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A Nutrition Perspective on the Ketogenic Diet as Therapy for Malignant Brain Cancer

Meredith Morgan

Abstract

Glioblastoma multiforme is the most deadly primary brain tumor. Current therapies have not demonstrated improved outcomes for patients; generally the median life expectancy is 8–15 months. Due to brain tumor cells dependence on glucose as a sole energy source, there is potential to target treatments towards glucose metabolism. The ketogenic diet (KD) is a high fat, low carbohydrate diet that has proven successful in the animal model. However, human studies are limited and there currently is not enough research to conclude the KD is an effective therapy. A few aspects need to be addressed for inclusion in protocols of future studies: (1) when to initiate the KD during treatment; (2) how much carbohydrate per day to provide to patients; (3) how to ensure patient compliance to diet; (4) the optimum duration of the diet; (5) how to mitigating patient weight loss. In addition, the registered dietitian nutritionist (RD or RDN) is a vital, and underutilized, member of the health care team. The inclusion of a RD to future KD protocol, as well as oncology practices, can enhance patient outcomes and help future patients overcome barriers when adhering to the KD.

Keywords: nutrition, ketogenic diet, glioblastoma multiforme, registered dietitian nutritionist, brain cancer

1. Introduction

In 2013, it was estimated that there were 23,130 cases of primary brain cancer in the United States and 14,080 deaths from the disease [1]. One type of tumor is glioblastoma multiforme (GBM), which is the most deadly primary brain tumor in children and adults [2]. Most cases of GBM occur in patients over the age of 50 years old [3]. Current median life expectancy for these patients is 8–15 months; 1 year survival is 34.6% and 5 year survival is less than 5% [1, 3]. Standard treatment is typically palliative in nature and includes surgery (maximal tumor resection), radiation, as well as chemotherapy [2, 3]. While there are new therapies, which include gene therapy, immune modulating therapy and anti-angiogenic therapy, these have not demonstrated improved outcomes for this disease [4]. Overall, the current aims of therapies are to increase life expectancy and enhance quality of life [3].

Patients with cancer often have a “wide range of nutrition related problems” [5]. These nutritional issues may occur anywhere along the digestive tract—from salivary dysfunctions to changes in stooling and often involve weight loss [5]. Other

patients may be at higher risks of developing morbidities such as “diabetes, adipositas, hyperlipidemia or cardiovascular disease” related to cancer therapies [5]. Patients with head and neck cancers have a high risk of mortality (50%) and many of these patients suffer from malnutrition [6]. This is often a result of the malignancy and may be attributed to loss of appetite, difficulties eating, weight loss as well as fatigue [6]. Malnutrition is an issue as it may cause setbacks in healing, such as weakened immune system, longer treatment times and increased complications along with the cancer [6].

When it comes to medical nutrition therapy (MNT), cancer patients are often “under-recognized and undertreated” as a patient population [5]. Data constantly demonstrates that patients with cancer that do not receive MNT have decreased likelihood of responding to therapies and success may be lower [5]. A registered dietitian nutritionist (RD or RDN) is trained to deliver nutrition facts as well as scientifically based nutrition education and counseling, while also considering educational levels and “psycho-oncological” influences [5]. Current nutrition recommendations correspond generally to patients with head and neck cancer, and there are no specific nutrition recommendations for patients with GBM. The ketogenic diet (KD) has shown promising results in the animal model for malignant brain tumors, but as of 2015, very few studies detail the treatment of primary brain tumors with the KD [1]. Currently, the data is limited whether the KD is effective for patients with GBM for improving outcomes and extending longevity. In addition, the question remains: should health professionals recommend the KD as a therapeutic treatment for patients with GBM?

2. Brain cell metabolism

The brain is a “metabolically active organ” that is almost completely dependent on glucose as its exclusive energy source [7]. Without the ability to locally store glucose, the brain relies on tight homeostasis of blood glucose to ensure adequate energy supplies [7]. Blood glucose concentrations are considered normal between 70 and 144 mg/dL, while any concentration over 200 mg/dL is considered hyperglycemic [7].

