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CLINICAL STUDY

Targeting metabolism with a ketogenic diet during the treatment of glioblastoma multiforme

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Abstract Retrospective data suggests that low serum glucose levels during the treatment of glioblastoma multiforme (GBM) may improve clinical outcomes. As such, many patients are implementing a ketogenic diet (KD) in order to decrease serum glucose flux while simultaneously elevating circulating ketones during radiation therapy and chemotherapy for the treatment of GBM. With IRB approval, a retrospective review of patients with high-grade glioma treated with concurrent chemoradiotherapy and adjuvant chemotherapy was carried out from August 2010 to April 2013. Serum glucose and ketone levels, dexamethasone dose, and toxicity of patients undergoing a KD during treatment were also assessed. Blood glucose levels were compared between patients on an unspecified/standard diet and a KD. Toxicity was assessed by Common Terminology Criteria for Adverse Events version 4. In total, 53 patients were analyzed. Six underwent a KD during treatment. The diet was well tolerated with no grade III toxicity and one episode of grade II fatigue. No episodes of symptomatic hypoglycemia were experienced. Four patients are alive at a median follow-up of 14 months. The mean blood glucose of patients on a standard diet was 122 versus 84 mg/dl for those on a KD. Based on this retrospective study, a KD appears safe and well tolerated during the standard treatment of GBM. Dietary restriction of carbohydrates through a KD reduces serum glucose levels significantly, even in conjunction with high dose steroids, which may affect the response to standard treatment and prognosis. Larger prospective trials to confirm this relationship are warranted.

Keywords High-grade glioma · Ketogenic diet · Temozolomide · Radiation therapy

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Introduction

The prognosis for patients diagnosed with glioblastoma multiforme (GBM) remains dismal, with a median survival of 15 months [1]. While GBM is the most common primary brain tumor, treatment advances have been limited with the standard of care remaining unchanged for several decades. As such, novel treatments are frequently sought by both the physician and patient. One such modality gaining popularity is carbohydrate restriction (CR) and the ketogenic diet (KD). Several decades ago, Nobel Prize laureate Otto Warburg presented his theory describing mitochondrial deficiency and a reliance on anaerobic glycolysis as a hallmark of cancer cell metabolism [2]. Recent data reveal that malignant cells

exhibit increased glucose uptake due to overexpression of glucose transporter-1 [3] and hexokinase [4]. This metabolic reliance on glucose is the mechanism with which positive emission tomographic scans measure tumor metabolism by quantifying 18-F-2-fluoro-2-deoxyglucose uptake, and correspondingly, elevated glucose uptake in cancer cells portends a poor prognosis [5]. The ability of normal cells to derive energy from ketone bodies distinguishes them from that of cancer cells, and more specifically glioma cells, and results in a dependence on glucose metabolism by these malignant cells [6, 7].

Recent data also reveal that elevated serum glucose levels during the treatment of GBM are associated with decreased survival, potentially illustrating the dependence of glucose by gliomas and the metabolic nature of these tumors [8, 9]. A common treatment modality for symptomatic glioma patients during adjuvant therapy is steroids, which potently raise serum blood glucose levels due to their glucocorticoid effects.

As such, a KD continues to gain popularity as a potential exploitative mechanism due to the metabolic discrepancy between glioma and normal brain cells, as well as the ability to potentially decrease circulating serum glucose and insulin levels [10]. Animal studies have revealed that increasing serum ketone levels above 1 mmol/L through carbohydrate deprivation of 50 g/day or less increases expression of monocarboxylic acid transporters in brain cells [11], leading to the substantial transfer of ketones across the blood brain barrier for energy consumption [12] and a potential decrease in glucose available for glioma intake. As a result, the present study will assess preliminary the safety of a KD as well as the effect on glucose levels in patients during the treatment of GBM with radiation therapy (RT) and chemotherapy.

Materials and methods

After receiving institutional review board approval, a retrospective review was performed analyzing the records of all high grade glioma patients with serial non-fasting glucose levels and quantitative or qualitative serum ketone levels available between March 2010 and April 2013. Only patients with histological diagnosis of World Health Organization grade III–IV gliomas were included in the study. All surgical and RT treatment records were reviewed along with imaging studies and laboratory values. Patients were excluded if at least two values of blood glucose and, for patients on a KD, two serum or urine ketone values could not be verified or ketosis confirmed in the patient's treatment record.

