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Long-term monitoring of the ketogenic diet: Do's and Don'ts

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Summary The ketogenic diet (KD) is an effective treatment for epilepsy and like other treatments it is not without side effects. The side effects encountered are related to the diet composition and the radical metabolic changes that results from a high fat, low carbohydrate and protein diet. Short-term side effects are well documented. Long-term side effects are not as well documented but since the last ''international symposium on dietary therapies for epilepsy and other neurological disorders'', there are now more prospective and longitudinal data. Monitoring practices and treatments will be discussed and compared to the International Ketogenic Diet Consensus Statement (IKDCS) from 2008.

There are no treatments without side effects and the ketogenic diet (KD) is not an exception. Several questions should be addressed when evaluating side effects. First, is the side effect truly due to the treatment or perhaps a result of the underlying disorder? Is the side effect transient and could disappear once the KD is discontinued? Are there true risks of using the KD that must be weighed against the benefits and reassessed periodically during the treatment? The strong seizure reducing effect of the KD should not detract from monitoring when it is needed.

Humans are omnivores and our current fast food diet, often composed of highly processed carbohydrates, fats and protein is not healthy, but the 90% fat, 7% protein and 3% carbohydrate diet that comprises the classical KD, is nutritionally the ''outlier'' of all diets. The KD lacks vitamins, trace-minerals and electrolytes unless it is properly supplemented (Zupec-Kania and Zupanc, 2008). The metabolic changes induced by the KD are both radical and diffuse, forcing every cell in the body to rely primarily on beta oxidation rather than glycolysis for energy production. In the process, the KD produces a compensated metabolic acidosis and affects hormonal pathways, genetic regulation as well as neurotransmitters production etc. (Schwartzkroin, 1999; Yudkoff et al., 2008). Our KD management practice of restricting calories and protein, its primary use in growing children and a treatment period that may exceed the typical two to three years, reinforces the need for monitoring.

The use of the KD has continued to increase since the first international conference in dietary therapies for epilepsy and other neurological disorders, in 2008. Following this conference, the international study group consensus statement was published (IKDCS) (Kossoff et al., 2009). The purpose of the document was to give directions for KD management by sharing the experience and practices from the larger centers

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across the world. The opinions expressed were based on center-based clinical practices, supported by retrospective case series and occasional prospective studies. Nonetheless, this document represents an important beginning for future work and still serves as a ''guideline'' for centers managing the KD across the world.

Since the last meeting, there have been a few more prospective studies with information regarding side effects from the KD that we can add to our management and monitoring skills. Long term side effects discussed here are usually encountered after the initial three months treatment and include; hyperlipidemia, GI issues, renal calculi, growth failure, bone health, deficits of vitamins, minerals and trace elements (Table 1).

Frequency of evaluations

In general most centers will evaluate a child in the outpatient clinic every three months the first year, and then every six months. Children younger than one year and those with growth and feeding issues are evaluated more frequently.

Hyperlipidemia

Hyperlipidemia is a common side effect, and occurs in up to 60% of all children treated with the KD. It can occur at any time of the treatment period, even shortly after the initiation of the diet. Genetics and the composition of the fat in the child's diet appear to play important factors in the development of hyperlipidemia. In that sense there are fats that are ''good, bad or ugly''. The traditional KD used mainly saturated fats and 50% of the fat calories are given as cream since cream easily can be incorporated into recipes (whipped cream, ice cream, soups, soufflés, sauces, dressing, etc.). The everyday challenge of the KD is to ''hide the fat'' and keep the diet palatable. Eggs, bacon and protein sources high in saturated fats are often used to minimize the amount of fat added to each meal to keep the ratio unchanged. Such traditional or classic KD will cause hyperlipidemia, with elevation in triglycerides and cholesterol, LDL, VLDL and decrease in anti-athrogenic-HDL (Dekaban, 1966; Chesney et al., 1999; Sharman et al., 2002; Fraser et al., 2003; Kwiterovich et al., 2003; Cunnane, 2004; Kang et al., 2004; Groesbeck et al., 2006; Dahlin et al., 2007; Nizamuddin et al., 2008; Zupec-Kania and Zupanc, 2008; Fenton et al., 2009; Porta et al., 2009).

