

A Systematic Review of Randomized Controlled Trials Investigating the Therapeutic and Adverse Effects of the Ketogenic Diet Across Various Health Conditions

KAREN PENDERGRASS¹ 

Pendergrass, K.(2019) **A Systematic Review of Randomized Controlled Trials Investigating the Therapeutic and Adverse Effects of the Ketogenic Diet Across Various Health Conditions.** *Ketogenic Diet Research*. The Paleo Foundation.

¹Department of Standards, Paleo Foundation, Encinitas, CA

Correspondence

Karen E. E. Pendergrass
Department of Standards, Paleo Foundation, Encinitas, CA

Contact

¹Email: karen@paleofoundation.com

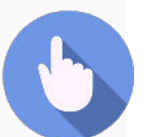
¹Twitter: @5WordsorlessKP

TABLE OF CONTENTS


KETOGENIC DIET RCTs

STATEMENT OF PURPOSE	3
ACKNOWLEDGMENTS	4
MEDICAL DISCLAIMER	5
INTRODUCTION	6
HISTORY	7
TERMINOLOGY	9
REFERENCES	28

RCTs	9
WHAT ARE RCTs?	9
DIABETES	10
WEIGHT LOSS	10
CANCER	12
EPILEPSY	12
AUTISM	16
EXERCISE	17
SAFETY	18
GLOBAL DEVELOPMENT DELAY	18
METABOLISM	19
CARDIOVASCULAR RISK	20
INFANTILE SPASMS	21
POTENTIAL APPLICATIONS	22
AMYOTROPHIC LATERAL SCLEROSIS (ALS)	22
MANIC DEPRESSIVE BIPOLAR DISORDER	23
GLUT1 DEFICIENCY DISORDER	24
CONCLUSIONS	25
NEXT STEPS FOR RESEARCH	25
ALTERNATIVE KETOGENIC DIETS	26
ADVERSE EFFECTS	27
IMPROVING TOLERABILITY	27
MECHANISMS OF ACTION	27



STATEMENT OF PURPOSE



While the amount of data regarding the influence of a ketogenic diet accumulates, there is also a need to improve the availability and accuracy of information to those in both a clinical sense, and to others who are responsible for the dissemination of information regarding ketogenic diet nutrition.

In this ketogenic diet research review, we examine all 32 of the available published randomized controlled trials (RCTs) involving the ketogenic diet, as well the potential clinical utility of the diet in other disorders, and potential adverse effects.


The purpose of this research review is to offer a large amount of information in as little time as possible, and to help broaden collective perspectives on the ketogenic diet.

Enjoy.



ACKNOWLEDGMENTS

The authors would like to acknowledge the following organizations:



In 1993, the ketogenic diet offered an effective therapeutic treatment for Charlie Abraham's intractable epilepsy. In 1994, The Charlie Foundation for Ketogenic Therapies was founded by his father Jim Abrahams who also produced the 1997 drama film "First Do No Harm," effectively renewing interest in the clinical applications of the Ketogenic Diet. We would like to thank the Charlie Foundation for their continued support and education for families affected by epilepsy.

Our greatest acknowledgment is to the dedicated researchers who produced the ketogenic diet studies covered in this review, and to the institutions that funded the research efforts that made this review possible.



MEDICAL DISCLAIMER

This document is provided by Paleo Certified, Inc. for educational purposes only. The opinions, findings, conclusions, and recommendations expressed in this document are not intended to diagnose, treat, cure, or prevent any disease.

Information in this document does not constitute medical advice. Please consult a medical or health professional before you begin any exercise, nutrition, or diet-related program, or if you have questions about your health.

KETOGENIC DIET RESEARCH

A Systematic Review of RCTs Investigating the Therapeutic and Adverse Effects of the Ketogenic Diet Across Various Health Conditions

Karen Pendergrass¹

¹Department of Standards, Paleo Foundation, Encinitas, CA

Correspondence

Karen E. E. Pendergrass
Department of Standards, Paleo Foundation, Encinitas, CA

Contact

¹Email: karen@paleofoundation.com

¹Twitter: [@5WordsorlessKP](https://twitter.com/5WordsorlessKP)

Abstract

'Food is medicine' is an ancient, yet still relevant concept that perfectly illustrates the exploration and findings of the ketogenic diet and its effect on human metabolism. The use of the ketogenic diet in treating epilepsy has been well established for many decades. However in more recent years, an increasing amount of evidence suggests that various ketogenic diets have a therapeutic role in other disease states as well, but also a grave potential for adverse effects.

KEYWORDS

Classic Ketogenic Diet, Modified Atkins Diet, Medium-Chain Triglycerides, Medium-Chain Triglyceride Diet, Randomized Controlled Trials (RCTs)

1 | INTRODUCTION

Classical ketogenic diets are characterized by a reduction in carbohydrates usually to less than 50 grams per day, and a relative increase in the proportions of protein and fat. The knowledge that has been accumulated in the past century in regards to the metabolic effects of classic ketogenic diets began with the need for a better alternative to starvation diets to treat epilepsy.

However in more recent years, an increasing amount of evidence suggests that ketogenic diets have a therapeutic role in other disease states as well. The positive results of these studies demonstrate the importance of this direction for research, as a ketogenic diet intervention may aid in reducing the reliance on pharmaceutical treatments, or provide adjunctive treatments which have both positive economic and social implications.

While the amount of data regarding the influence of nutrition on health status and disease prevention accumulates, there is also a need to move the needle more by way of improving the availability of information to those in both a clinical sense, and to others who are responsible for the dissemination of information about ketogenic diet nutrition.

As such, in this ketogenic diet research review, we examine the 32 available randomized controlled studies involving the ketogenic diet and their findings, as well the potential clinical utility of the ketogenic diet in other disorders, and potential adverse effects.

• WHAT IS KETOSIS

The hormone insulin activates key enzymes in metabolic pathways which store energy derived from carbohydrates. When an absence or scarcity of dietary carbohydrates occurs, a subsequent reduction in insulin levels lead to a reduction in lipogenesis (the metabolic formation of fat), and fat accumulation. After a few days of drastically reduced carbohydrate consumption (below 50 grams/day), glucose reserves become insufficient for fat oxidation and are therefore unable to supply glucose to the central nervous system.

However, the central nervous system cannot utilize fat for energy, and after 3–4 days without carbohydrate consumption, the central nervous system is 'forced' to find an alternative energy source, leading to the increased production of ketone bodies acetoacetate, β -hydroxybutyric acid and acetone in a process called ketogenesis, occurring principally in the mitochondrial matrix of the liver.

Ketogenesis occurs during periods of prolonged fasting, in type 1 diabetes, and in individuals following high-fat/low-carbohydrate diets. The main ketone body produced in the liver is acetoacetate, but the primary circulating ketone is β -hydroxybutyrate.

Under conditions of adequate dietary carbohydrate intake, free acetoacetic acid is typically low, and rapidly metabolized by various tissues such as the skeletal and heart muscles. However, in conditions where acetoacetic acid is overproduced, it is converted to the other two ketone bodies leading to the presence of ketone bodies in the blood and urine that act as an alternative metabolic substrate to glucose, supplying energy to the central nervous system.

It is important to note that ketosis is a completely different physiological mechanism than its similar-sounding pathological counterpart ketoacidosis, which is seen in individuals with type 1 diabetes.

In physiological ketosis which occurs during very-low-calorie or low carbohydrate ketogenic diets, ketone concentrations reach maximum levels of 7/8 mmol/l and do not go higher because the central nervous system must use these molecules for energy in place of glucose. Subsequently, there is no change in pH.

However, in uncontrolled diabetic ketoacidosis, ketone concentrations can exceed 20 mmol/l while lowering the blood pH which can be very dangerous.

2 | HISTORY OF THE KETOGENIC DIET

In biblical times and in the times of Hippocrates, the Greek 'father of medicine', fasting was used as a means to treat epilepsy, but remained poorly understood for millennia. Before the understanding of the mechanisms of fasting, physicians also used starvation clinically to treat epilepsy.

The following is a brief history of how food deprivation as a treatment for epilepsy unfolded in the 1920s into the use of the ketogenic diet for epilepsy as we know it today.

Dr. Guelpa and Dr. Marie: French physicians who authored the first scientific report on the value of fasting in epilepsy in 1911. Marie and Guelpa described a cyclical fasting regimen of four days of fasting and purging, followed by four days of a restricted vegetarian diet. [1].

• KETOSIS VS. KETOACIDOSIS

Bernarr Macfadden: A physical fitness guru/cultist who believed that any disease could be cured through exercise and fasting. This included asthma, diabetes, prostate cancer, impotence, paralysis, liver and kidney disease, as well as epilepsy [3].

Dr. Hugh W. Conklin: An American osteopathic physician and assistant to Macfadden who adopted Macfadden's beliefs and methods of fasting to treat his patients with epilepsy. His impressive and positive results drew attention from other pioneers [4, 5].

H. Rawle Geyelin: An American endocrinologist who was the first to report his use of fasting as a treatment for bromide and phenobarbital-resistant epilepsy to the American Medical Association (AMA) in 1919 [6]. Geyelin was most interested in discovering the mechanisms that made fasting such an effective treatment for epilepsy [7].

Dr. A. Goldbloom: A Canadian physician (and skeptic of Dr. Conklin) who treated patients with fasting, but noticed that when the fasting period ended, the seizures returned for some. He wrote, "It would seem from this case that the starvation treatment is effective only while it is continued and while the patient remains in bed, but that it has no enduring qualities [8]."

HTH: A boy who had grand mal seizures that were treated with fasting who was initially presented to the AMA convention by Dr. Geyelin. HTH was placed on a "Water Diet" fast for 3-4 weeks to treat his epileptic seizures. During the fasting period, his seizures disappeared. However, his seizures returned after the conclusion of the fast as Dr. Goldbloom suggested they might. Luckily for the boy and for the rest of the world with epilepsy, HTH was the nephew of pediatric physician Dr. John Howland, and son of a very wealthy Charles Howland [9, 10].

Dr. John Howland: Professor of pediatrics at Johns Hopkins, and director of the Harriet Lane Home for Invalid Children. In 1915, his brother Charles Howland donated five thousand dollars (the equivalent of more than \$120,000 today) to support research on the mechanisms of fasting in the treatment of epilepsy due to worries of his son HTH's intractable seizures that were not cured with starvation by Dr. Conklin [9 - 12].

Dr. Stanley Cobb and W.G. Lennox: Dr. Stanley Cobb was an associate professor of neuropathology at Harvard and physician who was in the audience during the presentation given by Geyelin to AMA.

