# The Ketogenic Diet as a Potential Treatment for Juvenile Huntington's Disease

Lauren A. Neal* and Jennifer Larimore

The ketogenic diet (KD) is a low-carb, high-fat diet that has been used for decades for not only weight loss, but the treatment of many neurological conditions. KD is most associated with the treatment of epilepsy because it reduces seizure frequency. Additionally, there is increasing evidence that KD could provide some relief of symptoms for other severe neurological disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and amyotrophic lateral sclerosis (ALS). Juvenile Huntington's disease (JHD) is a rare form of Huntington's Disease (HD) that affects individuals under the age of 21. JHD is commonly treated with pharmaceuticals that have adverse side effects which can affect the developing brain. There is the need to develop or implement treatments that have high efficacy without the negative side effects to protect the developing brains of those suffering from JHD. This review proposes the ketogenic diet as a promising treatment for JHD, due to its effects on symptoms seen in both JHD and other neurological disorders. There is the need to develop or implement treatments that have high efficacy without the negative side effects to protect the developing brains of those suffering from JHD.

Huntington's Disease (HD) is a neurological disorder characterized by several motor and cognitive symptoms. HD primarily affects the Caucasian population with a prevalence of around 1/10,000-1/20,000 (Roos, 2010). Adult-onset HD is heavily associated with chorea, characterized by unnecessary movement. Researchers in various fields have been exploring the pathogenesis, progression, and treatment options of the disease for many years. The majority of the research on disease pathogenesis examines adult-onset HD, which is arguably the most prevalent, with few studies considering the children and teens that are also affected by the disease. Juvenile Huntington's Disease (JHD) is characterized by the onset of HD in an individual under the age of 21. Although the exact prevalence of the condition is unknown, the literature suggests that JHD affects around 10 per 10,000 children worldwide (Gonzalez-Alegre and Afifi, 2006). In cases of HD alone, children and teens with JHD are thought to make up nearly 5% of the total (Quarrell et al., 2012).

Adult-onset HD and JHD are both associated with an abnormally high number of CAG trinucleotide repeats in the HTT gene. These CAG repeats are eventually cleaved into small, toxic proteins that aggregate and impair proper cellular function, leading to a number of the phenotypes associated with HD. As the mutations that cause this abnormal addition of repeats are passed down from generation to generation, the total number of trinucleotide repeats will increase. In healthy individuals, the sequence is repeated approximately 20 times, but in HD, the number is nearly doubled (Myers, 2004). In JHD, there are usually an even higher number of repeats ranging from 50 to 80 (Myers, 2004). Additionally, there is an inverse relationship between the number of CAG trinucleotide repeats and the average age of onset (Myers, 2004). This finding suggests that as time progresses, there will be an increase in the number of children with JHD.

JHD presents itself with a number of varying symptoms that differ from the symptoms seen in adult-onset HD. One of the most prevalent symptoms seen in JHD cases is seizure activity (Brackenridge, 1980; Gambardella et al., 2001; Cloud et al., 2012). Motor symptoms that present themselves early are dystonia, bradykinesia, and parkinsonian features (Quarrell et al., 2013). Many cognitive and psychiatric symptoms are seen in the disease, including but not limited to, mood disorders, problems in school, and anxiety (Ribai et al., 2007). JHD becomes difficult to diagnose based on the symptoms presented because the deficits may share similar traits to those implicated in puberty. Research involving JHD is minimal, contributing to the lack of knowledge of signs and symptoms resulting in misdiagnosis of the condition.

The current treatments for JHD include pharmaceuticals, psychotherapy, and physical therapy for motor deficits. Antidepressant, anxiolytic, and antipsychotic drugs are commonly prescribed for the treatment of the cognitive symptoms commonly

seen in cases of JHD (Quigley, 2017). Although these drugs are approved for particular uses in adults by the FDA, prescribing these drugs to children comes with some challenges. Researchers have examined the usage of antipsychotics in children and have determined that 1) they are mostly prescribed for the treatment of conditions not related to psychosis and 2) there can be a number of adverse side effects or increased risks in children that take these medications (Andrade et al., 2011; Penfold et al., 2014; Correll, 2011). A study conducted by Correll explored the effects of using standard antipsychotic treatment for children with schizophrenia to which the lab observed a significant increase in risk for developing metabolic disorders as well as drug-induced motor deficits, also known as extrapyramidal symptoms (Correll, 2011). JHD remains incurable, highlighting the need for treatments that are not only effective but also come without the adverse side effects.

