



## RESEARCH PROGRESS REPORT SUMMARY

**Grant 02252:** Investigating a Ketogenic Medium-Chain Triglyceride (MCT) Supplement for the Treatment of Drug-Resistant Canine Idiopathic Epilepsy and Its Behavioral Comorbidities

**Principal Investigator:** Holger Volk, DVM, PhD  
**Research Institution:** Royal Veterinary College, University of London  
**Grant Amount:** \$87,484  
**Start Date:** 5/1/2016      **End Date:** 9/30/2019  
**Progress Report:** FINAL

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### Original Project Description:

Canine epilepsy is a chronic neurological condition, often requiring lifelong medication with anti-epileptic drugs (AEDs). Despite appropriate treatment with available AEDs, seizure freedom may not always be achievable. Indeed, over two thirds of dogs with epilepsy continue to have seizures long-term and around 20-30% remain poorly controlled on standard AEDs. The hardest to treat dogs are termed 'refractory' or 'drug-resistant' patients. There is an urgent need to develop alternative treatments to improve the quality of life (QoL) of drug-resistant patients. The ketogenic diet, originally characterized as high in fat and low in carbohydrates, has been a successful treatment in children with epilepsy for several decades, decreasing seizure activity and even leading to seizure freedom in drug-resistant patients. Recent research has identified that a component of the ketogenic diet, a medium-chain fatty acid (MCT) called C10 has direct anti-seizure effects on the brain. The investigators will assess whether dietary supplementation with ACT oil containing C10 for dogs with drug-resistant epilepsy will reduce seizure frequency and/or severity. As epilepsy has multiple impacts on QoL beyond seizure frequency, the researchers will also investigate whether the MCT supplement alters the side effect profile of AEDs, improves behavioral problems associated with epilepsy (e.g. anxiety) and cognition, and improves the stress levels of the affected dog. If successful, MCT supplements could provide a new tool for canine epilepsy treatment.

### Publications:

Berk, B. A., Packer, R. M. A., Law, T. H., & Volk, H. A. (2018). Investigating owner use of dietary supplements in dogs with idiopathic epilepsy. *Research in Veterinary Science*, 119, 276–284. <https://doi.org/10.1016/j.rvsc.2018.07.004>

Berk, B. A., Packer, R. M. A., Law, T. H., Wessmann, A., Bathen-Nöthen, A., Jokinen, T. S., Knebel, A., Tipold, A., Pelligand, L., & Volk, H. A. (2019). A double-blinded randomised dietary supplement crossover trial design to investigate the short-term influence of medium chain fatty acid (MCT) supplement on canine idiopathic epilepsy: Study protocol. *BMC Veterinary Research*, 15(1), 181. <https://doi.org/10.1186/s12917-019-1915-8>

Packer, R. M. A., Volk, H. A., & Fowkes, R. C. (2017). Physiological reactivity to spontaneously occurring seizure activity in dogs with epilepsy and their carers. *Physiology & Behavior*, 177, 27–33. <https://doi.org/10.1016/j.physbeh.2017.04.008>

Watson, F., Packer, R. M. A., Rusbridge, C., & Volk, H. A. (2019). Behavioural changes in dogs with idiopathic epilepsy. *Veterinary Record*, vetrec-2018-105222. <https://doi.org/10.1136/vr.105222>

Berk, B. A., Law, T. H., Packer, R. M. A., Wessmann, A., Bathen-Nöthen, A., Jokinen, T. S., Knebel, A., Tipold, A., Pelligand, L., Meads, Z., & Volk, H. A. (2020). A multicenter randomized controlled trial of effect of medium-chain triglyceride dietary supplementation on epilepsy in dogs. *Journal of Veterinary Internal Medicine*. <https://doi.org/10.1111/jvim.15756>

Berk BA, Law TH, Packer RMA, Wessmann A, Bathen-Nöthen A, Jokinen TS, Knebel A, Tipold A, Pelligand L, Meads Z, Volk HA. A “Medium-chain triglycerides dietary supplement improves cognitive abilities in canine epilepsy.” *Epilepsy and Behavior*, under review (addressed minor comments).

