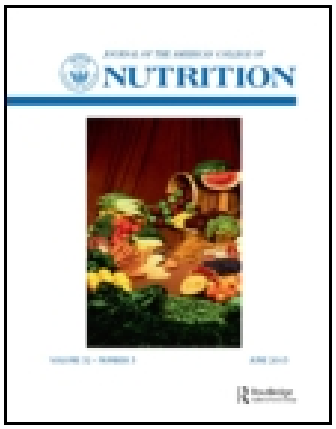

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Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports.

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Clinical and Laboratory Pearl

Effects of a Ketogenic Diet on Tumor Metabolism and Nutritional Status in Pediatric Oncology Patients: Two Case Reports

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Objective: Establish dietary-induced ketosis in pediatric oncology patients to determine if a ketogenic state would decrease glucose availability to certain tumors, thereby potentially impairing tumor metabolism without adversely affecting the patient's overall nutritional status.

Design: Case report.

Setting: University Hospitals of Cleveland.

Subjects: Two female pediatric patients with advanced stage malignant Astrocytoma tumors.

Interventions: Patients were followed as outpatients for 8 weeks. Ketosis was maintained by consuming a 60% medium chain triglyceride oil-based diet.

Main outcome measures: Tumor glucose metabolism was assessed by Positron Emission Tomography (PET), comparing [Fluorine-18] 2-deoxy-2-fluoro-D-glucose (FDG) uptake at the tumor site before and following the trial period.

Results: Within 7 days of initiating the ketogenic diet, blood glucose levels declined to low-normal levels and blood ketones were elevated twenty to thirty fold. Results of PET scans indicated a 21.8% average decrease in glucose uptake at the tumor site in both subjects. One patient exhibited significant clinical improvements in mood and new skill development during the study. She continued the ketogenic diet for an additional twelve months, remaining free of disease progression.

Conclusion: While this diet does not replace conventional antineoplastic treatments, these preliminary results suggest a potential for clinical application which merits further research.

INTRODUCTION

Certain tumors, particularly those associated with the central nervous system (e.g., astrocytomas, glioblastomas, and schwannomas) rely on glucose as the predominant source of energy [1, 2]. The apparent reason for such glucose dependency is the lack of key mitochondrial enzymes, thereby limiting the ability of the tumor to utilize alternative energy sources, principally ketone bodies, as the major source of fuel [3, 4]. The elevated glucose consumption (i.e., glycolysis) by the tumor tissue results in a non-productive cycle between the tumor and the host, draining host energy reserves to provide the ATP necessary for increased gluconeogenesis [5]. This "Cori-cycle" like activity may be a contributing factor to cachexia associated with many cancers [6]. In theory, decreasing availability of glucose to the tumor would not only be detrimental to tumor metabolism but disrupt the non-productive energy drain as well. One way to accomplish this would be to switch from a carbohydrate-based to a fat-based (i.e. ketogenic) diet.

Only one investigation with cachectic cancer patients has addressed whether a ketogenic diet can decrease nitrogen loss and reduce the supply of glucose for tumor energy metabolism [7]. Five adult patients were fed enterally via nasogastric tube for a 7-day period. Results demonstrated that a ketogenic diet containing 14% protein, 16% carbohydrate, 70% medium chain triglyceride (MCT) oil supplemented with D-3-hydroxybutyrate at 4 mmole/kg/day induced a ketotic state. The diet was well tolerated, maintained these individuals in positive nitrogen

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Abbreviations: FDG = [Fluorine-18] 2-deoxy-2-fluoro-D-glucose

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balance, and induced significant weight gain during the 7-day period [7].

Whether these observed changes in energy substrate concentrations might lead to an alteration in tumor glucose metabolism or effect nutritional status during a longer trial period remained to be determined. Therefore, our objective was to assess the effects of systemic ketosis induced by a MCT oil-based diet on nutritional status, tumor metabolism, and quality of life in select pediatric oncology patients. Initiating a ketogenic diet to shift the prime substrate for energy metabolism from glucose to ketone bodies may decrease the availability of glucose to the tumor, possibly interfering with tumor metabolism, while maintaining the patient's nutritional status.