Two studies have analyzed the specific fatty acids and phospholipids changes induced by the KD (Fraser et al., 2003; Dahlin et al., 2007). Both studies found elevations in the polyunsaturated fatty acids (PUFA's). Frazier's patients showed a greater increase in Arachidonic acids than Docohexaeonate. To try to improve the fatty acid profile Dahlin's group added supplementation with Omega 3-FA (fish oils) 1—2 g four times/day, which resulted in a progressive decrease in the omega-6 to omega-3 ratio with normalization of the essential fatty acid profile, potentially reducing any cardio-vascular risk.

Fenton et al. showed that by modifying the meals, using less saturated fats, and by decreasing the cholesterol intake, a normal lipid profile can be obtained even on a 90% fat diet (Fenton et al., 2009). The children reduced their intake of butter and cream, increased their use of oils, substituted egg whites for whole eggs etc. Although hyperlipidemia is common, it is not a reason for discontinuing the KD. With proper counseling from the dietician regarding the fat and cholesterol sources in the child's meals a normal lipid profile can and should be achieved in most children.

If hyperlipidemia persists despite these adjustments lowering of the ratio should be considered. The IKDCS suggest monitoring every three months with fasting lipid profile.

Cardiac disease

There has been no study systematically evaluating the cardiovascular risks of the KD or assessments of the coronary arteries of adults who were on the KD as children. The cardiac diseases reported are case studies and include cardiomyopathy from a selenium deficient state, complications from a prolonged QT interval and suspected mitochondrial disorders (Best et al., 2000; Bergqvist et al., 2003; Kang et al., 2004; Bank et al., 2008). There are currently no recommendations from the IKDCS for separate evaluations such as EKG, ECHO or carotid ultrasound. DRI recommendations should be met for all vitamins, minerals and trace elements when the diet is calculated and supplementation is planned.

Linear growth failure

Linear growth on the ketogenic diet has been a controversial topic and the results have been variable, ''some children on the KD grow normally'' (Vining et al., 2002). Much of the published literature is based on retrospective chart reviews, data collected in clinics, or survey results. Height is a difficult test to perform accurately in a healthy child and cognitive disabilities makes it more challenging. A good growth study requires measurements in triplicate, by one or two trained anthropometrists, and the duration of the study needs to be long enough to show a change, probably more than 6 months, preferably one year.

There is now a growing body of evidence that the KD may affect growth particularly the linear growth velocities (Couch et al., 1999; Vining et al., 2002; Williams et al., 2002; Liu et al., 2003; Peterson et al., 2005; Bergqvist et al., 2008; Neal et al., 2008). There are several factors that may contribute. The diet is restricted both in regards to calories and protein. Starvation and caloric restriction are both known to reduce growth. Protein intake may also affect growth status. Neal et al. compared the growth in children with intractable epilepsy who were treated with the KD and the medium chain triglyceride ketogenic diet (MCT KD) which allows for relatively more protein than the traditional KD, 1.67 g/kg/day compared to 1.13 g/kg/day (Neal et al., 2008). In this study both groups were followed prospectively over 12 months. Both groups had a decrease in height (HAZ) and weight Z-scores (WAZ) after an initial 6 months of stability. The deceleration in the WAZ and HAZ scores worsened over time. There was no difference between the traditional KD and MCT KD effect on growth status.

During preadolescent years linear growth velocity is primarily driven by insulin like growth factor-1 (IGF-1) and growth hormone. Spulber et al., measured IGF-1 before and

Table 1 Side effects, monitoring and suggested actions.

Side effect	IKDCS testing	Action
Frequency of evaluation team labs	Q 3 months—year 1 Q 6 months—year 2 Q 3—6 months	If less than one year old evaluate monthly Evaluate more frequently if there are problems
Hyperlipidemia	Lipid profile q 3 months	Change fat source, increase oil, decrease saturated fat Change the protein sources, reduce cholesterol Add omega-fatty acids Consider reducing ratio
Cardiac disease	CAD? Selenium—whole blood and plasma, q 3—6 months	Supplement additional selenium Follow levels
Growth failure	Weight and height with each visit. Lower leg length in child with cerebral palsy Prealbumin/albumin q 3—6 months	Increase protein and calories. Observe change? Continued deceleration in height Time to decrease ratio? Endocrinology evaluation? IGF-1? GH
Gastro-intestinal disorders	GERD Constipation Impaction Fatty liver/pancreatitis	H2 blockers, pump inhibitors Increase fluids Increase oil intake, polyethylene glycol, add fiber Enemas × 3—5 days LFT with KD labs, q 3—6 months Amylase and lipase if abdominal pain
Nephrolithiasis Uric acid stones	Urine multistix home monitoring Urine Ca/Cr ratio q 3—6 Urine analysis and culture Renal UTS, CT of abdomen	Increase hydration Add citrates to neutralize urine PH Nephrology/urology evaluation d/c AED with CAI qualities
Electrolyte, vitamin, mineral trace mineral deficits	Q 3—6 months CMP, Mg, PO4 Vitamins D (25-OH-D) q 6 months	Dietary analysis of current diet and supplements Correct supplementation if levels in blood low
Bone health	Osteopenia, osteoporosis, history of fractures, AED's and cerebral palsy Yearly DEXA	DEXA AP and whole body with pediatric reference data. If abnormal, check calcium intake, vitamin D level and intake, magnesium levels and intake. Adjust supplementation. Help from GI nutrition, endocrinology. Non-ambulating, use stander daily.