All patients received routine laboratory tests, including complete blood counts and basic metabolic panels at the time of surgery. Patients then received at least biweekly labs during RT and temozolomide (TMZ) treatment. Several patients on the KD had blood ketone lab values ordered by the treating physician (LabCorp, Philadelphia, PA). All other patients on the KD were encouraged to take bi-weekly serum ketone blood tests using the NovaMax glucometer (Nova Diabetes Care, Billerica, MA). All lab values and finger stick results were reviewed at the time of follow-up. Toxicity from the KD was assessed by the Common Terminology Criteria for Adverse Events version 4.

Table 1 Daily macronutrient consumption

Food names	Calories	Fat (g)	Carbohydrates (g)	Protein (g)
Breakfast				
Coffee	2	0	0.1	0.2
Cream	117	10.3	3.9	2.7
Three eggs	262	20.3	1.3	18.7
Bacon	54	4.2	0.1	3.7
Broccoli, cooked	16	0.8	2.1	0.7
Lunch				
Greek salad	212	14.6	6.7	14
Olive oil	239	27	0	0
Dinner				
Coconut oil	234	27.2	0	0
Kale, cooked	138	8.4	14.7	4.9
Salmon, cooked	118	3.7	0	19.9
Snack				
Macadamia nuts	406	43.1	7.3	4.4
Total	1,799	159.6	36.2	69.3

At our institution, patients who underwent a KD during treatment generally used several sources to guide treatment, including the *Atkins Diet for Seizure Control* and the *Art and Science of Low Carbohydrate Living* books to advise on methods and techniques for reducing carbohydrates to levels below 50 g /day, though methods were individualized. If patients were not achieving an adequate level of ketosis, they generally lowered carbohydrate levels in a stepwise manner to levels below 30 g /day while simultaneously limiting protein consumption in a similar stepwise fashion. Tracking of compliance was achieved via analyses of biweekly metabolic labs, including serum beta hydroxybutyrate levels, or daily ketone urine strips (Bayer Corporation, Moon, PA), and blood finger stick tests for serum ketones using a NovaMax glucometer. This also provided serum glucose values to assess for hypoglycemia. Urine ketone strips were generally used within the first 2 weeks of initiation of the diet. After this point, they were replaced by finger sticks that were performed by the patients at home, as urine strips are less accurate at

Dietary Component	Grams	Calories	%-Calories
Total Calories		1,799	
Fat	159.6	1,387	77
Saturated	57	496	28
Polyunsaturated	13.9	123	7
Monounsaturated	78.1	676	38
Carbohydrate	36.2	136	8
Dietary Fiber	12.5		
Protein	69.3	275	15

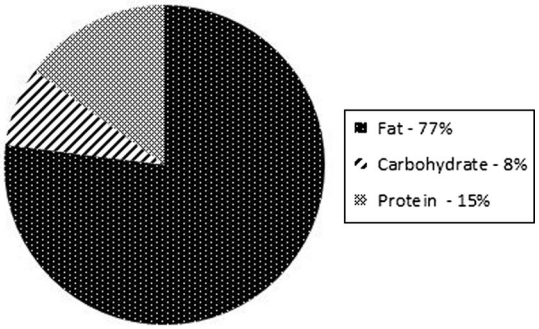

Fig. 1 Typical macronutrient composition while on a ketogenic diet

measuring ketones after 2 weeks on a KD. Ketosis was confirmed by the treating physician in reviewing patient logs regarding ketone levels from urine strips and finger sticks. Dietary information was tracked by several patients and their families on a daily basis using online software (Fitday.com), and was reviewed as well. A typical daily macronutrient composition and meal is provided in Table 1 and Fig. 1, respectively. The KD was patient-driven and, as the patients approached the treating physicians regarding the diet, guidance was merely provided during treatment.