MATERIALS AND METHODS

Two pediatric oncology patients, diagnosed with nonresectable advanced stage disease with measurable but nonprogressive tumor after therapy, participated in an 8-week pilot study. Each patient served as her own control. Informed written consent was obtained from parents or guardians for each patient. The protocol was approved by the University Hospitals of Cleveland–Institutional Review Board.

Historically, a MCT oil-based diet was used to control epileptic seizures in pediatric patients [8]. For this protocol, the MCT oil-based diet was adapted to provide 60% MCT oil, 20% protein, 10% carbohydrate and 10% dietary fat as percentage of total kilocalories. MCT oil (Mead Johnson/Bristol-Myers Co., Evansville, IN) was used as the primary diet lipid source. MCT oil was chosen because it is more rapidly hydrolyzed to fatty acids than are long chain triglycerides derived from dietary fats, thereby facilitating a stronger state of ketosis [9].

Energy levels were calculated at 120% of the Recommended Dietary Allowances (RDA) for age to prevent possible weight loss often noted upon initiation of a ketogenic diet [10]. The diet, normally deficient in B-complex vitamins, vitamin D, calcium, iron and other minerals due to its restrictive nature, was supplemented to meet RDA requirements for age and sex [11].

The patients were gradually introduced to the ketogenic diet over a 5-day period as inpatients at the General Clinical Research Center (CRC) of UHC. A dietary manual containing recipes and a food exchange list was developed for each patient to assist with education and compliance. Fasting baseline blood values, dietary intake data, and Positron Emission Tomography (PET) data were collected upon admission.

Following establishment of ketosis and dietary tolerance, the patients were discharged to continue the diet at home. During the next 8 weeks, data collection occurred during weekly outpatient appointments. Height or recumbent length, and weight were recorded by the CRC protocol nurse at the initiation of each visit [12]. During the trial, the patient's families also were contacted by telephone to provide assistance with appropriate procedures and encourage dietary compliance. Patients returned to the outpatient clinic for final evaluation and a second PET scan at the end of the trial period.

Dietary assessment consisted of one quantitative diet history taken at the start of the study and six 3-day food records collected during the trial. Intake data were coded and analyzed to determine values for kilocalories, protein, and selected nutrients using the Highland View Hospital-Case Western Reserve University Nutrient Data Base, (Revision 11, August 1, 1991; Cleveland, OH). Adequacy of the diet was assessed by comparisons to the 1990 RDA [13].

Blood and serum samples were analyzed by the CRC Core Laboratories, and the Clinical Chemistry Laboratories, Division of Clinical Pathology, University Hospitals of Cleveland. All procedures complied with the National Committee for Clinical Laboratory Standards. Serum glucose was measured by an oxidative method using a Beckman Glucose Analyzer 2 [14]. Serum lipids (total cholesterol, triglycerides) were analyzed using the Automated Technicon Chem I. The Roche Cobas-Bio Centerfugal Automated Analyzer was used to measure serum free fatty acids [15], serum ketones (β-hydroxybutyrate, acetoacetate) [16, 17] and high-density lipoprotein (HDL)-cholesterol, while low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) values were calculated [18].

PET analysis was performed using a Super PETT 3000 (PETT Electronics, St. Louis, MO). Patients were sedated during the scan period and passively restrained using normal Computed Tomography/Magnetic Resonance Tomography (CT/MRI) restraining techniques. A 30-minute attenuation scan was performed using an on-board rotating source of ^{68}Ge (germanium) prior to administration of FDG intravenously. The fluorine-18 2-deoxy-2-fluoro-D-glucose (FDG) was prepared on site by the PET facility staff. Injection of the FDG label and blood sampling were done according to standard procedures [19]. The FDG dose was based on weight (kg), ranging approximately 1.0 – 2.0 mCi F-18 labeled FDG per subject. FDG uptake was measured at 45–55 minutes after injection. The scanner was operated in a low resolution mode, producing seven contiguous planar slices, 14 mm thick. The effect of partial volume on measured radioactivity levels was minimal since the tumors were adequate in size.