He and his colleague Lennox were enlisted by the parents of HTH and Dr. John Howland in to further study the mechanisms of fasting on epilepsy [9]. Cobb and Lennox conducted several studies on fasting and had reported several significant findings, noting that levels of the ketone bodies β -hydroxybutyrate, acetoacetate, and acetone are elevated in the peripheral blood and in the urine [10].

R.T. Woodyatt: Diabetes Researcher in 1921, around the time of the studies of Cobb and Lennox, authored a review article about dietary manipulations for diabetes stating that acetone, acetic acid, and beta-hydroxybutyric acid (BHB) appears in subjects via fasting, or via a diet containing too low a proportion of carbohydrate and a high proportion of fat [13].

Dr. Wilder: Physician from the Mayo Clinic who originally coined the term "Ketogenic diet." [17] Based on the work by Woodyatt and Geyelin, Wilder proposed that the benefits of fasting could be obtained if ketone bodies had been produced by other means, such as eating a diet that was rich in fat and low in carbohydrate [14].

Wilder was the first to suggest that the ketogenic diet may be as effective as fasting, and could be maintained for an extended period to compensate for the disadvantages of prolonged fasting periods. The following day in 1921 after his proposal, a report was issued describing the success in seizure control of three patients of the Mayo Clinic using a ketogenic diet as a treatment instead of fasting.

In 1924, The Mayo Clinic began treating adults with epilepsy with the revolutionary “ketogenic diet.” [15-17].

3 | TERMINOLOGY

KD – Classic Ketogenic Diet

MAD – Modified Atkins Diet

MCT – Medium-Chain Triglycerides

MCTD – Medium-Chain Triglyceride Diet

LDL – Low-Density Lipoprotein

HDL – High-Density Lipoprotein

RCT- Randomized Controlled Trials

CICO- Calories-In Calories-Out theory

PUFA- Polyunsaturated Fatty Acids

DHA- Docosahexaenoic Acid

4 | RANDOMIZED CONTROLLED TRIALS

• RANDOMIZED CONTROLLED TRIALS (RCTS)

While some studies may detect associations between an intervention and an outcome, it can be difficult to rule out the possibility that the association was caused by another unknown factor.

However, the randomization that occurs in Randomized Controlled Trials (RCT) reduces the possibility of systematic errors, and are the most rigorous way of determining whether a cause-effect relation exists between treatment and outcome, and the extent to which specific, planned impacts are being achieved.

RCTs are quantitative, comparative, controlled experiments in which a group of investigators study two or more interventions in a series of participants who are allocated randomly to each intervention group with several important features, such as:

- Random allocation to intervention groups.
- Neither the patients nor the trial conductors are aware of which treatment was given to which patients until the study has completed.
- Intervention groups are treated identically except for the experimental treatment.
- Patients are analyzed within the group that they were allocated, whether they experienced the intended result or not.
- The analysis of the results focuses on estimating the effect size between different groups.

While many published studies have investigated the ketogenic diet, RCTs are the most stringent way of determining whether a cause-effect relation exists between the intervention and the outcome. For this reason, this research review will focus on the outcomes of these types of studies.

• TYPE II DIABETES

In 2017, the CDC reported that more than 100 million Americans, or 1/3 of the US population had prediabetes or diabetes, and was the leading cause of death in 2015. Worldwide, diabetes affects more than 422 million people, and is the leading cause of blindness, kidney failure, heart disease, and stroke. Clearly, diabetes is a serious health problem, but it can often be managed through physical activity, diet, and medication [18].

The findings of the reviewed studies suggest that the ketogenic diet may improve symptoms of Type II Diabetes.

Study: *“An Online Intervention Comparing a Very Low-Carbohydrate Ketogenic Diet and Lifestyle Recommendations Versus a Plate Method Diet in Overweight Individuals With Type 2 Diabetes: A Randomized Controlled Trial.”*

Findings: Individuals with type II Diabetes improved glycemic control and lost significantly more weight after they had been randomized to a very low-carbohydrate ketogenic diet and lifestyle program compared to a conventional low-fat diabetes diet program [19].

Study: *“Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus.”*

Findings: The very low-calorie ketogenic diet intervention was the most effective in reducing body weight and improvement in glycemic control compared to a standard hypocaloric diet and was well tolerated in Type II Diabetes patients [20].

• WEIGHT LOSS

The first law of thermodynamics— also known as the law of conservation of energy— has in effect controlled the concepts and conventional wisdom of weight loss (colloquially known as the Calories-In/Calories-Out theory (CICO) for over a century— resulting in a notable difficulty in accepting other potential ways of thinking.

Also adhering to conventional wisdom regarding weight loss and caloric deficit concepts, the US Department of Agriculture (USDA) has concluded that reducing calories alone results in weight loss, and that weight loss is independent of the macronutrient composition of the diet. Many educated following USDA guidelines also maintain the belief that the macronutrient composition of one’s diet is irrelevant to weight loss, provided that the calories remain in a deficit to caloric expenditure.

However, in sharp contrast with these views, the majority of ad-libitum studies demonstrate that subjects who follow a low-carbohydrate diet lose more weight during the first 3–6 months compared with those who follow more macronutrient-balanced diets.

While the exact metabolic mechanisms are not yet fully understood, some researchers suggest that macro-nutrient manipulations increase satiety and therefore reduces caloric intake, while others suggest that a distinct metabolic advantage is occurring.

Nevertheless, the outcomes of the following studies should raise further interest in the exploration of the ketogenic diet and its weight loss potential.

Study: *"Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease."*

Findings: Of those who completed the study, the analysis revealed that from the beginning (15 days) until the end of the observation, the weight reduction observed in the very-low-calorie-ketogenic diet was double that of the low-calorie diet [21].

Study: *"Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity."*

Findings: In a group of obese patients, the VLCK diet was significantly more effective than a standard low-calorie diet. At one year follow-up in the group with a VLCK diet, most of the patients lost more than 10% of their initial weight. However, lean mass was well preserved [22].

Study: *"Very-low-calorie ketogenic diet with amino acid supplement versus very low restricted-calorie diet for preserving muscle mass during weight loss: a pilot double-blind study."*

Findings: The pilot study found that a VLCKD was highly effective in terms of body weight reduction without inducing lean body mass loss, thus preventing the risk of sarcopenia. Further, the results show that a low-carbohydrate diet, associated with a decreased caloric intake, is effective in weight loss [23].

Study: *"Effect of DHA supplementation in a very low-calorie ketogenic diet in the treatment of obesity: a randomized clinical trial."*

Background: An increased ratio of dietary omega-6 : omega-3 polyunsaturated fatty acids (PUFAs) has been linked to the risk of chronic inflammatory diseases. Studies have identified docosahexaenoic acid (DHA) as a precursor to a potent anti-inflammatory eicosanoids, known as resolvins and protectins, which actively help terminate an inflammatory response.

Findings: Using a controlled, open design clinical trial, the patients of this study were randomized to receive either a very low-calorie ketogenic diet (VLCK) or an isocaloric VLCK diet without DHA (control group). The main finding of this study was that the very low-calorie ketogenic diet supplemented with DHA group improved inflammation-resolving eicosanoids compared with the isocaloric VLCK diet group, and was effective in inducing loss of body weight [24].

Study: *"Metabolic impact of a ketogenic diet compared to a hypocaloric diet in obese children and adolescents."*

Findings: Children and adolescents on the hypocaloric diet were instructed to reduce their caloric intake by 500 calories daily while deriving 28%–33% and 50%–55% of these calories from fat and carbohydrates, respectively.

Both groups had significant reductions in weight and fat mass, however, the ketogenic group had more pronounced improvements in weight loss and metabolic parameters than the hypocaloric diet. The authors conclude that the ketogenic may be a feasible and safe weight loss intervention for children [25].

Study: *"Effects of a very-low-calorie diet on body composition, metabolic state, and genes expression: a randomized double-blind placebo-controlled trial."*

Findings: This is the first study that analyzed body composition, metabolic profile, inflammation, and expression of oxidative stress genes after the administration of a very low carbohydrate ketogenic diet (VLCKD). Results of the study show the efficacy of a VLCKD with synthetic protein replacement for the reduction of cardiovascular risk, without the development of sarcopenia, or the activation of inflammatory and oxidative processes [26].

• CANCER

Approximately 1.7 million people were diagnosed with cancer in the United States in 2018, and more than 600,000 died from the disease according to the National Cancer Institute [27].

Most patients diagnosed with cancer will receive chemotherapy or radiation treatment, and patients undergoing treatment experience a multitude of symptoms, including fatigue, pain, difficulty breathing, nausea, appetite loss, and unintentional weight change.

Common cancer treatments may affect one's diet, however, some dietary changes can exacerbate other treatment related symptoms. It has been suggested that a specific dietary intervention during radiotherapy could have positive effects on body composition and even protect normal tissue from ionizing radiation.

While only one RCT exists in 2019, the outcomes of this trial suggests that a ketogenic diet could be considered an alternative to food abstention in oncological patients.

Study: *"Impact of a ketogenic diet intervention during radiotherapy on body composition: II. Protocol of a randomized phase I study (KETOCOMP)."*

Background: It can be expected that chemotherapy has an impact on body composition, due to its associated reduced energy intake, increased energy turnover, and inflammatory processes that often result in increases in skeletal muscle breakdown, among other things.

Findings: Previous studies found that a ketogenic diet (KD) during the course of radiotherapy (RT) was feasible and led to a preservation or favorable changes of body composition. This study found that morning irradiation after an overnight fast with a ketogenic breakfast consisting of an medium-chain triglyceride (MCT) drink diminished the expected decrease of phase angle (PA), an indicator of cell wall integrity, during the course of radiotherapy treatment [28].

• EPILEPSY

Epilepsy is a neurological disorder that is treated with antiepileptic drugs (AEDs) in the majority of the

patients, and affects nearly 1% of American children. However, AEDs are not always efficacious. About one-third of patients suffer from intractable epilepsy.

Further, patients often experience side effects that lead to discontinuation of the drug for these patients. While the efficacy of the ketogenic diet as a treatment for epilepsy is already well established, further investigations of the alternative nonpharmacological treatment is necessary to understand its mechanisms as an anticonvulsant, as well as its long-term efficacy and potential adverse effects.

Study: *"A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy."*

Findings: This trial provides class I evidence that the ketogenic diet is an effective therapy in children and adolescent patients with refractory epilepsy compared with care as usual (CAU). The most often reported side effects are gastrointestinal symptoms, and authors noted that lipid profiles showed only a significant increase of total cholesterol at 6 weeks. Of significance, patients treated with the KD had a seizure reduction of at least 50% and a relevant reduction in seizure severity [29].