Serum glucose levels starting at surgical excision and throughout RT were collected and averaged. Serum glucose levels in patients before and during the KD were compared using a *t* test, with a p value of less than 0.05 considered significant. Medication usage, including steroid doses were assessed and compared. Surveillance MRI of the brain was used to assess tumor recurrence utilizing the Revised Assessment in Neuro-Oncology (RANO) criteria. MRI results that were suspicious for recurrence were reviewed at our multidisciplinary tumor board incorporating neurosurgeons, radiation oncologists, neuro-radiologists, and neuro-oncologists. Biopsy was not required for the diagnosis of recurrence.

Results

Patient characteristics

A total of 134 patients underwent treatment for high grade glioma from August 2010 to April 2013. All patients underwent maximally feasible tumor resection and debulking via craniotomy, followed by RT to 60 Gy in 2 Gy fractions administered concurrently with TMZ. TMZ was continued adjuvantly starting 1 month after the completion of chemoradiation if there was no sign of definitive progression. Of these patients, 53 had adequate serum glucose values for analysis. No patient had a diagnosis of diabetes nor were any patients taking diabetic medications at presentation or during treatment. Prior to initiating treatment, all patients were consuming an unspecified standard American diet.

In total, six patients underwent a KD during treatment (Table 2). The remaining patients continued on an unspecified standard American diet. All patients on a KD were diagnosed with histologically confirmed GBM. One patient received cediranib during RT in conjunction with TMZ and another had a gliadel wafer placed at resection. Four patients underwent a KD during chemoradiation, and three continued during adjuvant TMZ. Two of the six patients began a KD after chemoradiation, during adjuvant TMZ treatment. The length of time with which each patient underwent the KD is described in Table 2.

Toxicity

The KD was well tolerated in all patients with no instance of grade III or higher toxicity. Grade I constipation occurred in two patients during the initiation of the diet. All patients experienced alopecia during RT and in those that underwent the diet during RT, four patients experienced grade I fatigue. Patient 5, who initiated the KD after RT, experienced grade II fatigue. This was in conjunction with a reduction in caloric intake by 30 % while on the KD. Patient one had a history of methylenetetrahydrofolate reductase (MTHFR) deficiency and experienced deep venous thrombosis during treatment. Serum glucose levels remained within normal ranges throughout treatment for all patients. One patient experienced a serum glucose level of 65 during finger stick, but was asymptomatic. No episodes of hypoglycemia were experienced by any patients and acute glucose replacement was not required at any point during treatment.

Weight loss is described in Table 2. It was minimal in the majority of patients; however, two experienced larger amounts of weight loss. One patient lost 27 lbs, though this was intentional as he weighed 287 lbs at initiation of the KD, and another lost 46 lbs. He was on a calorie-restricted

Table 2 Patient characteristics

Patient	1	2	3	4	5	6
Age	34	62	47	58	61	61
Location	Frontal	Multifocal	Frontal	Temporal	Temporal	Temporal
Extent of surgery	GTR[a]	Biopsy	GTR	STR	STR	GTR
Histology	GBM	GBM	GBM	GBM	GBM	GBM
Tx. during RT	TMZ	TMZ	TMZ	TMZ	TMZ	TMZ[c]
Dex.	Yes	Yes	No	Yes	No	No
Follow up (months)	11.9	6.3[b]	9.4	5	12	20.3[b]
Time of recurrence (months)	9.4	None	None	None	None	17
KD initiated	Before/during/ after RT	During RT	During/after RT	During/after RT	After RT	After RT
KD length (months)	9	3	8	4	7	12
Toxicity	Grade I fatigue, alopecia, DVT	Grade I GI, grade I fatigue, alopecia	Grade I fatigue, alopecia	Grade I fatigue, alopecia	Grade II fatigue, alopecia, weight loss, single episode nephrolithiasis, grade I constipation[d]	Alopecia
Pre-KD weight (lbs)	162	171	172	287	200	142
Weight last follow up (lbs)	157	171	157	260	154	130
Weight change (lbs)	5	1	13	27	46[d]	12
Ketone values (mg/dl)	Conf	14.1	Conf	Conf	5.6	Conf

Tx treatment, *Dex* dexamethasone, *RT* radiation therapy, *KD* ketogenic diet, *GTR* gross total excision, *STR* subtotal resection, *GBM* glioblastoma multiforme, *TMZ* temozolomide, *GI* gastrointestinal, *DVT* deep venous thrombosis, *Conf* confirmed ketosis from urine/blood stick tests on follow-up encounters

[a] Gliadel wafer placed at surgery

[b] Patient expired at this time

[c] Patient also received cediranib on clinical trial

[d] On calorie restricted ketogenic diet

KD, and at one point his weight dropped from 200 to 147 lbs. His average serum glucose value was 88 mg/dl. All other patients did not purposefully limit caloric consumption.

