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The ketogenic diet as a promising adjunctive therapy for glioma a comprehensive review

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Abstract

Gliomas are the most prevalent primary tumors of the brain and spinal cord. Regrettably, the prognosis, especially for high-grade gliomas, remains quite bleak. In recent decades, there's been a growing trend to replace or combine radiotherapy with chemotherapy, targeted therapy, and personalized treatment for different patients. For example, carboplatin and vincristine are considered standard treatments for some patients with unresectable pediatric low-grade gliomas. In recent years, ketogenic diet (KD) has emerged as a promising investigational therapy for CNS tumors, with researchers exploring its use in conjunction with existing treatment modalities. This review article delves into the mechanisms underlying KD's potential therapeutic effects on glioma and its efficacy, safety profile, and overall role in glioma treatment.

Keywords: Ketogenic Diet, Gliomas, Metabolism

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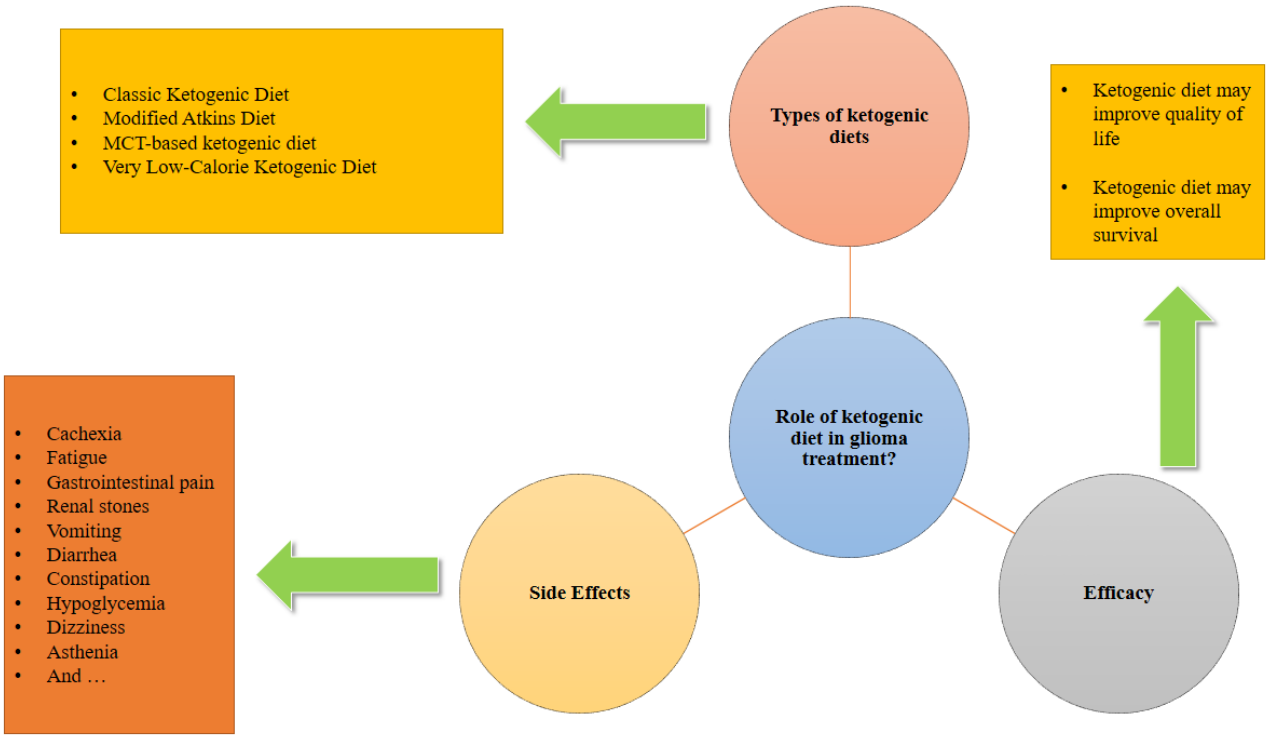
Graphical abstract



