Epilepsy Research (2012) 100, 267—271

journal homepage: www.elsevier.com/locate/epilepsyres

Carnitine, nutritional supplementation and discontinuation of ketogenic diet therapies

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Received 3 May 2011; received in revised form 1 April 2012; accepted 2 April 2012
Available online 15 June 2012

KEYWORDS
Ketogenic therapies;
Carnitine;
Supplementation;
Discontinuation

Summary Nutritional adequacy of a prescribed diet is integral to clinical implementation of the ketogenic diet therapies in intractable epilepsy. This review discusses the evidence for using additional carnitine and the importance of full micronutrient supplementation. The optimal duration of a diet therapy is also discussed, drawing on results of an internationally applied questionnaire.

Carnitine

The ketogenic diet (KD) is a high fat, low carbohydrate dietary regimen used since the 1920s (Wilder, 1921). It is designed to imitate the metabolic changes occurring during fasting and has been shown to be successful in treating intractable epilepsy (Freeman et al., 1998; Lefevre and Aronson, 2000; Henderson et al., 2006; Neal et al., 2008). The classical KD is usually prescribed at a ratio of 3 or 4 g of fat to every 1 g of carbohydrate and protein combined, thus providing 87—90% of total calories from fat, which is predominately from long chain sources. The transport of these long chain fatty acids into the mitochondria for subsequent β-oxidation requires their esterification by carnitine, a small water-soluble amino-acid derivative that is both synthesized in the body and provided from dietary sources, and mainly stored in muscle. L-Carnitine is the only biologically active isomer form of carnitine. Carnitine deficiency has been widely reported in epilepsy patients being treated with valproic acid (Anil et al., 2009; Hamed and Abdella, 2009), although this has been questioned in other studies (Hirose et al., 1998; Fung et al., 2003). As carnitine is well-absorbed from food, the main dietary sources being animal based such as milk, meat and eggs, these differences seen in valproic acid studies may influenced in part by the health status and therefore dietary intake of the population being studied. The effect of other anticonvulsants on carnitine levels is less widely reported. There have been suggestions that carbamazepine and phenobarbital may also deplete carnitine levels (Castro-Gago et al., 1998) especially if used in a polytherapy regime that includes valproic acid (Verrotti et al., 1999). Monotherapy with oxcarbazepine or carbamazepine has not been reported to cause problems (Kurul et al., 2003).

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http://dx.doi.org/10.1016/j.eplepsyres.2012.04.021

It has been suggested that the KD may also induce deficiency due to the high fat content (De Vivo et al., 1998). Few studies have examined this question. Berry-Kravis et al. (2001) reported plasma total carnitine levels in 46 patients (age range 1—24 years); this included eight already on the KD at the time of commencing the study and 38 who were followed from KD initiation. Three of the latter group were started on carnitine supplementation at baseline due to low levels. A further six of the 46 patients (18%), who were not started on carnitine at baseline, developed low carnitine levels and needed supplementation. None showed any clinical signs of carnitine deficiency, and there was no worsening of seizure control with low carnitine levels. The average total carnitine in patients who were never carnitine supplemented was lower after one and six months on the diet than at baseline, but this then increased again by 12 and 24 months. The conclusions from this study were that although total carnitine does decrease over the first few months of KD treatment, and in some patients, dip into the deficiency range, it then normalizes with no evidence of a continued decline. One other study measured plasma free carnitine levels in 164 epilepsy patients (age 1 month — 6 years), of which 11 were on the classical KD. None of these 11 diet patients developed abnormal levels of free carnitine (Coppola et al., 2006).

Carnitine levels in children on other types of KD therapy have not been reported. The medium chain triglyceride (MCT) KD should present less of a risk for deficiency as medium chain fatty acids are transported directly into the mitochondria for oxidation without the need for carnitine. A randomized trial found classical and MCT KD protocols to be comparable in efficacy and tolerability in children (Neal et al., 2009); as part of this trial carnitine levels were measured and results are pending.