For patients with GBM, blood glucose concentrations have been found to average 459 mg/dL [7]. In part, this may be due to high dose of glucocorticoids to help with peritumor associated edema [8, 9]. Glucocorticoids usage results in impaired glucose transport and high plasma glucose [8]. In addition, glucose metabolism is higher in environments with poor blood supply, such as acidic and hypoxemic environments [7]. This may be attributed to the Warburg effect. This effect is part of the aberrations observed in cancer cell metabolism; it involves a switch from oxygen dependent oxidative phosphorylation to “glucose intensive” anaerobic glycolysis for ATP production [7]. This results in the production of essential proteins, lipids and nucleic acids required for cell growth under hypoxic conditions [7]. Tumors in microenvironments are negative indicators of “therapeutic response” and overall survival [7]. Previous work has demonstrated that cancer cells have enhanced aptitude to defy damage from radiation when in hyperglycemic environments [10]. Unfortunately, due to high mortality rate, and decreased likelihood of patients developing diabetes in the long term, hyperglycemia is not managed by intensive therapies; rather, the goal is to avoid acute complications [8]. However, previous studies have demonstrated that higher amounts of glucose in the brains of cancer patients is correlated to a shorter survival [7, 8]. Other reports have demonstrated that the higher the glucose levels, the faster the tumor growth [9]. Glioma cells have previously been shown to display a “threefold increase” in the rate of glycolysis

compared to normal astrocytes and when glucose is removed; this leads to apoptosis in tumor cells, compared to normal cells [11].

When the brain has decreased access to glucose, it is able to metabolize ketone bodies (acetoacetate and β -hydroxybutyrate) for energy [9]. This occurs as the liver transforms fat into ketone bodies and fatty acids. The ketone bodies then circulate to the brain and substitute glucose as the brain's energy source [4]. The benefit is that as brain tumor cells are completely dependent on glucose to perform glycolysis, they are unable to metabolize ketones. The latter is due to impaired mitochondria [2]. Another benefit is that ketones may be toxic to some tumor cells by decreasing free radicals from oxygen and improving metabolism in healthy cells [9]. Therefore, focusing anti-tumor treatments on glucose metabolism may be beneficial for GBM patients' outcomes [2].

2.1 The ketogenic diet

The ketogenic diet (KD) was established in the 1920s and consists of a high fat content while providing a low carbohydrate content [2, 10]. It is best executed under medical supervision; it has been effective for treating children with epilepsy and may be successful in neurodegenerative diseases such as Alzheimer's and Parkinson's [2, 12]. The diet is successful as it mimics the fasting state by increasing the level of ketones circulating in the blood, while decreasing circulating glucose; this diet also avoids malnutrition in patients [2, 10]. The KD typically consists of 90% fat, with the remaining 10% contributed by both protein and carbohydrate [13]. Protein is indispensable in the diet, but too much protein can result in the transformation to glucose via gluconeogenesis and act metabolically as a carbohydrate [13]. It has previously been demonstrated that extremely malnourished oncology patients that were given a diet consisting of 44 kcal/kg, where medium chain triglycerides provided 70% of the macronutrient content, had no significant changes in nitrogen balance or protein synthesis [13].

Using the KD as a therapeutic approach for malignant brain cancer rests on the assumption that brain tumors do not have the necessary enzymes to oxidize ketones, and are based on successful rodent studies [4]. However, a recent study contradicted previous findings and reported that rodent brain tumors were able to metabolically change and the "up regulation of the ketone body monocarboxylate transporter," which "facilitated the uptake and oxidation of ketone bodies in the gliomas" [4]. To date, there are very few human studies and most of them have small sample sizes [4]. Using the KD as the sole treatment or part of the treatment may be effective against GBM, and has been suggested and discussed in previous literature [3, 9, 14].

Another idea worth noting is that the treatment of GBM with the KD may be enhanced by a calorie restriction; this idea has been shown to prevent tumor progress in a range of models [15]. Schwartz et al. provided a calorie restriction after calculating energy needs based on ideal body weight, then providing 20–25 kcals/kg with a 20% restriction in kcals per day [1]. A calorie restriction typically provides a 20–40% reduction in daily calories. During calorie restriction, serum levels of glucose and insulin decrease while fat breakdown increases. This eventually activates peroxisome proliferator-activated receptor- α (PPAR- α), which hinders glycolysis and fatty acids production. PPAR- α also stimulates transcription of enzymes that promote ketogenesis and fatty acid oxidation in the mitochondria and peroxisome [13]. For the tumor cells, which lack the enzymes needed to metabolize ketones, energy in the form of adenosine triphosphate (ATP) can no longer be produced via glycolysis; the cells also lack the ability to compensate via oxidative phosphorylation, which deprives the cell of ATP and means for growth [13]. A calorie restriction

may be a beneficial aspect along with the KD, but is not consistently explored in KD studies. A few concerns should be addressed when considering the KD as a therapeutic treatment for patients with GBM: carbohydrate content of diet; compliance to diet; when to initiate the diet; duration of diet; quality of life, and involving a RD with the treatment protocol to improve outcomes.