Introduction

Brain and other central nervous system (CNS) tumors, though uncommon, have a significant impact on mortality and morbidity across all age groups. Despite decades of research into the causes of brain and CNS tumors, no single risk factor has been identified as a major contributor. These tumors are unique due to their complex histological structure (1). Gliomas are the most prevalent primary tumors of the brain and spinal cord. Regrettably, the prognosis, especially for high-grade gliomas, remains quite bleak (2). Histologically, brain and CNS tumors share characteristics of normal glial cells and are often named based on these similarities. However, the exact origin of gliomas remains a topic of research, with potential sources including normal glial cells, glial or neural precursors, stem cells, or other cell types (3). Gliomas are the most prevalent primary malignant brain tumors globally, often originating from glial cells within the brain but also affecting other parts of the central nervous system (CNS). The latest WHO classification categorizes diffuse gliomas in adults into three main groups: astrocytoma IDH-mutant (grades 2, 3, or 4), oligodendroglioma IDH-mutant and 1p/19q co-deleted (grades 2 or 3), and glioblastoma (GBM) IDH-wildtype (grade 4). GBM, the most aggressive form, carries a dismal prognosis with a median overall survival of less than two years and a five-year survival rate of only 10% (4,5).

The prognosis for WHO grade 1 and 2 gliomas is the most promising, with differences based on molecular phenotype. IDH-mutant and 1p/19q co-deleted tumors (oligodendroglioma) have the best prognosis, followed by IDH-mutant and 1p/19q intact tumors, and then IDH-wildtype tumors. While a 'wait and see' approach was previously considered safe for low-grade gliomas, recent trials suggest that surgical resection should be performed as soon as possible to avoid tumor progression and accurately identify molecular subtypes (6,7).

Patients with GBM face a burdensome treatment regimen. Standard care involves surgical resection of the tumor, followed by six to nine months of radiation therapy and chemotherapy. Nevertheless, due to GBM's aggressive and highly vascular nature, the disease frequently recurs within six months of treatment (8,9).

Repeated cycles of standard therapy, including radiation therapy and temozolomide, are often used to treat disease progression. However, these treatments can lead to significant side effects, such as inflammation and edema in the brain (9–11). These symptoms often precede seizures and other neurological complications, which can adversely affect survival (10,12). Given the limitations of current GBM therapies, researchers are seeking new and improved treatments to prolong patient survival.

Scientists have been exploring the link between cancer metabolism and treatment resistance for nearly a century (13). In the 1950s, Nobel Prize winner Otto Warburg made a significant contribution to the field of cancer metabolism. Warburg discovered that cancer cells use a metabolic pathway called "aerobic glycolysis" to generate energy from glucose, even in the presence of oxygen (13,14). Warburg's findings indicate that cancer cells employ metabolic pathways that prioritize speed over efficiency, resulting from impaired mitochondrial respiration. This implies that cancer cells may not have the capacity to metabolize ketones (12). Warburg's findings are renowned and often cited in cancer research, and his conclusions have been termed the "Warburg Effect." (12,14–18). This discovery has been instrumental in the development of new cancer therapies, including dietary interventions such as calorie restriction (CR) and the ketogenic diet (KD) (15).

In recent years, KD has emerged as a promising investigational therapy for CNS tumors, with researchers exploring its use in conjunction with existing treatment modalities. (19). KD, or 'simulated fasting,' emerged around 1920 as a potential treatment for seizures. Its origins can be traced back to ancient Greek physician Hippocrates, who used fasting to manage seizure disorders. In 1911, French doctors Guelpa and Marie formalized the use of fasting for epilepsy. By 1921, researchers suggested that fasting and ketogenic diets could elevate ketone levels in healthy individuals, leading to potential therapeutic benefits for children with epilepsy (20,21). A growing body of research suggests that the ketogenic diet (KD) may be beneficial for managing a wide range of health conditions, including neurological disorders like epilepsy, migraine, Alzheimer's, motor neuron disease, autism, multiple sclerosis, and Parkinson's, as well as non-neurological conditions such as diabetes, obesity, cancer, acne, and polycystic ovary syndrome (22,23). Furthermore, the ketogenic diet remains the primary treatment option for certain metabolic disorders, including glucose transporter protein 1 (GLUT-1) deficiency syndrome, complex 1 mitochondrial disorders (C1MDs), and pyruvate dehydrogenase deficiency (24) (Figure 1).