Study: *"Risk of seizure recurrence after achieving initial seizure freedom on the ketogenic diet."*

Background: In previous short-term outcome studies, 15–20% of patients with intractable epilepsy achieved seizure freedom, and one-third achieved >90% seizure reduction. The objective of this study, however, was to examine the likelihood of sustained seizure freedom in the long-term on the ketogenic diet.

Findings: This study gives evidence to support the continued use of a ketogenic diet in patients with initial

seizure freedom even after breakthrough seizures, as even the frequency of the breakthrough seizures were not a return to baseline frequency in the patients [30].

Study: *"Cognitive and behavioral impact of the ketogenic diet in children and adolescents with refractory epilepsy: A randomized controlled trial."*

Findings: This RCT shows a positive cognitive and behavioral effect of the ketogenic diet intervention in children and adolescents. With respect to mood, patients on the ketogenic diet showed higher levels of mood problems at baseline. However, levels of mood-disturbed behavior diminished, and at the 4-month follow up it was noted that there was an overall reduction in anxiety/tension/hostility in the patients randomized to the ketogenic diet, independently of seizure control. The study also found that the group had increased productivity, and cognitive test results also revealed a higher receptive vocabulary [31].

Study: *"Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy."*

Background: The ketogenic diet (KD) is an established treatment for drug-resistant childhood epilepsy. However, the ketogenic diet may be too difficult to implement in pediatric patients because of its restrictive nature and has potential side effects. A more easily applied alternative dietary therapy has also been utilized for epilepsy patients. This study aimed to compare the two dietary approaches.

Findings: This study evaluated the classic ketogenic diet, but found that it did not have a definite advantage in terms of efficacy. Instead, the Modified Atkins Diet had advantages with respect to better tolerability and fewer side effects. However, in the patient group aged <2 years, the benefits of the ketogenic diet were more pronounced than compared with those consuming a modified Atkins Diet [32].

Study: "A pragmatic study on efficacy, tolerability and long-term acceptance of ketogenic diet therapy in 74 South Indian children with pharmaco-resistant epilepsy."

Background: An international consensus was established in 2009 recommending the use of a ketogenic diet in children after two trials of antiepileptic drugs in cases of intractable epilepsy. Even though the efficacy of KD is fairly well established in the management of drug-resistant epilepsy in children, it is still only being recommended to a few selected areas in the world. Many factors contribute to this scenario, including the lack of awareness among physicians and caregivers. However, another roadblock of the ketogenic diet as a treatment for intractable epilepsy is cultural acceptance and viability given local food preferences.

Note: The typical south Indian diet is very rich in carbohydrates, especially rice. Severe restriction of rice makes the diet unpalatable, posing a threat to the adherence to a ketogenic diet for individuals with epilepsy, especially for long-term maintenance. Further, there is a lack of cultural acceptance for the treatment. Authors noted that a less restrictive alternative approach may improve acceptability and long-term adherence. However, in areas like Kerala, the significant amount of fish products consumed, and the use of coconut oil as a traditional cooking medium may have aided in cultural acceptability and success of the patients in this region.

Findings: The Ketogenic Diet may be a safe and effective option for children with intractable epilepsies, even while on a traditional carbohydrate-rich South Indian diet. However, this study clearly points out that the successful introduction of a ketogenic diet therapy in any population will need to consider the dietary preferences of the local culture to have a successful intervention [33].

Study: "Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open-labeled study."

Background: The ketogenic ratio of lipids to non-lipids may play an important role in the efficacy and tolerability of ketogenic diets (KD). This study was the first of its kind to compare the efficacy and tolerability of 2.5:1 versus 4:1 lipid to non-lipid ratio ketogenic diet in children with intractable epilepsy.

Findings: Researchers found comparable efficacy in reducing seizure frequency and severity, as well as comparable tolerability and biochemical profiles between both the diets. However, one notable exception was a trend ($p = 0.06$) towards higher cholesterol and HDL in the 2.5:1 group, not the 4:1 group [34].

Study: "An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: An interim analysis."

Background: Epilepsy is a costly condition. In 2004, the total costs of epilepsy in Europe was €15.5 billion, with indirect costs being the single most dominant cost category (€8.6 billion.) In The Netherlands, the direct medical costs were €248 million in 2011, which is 0.3% of the health care budget. Although the majority of patients with epilepsy can be treated with antiepileptic drugs (AEDs), about 30% of patients have intractable epilepsy.

Objectives: Cost-compare the ketogenic diet (KD) to care as usual (CAU) in children and adolescents with intractable epilepsy: an evaluation of economic and social perspectives in an RCT.

Findings: Children with refractory epilepsy, randomized to the KD group had a significant reduction in seizures compared to children in the CAU group, 50%, and 18.2% respectively. However, costs per patient in the CAU group were €15,245 compared to €20,986 per patient in the KD group, resulting in an incremental cost-effectiveness ratio (ICER) of €18,044 per responder. However, no benefits in terms of quality-adjusted life years (QALYs) were found and, therefore, the authors determined that the cost per QALY increase was found to be high above any acceptable ceiling ratio.

Note: The authors concluded that the ketogenic diet is therefore not a cost-effective intervention when including the quality-adjusted life years. The authors further suggested that although the KD group had a significant reduction in seizures when compared to the care as usual group, the ketogenic diet's lack of effectiveness in terms of quality of life suggests that the diet may be an ineffective way of treating patients with epilepsy from an economic standpoint [35].

Study: *"A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy."*

Background: The ketogenic diet was first designed to induce a similar metabolic response as fasting, with the ketone bodies β -hydroxybutyrate and acetocetate becoming the primary energy source for the brain in the absence of adequate glucose supply. However, there are two main ways of implementing a ketogenic diet. First, the classical ketogenic diet is based on a ratio of fat to carbohydrate and protein, usually 3:1 or 4:1, with the fat provided by long-chain triglycerides.

The classical ketogenic diet restricts both carbohydrates and protein. However, a modified ketogenic diet using MCT as an alternative fat source yield more ketones per kilocalorie of energy than long-chain triglycerides. Further, MCT is absorbed more efficiently, and its increased ketogenic potential means that less fat is needed in the MCT diet, allowing also allowing for more dietary carbohydrate and protein.

Findings: This study reports the results of the first randomized trial comparing the classical and MCT versions of the ketogenic diet in the treatment of drug-resistant epilepsy, and found that the classical ketogenic diet does not show any advantages over the MCT diet in terms of efficacy. However, in terms of tolerability, there were increased reports of lethargy and vomiting, and constipation with the use of the classical ketogenic diet protocol [36].

Note: Most studies on the efficacy of the ketogenic diet have involved the classical ketogenic diet and not the MCT diet.

Study: *"A randomized trial of a medium-chain TAG diet as a treatment for dogs with idiopathic epilepsy."*

Background: Despite antiepileptic drug treatment, like humans, approximately one-third of dogs with epilepsy continue experiencing seizures. A 6-month prospective, randomized, double-blinded, placebo-controlled, cross-over dietary trial was designed to evaluate the efficacy and tolerability of a ketogenic medium-chain TAG diet (MCTD) in chronically antiepileptic drug-treated dogs with idiopathic epilepsy.

Note: The medium-chain TAG diet consists of caprylic acid, capric acid, lauric acid, and medium-chain triglycerides.

Findings: In conclusion, the data shows antiepileptic properties commonly associated with ketogenic diet, and provides evidence for the efficacy of an MCTD as used in this study as a therapeutic option for the treatment of intractable epilepsy in dogs [37].

Study: *"Effects of a ketogenic diet on ADHD-like behavior in dogs with idiopathic epilepsy."*

Background: Epilepsy is a common chronic neurological disorder in dogs as well as in humans. External factors associated with diet and the dog's lifestyle may also have an impact upon the seizure activity and behavior.

The aims of this study were to describe the behavioral profile of dogs with idiopathic epilepsy (IE) while on a standardized non-ketogenic placebo diet to determine whether ADHD-like behaviors are present, and to examine the effect of a medium chain triglyceride diet (MCTD) on the behavioral profiles of dogs with idiopathic epilepsy.

Findings: The study found that the use of the MCTD reduced one of these ADHD-related behaviors, chasing, and reduced stranger-related fear which suggests that the Ketogenic diet intervention may have further anxiolytic properties in dogs with idiopathic epilepsy. [38]

• AUTISM

Autism or Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by varying impairments in social communication and behaviors that may affect as many as 2% of the children in the United States, and new reports find that the incidence may be rising significantly. [39]

Symptoms of ASD include adverse behaviors such as anxiety, attention problems, impulsivity, and self-injurious behavior. Therapists often attempt to modify behaviors and enhance functional communication, but limited improvements occur with behavioral therapy, and behavioral therapy does not address core symptoms of ASD.

Several pharmacological options for reducing behavioral symptoms in patients with autism exist. Leading among these drugs are FDA-approved atypical antipsychotic medications such as Risperidone and Aripiprazole. However, these pharmacologic treatments carry risk of adverse effects, and only display a modicum of effectiveness. Thus, there is an increasing need to study novel, and safe interventions as potential alternative treatments for autism.

Study: *"Ketogenic diet versus gluten free casein free diet in autistic children: a case-control study."*

Background: The ketogenic diet is gaining attention due to its proven effect on neurological conditions like epilepsy in children, and the gluten-free, casein-free diet

(GFCF) is a popular special diet used for ameliorating gastrointestinal manifestations of ASD such as bloating, diarrhea, and discomfort that may impact behavior in autistic children. This study aimed to evaluate a modified ketogenic diet vs the gluten-free, casein-free diet in terms of efficacy in ameliorating symptoms and severity of ASD.

Findings: All patients were given a neurological examination, Childhood Autism Rating Scale (CARS) rating, and Autism Treatment Evaluation Test (ATEC) scale assessments before and 6 months after starting the diet they were randomized to. In short, both the ketogenic diet and GFCF groups showed significant improvement in both ATEC and CARS scores in comparison to the control group.

Thus, the authors concluded that a modified ketogenic diet and gluten-free, casein-free diet may safely improve autistic symptoms and severity, and could be recommended for children with ASD. [40]

• EXERCISE

Study: *"Efficacy of ketogenic diet on body composition during resistance training in trained men: a randomized controlled trial."*

Findings: 24 healthy men with more than 2 years of continuous experience in overload training participated in this randomized controlled study. The results found that the subjects who underwent resistance training during a ketogenic diet experienced a greater reduction in fat mass and visceral adipose tissue compared to their non-ketogenic diet counterparts.