KD is a low-carb, high-fat diet made up of meat, fatty fish, eggs, butter and cheese, nuts and seeds, avocados, and healthy oils (Masood and Uppaluri, 2018). KD became recognizable in the medical community in the 1920s, where it was introduced as a potential treatment for epilepsy (Wheless, 2008). The mechanism behind KD is that it places the body in a state of ketosis, meaning the body uses ketones as a source of energy when carbohydrates and glucose levels are depleted. Nutritionists and clinicians call this "nutritional ketosis". The release of ketones into the blood is a slow process that does not alter blood pH, making it safer compared to ketoacidosis, a serious complication of diabetes caused by excessive ketone release (Westerberg, 2013). Ketones are also able to cross the blood-brain barrier, a challenge when developing pharmaceutical drugs, and decrease free radical damage (Veech, 2004; Masood and Uppaluri, 2018). It has also been observed that a substantial amount of ketone bodies in the blood may be able to impact the balance of excitatory and inhibitory input in the central nervous system (Yudkoff et al., 2005). As mentioned earlier, the KD has been used frequently as a non-pharmaceutical treatment for epilepsy, in addition to a number of other neurological conditions including Alzheimer's disease, Parkinson's disease, and ALS (Huttenlocher et al., 1971; DeVivo et al., 1978; Dunwiddie and Worth, 1982; Trauner, 1985; Schwartz et al., 1989; Klepper et al., 2005; Hartman et al., 2007, Wang et al., 2005, Yudkoff et al., 2005; Bough et al., 2006; Balietti et al., 2010; Masino et al., 2011; Zarei et al., 2015; Shaafi et al., 2016). This review proposes that implementing a strict regimen of the KD to children with JHD may potentially provide therapeutic effects to the main symptoms of the condition during the progression of the disease.

## 2. Supporting Data

### 2.1 Ketogenic diet in epilepsy.

In human patients that suffer from epilepsy, KD has been researched heavily to explore the efficacy of the diet. One clinical study conducted explored a variant of the KD called the medium-chain triglyceride diet (MCTD) on children ranging from 2-16 (n=43) (Liu, 2008). A majority of the children on the diet had a 50-90% reduction in their seizure activity, and 21% of the children having been reported as seizure-free before the end of the trials which lasted between 2 months and 5 years (Liu, 2008). A number of studies have concluded that MCTD serves as an excellent seizure suppressor in a number of children; however, the diet is strongly associated with gastrointestinal issues as an adverse side effect (Huttenlocher et al., 1971; Trauner, 1985; Schwartz et al., 1989).

GLUT-1 deficiency syndrome results in epilepsy and developmental delay. The syndrome is characterized by low levels of glucose in the brain, leading to decreased brain metabolism (Marin-Valencia et al., 2012). KD implementation shifts the brain to use ketone bodies as the primary source of energy, which restores normal brain metabolism in approximately 67% of the patients in this study with the condition (Klepper et al., 2005). The study conducted by Klepper et al. demonstrated that out of 15 patients with GLUT-1 deficiency, 10 remained seizure-free after 2 ½ years on KD (2005). Another study also indicated that beginning the KD between the ages of 3.5 to 132 months was able to adequately control seizure activity for a variety of gene mutations that resulted in GLUT-1 deficiency (Wang et al., 2005).