IKDCS = International ketogenic diet consensus statement, 2008; AED = anti epileptic drug; CAI = carbonic anhydrase inhibitor; DEXA = dual energy X-ray absorptiometry; AP = anterior posterior; WB = whole body.

after one year after the KD and found that the levels of IGF-1 dramatically decreased, compared to before the KD (Spulber et al., 2009). The decrease correlated with the deceleration in height velocity. Low IGF-1 is therefore most likely the primary cause for the deceleration in height velocity seen with the KD. Catch up growth is often mentioned in the children who have discontinued the KD. In a survey study of 101 children who had been on the KD in the past 0.8—14 years (Patel et al., 2010) reported that children younger than 18 year the mean HAZ = −1.28 and WAZ = −0.79, were both still significantly below normal (normal = *Z*-score of 0).

The IKDCS suggest that weight and height measurements should be obtained for each follow up visit. In children with cerebral palsy who can't stand or have contractures other standardized measurements should be used to measure the growth, such as lower leg length (Bell and Davies, 2006). Families who are considering the KD should be counseled on the risk of growth retardation when discussion about using the KD is first introduced. When growth retardation occurs, protein intake should be maximized, consideration for ratio decrease and caloric adjustments made if possible. There is no published data on growth hormone use and the KD.

Gastro intestinal disorders

Gastro intestinal (GI) problems are common since the KD lacks fiber and bulk, and GI problems may occur in up to 3/4 of all KD patients. Gastro-esophageal reflux disease (GERD) and constipation are most commonly seen and occur because fat lowers the esophageal sphincter tone, slows gastric emptying and decreases intestinal transit time. Fluid restrictions will worsen these symptoms. The ketone bodies may induce anorexia or feeding refusal. There are case reports of pancreatitis, fatty liver and gallstone disease (Hassan et al., 1999; Stewart et al., 2001; Kang et al., 2004, 2005; Jung et al., 2008). There is no data published on peptic ulcer disease.

The IKDCS recommends that all children who are about to start the KD should have a thorough GI history taken. If GI problems are present, then interventions should be started before the diet is initiated. Jung et al. showed in their study that by treating the GI problems tolerance of the KD can be improved (Jung et al., 2008). Mild GERD can be treated with H2 blockers or pump inhibitors, constipation is treated by liberalizing the fluid intake, using more oils rather than saturated fats, use of non absorbable fiber, use of polyethylene—glycol. Treatment of impaction often involves several days of serial enemas. A good abdominal exam during the follow up visit should document liver size and excessive stool. For children with complicated GI issues seek help from your GI colleagues before initiating the KD.

Nephrolithiasis

Nephrolithiasis occur in up to 10% of the KD patients (Kielb et al., 2000; Kossoff et al., 2002; Kang et al., 2004; Sampath et al., 2007). Uric acid stones are more common than the calcium oxalate stones. The KD results in many metabolic changes that predisposes to nephrolithiasis; uric acid levels are elevated, the ketone bodies are acidic and when spilled in the urine results in an acidic urine PH, hypercalciuria, and low urine citrates all contribute to kidney stone formation (Furth et al., 2000). The risk may increase during dehydration. Anti epileptic mediations that have secondary mechanisms such as carbonic anhydrase inhibitor's could further increase this risk of nephrolithiasis. However, the single study that has looked at this relationship did not find an increased risk for stones with these medications, however, use of citrates while on the KD reduced the risk for stone formation (Sampath et al., 2007). The IKDSG suggest preventative use of citrates (brand formulation is important as many commercially available citrates contain carbohydrates) routine monitoring for renal stones during each follow up visits with a urine analysis and urine calcium creatinine ratio. Fluid restriction is no longer used by most centers in KD management. Good hydration is suggested to further minimize the risk of stone formation.