Outcomes

Four of the six patients are alive at a median follow-up of 14 months. Time to recurrence/progression was 10.3 months. Patient 2 had a multifocal GBM and died at 6.3 months after diagnosis. She underwent a KD during concurrent RT and TMZ and discontinued during adjuvant treatment. Patient 6 died at 20 months, 3 months after she was found to have recurrence. She was treated with carboplatin at recurrence. Of the remaining patients, two recurred and are under treatment with bevacizumab, and patient 6 recurred at 7 months and underwent resection and reirradiation. Patient 5 began the KD immediately after concurrent RT and TMZ, with stricter limitations on carbohydrate intake, limiting to an average of 20 g /day. MRI at 1 month after concurrent treatment revealed progression/post-radiation changes, which have since resolved. He remains without evidence of recurrence at 12 months from treatment.

Serum glucose levels

The mean serum glucose of all patients during treatment was 122 mg/dl (range 83–278 mg/dl). The average non-fasting serum glucose of patients on a KD ($n = 4$) during RT was 84 mg/dl (range 76–93 mg/dl), decreased from a value of 142.5 mg/dl (range 82–181 mg/dl, $p = 0.02$) prior to initiation of the diet and 1 week before RT. Of those patients on a standard diet, the average serum glucose of those on steroids ($n = 16$) and not on steroids ($n = 31$) was 130 and 109 mg/dl, respectively.

Two patients undergoing chemoradiation were taking high dose dexamethasone of 6 and 10 mg/day. Their mean

non-fasting blood glucose levels during treatment were 85 and 82 mg/dl, respectively, while on steroids. Patient 4 experienced an increase in his serum glucose to 103 mg/dl when placed on steroids during week 4 of RT. This was the highest blood glucose value experienced by any patient on the KD, though this value acutely lowered to 88 mg/dl. He discontinued the diet 1 week after RT for a short duration, and his blood glucose again rose to 129 mg/dl.

Discussion

This is the first study assessing CR and a KD in a series of patients undergoing treatment for GBM. The diet was well-tolerated in all patients with no grade III toxicity, and with the only non-fatigue or alopecia toxicity occurring as grade I constipation and one case of nephrolithiasis. The grade I fatigue and alopecia were likely related to RT and not necessarily the dietary intervention. The patient who experienced grade II fatigue was following a calorie-restricted KD, which led to significant weight loss and fatigue. This finding may provide caution to strictly restricting calories during the diet. One patient with MTHFR deficiency experienced a deep venous thrombosis during RT and TMZ, however, it is difficult to elucidate if this was influenced by a KD as patients with GBM are prone to vascular thrombosis [13], as are patients with MTHFR deficiency [14]. While several patients experienced blood glucose levels in the 60 s during treatment, none were symptomatic. This is likely explained by significant ketone production and a switch from glucose to ketone utilization by neurons, as has been previously described [15].

While a KD has been shown to be safe in randomized studies assessing patients without cancer [16], a recent study has exhibited a similar safety profile in patients with advanced cancer [17]. However, in this study no patients were undergoing chemotherapy or RT during the dietary intervention. The data presented here is of importance as patients are currently pursuing a CR and a KD to supplement chemotherapy and RT in increasing numbers at our institutions.