Long-term studies that explore KD over a period of time have been conducted in patients with epilepsy. In a study that observed the efficacy of KD in children 3 or 6 years after beginning the diet, 27% of the original cohort (n=150) had over 90% seizure reduction, with 13% having a complete loss in seizure activity (Hemingway et al., 2001; Barañano, 2008). Marsh et al. demonstrated that in a cohort of 150 children, 22% of the children had become seizure-free when assessed 3 to 6 years after discontinuation of KD for difficult to treat seizures (2006). These long-

term studies not only highlight the efficacy of KD in patients with epilepsy but also demonstrate that there may be disease-modifying characteristics that can be attributed to KD. The number of children with long-term relief after stopping the diet is an important finding that should be researched further to truly understand the long-term mechanisms behind KD.

The efficacy of the KD has been explored numerous times in rodent models of epilepsy due to its proposed ability to protect against seizure activity. A study conducted by Masino et al. demonstrated that administering the KD for 4 weeks of suppressed seizure activity in mice by increasing the levels of adenosine in the brain (2011). Adenosine is a known anticonvulsant in rodents (Dunwiddie and Worth, 1982). In mouse models of epilepsy stemming from reduced adenosine and normal levels of adenosine kinase (ADK), which clears adenosine from the cell, implementing the KD was able to eradicate seizure activity. The researchers observed that the KD reduced levels of ADK, increasing the activation of adenosine receptors which provided anticonvulsant effects (Masino et al., 2011). The ability of the KD to act as an anticonvulsant makes it a compelling potential treatment that can significantly improve the quality of life for individuals with JHD.

During seizures, there is a disruption in the balance between excitatory and inhibitory input, or E-I balance, that is controlled by the release of Glutamate and GABA, respectively. In many seizures, there is a proportionally larger amount of excitatory input, resulting in hyperexcitability of a neuron which makes it prone to firing at unnecessary times (Bromfield et al., 2006). The implementation of the KD for 4 days in rodent models of seizure activity has also been effectual in the maintenance of the E-I balance in the nervous system (Yudkoff et al., 2005). Ketosis as a result of KD results in increased levels of acetyl-CoA in the brain in rat models (Yudkoff et al., 2005). Yudkoff et al. observed that the increase in acetyl-CoA ultimately resulted in increased levels of GABA and Glutamine, a precursor to GABA, due to more glutamate being available for the synthesis of other compounds (Yudkoff et al., 2005; Hartman et al., 2007). This study demonstrated that using ketones as the major source of energy to the brain can increase inhibitory neurotransmitters, further explaining another mechanism by which the KD provides therapeutic relief.

Rodent models of epilepsy have shown the therapeutic effects of KD on seizure activity, one of the common symptoms of JHD (Brackenridge, 1980; Gambardella et al., 2001; Cloud et al., 2012). Honing research in on the cellular mechanisms that KD impacts can provide a framework for future exploration of JHD and other potential treatments for the disease. Because of the lack of research on JHD, specifically, relying on previous research that explores KD is vital for JHD research to progress. In this case, it is apparent in a chronic seizure model that KD can be a reliable treatment to alleviate the symptoms.

**2.2 Ketogenic diet in neurological disease models**

Besides epilepsy, the efficacy of the KD has been explored in many other neurodegenerative and neuromuscular disorders. A study exploring the effect of the KD on mouse models of Alzheimer's disease (AD) found that KD was able to rescue motor deficits observed in 5-month-old AD mouse models over the course of 3 months (n=10), but could not restore memory deficits (Brownlow et al., 2013). The researchers attribute the improvement in motor activity to increased metabolic efficiency of the muscles after the implementation of the KD (Brownlow et al., 2013). The formation of ketone bodies has also been shown to encourage mitochondria biogenesis in rat models of AD, thereby restoring normal bioenergetic properties of neurons (DeVivo et al., 1978; Bough et al., 2006; Balietti et al., 2010). Although the specific role of mitochondrial dysfunction in JHD has not been previously described, there have been numerous studies implicating mitochondria in adult-onset HD showing that there may be a connection of bioenergetic efficiency and the KD (Chan, 2006; Damiano et al., 2010).