Electrolyte, vitamin, mineral and trace element deficits

Electrolyte, vitamin, mineral and trace element deficits may occur if the KD is not properly supplemented, if the parents fail to administer the supplements, or the child has malabsorption. The older supplements were inadequate in the trace element contents and in a few children resulted in a deficient states (Bergqvist et al., 2003). Some of these deficits have been corrected. The optimal KD supplementation has not been determined. Children placed on the KD often have other medical problems; they may be frail and already have inadequate nutritional status. It is a great responsibility for the KD team (primarily the dietician) to make sure the child's nutrition is maximized while on the KD. The IKDCS specifically states that the child's nutritional status should be assessed before the KD. The KD should be supplemented to meet DRI recommendations for gender and age. Further, that periodic assessment of the KD and supplements are necessary.

Osteoporosis/osteopenia and fractures

Bone health is becoming an increasing concern in our children. Epilepsy increases the risk for fractures both from falls and AED use (Vestergaard, 2005). Antiepileptic medications cans cause rickets and osteoporosis by interfering with vitamin D function, calcium absorption or directly affecting bone remodeling (Fitzpatrick, 2004; Shellhaas et al., 2010). There is now an increasing amount of data suggesting that AED use predisposes the epilepsy patient to poor bone health and that duration of treatment and poly pharmacy increases this risk (Sheth et al., 2008).

The KD results in reduction in seizures, hence probably falls and injuries. Most importantly it allows us to reduced AED use. Infact, 20—60% of children on the KD for more than one year are treated with the KD alone (Hemingway et al., 2001; Kang et al., 2005; Groesbeck et al., 2006). Bergqvist et al, showed that >50% of children with intractable epilepsy who were about to start the KD, had insufficient vitamin-D status (25-OH-vitamin-D < 32 ng/dL), placing them at risk for osteopenia. Supplementation with low dose vitamin-D, (400 IU in the multivitamin) while on the KD for the 15 month, normalized their vitamin-D status (Bergqvist et al., 2007).

In spite of these bone preserving changes, osteopenia and fractures have now been reported in several studies of the longer term side effects associated with the KD (Hahn et al., 1979; Kang et al., 2004; Groesbeck et al., 2006). Bone changes take time to develop; perhaps not surprisingly, a seven-month short-term study did not find any changes (Bertoli et al., 2006).

A 15-month longitudinal prospective study used dual energy X-ray absorptiometry (DEXA) every 3 months to measure bone mineral content (BMC) in children on the KD. Whole body and spine BMC for-age and height declined with more than −0.5 Z-score/year while height declined −0.5 Z-score/year (Bergqvist et al., 2008). These changes occurred in spite of fewer AED and improved vitamin D status, suggesting a vitamin D independent mechanism. There may be several mechanisms involved and acidosis may play an important role. The ketone bodies are acidic, yet the PH is usually normal, but bicarbonate is low. These changes indicate an insufficient production or increased need for bicarbonate while on the KD. The acid environment may prevent normal BMC accrual and also affect the linear growth, which is now documented in several studies (see

growth above). IGF-1 is important for bone formation and there is evidence that IGF-1 becomes suppressed during the KD (Laron, 2001; Spulber et al., 2009). It is likely that the failure to accrue bone mineral content while on the KD is multi-factorial and may also include disruptions of the growth hormone axis.

The IKDCS recommendations for DEXA and vitamin D monitoring as optional. With this new information, our center performs a DEXA yearly and vitamin D every 6 months while the child is on the KD. For children with decreasing BMC-age and height adjusted Z-scores, calcium and vitamin D supplementations are maximized and exercise strongly encouraged. Children with who are not able to ambulate should use a stander to promote weight bearing to maximize their bone health.

In summary, the ketogenic diet is an ''outlier of diets'' resulting in diffuse metabolic shifts affecting every cell in the body. Many side effects can be prevented by careful monitoring and management of the diet. Some long-term side effects may not be preventable and the ''benefits'' will have to be reassessed periodically, particularly in children who remain on this treatment longer than the usual 2—3 years.

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