This indicates that a ketogenic diet may be an effective and safe alternative dietary approach to decrease fat mass and visceral adipose tissue without decreasing lean body mass. However, the authors suggest that the ketogenic diet may not be useful for increasing muscle mass during positive energy balance in men undergoing resistance training for 8 weeks. [41]

Study: *"Keto analogue and amino acid supplementation affect the ammoniaemia response during exercise under ketogenic conditions."*

Background: Ammonia is highly toxic to humans and can cross the blood-brain barrier, which can lead to decreased cerebral function, neuro-psychiatric disorders, and even death in some cases. Ammonia-mediated excitotoxicity has also been implicated in damage to the central nervous system. Several studies have suggested that increased ammoniaemia, or hyperammonaemia, also occurs during various types of exercise, and is related to both central and peripheral fatigue. Further, it has been found in previous studies that a low-carbohydrate diet increases the production of ammonia during exercise. As such, the **study** aimed to determine the effect of keto analogues and amino acids (KAAA) supplementation on ammonia production in subjects eating a low-carbohydrate diet who exercise.

Findings: Exercise-induced hyperammonaemia can successfully be reduced through supplementation with either amino acids or combined keto analogues and amino acids (KAAA). [42]

Study: *"The effects of a ketogenic diet on exercise metabolism and physical performance in off-road cyclists."*

Findings: High-volume training on a ketogenic diet increases fat metabolism during exercise, reduces body mass and fat content, and decreases post-exercise muscle damage. These results suggest that long-term high-fat diets may be favorable for endurance athletes during preparatory seasons when high volume and low to moderate intensity training is most common. [43]

• SAFETY

Data suggests that the ketogenic therapy is successful in children with intractable epilepsy, but many questions remain. For example, what are the mechanisms of action in the ketogenic diet? What are the potential physiologic derangements that may be produced by ketosis? Are there potential negative effects of adhering to the ketogenic diet for a prolonged period of time? Many questions must be answered if the ketogenic diet is to become an established therapy in adult epilepsy.

Study: *"Efficacy and safety of very-low-calorie ketogenic diet: a double-blind randomized crossover study."*

Background: Calorie restriction is the most effective in quick weight loss, under medical control. Since the popularity of short-term, very-low calorie, ketogenic diet (VLCKD) is increasingly high among obese patients, it has become important to understand the efficacy and safety of the diet. This study aimed to evaluate the safety of a low-calorie ketogenic diet in terms of weight loss.

Findings: This study found that a very low calorie ketogenic diet was able to be used safely for a period of 3 weeks to significantly stimulate fat loss, and improve

metabolic biomarkers without the risk of increasing the possibility of cardiovascular, renal, and hepatic disease. However, this study was limited in the number of subjects and study period. Nevertheless, it does offer evidence regarding the safety and important clinical implications in the administration of a very-low-calorie ketogenic diet.

Note: The 3 week VLCKD program did not induce any negative changes in the nutritional state of the global measurements observed. This included bone mineral content, which is important as previous mouse models suggested that there was evidence of bone mass density reduction. [44]

• GLOBAL DEVELOPMENTAL DELAY

Study: *"Prospective study of ketogenic diet in treatment of children with global developmental delay."*

Background: Global Developmental Delay (GDD) is the general term used to describe a condition that occurs during the developmental period of a child between birth and 18 years, when the child does not reach developmental milestones in all or most areas at the expected times. GDD usually results in the child having lower intellectual functioning than what is perceived as normal. This study aims to examine the effect of the ketogenic diet on neurobehavioral, social, and emotional development in children with global developmental delay.

Findings: The ketogenic diet can improve the neurobehavioral development and behavioral and emotional behaviors in children with GDD, with few adverse effects [45].

• METABOLISM

Study: *"Effects of Twenty Days of the Ketogenic Diet on Metabolic and Respiratory Parameters in Healthy Subjects."*

Background: Despite the widespread use of the ketogenic diet, its effect on respiratory function is still not well investigated. One of the metabolic effects of the ketogenic diet is higher than the usual oxidation of fats, which reduces the respiratory exchange ratio (RER) values. Study authors hypothesized that the ketogenic diet decreases RER and metabolic CO₂ production which may lead to decreased arterial carbon dioxide partial pressure (PETCO₂), which may make the ketogenic diet a potential adjunctive therapy for managing patients with respiratory failure.

This study aimed to investigate the potential for weight loss and improved respiratory function in healthy subjects on a ketogenic diet vs a Mediterranean diet.

Findings: The main findings of the study are that (1) the ketogenic diet significantly decreased the value of respiratory exchange ratio RER; (2) the ketogenic diet significantly decreased carbon dioxide end-tidal partial pressure (PETCO₂); (3) the ketogenic diet had no significant effect on resting energy expenditure, oxygen consumption, carbon dioxide production, or expired total ventilation; and (4) the ketogenic diet significantly decreased body mass and body fat mass.

Thus, the authors concluded that the ketogenic diet may be beneficial for patients with increased carbon dioxide arterial partial pressure due to respiratory insufficiency or failure. [46]

Study: *"The effect of the classical and medium-chain triglyceride ketogenic diet on vitamin and mineral levels."*

Background: Nutritional deficiency can be a risk for individuals with chronic medical conditions such as intractable epilepsy as a result of the long-term use of antiepileptic medications such as valproate and Lamotrigine, or pre-existing difficulties feeding.

This study aimed to examine the risk of nutritional deficiency in children on the restrictive ketogenic diet. This study aimed to examine plasma levels of vitamin A, E, zinc, selenium, and magnesium over the course of 12 months in children on the ketogenic diet and the medium chain triglyceride (MCT) diet. Study authors wanted to determine whether there were any significant changes in these indices in children on the classical ketogenic diet, the MCT diet, and children of a similar age.

Findings: Mean plasma vitamin A decreased in the classical ketogenic diet group, but significantly increased in the MCT group. No significant changes in plasma zinc were seen at 12 months, although mean plasma selenium and magnesium decreased. These findings are interesting, as high-fat foods tend to be high in vitamin A, and it unclear why plasma vitamin A decreased in children on the classical ketogenic diet, and increased in the MCT diet.

Nevertheless, it is known that excessive vitamin A supplementation can cause hypervitaminosis, which is associated with adverse effects such as skeletal and intracranial abnormalities. Therefore, these findings suggest a potential need for the reformulation of vitamin supplements to meet the requirements of the two different dietary approaches. [47]

Study: *"Acetone as a biomarker for ketosis buildup capability—a study in healthy individuals under combined high fat and starvation diets."*

Background: Both fasting and high-fat diets have been used successfully in clinical settings to help individuals lose weight. These interventions are known to increase the level of ketones within the blood. However, much remains unknown about the effects of macronutrient manipulation on blood ketone levels. The purpose of this study was to see how macronutrient and energy manipulation would impact ketone levels, which rather than being measured directly, were measured by acetone, which has been validated as an accurate proxy measure of ketone levels within the body.

Findings: The study found that when individuals consumed a diet with 79% or 90% fat, they had higher acetone levels than when consuming a diet consisting of 29% fat. The researchers were not able to discern a difference in acetone levels when individuals were on a diet with 79% fat or 90% fat. They suggest that diets with very high amounts of fat (such as 90%) may not be needed for clinical interventions.

Note: However, it's worth noting that due to the small sample size, the researchers may not have had enough statistical sensitivity to detect a difference between the high-fat diets with regards to their effects on acetone, and thus ketone levels. [48]

Study: *"Glucose uptake by the brain on chronic high-protein weight-loss diets with either moderate or low amounts of carbohydrate."*

Background: Previous dietary studies have shown that high-protein diets used in conjunction with low-carbohydrate diets lead to reduced hunger and food intake. However, little is known about the mechanisms behind this phenomenon.

This study aimed to see whether any possible differences in hunger between a high-protein, low-carbohydrate diet (22 g/d) and a high-protein, medium-carbohydrate (182 g/d) could be attributed to glucose or ketone metabolism, especially in key areas of the brain involved in the regulation of hunger.

Findings: Both groups experienced weight loss and the high-protein, the low-carbohydrate group experienced less hunger than the medium-carbohydrate group. However, despite a 9-fold difference in carbohydrate intake, the authors were unable to detect a difference between groups with regards to energy utilization by the brain in areas that were analyzed. This may also be due to the small sample size of the study, thus larger studies are needed. [49]

• CARDIOVASCULAR RISK

Study: *"Effects of n-3 polyunsaturated fatty acids (ω -3) supplementation on some cardiovascular risk factors with a ketogenic Mediterranean diet."*

Background: the ketogenic diet (KD) has become a widely used nutritional approach for weight loss. Some of the ketogenic diet's positive effects on metabolism and cardiovascular risk factors are similar to those seen after omega-3 polyunsaturated fatty acid supplementation. This study aimed to examine the effects of a ketogenic Mediterranean diet with phytoextracts combined with omega-3 supplementation on cardiovascular risk factors and inflammation.

Findings: The results did suggest a positive synergistic effect of a Mediterranean ketogenic diet with phytoextracts on body composition, cardiovascular risk factors, and inflammatory markers. Supplementation with ω -3 fatty acids significantly improved the effects of a ketogenic diet

on triglycerides, insulin, and adiponectin, and also decreased inflammatory mediators interleukin 1 beta (IL-1 β), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF- α). [50]

Study: *“Circulating proprotein convertase subtilisin kexin type 9 has a diurnal rhythm synchronous with cholesterol synthesis and is reduced by fasting in humans.”*

Background: Genetic variants of proprotein convertase subtilisin kexin type 9 (PCSK9) influence plasma low-density lipoprotein (LDL) cholesterol in humans, accounting for both hypercholesterolemia and hypocholesterolemia and altered coronary risk. It is known that fasting plasma levels of PCSK9 correlate positively with LDL cholesterol levels in healthy and diabetic patients. This study aimed to examine the influence of hormonal, diurnal, and dietary changes from food deprivation or a ketogenic diet on the function of PCSK9.

Findings: The study found that fasting strongly reduces circulating PCSK9 in healthy humans, occurring concomitantly with suppressed cholesterol synthesis. Despite these changes to circulating PCSK9, the study found that LDL cholesterol levels were not reduced. However, growth hormone which is known to be increased during fasting in humans, was found to reduce circulating PCSK9 in parallel to LDL cholesterol levels. [51]

• INFANTILE SPASMS

Infantile spasms, or West Syndrome, is a specific type of seizure most often seen in the first year of life. Spasms most often occur upon awakening and tend to occur in multiple clusters, with hundreds of seizures per day. Disorders such as birth injury, metabolic disorders, and genetic disorders are known to be the underlying cause of infantile spasms. However, in some children, no cause can be found.