KD's efficacy has also been investigated in models of Parkinson's disease (PD). A symptom of JHD is the onset of Parkinsonian symptoms (Quarrell et al., 2013). Shaafi et al. compared motor deficits in rat models of PD that were treated with KD to rat models that were treated with pramipexole for 14 or 25 days, a known medication for the motor symptoms of PD (2016). Enhanced motor activity was observed in the rats between the ages of 12 and 14 weeks treated with KD for 14 or 25 days, however, this was not a statistically significant finding (Shaafi et al., 2016). It was also found that if medications were taken at the same time as KD was administered; the motor function was enhanced even further, highlighting the complementary mechanisms of KD with medications (Shaafi et al., 2016).

Amyotrophic lateral sclerosis (ALS) is character-

ized by motor neuronal loss resulting in muscle weakness and bradykinesia (Zarei et al., 2015). KD has been explored as a potential treatment for the symptoms and disease progression of the variant of ALS caused by mutations in SOD1. KD was first proposed as a promising treatment for the symptoms of ALS due to its interactions with mitochondria and its ability to preserve motor function and motor neuron numbers (Siva, 2006). Transgenic mouse models for ALS were fed a strict KD beginning at 50 days old and were observed to have slower disease progression and a longer lifespan than those who were not fed KD (Zhao et al., 2012). Another study demonstrated that KD beginning at 50 days old played a significant role in promoting ATP synthesis, which provided therapeutic relief to mouse models of ALS (Zhao et al., 2006).

## 3. Conclusion

Studies have described the promising role of the KD in the treatment of numerous conditions that affect the nervous system. As aforementioned, most of the research on KD effects has been in conditions with similar symptoms as HD and JHD. The therapeutic capacity of KD in treating symptoms of HD has not been explored in-depth, but one study has demonstrated that KD is able to delay the weight loss associated with HD, and found no negative behavioral or physiological effects (Ruskin et al., 2011). The findings from that study provide foundational information that encourages further research to be conducted in HD models. The research that has been done on KD and its effect on other neurological diseases further support the idea that KD may be a promising treatment for JHD.

KD is associated with multiple of positive characteristics that make it a viable option for JHD treatment. Because the diet consists of foods that are commonly consumed by the general population, KD is viewed as a very accessible treatment. Dietary treatments, which fall under the category of complementary and alternative treatments, are administered to children at higher rates than adults to treat a wide variety of conditions including attention-deficit/hyperactivity disorder (ADHD), genetic conditions, and asthma (Madzhidova and Sedrakyan, 2019). The high rates of administration are often due to parents wanting another treatment option instead of strong pharmacological treatment affecting their child further than the condition they are trying to treat. Along with being considered safer alternatives to pharmacological interventions, most dietary treatments including KD can be administered to children from a young age and may even be easier to administer than medications. As shown in this review, there are a number of scientific studies that explore the efficacy and safety of KD in a number of conditions. Many studies have concluded that KD acts on a variety of cellular mechanisms to alleviate many physiological and neurological symptoms. Although a majority of the research has not been conducted in models of HD or JHD, the overlap in symptoms of the conditions still provides preliminary information on KD as a potential treatment for JHD.

With any treatment, there are also negative aspects that must be considered. In rodents, KD has been associated with the development of insulin resistance, liver disease, and the increased risk of type 2 diabetes, however, it has been found that negative side effects are usually short-lived (Kosinski and Jornayvaz, 2017). Additionally, there is no substantial research currently on the effect of KD in HD specifically, which calls into question the clinical relevance of the research to JHD. Furthermore, KD can be a fairly diverse diet, but food preference can get in the way of maintaining the diet into adulthood. The lack of research on KD efficacy in HD and JHD can be addressed by performing similar experiments that have been conducted for other conditions on mouse models for HD and JHD.

Overall, observing the effects of the KD on the progression and symptom frequency of JHD will provide more helpful information on the best avenue of treatment for those that suffer. Previous research has demonstrated that KD may have a positive impact on numerous conditions, so exploration of the effects in JHD is a logical future direction. Developing reliable models for JHD that can test the efficacy is also necessary for research to progress. Although there are no preventative measures against JHD, the implementation of the proper treatments can significantly improve the quality of life of those affected by the disease.