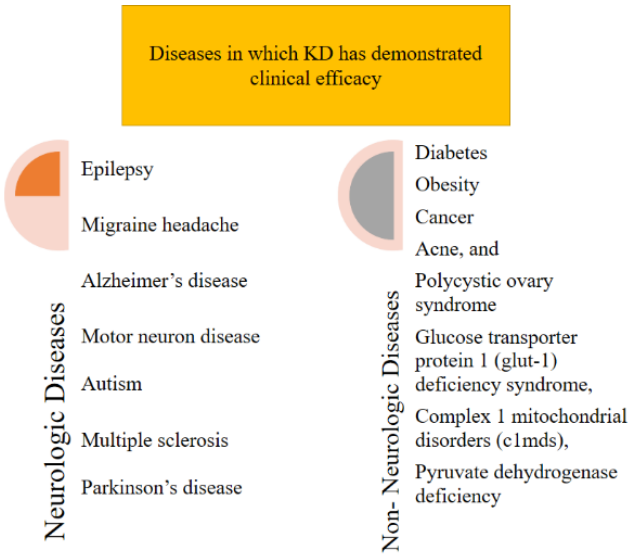


Figure 1. Diseases in which KD has demonstrated clinical efficacy.

The limited number of clinical trials investigating the ketogenic diet in GBM may be due to concerns regarding the quality of life and well-being of terminally ill patients, beyond diet tolerability and ketosis. Given the urgent need for novel cancer therapies for GBM, this review aims to explore the feasibility and efficacy of combining the ketogenic diet with standard GBM treatments. This review delves into the mechanisms underlying the ketogenic diet's potential therapeutic effects on glioma, as well as its efficacy, safety profile, and overall role in glioma treatment.

Methods

Search strategy

We conducted a comprehensive search of the MEDLINE database using precise MeSH terms such as “ketogenic diet” and “glioblastoma,” “ketogenic diet” and “gliomas,” “calorie restriction” and “glioblastoma,” “calorie restriction” and gliomas,” “diet intervention” and “glioblastoma,” “diet

intervention" and "gliomas," and finally, "low-carbohydrate diet" and "glioblastoma," "low-carbohydrate diet" and "gliomas".

Study selection and data extraction

We saved and uploaded all initial studies identified through our search into Mendeley software for title and abstract screening. Duplicate references were removed during this process. All eligible studies were reviewed in full by the author. We included only peer-reviewed, English-language articles published between 2009 and 2019. Study designs included in vivo pre-clinical research, patient case studies, randomized controlled trials, and retrospective studies focusing on GBM treated with a KD. We excluded non-peer-reviewed articles published before 2010. Our initial search yielded 126 results, which were narrowed down to 75 eligible studies. To ensure the highest relevance, we prioritized original research studies with a significant number of patients, providing robust evidence for the KD's potential effectiveness in glioma treatment.

Variety of Ketogenic Diets

There are several types of KD used in clinical practice:

1. **The Classic Ketogenic Diet (CKD)**

The Classic Ketogenic Diet (cKD) is a diet high in fat, very low in carbohydrates, and moderate in protein. It has a high ketogenic ratio, meaning the ratio of fats to carbohydrates and proteins is typically 3:1 or 4:1. This means you eat significantly more fat than carbohydrates and proteins (22,25,26); This is an isocaloric ketogenic diet (IKD) as defined by Trimboli et al. (26). Although the Classic Ketogenic Diet (cKD) is effective, it can be difficult to follow for both patients and their families. It requires strict adherence to a dietary protocol that can be time-consuming to maintain. The cKD is especially challenging for children, as they need to balance the ketogenic ratio with their increasing energy and nutrient requirements. Food refusal and low compliance can lead to inadequate nutrition and delayed growth in some children (27,28).

2. **The Modified Atkins Diet (MAD)**

The Modified Atkins Diet (MAD) is a variation of the original Atkins diet, created in the 1970s to address the rising obesity rates. MAD allows for a higher protein intake and doesn't require strict calorie counting. It also allows people to start the diet without fasting (29). The MAD offers increased flexibility and palatability by maintaining a 1:1 ratio of fat to carbohydrates and protein. This means about 60% of calories come from fat, 30% from protein, and 10% from carbohydrates. MAD, along with the low glycemic index diet (LGIT), are less restrictive alternatives to the KD because they don't limit protein or calorie intake (22,25).