Standard first-line therapy for infantile spasms include several forms of hormonal therapy, or the anti-seizure medication vigabatrin. While these treatments can be highly effective, they can also have serious side effects making it important to explore other alternative therapies.

Study: *“Comparison of short- versus long-term ketogenic diet for intractable infantile spasms.”*

Background: While the ketogenic diet is accepted as a treatment for intractable epilepsy and infantile spasms, the ketogenic diet is not without adverse side effects.

To minimize the adverse effects, the study aimed to examine the different prognoses between a short-term 8-month ketogenic diet and a long-term, >2 year ketogenic diet in patients with refractory infantile spasms.

Findings: Short-term, 8-month group: 37.5% experienced nausea/vomiting, diarrhea/constipation. 50% experienced hypertriglyceridemia. 31% experienced hypercholesterolemia. 31% experienced hepatitis. 0% experienced osteopenia.

Long-term, 2-year group: 41% experienced nausea/vomiting, diarrhea/constipation. 33% experienced hyper-triglyceridemia. 29% experienced hypercholesterolemia. 25% experienced hepatitis. 20% experienced osteopenia.

After successful discontinuation of the ketogenic diet, the prognoses were compared between the group that maintained the diet for 8 months and the group that maintained the diet for >24 months. There was no significant difference in the including relapse tendency, correlated EEG findings, and development outcome data between the two groups. However, serious complications such as osteopenia, ureteral stones, and growth failure significantly occurred only in the long-term trial group. In effect, the utility of the ketogenic diet for 8 months is well-tolerated. However, prolonged ketogenic diet treatment has similar outcomes and recurrence rate, but with more serious complications. [52]

5 | OTHER POTENTIAL APPLICATIONS

• AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, universally fatal disease due to degeneration of motor neurons of the cerebral cortex and anterior horn of the spinal cord. It has claimed the lives of many, including physicist Stephen Hawking, heavyweight boxing champion Ezzard Mack Charles, and baseball legend Lou Gehrig who the disease is colloquially named after.

Most patients with ALS present with symptoms such as cramps, weakness, and muscle atrophy of the hands or feet. Later, weakness progresses to the forearms, shoulders, and lower limbs. Fasciculations, spasticity, hyperactive deep tendon reflexes, extensor plantar reflexes, clumsiness, stiffness, weight loss, fatigue, and difficulty controlling facial expression and tongue movements soon follow.

Other symptoms include hoarseness, dysphagia, and slurred speech. Then, as swallowing becomes more difficult, patients often choke on liquids.

Ultimately, death is most often caused by the failure of the respiratory muscles. 50% of patients with ALS die within three years of the onset, 20% live for five years, and 10% will have a 10- year survival rate. Survival for longer than 30 years is extremely rare [53].

In other words, ALS is a devastating degenerative disease with no known cure, and few treatment options exist. Treatments for ALS include glutamate blockers like riluzole, and muscle relaxers are given to reduce pain and discomfort. Like epilepsy, the exact pathological mechanisms that underlie ALS aren't fully understood either. But what is known is that mechanistically, ALS likely involves oxidative damage, glutamate excitotoxicity, inflammation, and mitochondrial membrane dysfunction in nerve cells [54-56].

Individuals with the disease have a mutation in the gene encoding copper/zinc superoxide dismutase (SOD1) [1]. So when a transgenic mouse model of ALS was created in which the gene SOD 1-G93A was overexpressed, it led to progressive muscle weakness and death resulting from respiratory failure, similarly to what occurs in humans with ALS. Studies on the mutant SOD 1-G93A mutant mice have given a lot of direction for future ALS studies, and treatment.

For example, in one study the SOD 1-G93A mutant mice were given a ketogenic diet and were found to have significantly higher motor neuron counts— and preserved motor function— compared to the control mice [57]. The authors also found that the mutant mice showed impaired electron transport chain function. However, administering the ketone body β -hydroxybutyrate restored activity in the

neurons where electron transport chain function was either already decreased, or had been blocked pharmacologically [58]. While these results are indeed impressive, this study did not indicate an increase in lifespan of the mutant mice.

However, a more recent study found that the mutant mice fed a ketogenic diet variant called the Deanna Protocol delayed disease progression, extended the life expectancy in the ALS mouse model, and demonstrated improved motor function compared to controls [59]. These results are promising and carry the possibility that by raising ketones, the ketogenic diet and its variants may benefit patients with ALS.

• MANIC DEPRESSIVE BIPOLAR DISORDER

The ketogenic diet is best known for its established efficacy in treating intractable epilepsy. However, the mechanisms of action involved in ketosis are complex and not fully understood. Though, it likely involves metabolic adaptation in cellular signaling pathways, decreased neuronal excitability, and neuroprotection. [58] As such, it is possible that the ketogenic diet may be an effective treatment for other neurological diseases other than epilepsy, such as Amyotrophic Lateral Sclerosis (ALS), Manic Depressive Bipolar Disorder, and GLUT1 Deficiency.

While these neurological diseases have little in common pathophysiologically, they each feature abnormalities in cellular energy metabolism. Altered cerebral energy metabolism points to altered mitochondrial function. Unfortunately, exploration into the therapeutic effects of a ketogenic diet on other neurological disorders like Manic Depressive Bipolar Disorder is preliminary. Therefore, their efficacy in treating disorders other than epilepsy in humans is speculative, but warrants investigation as a potential treatment, or adjunct treatment.

The phrase “manic depression” has its origins rooted in ancient Greece, where the term was used to describe symptoms of the mental illness often called ‘Bipolar Disorder.’ The Greeks believed that mental illnesses involved an imbalance among the “humors” stemming from when melancholy, heated by the fluxes of the blood, became its opposite, mania.

Manic-depressive (bipolar or biphasic) psychosis is a disorder in which the individual cycles between a state of mania —characterized by generalized euphoria, a flight of ideas, and hyperactivity — and a state of depression —characterized by a depressed mood, and decreased activity and cognitive function. Researchers of the disorder have referred to this cycle and observed brain activity as a “slow seizure [60].

What may be etiologically interesting are the currently accepted pharmaceutical interventions for Bipolar Disorder or Manic-Depressive illness. They are either antiepileptic drugs (like valproate, carbamazepine, lamotrigine) or have anticonvulsant potential (lithium). In other words, antiepileptic, anticonvulsant activity appears to also be related to mood stabilization in those with Bipolar disorder or Manic-Depressive illness [61].

Also related to mood stabilization are disturbances in electrolyte metabolism. The accumulation of intracellular sodium has also been linked with both mania and depression [62]. Notably, one of the commonalities of effective mood-stabilizing pharmaceuticals also appears to be their ability to inhibit sodium entry and accumulation [63].

However, because the ketogenic diet induces mild acidosis and extracellular hydrogen ions, it would mechanistically be expected to reduce intracellular concentrations of sodium. And, studies have shown that increasing the extracellular concentration of hydrogen ions resulted in reductions in neuronal excitability and neurotransmitter activity [64].

Further, increases in cerebral energy reserves from a ketogenic diet may increase ion pumps leading to alterations in membrane potential, as well as increased capacity to produce inhibitory neurotransmitters, as the ketogenic diet does for epilepsy.

For this reason, the ketogenic diet is theoretically useful for Manic Depressive disorder, but more information is still needed to determine the efficacy and safety of such a treatment.

• GLUT1 DEFICIENCY

Glucose is an essential source of energy for the brain. However, glucose is polar and cannot diffuse across the blood-brain barrier. In order to enter the cell, it must be transported across the membrane through a specific transporter. In a family of glucose transporters, one major protein transports glucose across the blood-brain barrier: the facilitated glucose transporter type I protein (GLUT1) [65].

In a resting state, adults use roughly 20% of their whole-body glucose for brain metabolism. In children, the demand for glucose in the brain is much higher, up to 80% of whole-body glucose utilization— or the equivalent of three to four times higher than it is in adults.

Because the demand for glucose is so high, any reduction in the supply to the developing brain will significantly impair brain function and development in a child [66].

And thus, the deficiency of the GLUT1 transporter to shunt glucose into the brain would lead to a cerebral “energy crisis” and result in the same.

In 1991, a rare genetic disorder was first described where infants presented with developmental delays, microcephaly, hypotonia, motor development problems, and low glucose concentrations in cerebrospinal fluids (hypoglycorrhachia) even in the presence of normal glycemic values, and seizures. The cause of this disorder was found to be the absence of the GLUT1 transporter protein [67- 70] .

At birth, babies with GLUT1 deficiency syndrome may be born with a normal sized head. However, due to the lack of glucose fueling the cerebral cells properly, the growth of the brain is slow and can result in microcephaly, developmental delays, and intellectual disability [71] . Unfortunately, there are other GLUT1 deficiency syndrome symptoms.

Most have other pronounced neurological problems, including spasticity, ataxia, confusion, lethargy, headaches, uncontrollable muscle twitches, and difficulty with speech. Of note, these symptoms seem to occur more frequently during periods of fasting [67].

Approximately 500 cases of GLUT1 transporter disorder have been reported since the disorder was first identified. New estimates suggest that it may affect nearly 1 in 90,000 and that the disorder may actually be underdiagnosed since many other neurological disorders share similar symptoms. Several conditions that were originally given other names are now recognized as mere variants of a GLUT1 deficiency include paroxysmal choreoathetosis with spasticity, paroxysmal exercise-induced dyskinesia and epilepsy, and early-onset absence epilepsy with mild intellectual disability [71].

The ketogenic diet may have the potential to be an effective treatment for GLUT1 deficiency, since ketone bodies are another viable energy source for the brain. Further, ketone bodies do not require the GLUT1 transporter protein to assist in crossing the cell membrane. Ordinarily, utilization of ketones by the brain is minimal. But on a ketogenic diet, ketone bodies replace glucose as fuel for the brain. The ketone bodies are then converted to acetyl-CoA, and then enter the Krebs cycle within brain mitochondria, leading to the production of adenosine triphosphate (ATP): the primary energy carrier in all of the living organisms on the planet.

Some preliminary evidence suggests that the ketogenic diet can help individuals with GLUT1 Deficiency Syndrome. One study of a family of three with a GLUT1 deficiency found that their seizures responded well to a ketogenic diet. It was also found that, unlike epilepsy, seizure frequency and severity of seizures worsened during fasting [67]. Because pharmaceutical treatment options are limited, the ketogenic diet is recommended as a first-line treatment for a GLUT1 deficiency.