Carnitine status is assessed by measuring plasma levels of either free carnitine or of a number of different esters, or acyl-carnitines. It has been suggested that deficiency in childhood epilepsy be defined as plasma free concentration of $\leq$20 μM or a ratio of acylated-to-free carnitine of $\geq$0.4, at an age of over 1 week post term (De Vivo et al., 1998). These were arbitrary values, and different centers may use different, age-dependent ranges for deficiency, frequently using a lower free carnitine cut-off. Although plasma levels are not a true reflection of total body stores, most of these being in muscle, the most useful plasma measure for determining carnitine status in patients on the KD is free carnitine. The acyl:free ratio is unlikely to be accurate as levels of acylcarnitines, including acetyl carnitine, will be greatly increased because of the increase in fat metabolism and ketosis that occur while on the diet. This will elevate the ratio, which is likely to reflect the level of ketosis, rather than an indication of carnitine status. Indeed, further supplementation with carnitine will have no effect on reducing the ratio, and may even cause it to increase due to increased formation of acetyl carnitine. It has been suggested that the ratio may normalize slightly with time on the KD, due to adaptations to the ketotic state (Berry-Kravis et al., 2001).

Despite current KD expert consensus that children on the KD should not be routinely supplemented with carnitine unless showing biochemical or symptomatic deficiency (Kossoff et al., 2009), a number of families of children using the diet do choose to use either medically prescribed or bought over-the-counter carnitine supplements, regardless of biochemical status, with frequent anecdotal reports of improved well-being, energy levels and seizure control. As true carnitine deficiency will impair oxidation of fatty acids in the mitochondria and ketone production, a drop in ketone levels would be expected. Anecdotal reports do suggest ketone levels may improve with additional carnitine supplementation, especially if previously showing unexplained falls, even if plasma carnitine levels are normal, indicating it may be a useful additional tool for dietary fine-tuning. Any supplements used should be of the L-carnitine form, be commenced at a low dose and increased gradually. De Vivo et al. (1998) recommended supplementing patients with biochemical deficiency at 100 mg per kg body weight per day, in three or four divided doses, up to maximum of 2 g/day. There may be poor absorption, diarrhoea or an increase in seizures if high doses are started without gradual build-up. A starting dose of 10 mg/kg is frequently used for patients on the KD, which is increased as needed; many children do not require above 50 mg/kg per day.

Nutritional supplementation

General nutritional supplementation for the KD is less controversial and well established within clinical implementation. The KD restricts intake of dairy products, fruit, vegetables, cereals and grain products. These high carbohydrate foods contain many of the 28 known essential micronutrients. The KD is deficient in major nutrients when compared to the Dietary Reference Intakes (DRIs). The DRIs are micronutrient standards established by the United States Food and Nutrition Board of the Institute of Medicine (National Research Council, 2002). These standards are designed to meet the needs of healthy people but do not take into account chronic medical conditions, drugs or diet therapies. In the UK, standards are provided by Dietary Reference Values (DRVs) (Department of Health, 1991).

When comparing the micronutrient content of varying ratios of KDs to the DRIs it is evident that the higher the fat content of the diet, the lower the micronutrient density. In a review of optimally selected foods, the 4:1 diet contained the lowest concentration of micronutrients, meeting only three of the 28 DRIs whereas the 1:1 diet (similar to Modified Atkins diet or Low Glycemic Index Treatment) contained the highest, meeting 12 of the 28 DRIs (Zupec-Kania and Spellman, 2008). Nutritional supplementation is recommended when the nutritional composition of a diet cannot meet the DRIs.

The potential for micronutrient deficiency during KD therapy is significant. Nutrients of major concern on a carbohydrate-restricted diet are thiamine, folate, pantothenic acid, calcium, phosphorus, iron, vitamin D and trace minerals. In addition, the omega-3 fatty acid content is marginal if the main sources of fat are animal derived (such as cream and butter). For individuals eating the oral KD, nutritional supplementation is necessary. Nutritional supplement(s) should be carbohydrate-free or contain minimal carbohydrate. Supplements that are designed for children typically contain significant carbohydrate therefore tablets, powders or capsules should be considered. For those who are receiving total nutrition in liquid form such as

bottle-fed infants or enterally fed individuals, the formula should be fortified. Additional supplementation may be necessary if a formula is used off-label, e.g. Ross Carbohydrate-Free formula (designed for infants) used for a child or adult or KetoCal (designed for children ages 1—10) used for infants, older children or adults.

In general, a multivitamin with minerals and trace minerals is prescribed along with a calcium-containing Vitamin D3 product. Phosphorus is not included in most multivitamin supplements and therefore a separate supplement should be considered to optimize bone mineralization. Phosphorus is also an acid buffer which can be beneficial with KD therapy when acidosis is present. Omega-3 fatty acids can be easily provided in polyunsaturated oils that are incorporated into the diet.