## References

Andrade, S.E., Lo, J.C., Roblin, D., Fouayzi, H., Connor, D.F., Penfold, R.B., Chandra, M., Reed, G., Gurwitz, J.H., 2011. Antipsychotic medication use among children and risk of diabetes mellitus. Pediatrics 128, 1135–1141. https://doi.org/10.1542/peds.2011-0855

Balietti, M., Giorgetti, B., Di Stefano, G., Casoli, T., Platano, D., Solazzi, M., Bertoni-Freddari, C., Aicardi, G., Lattanzio, F., Fattoretti, P., 2010. A ketogenic diet increases succinic dehydro-

genase (SDH) activity and recovers age-related decrease in numeric density of SDH-positive mitochondria in cerebellar Purkinje cells of late-adult rats. Micron 41, 143–148. https://doi.org/10.1016/j.micron.2009.08.010

Barañano, K.W., Hartman, A.L., 2008. The Ketogenic Diet: Uses in Epilepsy and Other Neurologic Illnesses. Curr Treat Options Neurol 10, 410–419.

Bough, K.J., Wetherington, J., Hassel, B., Pare, J.F., Gawryluk, J.W., Greene, J.G., Shaw, R., Smith, Y., Geiger, J.D., Dingledine, R.J., 2006. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. Ann. Neurol. 60, 223–235. https://doi.org/10.1002/ana.20899

Brackenridge, C.J., 1980. Factors influencing dementia and epilepsy in Huntington's disease of early onset. Acta Neurol. Scand. 62, 305–311.

Bromfield, E.B., Cavazos, J.E., Sirven, J.I., 2006. Basic Mechanisms Underlying Seizures and Epilepsy. American Epilepsy Society.

Brownlow, M.L., Benner, L., D'Agostino, D., Gordon, M.N., Morgan, D., 2013b. Ketogenic Diet Improves Motor Performance but Not Cognition in Two Mouse Models of Alzheimer's Pathology. PLOS ONE 8, e75713. https://doi.org/10.1371/journal.pone.0075713

Chan, D.C., 2006. Mitochondria: dynamic organelles in disease, aging, and development. Cell 125, 1241–1252. https://doi.org/10.1016/j.cell.2006.06.010

Cloud, L.J., Rosenblatt, A., Margolis, R.L., Ross, C.A., Pillai, J.A., Corey-Bloom, J., Tully, H.M., Bird, T., Panegyres, P.K., Nichter, C.A., Higgins, D.S., Helmers, S.L., Factor, S.A., Jones, R., Testa, C.M., 2012. Seizures in juvenile Huntington's disease: frequency and characterization in a multicenter cohort. Mov. Disord. 27, 1797–1800. https://doi.org/10.1002/mds.25237

Correll, C.U., 2011. Safety and tolerability of antipsychotic treatment in young patients with schizophrenia. J Clin Psychiatry 72, e26. https://doi.org/10.4088/JCP.9101tx5c

Damiano, M., Galvan, L., Déglon, N., Brouillet, E., 2010. Mitochondria in Huntington's disease. Biochim. Biophys. Acta 1802, 52–61. https://doi.org/10.1016/j.bbadis.2009.07.012

DeVivo, D.C., Leckie, M.P., Ferrendelli, J.S., McDougal, D.B., 1978. Chronic ketosis and cerebral metabolism. Ann. Neurol. 3, 331–337. https://doi.org/10.1002/ana.410030410

Dunwiddie, T.V., Worth, T., 1982. Sedative and anticonvulsant effects of adenosine analogs in mouse and rat. J. Pharmacol. Exp. Ther. 220, 70–76.

Gambardella, A., Muglia, M., Labate, A., Magariello, A., Gabriele, A.L., Mazzei, R., Pirritano, D., Conforti, F.L., Patitucci, A., Valentino, P., Zappia, M., Quattrone, A., 2001. Juvenile Huntington's disease presenting as progressive myoclonic epilepsy. Neurology 57, 708–711.