2.2 Exploring best practices

While the KD typically provides 90% fat, the amount of carbohydrate permitted during treatment tends to vary with each study [13]. In the human studies investigated, the carbohydrate content ranged from 10 grams (g) per day, up to 70 g per day [2, 16]. Previous studies using the animal model have demonstrated that by restricting carbohydrates to <50 g/day, ketone levels ≥ 1 millimoles per liter (mmol/L) enhances the expression of monocarboxylic acid transporters in the brain; this results in the movement of ketones through the blood brain barrier [13]. An issue with very restrictive dietary carbohydrate is that patients with malignant tumors have been documented to have higher rates of gluconeogenesis, which decreases the body's stores of lean mass and hurts the patient [16]. Therefore, cancer patients may benefit from slightly more carbohydrate, and not risk leaving ketosis [16]. In addition, more carbohydrate options increases the types of food that can be eaten, which helps with compliance [16]. Best practice may be to allow patients to eat around 50 g 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 [16]. It is not uncommon for studies to report that some participants had low compliance [4, 16]. However, a few participants found the KD was tolerable: the diet was rated as good by seven patients, moderate by three patients and poor by only one patient [16] and was reported to be "relatively well tolerated" [15]. One patient was reported to strictly adhere to the KD and a calorie restricted diet for 56 days [2]. For patients following the KD, it is important for strict adherence to the diet. For those with strict compliance to the KD, it was reported there was a partial response to treatment, and ketone bodies were found in the normal appearing white matter 8 months after starting the diet; although, this response was attributed to bevacizumab therapy and not the KD [4]. However, there may be other barriers that exist that hinder patients from strictly adhering to the diet. To help mitigate these barriers, the addition of a RD to the treatment team would be best practice; this will be discussed later in the chapter.

Having patients test their own ketone and glucose levels may help them to comply with the diet, as they can see if their levels are in goal range. The goal for GBM therapy is to have blood glucose ranges between 55 and 65 milligram per deciliter (mg/dL) for maximum therapeutic implications [2]. 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 [4]. Artzi et al. reported only three incidences where ketones were found in the brain using magnetic resonance spectroscopy (MRS): two times in the normal appearing white matter, at 4 and 25 months after starting KD, and one in the tumor area 13 months after starting KD; it was noted that participant compliance to the KD was low [4]. Compliance to the KD was measured either by urine analysis or by blood analysis. The goal for urine ketones was set >2 , while blood ketone goals were between 3 and 8 mmol/L [1, 4]. It was reported that 92% of patients that tested urine ketones 2–3 times per week achieved ketosis at least one during the study [15]. Schwartz et al. went further and also had their participants test their blood glucose at least two times per day. Goals for

blood glucose were between 50 and 70 mg/dL, which is a suggested best practice for maximum therapeutic effect [1]. A benefit to testing ketones via the blood is that the patient can also test blood glucose and have measureable results. While the goal for blood glucose is 50–70 mg/dL, it is important that patients keep track of blood glucose to avoid hypoglycemic events, which is defined as blood glucose <45 mg/dL [2]. Hypoglycemia is a concern because if it goes untreated it can lead to coma and death [17]. However, it has been reported that while following the KD, there was no issue with hypoglycemic events, and that patients that had elevated blood glucose prior to the study, ended up with normal levels after starting the KD [2, 16]. There is valid concern that ketosis, defined by urine or blood concentrations, may not be indicative of the brain and tumor usage of ketones. However, MRS may not be a tool available for all patients and providers. Best practice would be to have patients test blood glucose and ketones 2–3 times per day to help with measurable goals, help encourage compliance and to avoid any hypoglycemic events.