6 | CONCLUSIONS

• NEXT STEPS FOR KETOGENIC DIET RESEARCH

The Charlie Foundation was born out of the desire to spare children from the unnecessary suffering that Charlie Abrahams endured before he achieved seizure freedom with the ketogenic diet. His parents, Jim and Nancy Abrahams shared their story in 1994 on Dateline and through a 1999 movie called First Do No Harm.

Despite dramatic testimonials and a dedicated foundation, the ketogenic diet remained under-

utilized. In 2007, the Charlie Foundation estimated that fewer than 15 of the 200 children's hospitals in the United States had a ketogenic diet therapy program. However, several key break-throughs came in 2008. The Charlie Foundation had commissioned medical professionals with ketogenic experience to collaborate on guidelines for prescribing the diet. This culminated in a publication in *Epilepsia*, a prestigious international medical journal titled "Optimal Clinical Management of Children Receiving the Ketogenic Diet: Recommendations of the International Ketogenic Diet Study Group" [72].

The same year, a Class I study was published in *Lancet Neurology* confirming the ketogenic diet's efficacy as a treatment for epilepsy, and more positive Class I studies followed. From these publications, the use of ketogenic diet therapy spread rapidly worldwide, paving the way for a greater understanding of its benefits for other disorders.

Indeed, the past 10 years have been a period of massive growth and revitalization in the field of ketogenic diet study and metabolic therapy. However, it may just be the beginning of the work that is needed to evaluate the ketogenic diet thoroughly. The following are areas currently needing more investigation:

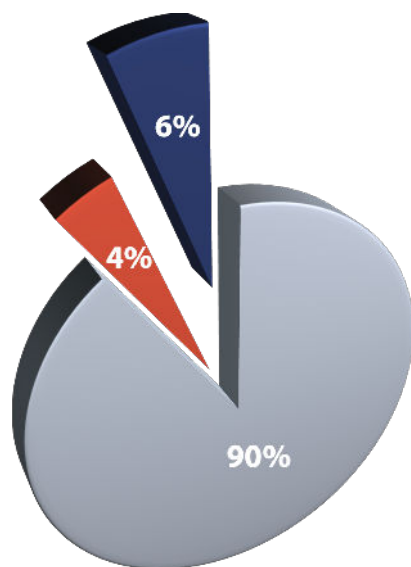
- Alternative Ketogenic Diets
- Adverse Effects
- Long-Term Safety
- Preventing Diet Discontinuation
- Mechanisms of Action
- Improving Tolerability
- Potential Therapeutic Applications

• ALTERNATIVE KETOGENIC DIETS

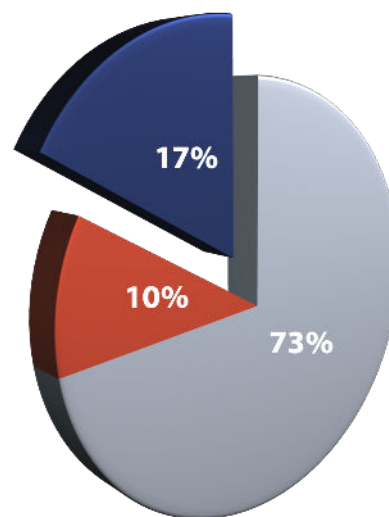
As the classical ketogenic diet [Figure A] approaches its centennial anniversary, the ketogenic landscape has expanded considerably both in its application and implementation. Although still extensively used today, the classical ketogenic diet therapy has also been used as the basis for development of alternative ketogenic protocols.

One ketogenic diet protocol gaining in popularity incorporates medium chain fatty acids, known as the Medium-Chain Triglyceride Diet (MCTD) [Figure B].

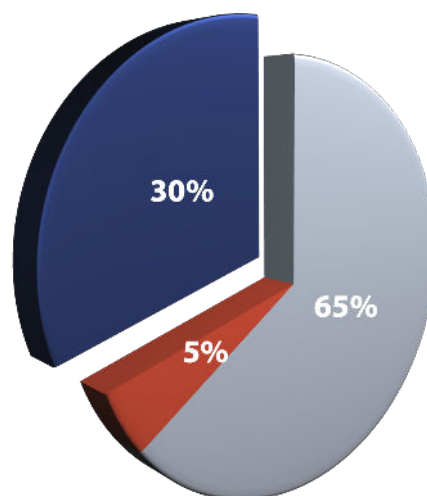
The MCTD is used for individuals who benefit from a greater carbohydrate allowance facilitated by the increased ketogenic potential of medium chain triglycerides. More recently, another less restrictive dietary approach has also been developed that allows for more protein, the modified Atkins diet (MAD) [Figure C].



A. ● FAT ● CARBOHYDRATE ● PROTEIN



B. ● FAT ● CARBOHYDRATE ● PROTEIN



C. ● FAT ● CARBOHYDRATE ● PROTEIN

Figure A. Percentage Fat, Protein, and Carbohydrate in the Classical Ketogenic Diet. **Figure B.** Fat (30%-60% MCT), Protein, and Carbohydrate in the MCTD. **Figure C.** Fat, Protein, and Carbohydrate in the Modified Atkins Diet. [71].

As worldwide use of the ketogenic diet continues to grow, it is clear that the alternative dietary protocols have an important place within the treatment options. The MAD in particular has emerged as a therapy with great potential for treating not only children, but also adults, and those in countries with more limited resources or traditionally higher carbohydrate diets. Further research will enable us to optimize protocols for clinical implementation to ensure the best possible outcome for those embarking on dietary treatment of epilepsy.

• ADVERSE EFFECTS

In general, the ketogenic diet is well tolerated, and on average, 60% of patients remain on the diet for over 6 months [72]. However, despite the high anticipations many hold for the the ketogenic diet and the numerous positive studies that have been published to date, the diet is not without adverse effects.

Adverse effects can be divided between common, and serious. Common side effects include constipation, vomiting, metabolic acidosis, vitamin/mineral deficiencies, lethargy, nausea, electrolyte imbalances, hypercholesterolemia, and hyper-triglyceridemia.

More significant side effects are not as common, but include stunted growth, hypoglycemia, kidney stones, pancreatitis, hepatitis, osteopenia, cardiomyopathy, and death [73-80].

While the ketogenic diet is an effective therapy for intractable epilepsy and certain metabolic and neurological disorders, these potential adverse effects must be weighed against the benefits. Further, the long-term effects of the ketogenic diet also need to be investigated thoroughly as data suggest that adverse events become more serious and more pronounced over time.

• IMPROVING TOLERABILITY

The ketogenic diet is a restrictive, and demanding diet that can be difficult to maintain, and tolerability of the ketogenic diet is the single-most important factor limiting individual acceptance for initiation [81-84].

Therefore, improving tolerability of the ketogenic diet is crucial to preventing diet discontinuation, warranting further investigation into methods for improving palatability, improving available foods that are compliant, as well as addressing cultural and social acceptance.

Note: The Keto Diet product market may be in a unique position to improve tolerability, especially in social and cultural environments that typically feature carbohydrate-rich “special occasion” types of foods. Standards for Keto Certified products were developed for adherence to a classical ketogenic diet, and are supported by a large body of scientific literature.

• MECHANISMS OF ACTION

In spite of a ketogenic diet therapy's ability to suppress refractory epilepsies for over a century, the ketogenic diet's underlying mechanisms of action are not fully understood. Metabolic hypotheses, amino acid hypotheses, ketone hypotheses, and the gut microbiome hypothesis have all been suggested to be responsible for its therapeutic effects [15, 85].

As such, the ketogenic diet remains a fertile area of study, including further elucidating these underlying mechanisms, discovering new potential therapeutic applications of the diet, and producing more studies to help develop new treatments aimed at improving sustainability and reducing adverse effects.

7 | REFERENCES

1. Wheless, J. W. (2008). History of the ketogenic diet. *Epilepsia*, 49, 3–5. doi:10.1111/j.1528-1167.2008.01821.x
2. Mark 9:14-29. King James Version.
3. Wheless, J. W. (2008). History of the ketogenic diet. *Epilepsia*, 49, 3–5. doi:10.1111/j.1528-1167.2008.01821.x
4. Lennox WG, Cobb S. (1928). Studies in epilepsy. VIII: The clinical effect of fasting. *Arch Neurol Psychiatr* 20:771-779. doi:10.1001/archneurpsyc.1928.02210160112009
5. Wheless, J. W. (2012). Dietary Therapies to Treat Epilepsy. *Epilepsy in Children and Adolescents*, 219–241. doi:10.1002/9781119998600.ch13
6. Schwartz, R. H., Eaton, J., Bower, B. D., & Aynsley-Green, A. (2008). ketogenic diets in the treatment of epilepsy: short-term clinical effects. *Developmental Medicine & Child Neurology*, 31(2), 145–151. doi:10.1111/j.1469-8749.1989.tb03972.x
7. Wheless, J. W. (2004). History and Origin of the Ketogenic Diet. *Epilepsy and the Ketogenic Diet*, 31–50. doi:10.1007/978-1-59259-808-3_2
8. Goldbloom A. (1922). Some Observations on the Starvation Treatment of Epilepsy. *Canadian Medical Association journal*, 12(8), 539–540. PMID: 20314170
9. Lennox, W. G. (1928). Studies in Epilepsy. *Archives of Neurology & Psychiatry*, 20(4), 771. doi:10.1001/archneurpsyc.1928.02210160112009
10. Wheless, J. W. (2004). History and Origin of the Ketogenic Diet. *Epilepsy and the Ketogenic Diet*, 31–50. doi:10.1007/978-1-59259-808-3_2
11. Magiorkinis, E., Diamantis, A., Sidiropoulou, K., & Panteliadis, C. (2014). Highlights in the History of Epilepsy: The Last 200 Years. *Epilepsy Research and Treatment*, 2014, 1–13. doi:10.1155/2014/582039
12. Swink TD, Vining EPG, Freeman JM. (1997). The ketogenic diet: 1997. *Adv Pediatr*;44:297-329. PMID: 9265974
13. Woodyatt, r. t. (1921). Objects and method of diet adjustment in diabetes. *Archives of Internal Medicine*, 28(2), 125. doi:10.1001/archinte.1921.00100140002001
14. Wilder, R. M. (1924). "Optimal" Diets for Diabetic Patients. *JAMA: The Journal of the American Medical Association*, 83(10), 733. doi:10.1001/jama.1924.02660100007003
15. Nylen, K., Likhodii, S., & Burnham, W. M. (2009). The ketogenic diet: Proposed mechanisms of action. *Neurotherapeutics*, 6(2), 402–405. doi:10.1016/j.nurt.2009.01.021
16. Höhn, S., Dozières-Puyravel, B., & Auvin, S. (2019). History of dietary treatment from Wilder's hypothesis to the first open studies in the 1920s. *Epilepsy & Behavior*, 101, 106588. doi:10.1016/j.yebeh.2019.106588
17. Kim, J.-M. (2017). Ketogenic diet: Old treatment, new beginning. *Clinical Neurophysiology Practice*, 2, 161–162. doi:10.1016/j.cnp.2017.07.001
18. "More than 100 million Americans have diabetes or prediabetes." Centers for Disease Control and Prevention. (2017) Accessed February 10, 2019 <https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html>
19. Moreno, B., Crujeiras, A. B., Bellido, D., Sajoux, I., & Casanueva, F. F. (2016). Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease. *Endocrine*, 54(3), 681–690. doi:10.1007/s12020-016-1050-2
20. Goday, A., Bellido, D., Sajoux, I., Crujeiras, A. B., Burguera, B., García-Luna, P. P., ... Casanueva, F. F. (2016). Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. *Nutrition & Diabetes*, 6(9), e230–e230. doi:10.1038/nutd.2016.36
21. Moreno, B., Crujeiras, A. B., Bellido, D., Sajoux, I., & Casanueva, F. F. (2016). Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease. *Endocrine*, 54(3), 681–690. doi:10.1007/s12020-016-1050-2