3. **Medium-Chain Triglyceride (MCT)**

Dr. Peter Huttenlocher and his research team made a significant innovation to the traditional KD by replacing some of the long-chain fats with medium-chain triglycerides (MCTs). MCTs are absorbed more efficiently and transported directly to the liver, leading to the production of more ketones per unit of energy compared to long-chain fats. This allows for a reduction in the overall fat content of the diet. While the traditional 4:1 ratio KD gets 90% of its energy from fat, the MCT-based KD typically gets 70-75% of its energy from fat (including MCTs and long-chain fats), allowing for more protein and carbohydrates (22,23).

4. **The Very Low-Calorie KD (VLCKD)**

The Very Low-Calorie KD (VLCKD) is a highly restrictive diet with a daily calorie intake of 600 to 800 calories. This diet is followed for a short period of up to 12 weeks and includes a minimum of 75 grams of protein per day. Carbohydrate intake is very limited, 30 to 50 grams per day, while fat intake is fixed at 20 grams, primarily from olive oil and omega-3 sources. The diet is designed to provide all necessary micronutrients according to European Food Safety Authority (EFSA) guidelines (22,30).

Our review indicates a dearth of comprehensive, standardized studies comparing the effects of various ketogenic diets on glioma patients. This scarcity can be attributed to the limited number of available randomized controlled trials on this topic.

How Ketogenic Diets Target Cancer: Mechanisms of Action

The ketogenic diet exerts its therapeutic effects through several mechanisms: cellular metabolic alterations, systemic and local inflammation reduction, decreased

reactive oxygen species (ROS), modulation of oncogenes and tumor suppressors, and epigenetic modulation. These mechanisms will be discussed in detail in the following sections.

Metabolic Targets

Cancer cells reprogram their metabolism to meet the heightened energy demands of rapid growth and proliferation, a phenomenon known as the Warburg effect (13). Ketogenic diets (KD) have demonstrated the potential to exert antitumor effects by targeting both intracellular and extracellular metabolic pathways. KD induces a decrease in blood glucose levels. Moreover, evidence suggests that it reduces insulin and IGF-1 levels, consequently inhibiting the anabolic signaling of the mTOR pathway (31,32). Intracellularly, ketone bodies, particularly beta-hydroxybutyrate, have multifaceted effects. Beta-hydroxybutyrate can be converted to acetyl-CoA, entering the Krebs cycle and supporting energy production in healthy cells. However, in neoplastic cells, impaired mitochondrial function prevents the efficient utilization of acetyl-CoA for ATP generation. As a result, acetyl-CoA may be redirected towards lipogenesis and cholesterol synthesis (33). Additionally, ketone bodies can competitively inhibit monocarboxylate transporters, leading to increased intracellular lactate levels and potentially affecting cancer cell growth and survival (34). Pyruvate kinase, a key glycolytic enzyme, is another intracellular target of KD in tumors. The M2 isoform of pyruvate kinase is overexpressed in cancer cells and contributes to their metabolic advantage (35,36). KD has been shown to inhibit the expression of this isoform, reducing energy production and promoting apoptosis in glioblastoma cells. Furthermore, KD downregulates other key glycolytic enzymes, such as hexokinase, lactate dehydrogenase, and pyruvate dehydrogenase, as well as the GLUT-1 transporter (37). In glioblastoma mouse models, KD has been shown to reduce the expression of HIF-1α and VEGF receptor 2, inhibiting angiogenesis and limiting tumor metabolic changes (38). KD also modifies the expression of AQP-4 and zonula occludens-1, reducing peritumoral edema (38) (Figure 2).

