gockel S, Wasser C, Pomeroy L, Wagener J, Gawryluk J, et al. The relationship among ATP, adenosine, and a ketogenic diet. *Neuroscience Meeting Planner*. San Diego, CA: Society for Neuroscience; 2007.
12. Zhao Z, Lange D, Voustantiouk A, MacGrogan D, Ho L, Suh J, et al. A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. *BMC Neurosci*. 2006;7:29.
13. Kaufmann P, Thompson JLP, Levy G, Buchsbaum R, Shefner J, Krivickas LS, et al. Phase II trial of coQ10 for ALS finds insufficient evidence to justify phase III. *Ann Neurol*. 2009;66:235–44.
14. Cudkowicz M, van den Berg L, Shefner J, Mitsumoto H, Mora J, Ludolph A, et al. Dexamipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomized, double-blind, phase 3 trial. *Lancet Neurol*. 2013;12:1059–67.
15. Rosenblum L, Trotti D. EAAT2 and the molecular signature of amyotrophic lateral sclerosis. *Adv Neurobiol*. 2017;16:117–36.
16. Blasco H, Mavel S, Corcia P, Gordon P. The glutamate hypothesis in ALS: pathophysiology and drug development. *Curr Med Chem*. 2014;21:3551–75.
17. Bellingham M. A review of the neuronal mechanisms of action and clinical efficiency of riluzole in treating amyotrophic lateral sclerosis: what have we learned in the past decade? *CNS Neurosci Ther*. 2011;17:4–31.
18. LeVerche V, Ikiz B, Jacquier A, Przedborski S, Re D. Glutamate pathway implication in amyotrophic lateral sclerosis: what is the signal in the noise? *J Recept Ligand Channel Res*. 2011;4:1–22.
19. Juge N, Gray JA, Omote T, Miyaji T, Inoue C, Hara H, et al. Metabolic control of vesicular glutamate transport and release. *Neuron* 2010;68:99–112.
20. Melo T, Nehlig A, Sonnewald U. Neuronal-glia interactions in rats fed a ketogenic diet. *Neurochem Int*. 2006;48:498–507.
21. Kallstig E, McCabe B, Schneider B. The links between ALS and NF- κ B. *IJMS*. 2021;22:3875.
22. Bright F, Chan G, van Hummel A, Ittner LM, Ke YD. TDP-43 and inflammation: implications for amyotrophic lateral sclerosis and frontotemporal dementia. *IJMS*. 2021; 22:7781.
23. Koh S, Dupuis N, Auvin S. Ketogenic diet and neuroinflammation. *Epilepsy Res*. 2020;167:106454.
24. Obrador E, Salvador-Palmer R, López-Blanch R, Jihad-Jebbar A, Vallés SL, Estrela JM. The link between oxidative stress, redox status, bioenergetics, and mitochondria in the pathophysiology of ALS. *IJMS*. 2021; 22:6352.
25. Writing Group; Edaravone ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a double-blind, placebo-controlled clinical trial. *Lancet Neurol*. 2017;16:505–12.
26. Orrell RW, Lane RJM, Ross M. Antioxidant treatment for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev*. 2005;1:CD002829.
27. Milder J, Patel M. Modulation of oxidative stress and mitochondrial function by the ketogenic diet. *Epilepsy Res*. 2012;100:295–303.
28. Kephart W, Mumford P, Mao X, Romero M, Hyatt H, Zhang Y, et al. The 1-week and 8-moth effects of a ketogenic diet or ketone salt supplementation on multi-organ markers of oxidative stress and mitochondrial function in rats. *Nutrients*. 2017;9:1019.
29. The ALSUntangled Group. ALSUntangled: introducing the table of evidence. *Amyotroph Lateral Scler Frontotemporal Degen*. 2015;16:142–5.

30. Zhao W, Varghese M, Vempati P, Dzhun A, Cheng A, Wang J, et al. Caprylic triglyceride as a novel therapeutic approach to effectively improve the performance and attenuate the symptoms due to the motor neuron loss in ALS disease. *PLoS One*. 2012;7:e49191.
31. Benatar M. Lost in translation: treatment trials in the SOD1 mouse and in human ALS. *Neurobiol Dis*. 2007; 26:1–13.
32. PatientsLikeMe. Available at: <https://www.patientslikeme.com/treatment/ketogenic-diet>. Accessed August 18, 2021.
33. Personal communication with Gleb Levitsky August 23, 2021.
34. Clawson R, Kimball R, Kossoff E, Chaudry V. Use of a ketogenic diet in a patient with amyotrophic lateral sclerosis. Presented at 2015 Northeast ALS Consortium Meeting in Clearwater Florida. 2015.
35. Wills A, Hubbard J, Macklin E, Glass J, Tandan R, Simpson E, et al. Hypercaloric enteral nutrition in patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet*. 2014;383: 2065–72.
36. Kang H, Chung D, Kim D, Kim H. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. *Epilepsia*. 2004;45:1116–23.
37. Wlodek D. Role of Ketogenic diets in neurodegenerative diseases. *Nutrients*. 2019;11:169.
38. Phillips M, Murtagh D, Gilbertson L, Asztely F, Lynch C. Low-fat versus ketogenic diet in Parkinson's disease: a pilot randomized controlled trial. *Mov Disord*. 2018;33: 1306–14.
39. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, Sikand G, Aspary KE, Soffer DE, et al. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: a scientific statement from the national lipid association nutrition and lifestyle task force. *J Clin Lipidol*. 2019;13:689–711.
40. Ballaban-Gil K, Callahan C, O'Dell C, Pappo M, Moshé S, Shinnar S. Complications of the ketogenic diet. *Epilepsia*. 1998;39:744–8.
41. Bueno N, de Melo I, de Oliveira S, Ataíde T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomized controlled trials. *Br J Nutr*. 2013;110:1178–87.
42. Diabetes UK. Available at: <https://www.diabetes.co.uk/keto/side-effects-of-ketogenic-diet.html>. Accessed August 25, 2021.
43. Janse van Mantgem MR, van Eijk RPA, van der Burgh HK, Tan HHG, Westeneng H-J, van Es MA, et al. Prognostic value of weight loss in patients with amyotrophic lateral sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry*. 2020;91:867–75.
44. Bank I, Shemie S, Rosenblatt B, Bernard C, Mackie A. Sudden cardiac death in association with the ketogenic diet. *Pediatr Neurol*. 2008;39:429–31.
45. Bioketo. Available at: <https://bioketo.com/cost-of-the-keto-diet/>. Accessed August 21, 2021.
46. Epilepsy Foundation. Available at: https://www.epilepsy.com/sites/core/files/atoms/files/517TSE_DietaryTherapies_Rev09-2018_FINAL.pdf. Accessed August 25, 2021.
47. Roehl K, Sewak S. Practice paper of the academy of nutrition and dietetics: classic and modified ketogenic diets for treatment of epilepsy. *J Acad Nutr Diet*. 2017; 117:1279–92.
48. Freeman J, Freeman J, Kelly M. *The ketogenic diet: a treatment for epilepsy*. Third Edition, NY, Demos Publishing, 2000.
49. Nutrition Care Manual. Available at: https://www.nutritioncaremanual.org/client_ed.cfm?ncm_client_ed_id=75. Accessed August 31, 2021.