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Ketogenic Diet for Malignant Gliomas: a Review

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Abstract

Purpose of Review In this review, we examine the postulated mechanisms of therapeutic effect of ketogenic diets in the treatment of gliomas, review the completed clinical trials, and discuss further directions in this field.

Recent Findings Cancers including gliomas are characterized by derangements in cellular metabolism. In vitro and animal studies have revealed that dietary interventions to reduce glucose and glycolytic pathways in gliomas may have a therapeutic effect. Early trials in patients with malignant gliomas have shown feasibility, but are not robust enough yet to demonstrate clinical applicability.

Summary Therapies for malignant gliomas of the brain are increasingly using a multi-targeted approach. The use of ketogenic diets and its variants may offer a unique and promising anti-glioma treatment by exploiting metabolic alterations seen in cancers including gliomas seen at the cellular level, which may work in concert with other therapies.

Keywords Glioma · Glioblastoma · Gbm · Astrocytoma · Ketogenic diet · Dietary intervention

Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor. Due to lack of effective therapies, patients with newly diagnosed glioblastoma have a median survival of only 14 months [1]. In the most current treatment paradigm, GBMs are treated with a combination of maximal safe resection followed by chemotherapy and radiation [2, 3]. Despite intense investigations of new therapies in recent years such as tumor-treating fields [4], immunotherapy [5], and vaccine therapy [6], the prognosis remains dismal. Currently, as no single new therapy appears to radically change the clinical course, there is great interest in combining newer treatments in the hopes that a synergistic effect can significantly improve outcomes. Additionally, the marked heterogeneity of glioblastomas likely leads to a variability of response to therapies. As such, new treatment approaches that attack the cancer from new angles while complementing existing therapies are particularly attractive.

One of the features of cancer cells is dysregulation of cellular metabolism. In adopting a highly proliferative state, cancer cells reduce the utilization of the citric acid cycle and oxidative phosphorylation for energy production and instead shift to glycolysis. This "Warburg effect" was demonstrated in 1927 [7] and is considered a hallmark of cancer [8], including GBM. This makes it an attractive therapeutic target, and there have been numerous efforts to exploit this across many cancer types. The ketogenic diet (KD) is the most common therapy used to target this cancer feature.

KD is a low-carbohydrate, high-fat diet that induces changes in body metabolism akin to a starvation state. This affects the levels of ketones, free fatty acids, insulin, glucagon, and glucose in the serum [9]. Ketogenic diets have been used for many years to treat neurologic conditions such as epilepsy, traumatic brain injury, and stroke [10], importantly demonstrating a biologic effect in the brain. Its efficacy is most established in the treatment of epilepsy, in which several randomized controlled trials (RCTs) revealed benefit in seizure control with various types of KDs. RCTs were performed employing a classic ketogenic diet [11], medium-chain fatty acid diet [12], and modified Atkins diet [13], with low glycemic index diet also suggesting benefit in another study [14].

Pathways/Mechanisms

Ketogenic diets raise serum ketone bodies (acetoacetate, 3-hydroxybutyrate, and acetone) in the serum and lower the utilization of glucose. Ketone bodies are then used as

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substrates in the citric acid cycle and oxidative phosphorylation in the mitochondria. Along the lines of the Warburg effect, it is thought that gliomas are more reliant on glucose and glycolysis than normal brain tissue [15], and therefore, may be susceptible to targeted energy deprivation with lowered glucose levels. Several studies have noted ultrastructural abnormalities in GBM mitochondria with aberrant or absent cristae and defects in membranes, including alterations in the composition of cardiolipins, an important lipid in the inner membrane [16]. These mitochondrial abnormalities suggest a compromise in the mitochondrial function of oxidative phosphorylation, which uses reduced cofactors to yield adenosine triphosphate (ATP) via oxygen carriers. Consequently, a fermentative state such as glycolysis would need to be utilized to a greater extent to meet cellular energy demands. The high lactate concentrations in GBMs [17] again suggest increased dependence on glycolysis. In addition to glucose, other fermentative fuels used may include glutamine for glutaminolysis [16], a process which also helps to generate anti-oxidants to reduce susceptibility to reactive oxygen species and generates byproducts aiding in cellular proliferation [18].

Numerous clinical studies have shown that hyperglycemia is associated with poorer progression-free and overall survival in patients with GBM, controlling for the presence of diabetes, steroid use, and other confounders [19], and may in fact independently contribute to worse outcomes. If this were the case, it would suggest that changes in body metabolism could affect outcomes in malignant gliomas. In fact, isocitrate dehydrogenase (IDH), a key enzyme in the citric acid cycle that converts isocitrate into alpha ketoglutarate, is mutated in a large subset of GBMs and most low-grade gliomas. The presence of this mutation is associated with a significantly less aggressive phenotype in gliomas [20, 21], which again suggests cellular metabolic changes are tied to prognosis in gliomas.