In addition to the need to supplement nutrients that are deficient in the diet, medications commonly used to treat epilepsy carry additional nutritional concerns. Adverse effects of many anticonvulsant medications include drowsiness, nausea, vomiting, and constipation; all which can interfere with nutritional intake. Several anticonvulsant medications interfere with the metabolism of Vitamin D leading to an increased risk of osteopenia and osteoporosis. Carbamazepine, ethosuximide, phenobarbitol, phenytoin and valproic acid have been associated with inhibited intestinal calcium transport, increased turnover of skeletal minerals, and/or synthesis of inactive forms of Vitamin D (Chung and Ahn, 1994; Baer et al., 1997; Pavlakis et al., 1998). These effects may be exacerbated by KD therapy (Bergqvist et al., 2007). Anticonvulsant medications that induce hepatic microsomal enzymes including phenobarbital, phenytoin and carbamazepime are associated with decreased folate levels (Kishi et al., 1997). Supplementation of folate concurrently with these medications can improve seizure control through enhancement of pharmacokinetics and pharmacodynamics (Lewis et al., 1995).

Selection of appropriate nutritional supplements requires knowledge of DRI recommendations for age as well as carbohydrate content of products. Clinical nutritionists and dietitians should be utilized to provide the optimal profile of micronutrient intake. One resource that provides a database of products with nutrient and carbohydrate information is KetoCalculator, a web-based program that is available to dietitians (KetoCalculator, 2011). Recommendations for each age group and Tolerable Upper Limit data are displayed to guide decisions on appropriate dosage of supplements.

Diet discontinuation: an international survey

A frequently asked question is what is the optimal duration of KD therapy? Doctors and dietitians have traditionally recommended that the KD be used for no longer than two years due to potential long term side effects, such as dyslipidemia, kidney stones, and decreased growth velocity (Groesbeck et al., 2006). Over the past 90 years of clinical use, the implementation of the diet has changed with the liberalization of calories and fluid restriction as well as vitamin and mineral supplementation (Kossoff et al., 2009). Despite the multitude of evidence proving efficacy of the diet over the short and long term, prospective data evaluating optimal treatment duration is currently unavailable. This is partly due to multiple variables within the diet including ratio, calories, medications, tolerability, seizure etiology, growth and individual patient characteristics. Therefore, the duration of dietary treatment is as much art as it is science. In order to determine how treatment duration differs between KD centers, an informal questionnaire was sent to approximately 100 international centers with the help of two KD charities, Charlie Foundation and Matthew's Friends. Thirty-one questionnaires were completed and returned from the US, UK, South Africa, Poland, and China. The following summary of results provides some indication of the current themes of diet discontinuation in global clinical practice.

When asked what criteria are used to determine length of treatment duration, all respondents reported that tolerance is a determining factor. The majority (79%) reported that age does not play a factor in treatment duration. However, a few participants noted that diet tolerability and compliance decreases during adolescence. During adolescence there is also variability in seizure frequency and phenotype associated with the hormonal changes of puberty and therefore some may choose to continue treatment during this uncertain time. Views were split on whether EEG results affect length of treatment with 44% stating they would continue the diet in the setting of seizure freedom if the EEG remained abnormal. Previous research indicates that 20% of patients will experience seizure recurrence within two years of stopping the diet, with a higher incidence in the setting of an abnormal EEG (Martinez et al., 2007).

The majority (75%) of responders reported that seizure types and epileptic syndromes do not affect length of treatment. The seizure types and syndromes that were reported to have an affect included: infantile spasms, Lennox Gastaut syndrome, Doose syndrome, Glut 1 deficiency, and PDH deficiency. Those with infantile spasms and Doose syndrome were thought to only need treatment for shorter durations, while the remaining seizure types and syndromes were thought to need greater than 2 years of treatment.

As the parents are the gate keepers of dietary treatment, it is no surprise that the majority reported that parental involvement affects their decision on treatment duration. Health professionals specializing in the KD may be experts in their fields, but parents are experts when it involves their own child's needs and abilities. Reports of how patients are tapered off the diet varied by treatment center. Tapering ranged from 2 weeks to one year and was based on the individual patients' seizure control, ketones and length of treatment. The three most common reported reasons for immediate discontinuation of the diet were noncompliance, supervised hospitalization, and illness.