Gonzalez-Alegre, P., Afifi, A.K., 2006. Clinical characteristics of childhood-onset (juvenile) Huntington disease: report of 12 patients and review of the literature. J. Child Neurol. 21, 223–229. https://doi.org/10.2310/7010.2006.00055

Hartman, A.L., Gasior, M., Vining, E.P.G., Rogawski, M.A., 2007. The Neuropharmacology of the Ketogenic Diet. Pediatr Neurol 36, 281–292. https://doi.org/10.1016/j.pediatrneurol.2007.02.008

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, 898–905.

Huttenlocher, P.R., Wilbourn, A.J., Signore, J.M., 1971. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. Neurology 21, 1097–1103.

Klepper, J., Scheffer, H., Leiendecker, B., Gertsen, E., Binder, S., Leferink, M., Hertzberg, C., Näke, A., Voit, T., Willemsen, M.A., 2005. Seizure control and acceptance of the ketogenic diet in GLUT1 deficiency syndrome: a 2- to 5-year follow-up of 15 children enrolled prospectively. Neuropediatrics 36, 302–308. https://doi.org/10.1055/s-2005-872843

Kosinski, C., Jornayvaz, F.R., 2017. Effects of Ketogenic Diets on Cardiovascular Risk Factors: Evidence from Animal and Human Studies. Nutrients 9. https://doi.org/10.3390/nu9050517

Liu, Y.C., 2008. Medium-chain triglyceride (MCT) ketogenic therapy. Epilepsia 49, 33–36. https://doi.org/10.1111/j.1528-1167.2008.01830.x

Madzhidova, S., Sedrakyan, L., 2019. The Use of Dietary Interventions in Pediatric Patients. Pharmacy 7, 10. https://doi.org/10.3390/pharmacy7010010

Marin-Valencia, I., Good, L.B., Ma, Q., Duarte, J., Bottiglieri, T., Sinton, C.M., Heilig, C.W., Pascual, J.M., 2012. Glut1 deficiency (G1D): epilepsy and metabolic dysfunction in a mouse model of the most common human phenotype. Neurobiol. Dis. 48, 92–101. https://doi.org/10.1016/j.nbd.2012.04.011

Marsh, E.B., Freeman, J.M., Kossoff, E.H., Vining, E.P.G., Rubenstein, J.E., Pyzik, P.L., Hemingway, C., 2006. The outcome of children with intractable seizures: a 3- to 6-year follow-up of 67 children who remained on the ketogenic diet less than one year. Epilepsia 47, 425–430. https://doi.org/10.1111/j.1528-1167.2006.00439.x

Masino, S.A., Li, T., Theofilas, P., Sandau, U.S., Ruskin, D.N., Fredholm, B.B., Geiger, J.D., Aronica, E., Boison, D., 2011. A ketogenic diet suppresses seizures in mice through adenosine A1 receptors. J Clin Invest 121, 2679–2683. https://doi.org/10.1172/JCI57813

Masood, W., Uppaluri, K.R., 2018. Ketogenic Diet, in: StatPearls. StatPearls Publishing, Treasure Island (FL).

Myers, R.H., 2004. Huntington's Disease Genetics. NeuroRx 1, 255–262.

Penfold, R.B., Stewart, C., Hunkeler, E.M., Madden, J.M., Cummings, J., Owen-Smith, A.A., Rossom, R.C., Lu, C., Lynch, F.L., Waitzfelder, B.E., Coleman, K.A., Ahmedani, B.K., Beck, A.L., Zeber, J.E., Simon, G.E., 2013. Use of Antipsychotic Medications in Pediatric Populations: What Do the Data Say? Curr Psychiatry Rep 15, 426. https://doi.org/10.1007/s11920-013-0426-8

Quarrell, O., O'Donovan, K.L., Bandmann, O., Strong, M., 2012. The Prevalence of Juvenile Huntington's Disease: A Review of the Literature and Meta-Analysis. PLoS Curr 4. https://doi.org/10.1371/4f8606b742ef3

