The Role of the Keto-genic Diet and Managing Seizures and Electrical Transmission in the Brain

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Glioblastoma multiforme (GBM) is the most deadly primary brain tumor in the United States (1). Current median life expectancy is 8-15 months (1, 3). Standard treatment is typically palliative in nature and while there are new therapies, improved long term survival needs verification (1,2,3). The ketogenic diet (KD) – described below, has shown promising results in animal models with malignant brain tumors, but few human studies detail results for treatment of primary brain tumors with the KD (4). Currently, the data that the KD alone for patients with GBM improves survival is limited since most patients are also on chemo/radiation therapies (3). However, secondary tumor associated seizure activities appear to be reduced in those patients on KDs (3).

The brain is almost completely dependent on glucose for energy (5). Blood glucose concentrations are considered normal between 70-144 mg/dL, while any concentration over 200 mg/dL is considered hyperglycemic (5). For patients with GBM, blood glucose concentrations have been found to average up to 459 mg/dL – secondary to tumor metabolism (5). Previous work has demonstrated that cancer cells can defy damage from radiation when in a hyperglycemic environment and that higher amounts of glucose is correlated to a shorter survival, and faster tumor growth (5,6,7,8).

When the brain has decreased access to glucose, it is able to metabolize ketone bodies for energy (8). Brain tumor cells are completely dependent on glucose to perform glycolysis, and are unable to metabolize ketones, due to impaired mitochondria (1). Ketones may be toxic to some tumor cells (8). Therefore, focusing anti-tumor treatments involving glucose metabolism may be of benefit for GBM patients (1). The Ketogenic Diet (KD) typically consists of 90% fat, with the remaining 10% contributed by both protein and carbohydrate (9). To date, there are very few human studies involving the KD as the sole treatment or a component of a treatment for GBM (2,3,8,10).

A few concerns should be addressed when considering the KD as a therapeutic treatment for patients with GBM: carbohydrate content of diet, initiation of diet, compliance to diet, duration of diet, quality of life, and involving a Registered Dietician (RD) in the treatment protocols. While the KD typically provides 90% fat, the amount of carbohydrate permitted during treatment tends to vary in the literature (9). Previous studies using the animal model have demonstrated that by restricting carbohydrates to <50 g/day results in ketone blood levels ≥1 millimoles per liter (mmol/L) which results in reduced ketone –related stimuli for seizure activity (9). Best practice may be to allow patients to eat around 50 grams of carbohydrate per day, which may improve adherence to the prescribed diet and improve treatment outcomes.

Compliance to the KD is an issue as it requires a lifestyle change, which may be difficult for some patients (11). It is not uncommon for studies to report that some participants had low compliance (3,11). For patients with strict compliance to the KD, there was a reported partial response to treatment (3). Having patients test their own ketone and glucose levels may help them to comply with the diet. The goal for GBM therapy is to have blood glucose ranges between 55-65 milligram per deciliter (mg/dL) (1).

To measure compliance to the KD, ketones are measured *via* urine analysis; however, there is evidence to show that urine concentrations are not reflective of the concentrations of ketones available to the brain for consumption (3). It was reported that 92% of patients that tested urine ketones 2-3 times per week achieved ketosis at least one during the study. Best practice would be to have patients test blood glucose and ketones 2-3 times per day to help with measurable goals. While the KD has been promising in the mouse model, the studies in human clinical trials have yet to clearly demonstrate that the KD is effective as a sole intervention. Part of the issue is that the KD has not been consistently used an isolated therapy, and many of the studies use KD concomitantly with other treatments (1,3,4,11). However, the KD may be most effective when used in combination with chemotherapy (12).

It has previously been reported that effects of the KD cannot be ascertained until after 8 weeks on the diet (11). Current recommendations state that dietary interventions should be started before cancer treatments then continue along with and after treatments (13). The KD is intended to meet the energy and nutrition requirements of oncology patients while also stimulating lean body mass recovery (9). In addition, seizure activity is reduced (12). While the KD, especially if paired with a calorie restriction, may cause weight loss, one of the goals during cancer treatment is preventing malnutrition. Malnutrition has been found to be the leading reason for interrupting the KD (14). Overall, the KD appears relatively safe for patients with GBM, may help increase longevity, and reduce seizures, although excessive weight loss may be a concern. It is important that patients following the KD have a balance of food choices to increase quality of life and mitigate weight loss while also adhering to the KD for best treatment outcomes.

When considering diet therapy in combination with anti-tumor treatments, it would be best practice to consult a registered dietitian or clinical nutritionist (RD or RDN) (16).The majority of the cancer patients that followed a special diet reported they adhered to it after receiving education from a registered dietitian (18).

There is a need to develop clinical trials involving GBM patients that include: 1) initiation of a KD composed of 50 grams of carbohydrate per day prior to chemotherapy and continue concomitantly with chemotherapy; 2) monitor blood levels for ketones and glucose daily to prevent hypoglycemia; 3) continue the KD for at least 8 weeks and 4) monitor weight loss. In addition, it would be best practice to include a registered dietitian nutritionist with the protocol to improve patient outcomes, educate patients on the KD,

monitor progress, calculate energy needs and identify potential barriers while following the KD.

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