Preclinical data have revealed that a KD may enhance current treatment modalities for gliomas, including RT [18]. Preclinical data have also demonstrated an increased survival in mice with gliomas on a KD [19] and a recent study revealed complete eradication of glioma tumor in 9 of 11 mice on a KD receiving RT versus 0 of 11 mice on a standard diet [20]. This study also revealed a significant decrease in serum glucose levels in those mice on the KD. Several retrospective studies have shown an important association between elevated serum glucose levels after resection of GBMs and a detriment in survival independent of steroid usage. One study revealed that 1–3 blood glucose spikes over 180 mg/dl led to a 6 month detriment in survival [9]. No patients undergoing a KD in the data presented in this study experienced a spike in blood glucose levels over this value, with the highest single value of 103 mg/dl. Another study revealed that as blood glucose levels rise, survival inversely declines, with the greatest survival in those with average levels below 94 mg/dl [8]. As shown in Table 3, all patients in this study experienced average glucose levels below this value, even during treatment with high-dosage steroids. Two patients had serum glucose levels of 172 and 181 mg/dl prior to the KD, which decreased to 82 and 76 mg/dl upon initiation of the diet, respectively. In one patient, immediately upon discontinuing the KD, his serum glucose rose to 129 mg/dl. While limited by sample size, the present study suggests dietary restriction of carbohydrates may abate hyperglycemia during the treatment of GBM.

Table 3 Blood glucose values throughout treatment

Patient	Blood glucose at time of surgery (mg/dl)	Blood glucose at start or RT (mg/dl)	Average blood glucose during RT (mg/dl)	Average daily decadron dose during RT (mg)	Maximum blood glucose value during RT (mg/dl)
1	78	82	85	8	99
2	146	172	82	10	90
3	152	181	76	0	77
4	135	None	93	1	103

RT radiation therapy

While preclinical data assessing a KD in conjunction with standard treatment is encouraging, it is remains unknown if a benefit will continue through a transition to the clinic. It is difficult to draw conclusions from survival data in this study or to make generalizable conclusions due to the small patient number. However, due to the rarity of this novel dietary intervention during GBM treatment, this study serves as the largest within the reported literature regarding the safety and outcomes of patients on a KD during the treatment of GBM. The only previously reported work of the KD in the treatment of gliomas was a case study of a patient treated for GBM [21] and two children with gliomas [22].

The exact mechanism by which CR or a KD may work to enhance cancer therapy remains unknown. Preclinical data have revealed that the insulin pathway, including insulin, insulin-like growth factor 1 (IGF-1), and the IGF receptor IGF-1R, have been associated with cancer initiation and progression [23]. This pathway is upregulated though dietary consumption of carbohydrates and the minimization of these dietary sources in general or with a KD is one potential mechanism. Additionally, IGF-1

modulates cell proliferation by upregulating IGF-1R, and can protect cells from apoptosis [24, 25]. Supplementing IGF-1 to cancer cells treated with radiotherapy and chemotherapy results in significantly decreased tumor kill [26]. As such, attempts to mitigate the insulin and IGF pathway and enhance RT have been attempted to increase treatment efficacy [18]. A recent clinical trial in patients with advanced cancer has revealed a significant decrease in the insulin pathway with CR [17]. Other data have revealed clinical and radiographic improvements in 8 of 12 patients with GBM after the downregulation of IGF-1R, including unexpected spontaneous regression of tumor [27]. Downregulation of IGF in other cancer subtypes increases their sensitivity to radiation treatment as well [28]. Additionally, methods to limit blood glucose levels in other, less metabolically active cancer sites dependent on the insulin pathway, have also been suggested [29].

Finally, it is unknown if a benefit can be derived simply from lowering blood glucose levels through minimal dietary changes and CR, or if a more aggressive threshold must be met through a KD [30]. Other data has suggested that a benefit may be derived from caloric restriction, which often accompanies a reduction in carbohydrate consumption [31]. Preclinical data over the past century has revealed a reduction on cancer induction and progression with caloric restriction, though the most frequent and significant effects were seen when carbohydrates were limited and even replaced with fat [18]. A pilot study in advanced cancer patients has recently revealed a significant decrease in serum insulin levels in patients on a low-carbohydrate KD [10], though it remains unclear if a simple reduction in dietary carbohydrate alone could also downregulate the insulin pathway in tumor cells.

Conclusion

Based on this retrospective study, a KD was safe and well tolerated in six patients during concurrent TMZ and RT and adjuvant temozolomide for the treatment of GBM. Dietary restriction of carbohydrates through a KD appeared to significantly reduce serum glucose levels, even in conjunction with high dose steroids, which may improve the response to standard treatment and prognosis. Larger prospective trials to confirm this relationship are warranted.

Conflict of interest None declared.

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