Additionally, glucose and glycolysis are thought to activate important pathways that prevent cell death. Overactivity of the Akt/PIK3/mTOR results in a proliferative state and is an important route that cancer cells exploit. In addition to other solid tumors, this pathway is overactive in many gliomas. Glucose and glycolysis may activate the tyrosine kinase Akt via prevention of activation of Bax, a pro-apoptotic protein [22]. In this manner, diets that reduce glucose and glycolytic activity may have an anti-proliferative effect on cancer independent of the Warburg effect.

Pre-Clinical Studies

Several studies have looked at the metabolic flexibility of gliomas with regard to energy utilization. One study implanted CT-2A mouse astrocytomas and U87 human gliomas in mice and subjected mice to a high-fat/low-carbohydrate ketogenic diet [23]. The authors found gene expression of mitochondrial enzymes including 3-hydroxybutyrate dehydrogenase was lower in tumor compared with contralateral brain. Another study looked at the in vitro expression of 3-hyrodybutyrate dehydrogenase and other ketone body-metabolizing enzymes in human glioma cell lines U87 and T98 [15]. Though mRNA and protein expression was evident, there was still absence of substantial 3-hydroxybutyrate metabolism. Additionally, administration of 3-hydroxybutyrate was unable to rescue glioma cell lines from glucose withdrawal-induced cell death. Interestingly, this study also demonstrated quantitatively a reduction in vessel microdensity in the KD treatment group in comparison with the standard diet group.

However, not all studies have supported the hypothesis that glioma cells cannot harness ketone bodies as metabolic substrates. One study used RG2 and 9L xenograft glioma rat models subjected to KD [24]. After injection of labeled ketone bodies, magnetic resonance spectroscopy revealed ketone body oxidation in the tumor equal to that in the normal brain. Additional histochemistry revealed upregulation of the transporter of the ketone body monocarboxylate in tumors. Additionally, another study suggested that for in vitro culture of gliomas, glucose restriction may actually enrich for glioma stem cells, the brain tumor-initiating cells that contribute to chemo and radioresistance and recurrences [25]. This phenomenon was mediated by co-opting high-affinity glucose transporter Glut3.

Pre-clinical in vivo studies examining KD for the treatment of solid cancer in other body locations have confirmed the potential of KD as an anti-cancerous. One meta-analysis looked at 59 studies that employed mouse and rat models and found that both caloric restriction and ketogenic diet showed effectiveness against cancer, with a pooled odds ratio of 0.20 (CI 0.12–0.34) [26]. Another study performed Bayesian random effects meta-analysis on 12 studies using mice on an unrestricted KD compared with standard diet and found a mean survival time ratio and hazard ratio of 0.85 and 0.55, respectively, both significant [27•]. Of note, however, the included studies using brain tumors had decreased benefit compared with studies of other body locations.

Pre-clinical in vivo studies to study the therapeutic effect of KD on gliomas have generally employed murine models. Twenty-four studies have been performed looking at tumor growth and survival, using a variety of nutritional restrictions: 12 studies employed a ketogenic diet, one used ketone supplementation, 9 used caloric restrictions, and 2 utilized short-term starvation [28•]. These studies were not only heterogeneous with regard to therapeutic diet; they differed in choice of subcutaneous versus intracranial glioma models and cell lines as well. Nevertheless, 17 of the 24 studies showed significant decrease in tumor size with the ketogenic or calorie restricted diet. Of the 16 studies performing survival analysis,

10 of these demonstrated significant increase in survival with the intervention. Examining surrogate endpoints, 19 of the 24 studies demonstrated decreased blood glucose levels, and 18 of 20 studies demonstrated increased serum ketone levels. Taken in total, there was a trend toward decreased blood glucose being associated with increased survival and decreased tumor growth ($P = 0.07$ by Fisher's exact test).

Pre-clinical studies have also looked at potentiating effects of KDs with other glioma therapies such as radiotherapy. One study used an intracranial bioluminescent mouse model with implanted gliomas and found that in mice who received a KD plus radiation, survival and tumor reduction appeared to markedly improve in a synergistic manner [29]. The KD alone therapy provided only modest benefit. Other anti-glioma therapies may be potentiated too. In another study complementing a clinical study [30], nude mice with implanted U87 gliomas received the VEGF inhibitor bevacizumab, an agent often employed in the treatment of recurrent GBM. The mice were placed either on standard diet or KD. The mice in the bevacizumab-KD group had prolonged survival (52 vs 58 days, $P \leq 0.05$) and a trend in reduction in tumor volume by MRI (23.9 mm^3 vs 13.8 mm^3) that did not reach significance. The KD diet alone did not produce a survival benefit in this study.