22. Moreno, B., Bellido, D., Sajoux, I., Goday, A., Saavedra, D., Crujeiras, A. B., & Casanueva, F. F. (2014). Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. *Endocrine*, 47(3), 793–805. doi:10.1007/s12020-014-0192-3
23. Merra G1, Miranda R, Barrucco S, Gualtieri P, Mazza M, Moriconi E, Marchetti M, Chang TF, De Lorenzo A, Di Renzo L. (2016). Very-low-calorie ketogenic diet with aminoacid supplement versus very low restricted-calorie diet for preserving muscle mass during weight loss: a pilot double-blind study. *Eur Rev Med Pharmacol Sci*. 2016 Jul;20(12):2613-21. doi: 10.3390/nu1102368
24. De Luis, D., Domingo, J. C., Izaola, O., Casanueva, F. F., Bellido, D., & Sajoux, I. (2016). Effect of DHA supplementation in a very low-calorie ketogenic diet in the treatment of obesity: a randomized clinical trial. *Endocrine*, 54(1), 111–122. doi:10.1007/s12020-016-0964-z
25. Partsalaki, I., Karvela, A., & Spiliotis, B. E. (2012). Metabolic impact of a ketogenic diet compared to a hypocaloric diet in obese children and adolescents. *Journal of Pediatric Endocrinology and Metabolism*, 25(7-8). doi:10.1515/jpem -2012-0131
26. Merra G1, Gratterer S, De Lorenzo A, Barrucco S, Perrone MA, Avolio E, Bernardini S, Marchetti M, Di Renzo L. (2017). Effects of very-low-calorie diet on body composition, metabolic state, and genes expression: a randomized double-blind placebo-controlled trial. *Eur Rev Med Pharmacol Sci*. 2017 Jan;21(2):329-345. PMID: 28165552
27. Cancer Statistics. (2018) National Cancer Institute. Accessed February 2019. <https://www.cancer.gov/about-cancer/understanding/statistics>
28. Klement, R. J., & Sweeney, R. A. (2016). Impact of a ketogenic diet intervention during radiotherapy on body composition: II. Protocol of a randomised phase I study (KETOCOMP). *Clinical Nutrition ESPEN*, 12, e1–e6. doi:10.1016/j.clnesp.2015.11.001
29. Lambrechts, D. A. J. E., de Kinderen, R. J. A., Vles, J. S. H., de Louw, A. J. A., Aldenkamp, A. P., & Majoie, H. J. M. (2016). A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. *Acta Neurologica Scandinavica*, 135(2), 231–239. doi:10.1111/ane.12592
30. Taub, K. S., Kessler, S. K., & Bergqvist, A. G. C. (2014). Risk of seizure recurrence after achieving initial seizure freedom on the ketogenic diet. *Epilepsia*, 55(4), 579–583. doi:10.1111/epi.12583
31. Lambrechts, D. A. J. E., de Kinderen, R. J. A., Vles, J. S. H., de Louw, A. J. A., Aldenkamp, A. P., & Majoie, H. J. M. (2016). A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. *Acta Neurologica Scandinavica*, 135(2), 231–239. doi:10.1111/ane.12592
32. Kim, J. A., Yoon, J.-R., Lee, E. J., Lee, J. S., Kim, J. T., Kim, H. D., & Kang, H.-C. (2015). Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. *Epilepsia*, 57(1), 51–58. doi:10.1111/epi.13256
33. Baby, N., Vinayan, K. P., Pavithran, N., & Grace Roy, A. (2018). A pragmatic study on efficacy, tolerability and long term acceptance of ketogenic diet therapy in 74 South Indian children with pharmaco-resistant epilepsy. *Seizure*, 58, 41–46. doi:10.1016/j.seizure.2018.03.020
34. Raju, K. N. V., Gulati, S., Kabra, M., Agarwala, A., Sharma, S., Pandey, R. M., & Kalra, V. (2011). Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: A randomized open labeled study. *Epilepsy Research*, 96(1-2), 96–100. doi:10.1016/j.eplepsyres.2011.05.005

35. De Kinderen, R. J. A., Lambrechts, D. A. J. E., Wijnen, B. F. M., Postulart, D., Aldenkamp, A. P., Majoie, M. H. J. M., & Evers, S. M. A. A. (2015). An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: An interim analysis. *Epilepsia*, 57(1), 41–50. doi:10.1111/epi.13254
36. Neal, E. G., Chaffe, H., Schwartz, R. H., Lawson, M. S., Edwards, N., Fitzsimmons, G., ... Cross, J. H. (2009). A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia*, 50(5), 1109–1117. doi:10.1111/j.1528-1167.2008.01870.x
37. Law, T. H., Davies, E. S. S., Pan, Y., Zanghi, B., Want, E., & Volk, H. A. (2015). A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy. *British Journal of Nutrition*, 114(09), 1438–1447. doi:10.1017/s000711451500313x
38. Packer, R. M. A., Law, T. H., Davies, E., Zanghi, B., Pan, Y., & Volk, H. A. (2016). Effects of a ketogenic diet on ADHD-like behavior in dogs with idiopathic epilepsy. *Epilepsy & Behavior*, 55, 62–68. doi:10.1016/j.yebeh.2015.11.014
39. Johns Hopkins University Bloomberg School of Public Health. "U.S. autism rate up 15 percent over two-year period: Researchers say racial and ethnic disparities are narrowing." *ScienceDaily*. ScienceDaily, 26 April 2018. Accessed February 2019.
40. El-Rashidy, O., El-Baz, F., El-Gendy, Y., Khalaf, R., Reda, D., & Saad, K. (2017). Ketogenic diet versus gluten free casein free diet in autistic children: a case-control study. *Metabolic Brain Disease*, 32(6), 1935–1941. doi:10.1007/s11011-017-0088-z
41. Vargas, S., Romance, R., Petro, J. L., Bonilla, D. A., Galancho, I., Espinar, S., ... Benítez-Porres, J. (2018). Efficacy of ketogenic diet on body composition during resistance training in trained men: a randomized controlled trial. *Journal of the International Society of Sports Nutrition*, 15(1). doi:10.1186/s12970-018-0236-9
42. Prado, E. S., de Rezende Neto, J. M., de Almeida, R. D., Dória de Melo, M. G., & Cameron, L.-C. (2011). Keto analogue and amino acid supplementation affects the ammoniaemia response during exercise under ketogenic conditions. *British Journal of Nutrition*, 105(12), 1729–1733. doi:10.1017/s000711451000557x
43. Zajac, A., Poprzecki, S., Maszczyk, A., Czuba, M., Michalczyk, M., & Zydek, G. (2014). The Effects of a Ketogenic Diet on Exercise Metabolism and Physical Performance in Off-Road Cyclists. *Nutrients*, 6(7), 2493–2508. doi:10.3390/nu6072493
44. Colica C1, Merra G, Gasbarrini A, De Lorenzo A, Cioccoloni G, Gualtieri P, Perrone MA, Bernardini S, Bernardo V, Di Renzo L, Marchetti M.. (2017). Efficacy and safety of very-low-calorie ketogenic diet: a double blind randomized crossover study. *Eur Rev Med Pharmacol Sci*. 2017 May;21(9):2274-2289. PMID: 28537652
45. Zhu DN1, Li P, Wang J, Yuan JY, Zhang GY, Liang JF, Wang MM, Zhao YX, An S, Ma N, Ma DD. [Prospective study of ketogenic diet in treatment of children with global developmental delay]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2017 Oct;19(10):1038-1043. doi:10.7499/j.issn.1008-8830.2017.10.002
46. Alessandro, R., Gerardo, B., Alessandra, L., Lorenzo, C., Andrea, P., Keith, G., ... Antonio, P. (2015). Effects of Twenty Days of the Ketogenic Diet on Metabolic and Respiratory Parameters in Healthy Subjects. *Lung*, 193(6), 939–945. doi:10.1007/s00408-015-9806-7
47. Christodoulides, S. S., Neal, E. G., Fitzsimmons, G., Chaffe, H. M., Jeanes, Y. M., Aitkenhead, H., & Cross, J. H. (2011). The effect of the classical and medium chain triglyceride ketogenic diet on vitamin and mineral levels. *Journal of Human Nutrition and Dietetics*, 25(1), 16–26. doi:10.1111/j.1365-277x.2011.01172.x