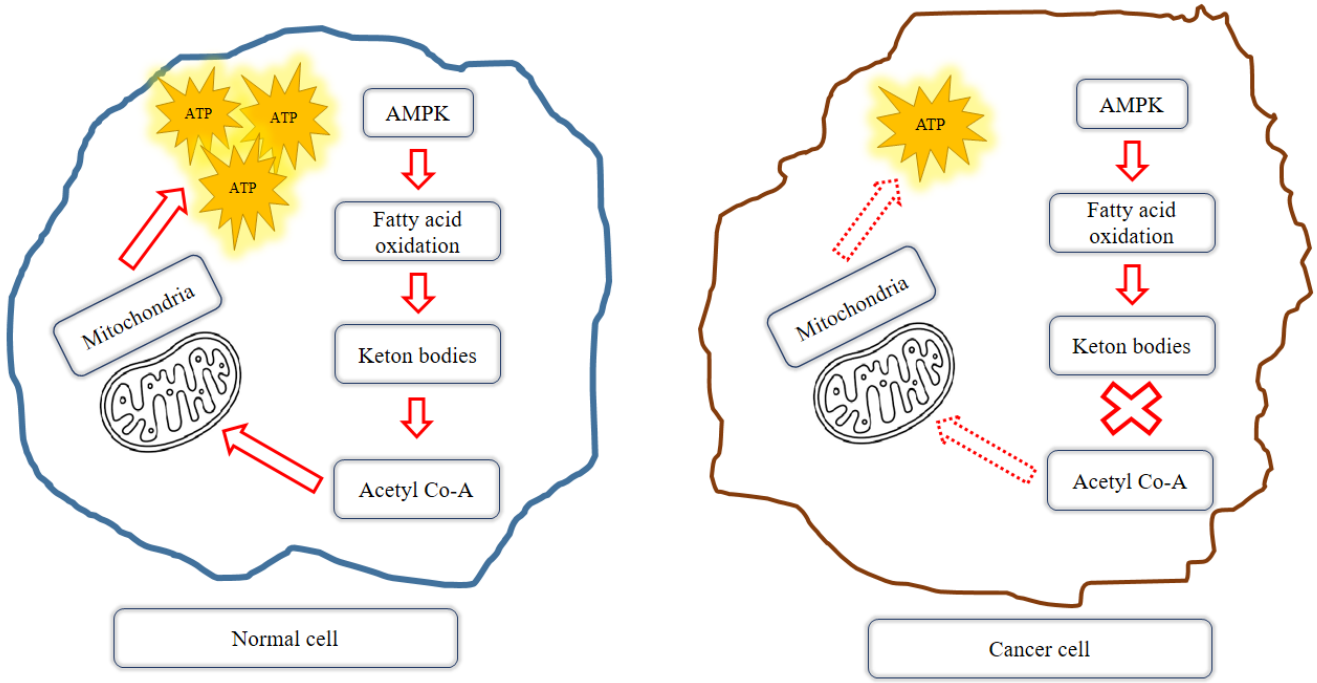


Figure 2. In normal cells on a ketogenic diet (KD), lower glucose levels lead to an increase in ketone bodies due to rising free fatty acids. This increases the level of acetyl-CoA in mitochondria, which is used to produce energy (ATP). However, in cancer cells on a KD, glycolysis is reduced, and mitochondria may be dysfunctional, hindering their ability to produce ATP (90). AMPK; Adenosine monophosphate-activated protein kinase.

Inflammation

Inflammation has emerged as a hallmark of cancer, characterized by increased local and systemic release of pro-inflammatory cytokines. This chronic inflammatory state is often driven by the hyperactivation of NF-κB and other transcription factors, promoting tumorigenesis and progression (39). Fatty acids, by activating the PPAR-alpha receptor, can inhibit the NF-κB signaling pathway, leading to downregulation of COX-2 and NOS, which are overexpressed in many tumors (40). Furthermore, ketogenic diets (KD), alone or in combination with the glutamine antagonist 6-diazo-5-oxo-1-norleucine (DON), have been shown to decrease TNF-α expression in glioblastoma models, reducing tumor growth, inflammation, and prolonging survival (41). The inflammasome, a multiprotein complex, plays a pivotal role in initiating inflammatory responses to pathogens or cellular damage, including cancer (42). Inhibition of the inflammasome has been shown to reduce tumor growth and prolong survival in glioma mouse models (43). Beta-hydroxybutyrate, a ketone body produced during KD, can inhibit NLRP3 inflammasome assembly and subsequent cytokine production, reducing inflammatory markers in central nervous system tumors (44). From an immunotherapeutic perspective, KD has been shown to enhance anti-tumor immune responses in glioblastoma mouse models. Specifically, KD can increase cytokine production and CD8+ T cell-mediated cytolysis, promote CD4+ T cell infiltration while maintaining normal levels of regulatory T cells, and decrease the expression of co-inhibitory molecules CD86 and PD-L1, thereby reducing tumor-mediated immunosuppression (45). Additionally, KD has been shown to reduce peritumoral edema and steroid requirements (17,38,46).