The PET images were compared to available CT and/or MRI scans to determine the region of interest (ROI) in each tumor. A background ROI was drawn as a mirror image of the original tumor ROI for the purpose of calculating a tumor-to-background ratio, in this case tumor to normal cortex. The average activity within each tumor site was corrected for radioactive decay and normalized for the dose administered and the patient's weight to yield the average dose uptake ratio. The final image intensity scale was reconstructed based upon the absolute values obtained between the pre- and post-trial scan [20–22].

CASE REPORT 1

Patient #1, a 3-year-old Caucasian female with positive history of prenatal alcohol and drug exposure, was diagnosed at age 18 months with Anaplastic Astrocytoma (Stage IV) extensively involving her entire spinal cord. She was enrolled in the Children's Cancer Study Group (CCG-945) protocol titled, "A Non-Randomized Study of the "Eight Drugs in One Day" Regimen in Children With New Newly Diagnosed Primary Spinal Cord Tumors, in Conjunction With Conventional Local and Neuroaxis Radiotherapy." Hyperfractionated radiation to the cranial/spine region was started the same month.

Continued failure to thrive, poor tolerance to oral feedings and declining body weight required the placement of a gastrostomy tube 2 months later. Radiation treatments totaling 3600 cGys whole neuroaxis (head and spine) were completed at age 20 months. A Broviac catheter was placed and chemotherapy started during the same month. However, hematopoietic and renal toxicity were considerable. At age 24 months, the subject experienced a single brief seizure episode for which she was hospitalized. Continued poor tolerance to oral and enteral intake, increased infections, toxicity, and deteriorating motor skills required a halt to chemotherapy treatments by age 25 months. The patient had received a total of six treatments before chemotherapy was discontinued. There was no evidence of tumor response to therapy or of tumor progression at the time standard therapy was stopped.

Treatment

Quantitative diet history analysis prior to enrollment in the study indicated a usual caloric intake of 600 Kcal/day (13% PRO, 52% CHO, 35% FAT) in a 50:50 enteral formula combination of PediaSure and Enrich (Ross Laboratories, Columbus, OH) prior to the start of the study. The diet was below the RDA for vitamin D and most minerals. The patient was below the fifth percentile for height (80 cm) and weight (11 kg) for her age group. For the study protocol, an enteral formulation of the ketogenic diet was developed for this patient's unique tolerance issues to provide 70 Kcal/kg and 4 tablespoons MCT oil. It was administered through the gastrostomy. As the trial continued, the caloric value was increased to 85 Kcal/kg and 5 tbsp MCT oil to encourage weight gain. The ketogenic formula consisted of MCT oil, Portagen (Mead Johnson/Bristol-Myers Co., Evansville, IN) and Pro-Mod protein supplement powder (Ross Laboratories, Columbus, OH) with added liquid vitamin and mineral supplements (Vita-Quick/Mini-Quick; Twin Laboratories, Ronkonkoma, NY).

Tolerance to the diet was established without difficulty in this patient within 5 days of introduction. Changes in blood values are shown in Fig. 1. The sudden fluctuations noted during the fourth week were associated with a sinus infection which briefly affected dietary compliance.

Blood and serum analyses (Table 1) indicated cholesterol, triglyceride, and free fatty acid levels were elevated in proportion to the length of time the patient was following the ketogenic diet. HDL-C, LDL-C, VLDL-C levels changed slightly but remained within normal limits. The changes in lipid levels, especially triglyceride levels, were attributed to the large percentage of MCT oil contained in the ketogenic diet.

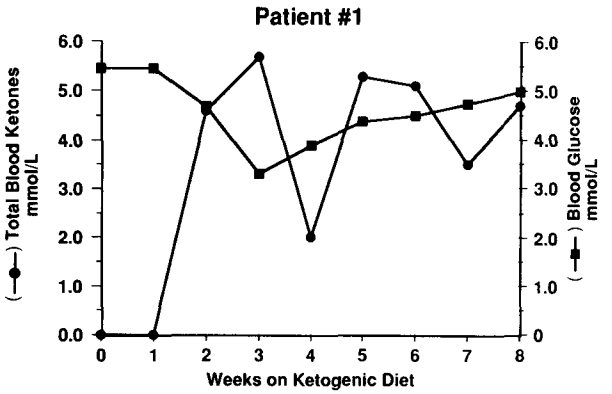

Fig. 1. Total ketone (β-hydroxybutyrate + acetoacetate) and blood glucose concentrations for Patient #1 collected during weekly clinic visits. Dietary compliance was compromised briefly during Week 4 due to a sinus infection.