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 as an isolated therapy and many of the studies use KD concomitantly with other treatments; therefore, the studies have not been able to conclude if the KD was an effective therapy [1, 2, 4, 16]. However, the KD may be most effective when used in combination with chemotherapy. Rieger et al. found that patients that received the KD and received bevacizumab had a median progression free survival of 20.1 weeks while patients receiving bevacizumab and not on the KD had a median progression free survival of 16.1 weeks [15].

The duration of the KD ranged greatly amongst the studies, and there does not appear to be a pattern for best practice. However, it has previously been reported that effects of the KD cannot be ascertained until after 8 weeks on the diet [16]. As mentioned previously, a case study reported on a patient following the KD and a calorie restriction for 56 days, then discontinued the KD and followed a low calorie diet for 5 months and was found to be disease free at that follow up [2]. Artzi et al. had dietary components that lasted from 2 months up to 31 months, although not all patients were able to follow the KD strictly [4]. Meanwhile, Reiger et al. had a median duration of 36 days for diet adherence and reported that patients followed the diet for 6.8 days out of the week. Schwartz et al. reported two participants followed the KD for 12 weeks, but there was no benefit to stopping tumor growth [1]. Meanwhile, there was evidence that the KD could be effective for longer “progression free survival;” in patients with stable ketosis, the median overall survival was 32 weeks, with a range from 6 to 86+ weeks [15]. Current recommendations state that dietary interventions should be started before cancer treatments then continue along with and after treatments; it also may be more successful if an intervention is if a registered dietitian is an active part of the treatment team [18].

Nutrition status and quality of life have a positive relationship and both are associated with survival [10, 19]. While most patients with GBM have a short life expectancy, it is important that their quality of life is maximized, and the quality of their diet is an important factor. Food is one of the few aspects of health that both patients and care givers continue to have control over, and is both a “mental and social act” that has many external influences [5]. Schmidt et al. investigated the quality of life for patients with different types of cancer on the KD. Quality of life was initially low for participants due to stage of tumor progression, but the KD was found to increase their quality of life over time. Symptoms of fatigue, pain and dyspnea amplified over time, but emotional function and insomnia improved. Previous side effects reported on the KD have included vomiting, fatigue, hunger and constipation; however, the study reported no incidence of hunger, meanwhile

nausea and vomiting were reported as infrequent [16]. In addition, the KD has been found to have no adverse neurological or physiological impacts for patients [2].

Another aspect of quality of life is weight loss. Ten to eighty-three percent of patients with cancer may have unwanted weight loss [5]. The KD in theory should mimic the benefits of long term fasting, while avoiding weight loss in the “oncological setting” [10]. The KD is intended to meet the energy and nutrition requirements of oncology patients while also stimulating lean body mass recovery [13]. From a nutrition perspective, unintentional weight loss is defined as $\geq 5\%$ in 1 month or $\geq 10\%$ in 6 months [18]. In the few studies that investigate the KD, most reported that participants lost weight [1, 2, 15, 16]. Zuccoli et al. reported on a patient that received the KD along with a calorie restriction and after 20 days had experienced a 13.4 pound (9.5%) weight loss, which is nutritionally significant based on malnutrition criteria [2, 20]. It is to be noted that this patient was on a calorie restriction of 600 calories per day [2]. Meanwhile, Rieger et al. reported a statistically significant weight loss of 2.2% overall for patients on the KD [15]. While the KD, especially if paired with a calorie restriction, may cause weight loss, one of the goals during cancer treatment is preventing malnutrition. Significant weight loss is one of the criteria used to diagnose malnutrition. Malnutrition has been found to be the leading reason for interrupted treatments [6].

Overall, the KD appears relatively safe for patients with GBM, and may help increase longevity, 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.

2.3 Role of registered dietitian in cancer treatment

It is essential for patients with head and neck cancers to follow nutrition advice for best “treatment and health outcomes” [6]. Patients that participated in a nutrition intervention during treatment were able to “maintain or improve nutritional status” as well as improving the rate of treatments completion, decreasing hospital visits, length of hospital stays and decreasing the amount of weight lost during treatment [6]. Unfortunately, patients with head and neck cancer are not always compliant with dietary advice, especially if dietary is not considered an essential part of the treatment by patients [6]. It has previously been reported that more participants received nutrition counseling after treatment (60.7%) compared to during cancer treatment (47.4%) [5].