48. Prabhakar, A., Quach, A., Zhang, H., Terrera, M., Jackemeyer, D., Xian, X., ... Forzani, E. S. (2015). Acetone as biomarker for ketosis buildup capability - a study in healthy individuals under combined high fat and starvation diets. *Nutrition Journal*, 14(1). doi:10.1186/s12937-015-0028-x
49. Loble, G. E., Johnstone, A. M., Fyfe, C., Horgan, G. W., Holtrop, G., Bremner, D. M., ... Welch, A. (2013). Glucose uptake by the brain on chronic high-protein weight-loss diets with either moderate or low amounts of carbohydrate. *British Journal of Nutrition*, 111(04), 586–597. doi:10.1017/s0007114513002900
50. Paoli, A., Moro, T., Bosco, G., Bianco, A., Grimaldi, K., Camporesi, E., & Mangar, D. (2015). Effects of n-3 Polyunsaturated Fatty Acids (ω -3) Supplementation on Some Cardiovascular Risk Factors with a Ketogenic Mediterranean Diet. *Marine Drugs*, 13(2), 996–1009. doi:10.3390/md13020996
51. Persson, L., Cao, G., Stahle, L., Sjöberg, B. G., Troutt, J. S., Konrad, R. J., ... Rudling, M. (2010). Circulating Proprotein Convertase Subtilisin Kexin Type 9 Has a Diurnal Rhythm Synchronous With Cholesterol Synthesis and Is Reduced by Fasting in Humans. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 30(12), 2666–2672. doi:10.1161/atvbaha.110.214130
52. Kang, H.-C., Lee, Y. J., Lee, J. S., Lee, E. J., Eom, S., You, S. J., & Kim, H. D. (2011). Comparison of short- versus long-term ketogenic diet for intractable infantile spasms. *Epilepsia*, 52(4), 781–787. doi:10.1111/j.1528-1167.2010.02940.x
53. Hulisz, D. (2018). Amyotrophic lateral sclerosis: disease state overview. *Am J Manag Care*, S320–S326. PMID: 30207670
54. Vucic, S., Rothstein, J. D., & Kiernan, M. C. (2014). Advances in treating amyotrophic lateral sclerosis: insights from pathophysiological studies. *Trends in Neurosciences*, 37(8), 433–442. doi:10.1016/j.tins.2014.05.006
55. Martin, L. J. (2011). Mitochondrial pathobiology in ALS. *Journal of Bioenergetics and Biomembranes*, 43(6), 569–579. doi:10.1007/s10863-011-9395-y
56. Ari, C., Poff, A. M., Held, H. E., Landon, C. S., Goldhagen, C. R., Mavromates, N., & D'Agostino, D. P. (2014). Metabolic Therapy with Deanna Protocol Supplementation Delays Disease Progression and Extends Survival in Amyotrophic Lateral Sclerosis (ALS) Mouse Model. *PLoS ONE*, 9(7), e103526. doi:10.1371/journal.pone.0103526
57. Zhao, Z., Lange, D. J., Voustianiouk, A., MacGrogan, D., Ho, L., Suh, J., ... Pasinetti, G. M. (2006). *BMC Neuroscience*, 7(1), 29. doi:10.1186/1471-2202-7-29
58. D'Alessandro, G., Calcagno, E., Tartari, S., Rizzardini, M., Invernizzi, R. W., & Cantoni, L. (2011). Glutamate and glutathione interplay in a motor neuronal model of amyotrophic lateral sclerosis reveals altered energy metabolism. *Neurobiology of Disease*, 43(2), 346–355. doi:10.1016/j.nbd.2011.04.003
59. Klein, S., & Wolfe, R. R. (1992). Carbohydrate restriction regulates the adaptive response to fasting. *American Journal of Physiology-Endocrinology and Metabolism*, 262(5), E631–E636. doi:10.1152/ajpendo.1992.262.5.E631
60. El-Mallakh, R. S. (1983). The Na, K-ATPase hypothesis for manic-depression. I. General considerations. *Medical Hypotheses*, 12(3), 253–268. doi:10.1016/0306-9877(83)90042-7
61. El-Mallakh, R. S., & Huff, M. O. (2001). Mood Stabilizers and Ion Regulation. *Harvard Review of Psychiatry*, 9(1), 23–32. doi:10.1080/10673220127873
62. Naylor, G. J., McNamee, H. B., & Moody, J. P. (1971) Changes in Erythrocyte Sodium and Potassium on Recovery from a Depressive Illness. *The British Journal of Psychiatry*, 118(543), 219–223. doi:10.1192/bjp.118.543.219

63. CCoppen, A., Shaw, D. M., Malleson, A., & Costain, R. (1966). *Mineral metabolism in mania*. *BMJ*, 1(5479), 71–75. doi:10.1136/bmj.1.5479.71
64. Balestrino, M., & Somjen, G. G. (1988). A concentration of carbon dioxide, interstitial pH and synaptic transmission in the hippocampal formation of the rat. *The Journal of Physiology*, 396(1), 247–266. doi:10.1113/jphysiol.1988.sp016961
65. Klepper, J., & Voit, T. (2002). Facilitated glucose transporter protein type 1 (GLUT1) deficiency syndrome: impaired glucose transport into the brain: a review. *European Journal of Pediatrics*, 161(6), 295–304. doi:10.1007/s00431-002-0939-3
66. Cremer, J. E. (1982). Substrate Utilization and Brain Development. *Journal of Cerebral Blood Flow & Metabolism*, 2(4), 394–407. doi:10.1038/jcbfm.1982.45
67. Brockmann, K., Wang, D., Korenke, C. G., Von Moers, A., Ho, Y.-Y., Pascual, J. M., De Vivo, D. C. (2001). Autosomal dominant GLUT1 deficiency syndrome and familial epilepsy. *Annals of Neurology*, 50(4), 476–485. doi:10.1002/ana.1222
68. Klepper, J., Wang, D., Fischbarg, J., Vera, J. C., Jarjour, I. T., O'Driscoll, K. R., & De Vivo, D. C. (1999). *Neurochemical Research*, 24(4), 587–594. doi:10.1023/a:1022544131826
69. Klepper, J. (2001). Autosomal dominant transmission of GLUT1 deficiency. *Human Molecular Genetics*, 10(1), 63–68. doi:10.1093/hmg/10.1.63
70. Seidner, G., Alvarez, M. G., Yeh, J.-I., O'Driscoll, K. R., Klepper, J., Stump, T. S., De Vivo, D. C. (1998). GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. *Nature Genetics*, 18(2), 188–191. doi:10.1038/ng0298-188
71. Pearson, T. S., Akman, C., Hinton, V. J., Engelstad, K., & De Vivo, D. C. (2013). Phenotypic Spectrum of Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS). *Current Neurology and Neuroscience Reports*, 13(4). doi:10.1007/s11910-013-0342-7
72. Kossoff, E. H., Zupec-Kania, B. A., Auvin, S., Ballaban-Gil, K. R., Christina Bergqvist, A. G., ... Blackford, R. (2018). Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open*, 3(2), 175–192. doi:10.1002/epi4.12225
73. Williams, S., Basualdo-Hammond, C., Curtis, R., and Schuller, R. (2002). Growth Retardation in Children with Epilepsy on the Ketogenic Diet. *Journal of the American Dietetic Association*, 102(3), 405–407. doi:10.1016/s0002-8223(02)90093-3
74. Bergqvist, A. G. C., Schall, J. I., Gallagher, P. R., Cnaan, A., & Stallings, V. A. (2005). Fasting versus Gradual Initiation of the Ketogenic Diet: A Prospective, Randomized Clinical Trial of Efficacy. *Epilepsia*, 46(11), 1810–1819. doi:10.1111/j.1528-1167.2005.00282.x
75. Kielb, S., Koo, H.P., Bloom, D.A., and Faerber, G.J. (2000). Nephrolithiasis associated with the ketogenic diet. *The Journal of Urology*, 164(2), 464–466. doi:10.1016/s0022-5347(05)67400-9
76. Kang, H. C., Chung, D. E., Kim, D. W., & Kim, H. D. (2004). Early- and Late-onset Complications of the Ketogenic Diet for Intractable Epilepsy. *Epilepsia*, 45(9), 1116–1123. doi:10.1111/j.0013-9580.2004.10004.x
77. Neal, E. G., Zupec-Kania, B., & Pfeifer, H. H. (2012). Carnitine, nutritional supplementation and discontinuation of ketogenic diet therapies. *Epilepsy Research*, 100(3), 267–271. doi:10.1016/j.epilepsyres.2012.04.021

78. Ballaban-Gil, K.R. "Complications of the Ketogenic Diet." *Epilepsy and the Ketogenic Diet* 1st Edition, edited by Carl E. Stafstrom et al. Springer New York, 2004, pp 123-128
79. Stewart, W. A., Gordon, K., & Camfield, P. (2001). Acute Pancreatitis Causing Death in a Child on the Ketogenic Diet. *Journal of Child Neurology*, 16(9), 682–682. doi:[10.1177/088307380101600910](https://doi.org/10.1177/088307380101600910)
80. Bergqvist, A.G.C, Schall, J.I., Stallings, V.A., and Zemel, B.S. (2008). Progressive bone mineral loss in children with intractable epilepsy treated with the ketogenic diet. *Am J Clin Nutr* 88, 1678–1684. doi:[10.3945/ajcn.2008.26099](https://doi.org/10.3945/ajcn.2008.26099)
81. Duchowny, M. S. (2005). Food for Thought: The Ketogenic Diet and Adverse Effects in Children. *Epilepsy Currents*, 5(4), 152–154. doi:[10.1111/j.1535-7511.2005.00044.x](https://doi.org/10.1111/j.1535-7511.2005.00044.x)
82. Ballaban-Gil, K., Callahan, C., O'Dell, C., Pappo, M., Moshe, S., & Shinnar, S. (1998). Complications of the Ketogenic Diet. *Epilepsia*, 39(7), 744–748. doi:[10.1111/j.1528-1157.1998.tb01160.x](https://doi.org/10.1111/j.1528-1157.1998.tb01160.x)
83. Vining, E. P. G. (1999). Clinical efficacy of the ketogenic diet. *Epilepsy Research*, 37(3), 181–190. doi:[10.1016/s0920-1211\(99\)00070-4](https://doi.org/10.1016/s0920-1211(99)00070-4)
84. Hemingway, C., Freeman, J. M., Pillas, D. J., & Pyzik, P. L. (2001). The Ketogenic Diet: A 3- to 6-Year Follow-Up of 150 Children Enrolled Prospectively. *PEDIATRICS*, 108(4), 898–905. doi:[10.1542/peds.108.4.898](https://doi.org/10.1542/peds.108.4.898)
85. Cabrera-Mulero, A., Tinahones, A., Bandera, B., Moreno-Indias, I., Macías-González, M., & Tinahones, F. J. (2019). Keto microbiota: A powerful contributor to host disease recovery. *Reviews in Endocrine and Metabolic Disorders*. doi:[10.1007/s11154-019-09518-8](https://doi.org/10.1007/s11154-019-09518-8)

Pendergrass, K. (2019) **A Systematic Review of Randomized Controlled Trials Investigating the Therapeutic and Adverse Effects of the Ketogenic Diet Across Various Health Conditions. Ketogenic Diet Research.** The Paleo Foundation.

This work is licensed under a [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/).