PET scan data indicated a decrease in FDG uptake by 21.77%, at the tumor site (Table 2). Periodic MRI scans indicated no change in tumor margins while she was following the ketogenic diet.

Patient #1 successfully completed the initial trial period with notable improvement. Marked progress in skill development (gait, mobility, speech, hand coordination) and mood justified extension of the initial trial period (Weeks 1–8). An addendum to the protocol was approved and she continued to be followed.

Patient #1 remained on the ketogenic diet for 12 additional months (Weeks 9–62) after the initial study period exhibiting no measurable progression of disease. She continued to improve her abilities to sit or stand without assistance, developed better control over bodily functions, and cooperated in attempts at toilet training. A specially designed walker allowed the subject to walk independently. She started school for the medically handicapped where she continued to develop new social

Table 1. Patient #1: Lipid Profile

	Week 1_A	Week 8	Week 39
	(mmol/L)	(mmol/L)	(mmol/L)
Total Cholesterol	4.32	4.45	5.09
HDL-C	1.21	1.56	1.48
LDL-C	2.30	1.68	2.51
VLDL-C	0.80	1.22	1.76
CHOL/HDL ratio	3.6	2.9	3.4
Triglycerides	1.89	2.66	2.91
Free fatty acids	0.51	1.24	3.40

$_A$ Week 1 baseline fasting blood samples drawn prior to initiating the diet.

Table 2. PET Data Results

PET scan	Ratio tumor:normal cortex$_A$	
	PATIENT #1	PATIENT #2
Week 1$_B$	0.7622	3.6418
Week 8	0.5963	2.8465
% CHANGE$_C$	−21.77%	−21.84%

$_A$ Dose Uptake Ratio — mCi × cc^{-1}/mCi × kg^{-1}.

$_B$ Week 1 baseline fasting blood samples drawn prior to initiating the diet.

$_C$ % Change = (Week 1 − Week 8)/Week 1 × 100.

and cognitive skills. Family members reported her overall quality of life greatly improved.

CASE REPORT 2

Patient #2, an 8.5-year-old Caucasian female, had no early medical indication of any significant problems. She was diagnosed at age 6 with Cerebellar Astrocytoma (Low Grade) after experiencing sudden, frequent headaches and difficulty in balance and coordination. Surgery 2 months later removed approximately 95% of her cerebellum. A ventricular peritoneal shunt was placed 2 months after surgery. Coordination problems redeveloped by age 8 years. A second surgery (posterior fossa craniectomy) occurred the same month for recurrent tumor which was reclassified as Cerebellar Astrocytoma (Grade III). Neurological deficits improved slightly after the second surgery.

Patient #2 was enrolled in protocol CCG-945 Regimen B. Hyperfractionated radiation therapy began after the second surgery. Radiation treatments totaling of 5400 cGys to the posterior fossa (right and left lateral portals) were completed three months later. Within 1 month after surgery, a Mediport catheter was placed and the chemotherapy protocol started. The patient followed a monthly chemotherapy treatment schedule. Patient #2 had high pitch frequency hearing loss secondary to chemotherapy (Cis-platin) toxicity. She had low blood magnesium levels which required additional supplementation. Patient #2 was entered on the ketogenic diet while still receiving chemotherapy, after having completed irradiation, when her tumor was radiologically stable by CT scan.

TREATMENT

Quantitative diet history data analysis prior to enrollment in the study indicated an average of 1900 Kcal/day (17% PRO, 43% CHO, 40% FAT). Nutrient intakes prior to enrollment were 100% or greater of RDA guidelines for all nutrients except biotin, vitamin E, and vitamin D which were between 50–70% of RDA guidelines. The patient was in the 25th–50th percentile for both height (128 cm) and weight (24 kg) for her age group.