When considering diet therapy in combination with anti-tumor treatments, it would be best practice to consult a registered dietitian. A registered dietitian nutritionist (RD or RDN) is a food and nutrition expert with a bachelor and/or master degree from an accredited university, and has taken coursework that has been approved by the Accreditation Council for Education in Nutrition and Dietetics. In addition, the RD has completed a 1200 hour supervised practice with rotation concentrations in clinical, community and food service management, and passed a national credentialing exam. RDs have to take continuing education credits, regarding up-to-date food and nutrition information, to maintain RD credentials. RDs also have the option to become certified in specific areas of practice; one such area is oncology [21]. RDs are trained to do assessments and give detailed nutrition educations. As part of the assessment, the RD assesses current weight and discusses weight history, discusses current nutrition symptoms, assesses diet history, and calculates protein and energy needs [22]. RDs use the nutrition care process, which is an internationally validated and accepted tool, which makes nutrition care more visible amongst the health profession and ensures access of information to qualified professionals [5].

The RD is an integral part of the health care team, and may be an underutilized resource. Maschke et al. found that cancer patients were more likely to receive nutrition advice from a dietitian if they were between ages 45–70 years old, and those patients between ages 27–45 years old received nutrition information from the internet, nurse or doctor. It would have been beneficial for more patients to see a dietitian as the most often reported questions was regarding a “healthy diet” as well as issues with fatigue and weakness [5]. Kiss et al. found that when the dietitian clinic was located separately from the oncology clinic, the RD was not included as part of the multidisciplinary team and patients did not attend the dietitians’ clinic. When the RD team was moved to be a part of the oncology team, it was found to improve communication amongst team members, resulting in the ability to quickly identify nutrition complications and reduce hospital admissions [22].

In regards to the studies administering the KD to patients, a RD was mentioned in a few studies as part of the protocol. Benefits of adding the RD as a part of the study protocol team is the ability to check in on patients more often, either via the phone or in the clinic, answer questions and refer patients to the doctor if there are medical treatment issues that arise. This can help take part of the burden off of the doctors [1]. In addition, it has been reported that when patients visited with a RD regularly, the percent of patients admitted to the hospital for nutrition related issues decreased from 12 to 4.5% and that hospital days decreased from 199 to 62 days [22]. The RD has the expertise and the experience to calculate energy and protein needs as well as diet plans to fit patient’s individual needs, which has some benefit [4]. To best highlight this, it is best to discuss the studies that do not involve a RD. For the two studies that did not provide patients with a RD, the study provided patients with instructions or a diet manual with a list of foods, the nutrition contents of foods, recipes and rules to follow when on the KD. Patients were left to their own devices to prepare meals and only one of the studies provided a daily menu [15, 16]. This could be one of the barriers that prevented patients from strictly adhering to the KD. Previous findings have shown that individualized diet counseling based on patients’ normal food preferences, along with head and neck cancer treatments, is a very successful way to improve patients’ nutrition status, nutrition intake and quality of life [19]. Maschke et al. reported that over half of their study respondents wanted nutrition information, which suggested there is a need for providing consistent and evidenced based MNT. In addition, they suggested that there is the potential for a strong partnership between RDs and oncologists to meet the “informational needs” of patients [5]. The majority of the cancer patients that followed a special diet reported they adhered to it after receiving education from a registered dietitian [5].

3. Conclusion

GBM is a deadly primary brain tumor and patients with this diagnosis have a limited life expectancy. The ketogenic diet has shown promising results in the animal model and in theory should work to target brain tumor cells’ glucose metabolism. However, it is difficult to draw conclusions on the effectiveness of the diet due to the limited number of studies, small sample sizes, and the inability to use the KD as an isolated therapy. More studies need to be performed before the KD can be recommended as a sole therapy for GBM, and using the KD as a therapy should occur only with direct medical supervision. Future research needs to include a standardized protocol for including KD in studies. Based on the current literature, best practice would include: (1) initiate KD prior to chemotherapy and continue concomitantly with chemotherapy; (2) KD composed of 50 grams of

carbohydrate per day; (3) patients test blood levels of ketones and glucose daily for compliance and to prevent hypoglycemia; (4) continue the KD for at least 8 weeks; (5) minimize patient 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 patient progress, calculate energy needs and help patients overcome potential barriers while following the KD.

Conflict of interest

No conflict of interests.

Notes

At time of publication, Meredith Morgan, is completing her supervised practice, and is anticipated to be a Registered Dietitian upon the completion of her dietetic internship.

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