When asked if any specific situations would prompt discontinuation of the diet, such as surgery, the majority of respondents reported that they would not discontinue the diet due to a surgical procedure. As indicated by prior research, patients need to be monitored appropriately throughout surgery, especially with regard to bicarbonate levels and treated accordingly (Valencia et al., 2002). Respondents noted that the following situations would prompt diet discontinuation: reflux, pancreatitis, food refusal, high dose steroid treatment and acute liver disease.

Opinions varied when determining how long after initiation of the diet should be given before discontinuation due to lack of efficacy. The majority stated that they would wait

3—6 months, but the results ranged from 1 to 6 months. During the first month of treatment patients have been reported to have an increase in seizures from their baseline, and therefore may be misleading to the actual efficacy of dietary treatment. It takes approximately one month to metabolically adjust to the changes that occur when transitioning from using carbohydrates to utilizing fat as the body's primary fuel source. Additional time is also indicated to fine tune the diet, optimizing it to each individual patient. There was no specific time after which respondents felt that treatment should be discontinued. Reported duration of long term treatment ranged from 2 to 21 years, with an average of 6 years.

While the responses to the questionnaire provide important insight into current clinical practice, conclusions about the optimal dietary treatment duration cannot be drawn based on these limited findings. Clinicians can reference guidelines provided in the 2009 consensus statement. This statement recommends that the diet be used for at least 3 months to determine efficacy before discontinuation, and discontinuation should be considered after 2 years, with longer duration indicated for patients with GLUT 1 and PDH deficiencies. It also recommends that patients have an EEG prior to discontinuation, given patients with active EEGs have a higher risk of seizure recurrence. Finally, unless there is an urgent need to taper, it recommends that the diet be tapered over 2—3 months by gradually lowering the ketogenic ratio to mimic the weaning of medications (Kossoff et al., 2009).

The results obtained through this informal survey are a summary of clinicians' opinions from a variety of centers from around the globe. As with any seizure treatment, the duration of dietary therapy should be based on the individual patient needs while maintaining their health and well being.

References

Anil, M., Helvaci, M., Ozbal, E., Kalenderer, O., Anil, A.B., Dilek, M., 2009. Serum and muscle carnitine levels in children receiving sodium valproate. J. Child Neurol. 24 (1), 80—86.

Baer, M.T., Kozlowski, B.W., Blyler, E.M., Trahms, C.M., Taylor, M.I., Hogan, M.P., 1997. Vitamin D, calcium and bone status in children with developmental delay in relation to anticonvulsant use and ambulatory status. Am. J. Clin. Nutr. 65, 1042—1051.

Bergqvist, A.G., Schall, J.I., Stallings, V.A., 2007. Vitamin D status in children with intractable epilepsy, and impact of the ketogenic diet. Epilepsia 48, 66—71.

Berry-Kravis, E., Booth, G., Sanchez, A.C., Woodbury-Kolb, J., 2001. Carnitine levels and the ketogenic diet. Epilepsia 42 (11), 1445—1451.

Castro-Gago, M., Eirís-Puñal, J., Novo-Rodríguez, M.I., Couceiro, J., Camiña, F., Rodríguez-Segade, S., 1998. Serum carnitine levels in epileptic children before and during treatment with valproic acid, carbamazepine, and phenobarbital. J. Child Neurol. 13 (11), 546—549.

Chung, S., Ahn, C., 1994. Effects of anti-epileptic drug therapy on bone mineral density in ambulatory epileptic children. Brain Dev. 16, 382—385.

Coppola, G., Epifanio, G., Auricchio, G., Federico, R.R., Resicato, G., Pascotto, A., 2006. Plasma free carnitine in epilepsy children, adolescents and young adults treated with old and new antiepileptic drugs with or without ketogenic diet. Brain Dev. 28 (6), 358—365.

Department of Health, 1991. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. HMSO, London.

De Vivo, D.C., Bohan, T.P., Coulter, D.L., Dreifuss, F.E., Greenwood, R.S., Nordli Jr., D.R, Shields, W.D., Stafstrom, C.E., Tein, I., 1998. L-Carnitine supplementation in childhood epilepsy: current perspectives. Epilepsia 39, 1216—1225.

Freeman, J.M., Vining, E.P.G., Pillas, D., Pyzik, P.L., Casey, J.C., Kelly, M.T., 1998. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics 102 (6), 1358—1363.

Fung, E.L., Tang, N.L., Ho, C.S., Lam, C.W., Fok, T.F., 2003. Carnitine level in Chinese epileptic patients taking sodium valproate. Pediatr. Neurol. 28 (1), 24—27.