The ketogenic diet designed for Patient #2 provided 2200 Kcal/day (88 Kcal/kg) and 11.5 tbsp MCT oil. A special "shake" was designed to incorporate most of the daily MCT oil allotment. In this manner, the quantity consumed could be easily measured and controlled. The shakes were made with a variety of flavoring agents, low-fat milk, water, and the MCT oil. The remaining allotment of oil was added to foods like scrambled eggs, tuna fish, salads, or casseroles with consideration to the patient's food preferences. Vitamin and mineral supplements (1 tablet each Twin Laboratories Animal Friends Chewable for Children, Ronkonkoma, NY and Os-Cal Chewable 500 mg Calcium, Marion Laboratories, Inc. Kansas City, MO) were added to the diet to insure appropriate nutrient intake levels.

Tolerance to the diet was established without difficulty in this patient within 5 days of introduction. She completed the protocol without any complications. Change in blood values over time are shown in Fig. 2. A chemotherapy treatment during Week 4 briefly affected dietary compliance.

Blood and serum analyses (Table 3) indicated cholesterol and free fatty acid levels increased. However, blood triglyceride levels actually declined during the same period. Lipoprotein levels for HDL-C increased slightly, while LDL-C and VLDL-C levels declined. Urine was tested with KETOSTIC Reagent Strips (Miles., Inc. Diagnostic Division, Elkhart, IN.) to corroborate the degree of dietary compliance and validity of blood ketone levels reported.

PET scan data indicated a decrease in FDG uptake by 21.84%, indicative of decreased glucose metabolism at the site of the tumor (Table 2).

DISCUSSION

A medium chain triglyceride (MCT) oil-based diet, considered non-invasive compared to more traditional antineoplastic

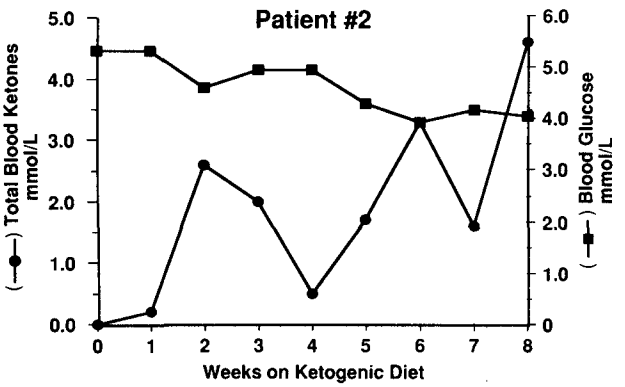

Fig. 2. Total ketone (β-hydroxybutyrate + acetoacetate) and blood glucose concentrations for Patient #2 collected during weekly clinic visits. Dietary compliance was briefly compromised during Week 4 due to a chemotherapy treatment. The start of school (and school lunches) also slightly affected dietary compliance during Week 7.

Table 3. Patient #2: Lipid Profile

	Week 1_A	Week 8
	(mmol/L)	(mmol/L)
Total cholesterol	6.03	6.65
HDL-C	1.82	2.07
LDL-C	3.54	2.95
VLDL-C	0.67	0.57
CHOL/HDL ratio	3.3	3.2
Triglycerides	0.53	1.22
Free fatty acids	0.53	1.22

$_A$ Week 1 baseline fasting blood samples drawn prior to initiating the diet.

regimens, was effectively implemented over an 8-week period in two pediatric oncology patients with advanced stage neoplasia. Detailed assessment of dietary intake data indicated the ketogenic diet with supplements met the overall energy and nutrient needs of both patients. Calorie and nutrient intake levels improved in each patient during the trial period compared to the month preceding it. Body weights were stabilized (Pt. #1 11 ± 0.5 kg, Pt. #2 24 ± 0.3 kg) thereby reversing the weight loss experienced by both patients prior to the start of the study.