Changes in fat metabolism and neurotransmitter composition is linked to a diet high in medium chain triglycerides. Under preparation for *PLoSone*.

#### **Presentations:**

European College of Veterinary Neurology annual conference 2017

#### **INVESTIGATING THE USE OF DIETARY SUPPLEMENTS IN DOGS WITH IDOPATHIC EPILEPSY**

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Epilepsy is the most common chronic neurological disorder in dogs. Diet has been shown to have a positive impact upon the seizure activity and behaviour of dogs with idiopathic epilepsy, and commercially available diets or dietary supplements (DS) are increasingly marketed to help manage a variety of health conditions. There remains a lack of data of diet and dietary supplementation of dogs with epilepsy, and how this could impact epilepsy management.

An online survey was designed to assess how and why owners of dogs with idiopathic epilepsy use diets and DS. In total, 186 valid responses were received. The study cohort consisted of mainly male neutered (45.2%), pure-breed (83.7%) dogs with a mean age (months)  $\pm$ SD of  $68.9 \pm 32.9$  months. Over half of owners (52.6%) administered DS; the most common being coconut oil (40.8%), milk thistle (35.7%), fish oil (34.7%), cannabidiol oil (15.3%) and Medium-chain Triglyceride (MCT) oil (13.3%). While only 20% of owners consulted their vet, the most common source advice on DS use was online owner support groups (50.5%). Beside the protection from potential drug side effects (57.3%), owners used DS to try and reduce seizure frequency (79.6%) and severity (56.3%).

As pharmacokinetic properties of anti-epileptic drugs can be influenced by other medications or diets, DS may also affect their efficacy, absorption and clearance. Owners commonly use DS, which should be considered when taking a history, as it might influence epilepsy management. Understanding the complex relationship of medication and diet will improve future management of epileptic patients.

European College of Veterinary Neurology annual conference 2018

#### **INVESTIGATING THE SHORT-TERM EFFECTS OF MEDIUM-CHAIN TRI-GLYCERIDES (MCT) SUPPLEMENT ON CANINE EPILEPSY IN DRUG-NON RESPONDERS**

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The influence of diets have been studied extensively in human epilepsy, however, there is a lack of comparative data in veterinary medicine. It has been shown that a medium-chain triglyceride (MCT) enriched diet has a positive effect on seizure control and behaviour in dogs with idiopathic epilepsy. However, it is unknown whether MCTs administered in the form of an add-on dietary supplement (DS) to a variable base diet will show similar positive effects.

A 6-month multi-centre, prospective, randomised, double-blinded, placebo-controlled cross-over trial was completed, comparing a MCT-DS with a standardised placebo-DS in a population of dogs with idiopathic epilepsy, chronically treated with antiepileptic drugs and reaching tier-2 diagnostic certainty. A 9%-MCT or placebo oil was added to the dogs' diet for three months, followed by the alternative oil for a further three months. Twenty-eight dogs completed this study and were included in further analysis. Seizure frequency was significantly lower when dogs were fed MCT-DS (median 2.51/month,

0-6.67/month) in comparison with the placebo-DS (2.67/month, 0–10.45/month;  $P=0.0147$ ). Seizure day frequency was also significantly lower during MCT-DS phase (1.68/month, 0-5.60/month vs. 1.99/month, 0–7.42/month,  $P=0.0101$ ). Two dogs achieved seizure-freedom, three additional dogs had  $\geq 50\%$  reduction and 12 had  $< 50\%$  reduction in seizure frequency. Eight dogs showed no response or a slight increase (8%).

In summary, these data show antiepileptic properties associated with MCT-DS when compared to a placebo and support former evidence for the efficacy of the MCTs as a nutritive, therapeutic option for a subpopulation of drug-non responsive epileptic dogs.

European College of Veterinary Nutrition annual meeting 2018

**Medium-chain triglycerides dietary supplement improves cognitive abilities in dogs diagnosed with idiopathic epilepsy.**

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**Introduction.** Idiopathic epilepsy (IE) can induce or accelerate the onset of cognitive dysfunction in dogs. A positive impact from dietary administered medium-chain triglycerides (MCT) has been shown to improve seizure control (1) and behavioral comorbidities (2) in epileptic dogs. MCTs have also been shown to improve cognitive function in older dogs (3; 4). However, it is unknown whether MCTs administered in the form of an add-on dietary supplement (DS) to a variable base diet can also improve cognitive function in dogs with IE. The study objective was to evaluate short-term effects occurring from MCT oil consumption on cognitive abilities in dogs diagnosed with IE.