Clinical Studies

Pre-clinical models demonstrating the promise of KDs as a general cancer treatment have prompted human clinical trials. In one systematic review [31], 13 studies were identified that examined endpoints of progression-free survival (PFS) and overall survival (OS), including two randomized controlled trials. Though limited by small numbers, four of the trials showed beneficial effects of the therapy. With regard to malignant gliomas, anecdotal reports hinted at potential therapeutic potential. One of the first reports of possible efficacy involved two pediatric patients with malignant astrocytomas who were started on a KD. Subsequently, blood glucose decreased and was accompanied by a twenty- to thirty-fold increase in serum ketones. FDG-PET scans indicated 21.8% average decrease in glucose uptake at the tumor site, and one patient exhibited symptomatic improvement [32]. While there is a dearth of clinical trials assessing the anti-glioma effect of KDs to date [33], there have been several feasibility studies completed. Table 1 provides a summary of these clinical series.

In the ERGO trial [30], 20 patients with recurrent GBM were given a low-carbohydrate KD. Three patients (15%) discontinued the diet due to poor tolerability. In the remaining 17 patients, serum ketosis was achieved in 12 of the 13 patients who were able to be evaluated. Median PFS was only 5 weeks, and median survival from enrollment was 32 weeks. Though serum ketosis was achieved, glucose levels were not significantly lowered. Use of dexamethasone increased during the treatment, which may have blunted the glucose-lowering effects of the KD.

In another feasibility trial [34], a modified Atkins diet was employed alongside standard radiation and temozolomide treatment after initial diagnosis. Twenty-nine patients were enrolled and numerous glioma types were included—one grade 2 oligdendroglioma, 2 grade 2 astrocytomas, 7 grade 3 anaplastic astrocytomas, and 19 grade 4 glioblastomas. Successful ketosis was achieved in all patients and the diet was well-tolerated, with only one patient (3.4%) having to abort the therapy. The diet was modified as needed by a dietician to successfully reach ketotic state. Twenty-five patients (86%) had reduction of BMI with the therapy. For the survival analysis in the GBM patients, 2 patients were excluded for insufficient follow-up. Of the remaining 17 patients, 2-year survival was 26.7% which was in line with expected survival with standard therapy [4].

A third feasibility study enrolled 9 patients who were undergoing initial standard chemoradiation and administered to them an exclusively liquid KD [35]. After the initial 6 weeks and completion of radiation, patients were switched to a solid KD with medium-chain triglyceride emulsions. Patients on dexamethasone were excluded. One patient dropped out of the study and 2 patients were not able to tolerate or adhere to the diet. Adequate ketosis (> 3 mmol/L) was reached in all remaining patients. The small numbers preclude any analysis of therapeutic effect, but the median survival was 12.8 months, lower than the expected 14.6 months with standard of care [1], despite the patients being generally young (median age 53.8 years). However, all patients were IDH wild-type glioblastoma, which carries a median survival half that of IDH mutant GBM [21]. Quality of life (QOL) was also assessed at baseline, during the study, and at conclusion with a standard EORTC form and a coping questionnaire. The exclusion of patients taking dexamethasone incurred significant selection bias, likely tilting to more favorable outcomes. In QOL assessment, some gastrointestinal complaints persisted throughout the study period.

A fourth feasibility study, the KEATING study [36], was a randomized prospective pilot study that enrolled GBM patients who were to undergo standard chemoradiation. The enrolled patients would be randomized to either a modified KD or a KD with medium-chain triglycerides. Out of 42 eligible patients, only 12 enrolled, and among the enrollees, 2 withdrew prior to the study beginning and 6 of the remaining 10 withdrew before the 3-month primary endpoint was reached. Three patients completed the 12-month intervention period. In follow-up qualitative study involving interviews of eligible patients and their caregivers, the authors determined QOL considerations were an important factor in limiting

Table 1 Clinical trials of KDs and gliomas

Study	Pathology	# pts	Dietary intervention	Tolerability	PFS	OS
ERGO trial, 2014	Recurrent GBM	20	Low-carb KD	85%	5 weeks	32 weeks
Woodhouse et al., 2019	New diagnosed gliomas	29 (19 GBM)	Modified Atkins	96.6%	NR	NR (GBM 2-year survival 26.7%)
Van der Louw et al., 2019	New diagnosed GBM	9	Liquid KD/KD + MCT	67%	NR	54.8 weeks
KEATING trial	New diagnosed GBM	12	Modified KD or KD + MCT	33%	14.4 weeks	67.3 weeks

PFS median progression-free survival, *OS* median overall survival, *GBM* glioblastoma, *KD* ketogenic diet, *MCT* medium-chain triglycerides, *NR* not reported

enrollment. The authors suggested a 6-week rather than 3-month dietary intervention may be more feasible in future studies.