Reactive Oxygen Species (ROS)

To support their growth, cancer cells undergo mitochondrial alterations that lead to increased production of reactive oxygen species (ROS) (37). While this ROS production and oxidative stress provide an evolutionary advantage for cancer cells by increasing mutation rates and generating diverse clones, it also poses a significant risk. If ROS levels exceed a critical threshold, the resulting oxidative damage can overwhelm the cancer cell's repair mechanisms, leading to cell death (47). This is the underlying principle of conventional therapies like radiotherapy and chemotherapy, which aim to induce irreparable damage in cancer cells (48). Ketogenic diets, by limiting glucose-6-phosphate availability, disrupt both glycolysis and the pentose phosphate pathway. The latter pathway is crucial for cancer cells as it provides NADPH, a cofactor essential for maintaining reduced glutathione levels and mitigating oxidative stress. However, this pathway also supports the synthesis of nucleotides, thus limiting tumor growth and proliferation (49). Interestingly, while ketogenic diets increase oxidative stress in cancer cells, they simultaneously promote an antioxidant response in healthy tissues. Beta-hydroxybutyrate, a ketone body produced during ketosis, can activate uncoupling protein 2 (UCP-2) in mitochondria, enhancing the cell's antioxidant capacity (50). In summary, ketogenic diets exhibit a dual effect: they synergize with conventional therapies by increasing oxidative stress in cancer cells, while simultaneously protecting healthy tissues through their antioxidant properties (51,52).

Epigenetic Modulation

The impact of ketogenic diets on the genome and gene expression is a relatively new and understudied area. Ketogenic diets may modulate gene expression both directly, by regulating DNA methylation (ketones increase adenosine levels, inhibiting DNA methylation (53), and indirectly, by altering histone modifications such as acetylation, methylation, phosphorylation, ubiquitination, and lysine beta-hydroxybutyrylation; the latter modification seems unique to ketone bodies. These epigenetic modifications could explain the ketogenic diet's ability to positively influence the expression of oncogenes and tumor suppressors (33,54,55). Another less explored but scientifically intriguing topic is the role of microRNAs (miRNAs). These small non-coding RNAs can regulate gene expression by binding to complementary mRNA sequences, leading to their degradation and silencing. MiRNAs are implicated in various pathological conditions, including cancer, where altered miRNA expression often results in upregulation of oncogenes and downregulation of tumor suppressors (50). In glioblastoma, specific miRNAs have been found to be dysregulated. For instance, studies have identified 256 significantly overexpressed miRNAs (primarily miR-10b, miR-17-92 clusters, miR-21, and miR-93) and 95

significantly under-expressed miRNAs (such as miR-7, miR-34a, miR-128, and miR-137) compared to healthy brain tissue (56). In glioblastoma mouse models, ketogenic diets have been shown to modulate the expression of various miRNAs, reducing tumor progression and increasing long-term survival (55,57,58).