**Animals, material and methods.** Cognitive effects of a MCT-DS were evaluated in a population of dogs with IE over a 3 months period in a 6-month multi-centre, prospective, randomised, double-blinded, placebo-controlled cross-over trial design. A metabolic energy requirement (ME) based amount of 9% MCT or control oil was supplemented to the dogs' diet for three months, followed by the alternative oil for another three months. A combination of scored (Table 1), non-invasive cognitive testing (5) and the owner-based Canine Cognitive Dysfunction Rating (CCDR) scale(6) was used to assess cognitive parameters under dietary intervention.

**Results and discussion.** The study was completed by twenty-eight dogs, of which eight-teen dogs completed two non-invasive cognition tests. Significant better performance was observed in the problem-solving task comparing MCT oil to control. The ability of finding a solution to get the treat under a box was significantly accelerated ( $1.5 \pm 0.99$  v.  $1.83 \pm 1.1$ ;  $p=0.0195^*$ ). However, neither in all

(N=28), nor in the cognitive testing population (N=18) differed the CCDR scores significantly between intervention periods.

Table 1. Scoring system for non-invasive cognitive test:

Food Searching Task 1 Problem Solving Task 2

- 1 Goes directly to the food in the corner. Successfully gets all food from box within 2 minutes.
- 2 Finds food within 1 minute. Tries to get food but is unsuccessful within time limit.
- 3 Searches but does not find the food. Sniffs around box but makes no attempt to get food.
- 4 Makes no attempt to search for the food. No attempt to get the food.

Conclusion. Further, larger scale studies are required into the effect of MCT in dogs with IE, but the current data suggests that MCT as DS is a promising nutritive add-on to improve cognitive function in dogs with IE.

References:[1] Law TH, et al. (2015), Br J Nutr 114, 1438-1447. [2] Packer RM, et al. (2016), Epilepsy Behav 55, 62-68. [3] Pan Y, et al. (2010), Br J Nutr 103, 1746-1754. [4] Pan Y, et al. (2018), Front Nutr 5, 127. [5] Gonzalez-Martinez A, et al. (2013) Vet J 198, 176-181. [6] Salvin HE, et al. (2011), Vet J 188, 331-336.

European College of Veterinary Nutrition annual meeting 2020

**Metabolic profile associated with the dietary supplementation of medium-chain triglyceride (MCT) in dogs with idiopathic epilepsy.**

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Introduction. Consumption of medium-chain triglycerides (MCT) has been shown to improve seizure control [1, 2], milder behavioral comorbidities [3] and improve cognitive abilities in epileptic dogs. However, the exact metabolic pathways affected by dietary MCT are poorly understood. Here, we aimed to identify the global metabolic changes associated with the consumption of a ketogenic supplement (MCT-DS) in dogs with idiopathic epilepsy (IE).

Animals, material and methods. Metabolic alterations induced by a commercial MCT-DS in a population of 28 dogs with IE were evaluated using 6-month multi-centre, prospective, randomised, double-blinded, placebo-controlled cross-over trial design [4]. A metabolic energy requirement-based amount of 9% MCT or control oil was supplemented to the dogs' stable base diet for three months, followed by the alternative oil for another three months. A validated, quantitative nuclear magnetic

resonance (NMR) spectroscopy platform was applied to pre- and postprandially collected serum samples comparing changes in the fat and protein metabolism between both DS and to baseline [5].