Quarrell, O.W.J., Nance, M.A., Nopoulos, P., Paulsen, J.S., Smith, J.A., Squitieri, F., 2013. Managing juvenile Huntington's disease. Neurodegener Dis Manag 3. https://doi.org/10.2217/nmt.13.18

Quigley, J., 2017. Juvenile Huntington's Disease: Diagnostic and Treatment Considerations for the Psychiatrist. Curr Psychiatry Rep 19, 9. https://doi.org/10.1007/s11920-017-0759-9

Ribaï, P., Nguyen, K., Hahn-Barma, V., Gourfinkel-An, I., Vidailhet, M., Legout, A., Dodé, C., Brice, A., Dürr, A., 2007. Psychiatric and cognitive difficulties as indicators of juvenile huntington disease onset in 29 patients. Arch. Neurol. 64, 813–819. https://doi.org/10.1001/archneur.64.6.813

Roos, R. A. (2010). Huntington's disease: a clinical review. Orphanet Journal of Rare Diseases, 5, 40. https://doi.org/10.1186/1750-1172-5-40

Ruskin, D.N., Ross, J.L., Kawamura, M., Ruiz, T.L., Geiger, J.D., Masino, S.A., 2011. A ketogenic diet delays weight loss and does not impair working memory or motor function in the R6/2 1J mouse model of Huntington's disease. Physiol. Behav. 103, 501–507. https://doi.org/10.1016/j.physbeh.2011.04.001

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

Shaafi, S., Najmi, S., Aliasgharpour, H., Mahmoudi, J., Sadigh-Etemad, S., Farhoudi, M., Baniasadi, N., 2016. The efficacy of the ketogenic diet on motor functions in Parkinson's disease: A rat model. Iran J Neurol 15, 63–69.

Siva, N., 2006. Can ketogenic diet slow progression of ALS? The Lancet Neurology 5, 476. https://doi.org/10.1016/S1474-4422(06)70462-8

Trauner, D.A., 1985. Medium-chain triglyceride (MCT) diet in intractable seizure disorders. Neurology 35, 237–238.

Veech, R.L., 2004. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. Prostaglandins Leukot. Essent. Fatty Acids 70, 309–319. https://doi.org/10.1016/j.plefa.2003.09.007

Wang, D., Pascual, J.M., Yang, H., Engelstad, K., Jhung, S., Sun, R.P., De Vivo, D.C., 2005. Glut-1 deficiency syndrome: clinical, genetic, and therapeutic aspects. Ann. Neurol. 57, 111–118. https://doi.org/10.1002/ana.20331

Westerberg, D.P., 2013. Diabetic ketoacidosis: evaluation and treatment. Am Fam Physician 87, 337–346.

Wheless, J.W., 2008. History of the ketogenic diet. Epilepsia 49 Suppl 8, 3–5. https://doi.org/10.1111/j.1528-1167.2008.01821.x

Yudkoff, M., Daikhin, Y., Nissim, Ilana, Horyn, O., Lazarow, A., Luhovyy, B., Wehrli, S., Nissim, Itzhak, 2005. Response of brain amino acid metabolism to ketosis. Neurochem. Int. 47, 119–128. https://doi.org/10.1016/j.neuint.2005.04.014

Zarei, S., Carr, K., Reiley, L., Diaz, K., Guerra, O., Altamirano, P.F., Pagani, W., Lodin, D., Orozco, G., Chinea, A., 2015. A comprehensive review of amyotrophic lateral sclerosis. Surg Neurol Int 6. https://doi.org/10.4103/2152-7806.169561

Zhao, Z., Lange, D.J., Voustianiouk, A., MacGrogan, D., Ho, L., Suh, J., Humala, N., Thiyagarajan, M., Wang, J., Pasinetti, G.M., 2006. A ketogenic

diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. BMC Neurosci 7, 29. https://doi.org/10.1186/1471-2202-7-29

Zhao, W., Varghese, M., Vempati, P., Dzhun, A., Cheng, A., Wang, J., Lange, D., Bilski, A., Faravelli, I., Pasinetti, G.M., 2012. 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 7, e49191. https://doi.org/10.1371/journal.pone.0049191