Despite the lack of prospective trials with sufficient patient numbers to detect an effect, there are several trials ongoing, with three trials recruiting and another 3 active (clinicaltrials.gov). These studies will hopefully bring greater clarity to many of the clinical questions that remain with KD in the treatment of gliomas.

Ongoing Areas of Study

Some clinical studies are enrolling patients with newly diagnosed gliomas while others are recruiting patients with recurrent gliomas and GBMs. Each of these patient groups provide different advantages for clinical study. In patients with recurrent gliomas, recruitment may be easier and KD as monotherapy can potentially be employed, allowing direct assessment of the intervention. However, recurrent gliomas will have undergone highly variant treatments, and this can result in highly disparate responses as well as limit generalizability. In the study of newly diagnosed gliomas, the tumors are uncontaminated by treatments other than surgery, and dietary intervention would have to be given alongside standard chemoradiation. Fortunately, based on the animal studies, KDs appear to function best as complementing rather than supplanting chemotherapies and radiation. In further studies that aim to investigate therapeutic effect, PFS will be an important endpoint. PFS may more directly measure objective biologic effect of the therapy, whereas OS in GBM can be affected by numerous factors such as choice and/or efficacy of second-line therapies, and goals of care decisions between patients and clinicians.

In addition to the usual endpoints of PFS and OS, future studies will also need to better assess the effect on KDs on QOL. Maximizing QOL is of utmost importance in GBM patients, as it remains a terminal disease. Lengthening PFS and OS with a decrease in QOL is a tradeoff few patients would choose. This important component was accounted for in the most recent clinical studies, and will continue to need emphasis.

A central impediment in assessing for clinical effect is the variance in the dietary intervention used in each study. It limits the ability to pool data and draw conclusions. The optimal diet would have the right balance of tolerability with ketosis and glucose levels. For instance, KD with strict caloric restriction may not be appropriate in patients with GBM, in whom QOL is important and who often struggle with poor nutritional intake. In some of the feasibility trials, adherence was difficult, even with intense dietary supervision. The modified Atkins diet appears to offer better adherence in treatment of epilepsy [37], but it is unclear what would be the optimal carbohydrate amount ideal for anti-cancer treatment. The appropriate length of the dietary intervention also will need to be determined. Although several of the clinical studies demonstrated patients were able to continue their diet beyond the prescribed intervention period, one study suffered from significant patient drop out and suggested a shorter intervention period [36]. Additionally, proper standardized biomarkers for appropriate ketosis will be needed across studies.

The use of dexamethasone can greatly palliate neurologic symptoms related to gliomas, but can interfere significantly with dietary interventions that aim for ketosis and lower blood glucose levels. Strictly excluding patients on dexamethasone from trials certainly would result in selection bias, and not allowing dexamethasone use during trials could result in either increased drop out or poorer QOL in the enrollees. Consequently, elucidating the relationship of dexamethasone on the anti-cancerous effects of KDs is an important area of future investigation. It may be that dexamethasone in smaller amounts may be sufficient for neurologic symptoms and not conflict with dietary intervention. For example, in immunotherapy trials for GBM, dexamethasone is limited to smaller doses but often not outright exclusionary [5].

The interaction between KD and the molecular landscape of gliomas also needs to be better elucidated. More and more, cancer treatment is being directed by the molecular and genetic characteristics of the tumor. Specifically in GBM, it would be important to know whether KDs have a differential effect

depending on the IDH mutation status of the tumor. As IDH mutant gliomas have disruption of the citric acid cycle, an important component of oxidative phosphorylation, KDs could potentially have a greater effect in this subset of gliomas. In one of the clinical trials [35], the overall survival results were disappointing after dietary intervention, but all the patients had IDH wild-type GBM. Perhaps, KDs are more effective in IDH mutant GBMs or GBMs with another molecular signature.

Conclusions

Ketogenic diets and its variants offer an attractive potential therapy for gliomas. They exploit the unique metabolic characteristics of cancer and its dependence on glucose and glycolysis. KDs are able to promulgate a biologic effect in the brain as evidenced by the established efficacy in neurologic disorders such as epilepsy. Animal studies have been promising and KDs and its variants appear to complement and synergize with rather than supplant current anti-glioma therapies. Though available human trials are few with low numbers precluding identification of therapeutic effect, these trials appear to demonstrate feasibility and safety with certain forms of KDs. Further clinical study is warranted.

Compliance with Ethical Standards

Conflict of Interest The authors do not have any potential conflicts of interest to disclose.

Human and Animal Rights and Informed Consent As this was a review paper, no human or animal research was conducted by the authors.

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