**Results and discussion.** The study was completed by twenty-eight dogs. Five dogs had an overall reduction in seizure frequency  $\geq 50\%$  five dogs (30%) classified as MCT responders (R), while 12 dogs showed  $\leq 50\%$  (21%; 6 – 42%); 3 dogs with no change and 8 dogs with an overall increase in seizure frequency per month (8%; 2 – 33%). Amino-acid metabolism was significantly influenced by MCT consumption compared to the control oil (alanine/BCCA decreased,  $p=0.008$ ; alanine/valine decreased,  $p=0.02$ ). While the amount of total fatty acids appeared similar ( $p=0.68$ ) between the MCT-DS and control oil, the relative amounts of individual fatty acids differed. During MCT supplementation, significantly increased concentrations of polyunsaturated ( $p=0.027$ ) fatty acids and arachidonic acid (C20:4n-6;  $2.4 \pm 0.9$  mmol/l vs.  $2.1 \pm 0.7$  mmol/l,  $p=0.02$ ) were observed compared to the control oil. Under both oils, the serum concentration of acetate was higher compared to baseline (MCT,  $p=0.02$ ; control,  $p=0.01$ ). Blood glucose levels were significantly lowered under MCT compared to baseline ( $4.6$  mmol/l vs.  $4.1$  mmol/l,  $p=0.01$ ).

**Conclusion.** In conclusion, these pilot data highlight the global metabolic changes in lipid, amino-acid and ketone metabolism as result of MCT supplementation. Elucidating the global metabolic response of MCT provides new avenues to develop better nutritional management with improved anti-seizure and neuroprotective efficacies for dogs with epilepsy, or other neurological disorders.

#### References:

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2. Berk BA, Packer RMA, Law TH, Wessmann A, Bathen-Nöthen A, Jokinen TS, Knebel A, Tipold A, Pelligand L, Meads Z et al: A multicenter randomised controlled trial of medium-chain triglyceride dietary supplementation on epilepsy in dogs. *JVIM* 2020, in press.
3. Packer RM, Law TH, Davies E, Zanghi B, Pan Y, Volk HA: Effects of a ketogenic diet on ADHD-like behavior in dogs with idiopathic epilepsy. *Epilepsy Behav* 2016, 55:62-68.
4. Berk BA, Packer RMA, Law TH, Wessmann A, Bathen-Nöthen A, Jokinen TS, Knebel A, Tipold A, Pelligand L, Volk HA: A double-blinded randomised dietary supplement crossover trial design to investigate the short-term influence of medium chain fatty acid (MCT) supplement on canine idiopathic epilepsy: study protocol. *BMC Vet Res* 2019, 15(1):181.
5. Ottka C, Vapalahti K, Puurunen J, Vahtera L, Lohi H: Characteristics of a novel NMR-based metabolomics platform for dogs. *bioRxiv* 2019:871285.

#### Report to Grant Sponsor from Investigator:



Canine epilepsy is a chronic neurological condition, often requiring lifelong medication with anti-epileptic drugs (AEDs). Despite appropriate treatment with available AEDs, seizure freedom may not always be achievable. There is an urgent need to develop alternative treatments to improve the quality of life (QoL) of drug-resistant patients, who may continue to experience unpleasant AED side-effects despite their lack of success. The project did investigate whether supplementing the diet of dogs with drug-resistant epilepsy with an MCT oil containing C10 will reduce seizure frequency and/or severity. As epilepsy has multiple impacts on QoL beyond seizure frequency, we also investigated whether the MCT supplement altered the side effect profile of AEDs the patient is already receiving, improves any behavioural problems associated with epilepsy (e.g. anxiety), cognition and improves the stress levels of the affected dog and their owner. The study showed that some dogs respond very well to MCT supplementation. Two dogs were free of seizures, 3 had  $\geq 50\%$  and 12 had  $< 50\%$  reductions in seizure frequency, and 11 dogs showed no change or an increase in seizure frequency. These data show antiseizure properties of an MCT-DS compared to a control oil and support former evidence for the efficacy of MCTs as a nutritive management option for a subpopulation of drug-resistant dogs with epilepsy. It appears that a subgroup of dogs responds better to MCTs than the whole population. We could also show that by supplementing the diet with MCT oil multiple drug side effects such as ataxia and sedation and cognition did improve. We have also identified interesting neurotransmitter changes in the urine showing that certain neurotransmitter might play a role in improving seizure control in dogs fed MCT. The untargeted metabolomics did not yield an interesting hit, but we could show by using a different targeted metabolomics approach that MCT result in a change in fat metabolism providing a different energy source, which was directly linked to seizure control.