Groesbeck, D.K., Bluml, R.M., Kossoff, E.H., 2006. Long-term use of the ketogenic diet in the treatment of epilepsy. Dev. Med. Child Neurol. 48, 978—981.

Hamed, S.A., Abdella, M.M., 2009. The risk of asymptomatic hyperammonemia in children with idiopathic epilepsy treated with valproate: relationship to blood carnitine status. Epilepsy Res. 86 (1), 32—41.

Henderson, C.B., Filloux, F.M., Alder, S.C., Lyon, J.L., Caplin, D.A., 2006. Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. J. Child Neurol. 21, 193—198.

Hirose, S., Mitsudome, A., Yasumoto, S., Ogawa, A., Muta, Y., Tomoda, Y., 1998. Valproate therapy does not deplete carnitine levels in otherwise healthy children. Pediatrics 101 (5), E9.

KetoCalculator Web site. https://www.ketocalculator.com (accessed 31.03.11).

Kishi, T., Fujita, N., Eguchi, T., Ueda, K., 1997. Mechanism for reduction of serum folate by anti-epileptic drugs during prolonged therapy. J. Neurol. Sci. 145, 109—112.

Kossoff, E.H., Zupec-Kania, B.A., Amark, P.E., Ballaban-Gil, K.R., Bergqvist, A.C.G., Blackford, R., Buchhalter, J.R., Caraballo, R.H., Cross, J.H., Dahlin, M.G., Donner, E.J., Jehle, R.S., Klepper, J., Kim, H.D., Liu, Y.M.C., Nation, J., Nordli Jr., D.R., Pfeifer, H.H., Rho, J.M., Stafstrom, C.E., Thiele, E., Turner, Z., Veggiotti, P., Vining, E.P.G., Wheless, J.W., Wirrell, E.C., Charlie Foundation, The Practice Committee of the Child Neurology Society, 2009. Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group. Epilepsia 50, 304—317.

Kurul, S., Dirik, E., Iscan, A., 2003. Serum carnitine levels during oxcarbazepine and carbamazepine monotherapies in children with epilepsy. J. Child Neurol. 18 (8), 552—554.

Lefevre, F., Aronson, N., 2000. Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. Pediatrics 105 (4), E46, 1-7.

Lewis, D.P., Van Dyke, D.C., Willhite, L.A., Stumbo, P.J., Berg, M.J., 1995. Phenytoin—folic acid interaction. Ann. Pharmacother. 29, 726—735.

Martinez, C.C., Pyzik, P.L., Kossoff, E.H., 2007. Discontinuing the ketogenic diet in seizure-free children: recurrence and risk factors. Epilepsia 48, 187—190.

National Research Council and National Academies of Sciences, 2002. Dietary Reference Intakes for Individuals, Vitamins, Minerals, Trace Minerals, Fiber, Essential Fatty Acids. National Academies Press, Washington, DC.

Neal, E.G., Chaffe, H.M., Schwartz, R., Lawson, M., Edwards, N., Fitzsimmons, G., Whitney, A., Cross, J.H., 2008. The ketogenic diet in the treatment of epilepsy in children: a randomised controlled trial. Lancet Neurol. 7, 500—506.

Neal, E.G., Chaffe, H.M., Schwartz, R., Lawson, M., Edwards, N., Fitzsimmons, G., Whitney, A., Cross, J.H., 2009. A randomised trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia 50 (5), 1109—1117.

Pavlakis, S.G., Chusid, R.L., Roye, D.P., Nordli, D.R., 1998. Valproate therapy: predisposition to bone fracture? Pediatr. Neurol. 19, 129—131.

Valencia, I., Pfeifer, H., Thiele, E.A., 2002. General anesthesia and the ketogenic diet: clinical experience in nine patients. Epilepsia 43, 525—529.

Verrotti, A., Greco, R., Morgese, G., Chiarelli, F., 1999. Carnitine deficiency and hyperammonemia in children receiving valproic acid with and without other anticonvulsant drugs. Int. J. Clin. Lab. Res. 29 (1), 36—40.

Wilder, R.M., 1921. High fat diets in epilepsy. Mayo Clin. Proc. 2, 308.

Zupec-Kania, B., Spellman, E., 2008. Micronutrient composition of the classic ketogenic diet. Paper Presented at: International Symposium on Dietary Therapies for Epilepsy and Other Neurological Disorders, Phoenix, AZ (Abstract 24).