It was anticipated that implementation of the MCT oil-based diet would create an elevation in blood ketone levels and a decline in blood glucose levels. Free fatty acids levels should also become elevated, reflecting the diet composition and amount of MCT oil used. The free fatty acids would then be transported to the liver for ketone body synthesis in turn allowing glucose to be replaced by ketone bodies as the primary fuel source in muscle tissue [9]. Since the diet would provide adequate energy and protein levels, gluconeogenic activity should decline. These expectations were confirmed by the monitored biochemical parameters.

Weekly blood tests were used to monitor compliance and tolerance of each patient. Blood ketone levels were extremely sensitive indicators of the degree of ketosis. Dietary modifications required during periods of illness or treatment were reflected in changes in blood ketone and glucose levels indicating a diminution in the state of ketosis. Slight modifications to the ketogenic diet were initiated as necessary to return the patient to a moderate to strong state of ketosis.

Because tumors consume glucose at higher rates than their normal tissue counterparts, FDG-PET imaging is able to accurately identify high grade metabolically active tumors [23]. In the brain, FDG-PET also has been utilized to distinguish between tumor recurrence and necrotic tissue [24], to estimate the extent of residual tumor after surgical resection [24, 25], to measure the metabolic or physiologic impact of radiation and chemotherapy on tumor and normal tissue [26–33], and to estimate patient prognosis [27]. When glucose utilization of high grade gliomas were compared to contralateral normal brain tissue, patients with tumor metabolic ratios greater than 1.4 had a median survival of 5 months while those with lower ratios had a median survival of 19 months [28].

The unique aspect of this study is the application of PET technology to assess changes in tumor glucose metabolism initiated by diet. FDG uptake decreased by approximately 21.8% during the 8-week diet regimen in both patients, indicative of overall decreased glucose metabolism, at the tumor site. Our data suggests that these changes were coincident with institution of the diet and not related to other treatment. Although both patients demonstrated similar decline in FDG uptake at the tumor site, only Patient #2 was receiving active chemotherapy (one treatment administered during Week 4 of the study). Both patients had completed irradiation treatment. PET studies assessing the effect of treatment indicate the greater the overall decrease in tumor metabolism following radiation or chemotherapy, the longer the period of clinical remission [29, 30]. In the most aggressive tumors, FDG uptake may actually increase within 24 hours after chemotherapy as cellular recovery from treatment induced injury occurs at the tumor site [31–33]. Therefore, the chemotherapy treatment for Patient #2 was coordinated into the study schedule to minimize any potential effect on FDG-PET evaluation.

The noted differences in calculated glucose uptake ratios between Patient #1 and Patient #2 may be attributed to differences in tumor grade, the degree of inflammation, edema, tissue necrosis, or fibroses present, or the extent of blood supply available to the tumors [34]. To minimize such differences, patients were matched by tumor type and grade as much as possible and were in a stable phase of treatment. Additionally, qualitative FDG-PET data in the form of glucose uptake ratios were used to assess changes between pre- and post-trial scans within each patient. Therefore, the data reported are believed to reflect the effects of dietary-induced ketosis. A study with a larger number of subjects is needed to resolve this question.

Notable clinical improvements in mood and new skill development by Patient #1 during the initial trial warranted extension of the study; she remained on the ketogenic diet for 12 additional months without further measured disease progression yet continued clinical improvement and enhanced quality of life.

The present investigation is an attempt to explore the effects of diet composition on tumor glucose metabolism in pediatric oncology patients. The MCT oil-based diet is able to meet the energy and nutrient needs of the pediatric cancer patient. Tolerance to the diet can be established in these patients without difficulty. PET data indicate a decline in FDG glucose uptake at the tumor site. At the time of publication, both patients remain in remission (5 and 4 years after diagnosis, respectively) and continue to enjoy a good quality of life.

CONCLUSION

A ketogenic diet can be successfully implemented in pediatric oncology patients as a means to effect tumor metabolism.

While the authors do not imply that this diet replaces conventional antineoplastic treatments, it may be an option for select patients as an adjunct to various antineoplastic treatments. These preliminary results, though not conclusive, suggest a potential for clinical application which merits further investigation.

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