Oncogenes and Tumor Suppressors

Metalloproteinases, a group of zinc-dependent endopeptidases, are responsible for breaking down the extracellular matrix. Cancer cells often overexpress these enzymes to facilitate local invasion and metastasis. Ketogenic diets have been shown to reduce the expression of MMP-2 and MMP-9, as well as vimentin (38). P53, a tumor suppressor gene, plays a crucial role in regulating cell proliferation, apoptosis, and genomic stability. While p53 is typically expressed at low levels and functions normally in healthy cells, it is often mutated and overexpressed in cancer cells, contributing to therapeutic resistance. Ketogenic diets can downregulate mutant p53 through deacetylation, inducing apoptosis in neoplastic cells (55,59–61). AMP-activated protein kinase (AMPK) is an enzyme that can activate tumor suppressors like p53, inhibiting cell growth and cycle progression. Various compounds, including metformin, curcumin, certain NSAIDs, and ketone bodies, have been shown to activate AMPK (55,62). Comparisons between ketogenic and standard diets in animal tumor models have revealed that ketogenic diets can downregulate pathways mediated by IGF-1, PDGFR, and EGF, which are frequently overexpressed in gliomas and activate Akt and mTOR. mTOR, in turn, activates transcription factors such as HIF-1, upregulating oncogenes, glucose transporters (GLUT), and glycolytic enzymes (51,63). Notably, ketogenic diets enhance tumor response to PI3K inhibitors (64).

Effect of KD on quality of life in patients with glioma tumors

Quality of life (QOL) is a complex concept with various interpretations. It reflects an individual's personal perspective on their life situation in relation to their goals and expectations. QOL encompasses all aspects of life, including psychological, social, and economic well-being, as well as relationships with the environment. It's best understood as the difference between one's current functional level and their ideal standard (65). A KD may improve QOL by reducing chronic pain, inflammation, and enhancing metabolic parameters (Table 1).

Table 1. Overview of studies that have investigated effect of KD on quality of life in patients with glioma tumors.

Reference	Type of Glioma	KD Duration	Quality of Life
(15)	Astrocytoma IDH-mutant grade III Astrocytoma IDH-wild type grade IV	14 months	N/A
(91)	Astrocytoma IDH-mutant grade II-III Oligodendroglia IDH-mutant 1p/19q deleted grade II-III Astrocytoma IDH-wild type grade IV	3 months	Improved
(86)	Astrocytoma IDH-mutant grade II-III Astrocytoma IDH-wild type grade IV	4 months	Improved
(88)	Diffuse Midline glioma, high grade	3 months	Decreased
(87)	Astrocytoma IDH-wildtype grade IV	3.5 months	Decreased
(66)	Diffuse Midline glioma, high grade	6.5 months	N/A
(92)	Astrocytoma IDH-wild type grade IV	6 to 26 months	Improved
(78)	Astrocytoma IDH-wild type grade IV	1 to 4 months	Decreased
(72)	Astrocytoma IDH-wild type grade IV	1 to 12 months	Improved

The Dark Side of KD: Potential Negative Effects and Risks

Adults with malignant glioma who follow a KD may experience common side effects, including gastrointestinal issues, weight loss, and a temporary

rise in lipid levels. Gastrointestinal symptoms like constipation, diarrhea, occasional nausea, and vomiting are typically mild and often improve over time. These effects can usually be managed through dietary adjustments, with guidance from a dietitian or nutritionist. Medical intervention is rarely required (66,67). Consuming smaller meals, increasing fiber intake, exercising, and drinking more fluids can help prevent or alleviate these gastrointestinal issues. While weight loss may be a desired outcome for overweight patients, those seeking to maintain or gain weight should adjust their caloric intake accordingly (68). Weight loss, particularly muscle mass loss (cachexia), is a significant concern in patients with malignant glioma. Cachexia can reduce tolerance to cancer treatments, impair lung function, and lead to lower survival rates. Research has shown that very low-carbohydrate diets, which induce ketosis, can lower levels of serum triglycerides, low-density lipoprotein, and total cholesterol while increasing high-density lipoprotein cholesterol in adults (69,70). Restricting carbohydrates and maintaining prolonged ketosis can lead to vitamin and mineral deficiencies. Taking a daily multivitamin and mineral supplement can help reduce the risk of these deficiencies (21,69,71). In one study, hydro-electrolyte disorders were found (72) and in another, a patient with an MTHFR mutation developed DVT (15). Studies examining the use of KD in cancer patients have yielded varied results regarding its impact on improving quality of life, cachexia, and fatigue (32,55).

Long-term use of KD may lead to mild side effects, such as gastrointestinal discomfort or kidney stones. These effects are often associated with medium-chain triglyceride (MCT) oils and can be minimized by consuming the KD in limited amounts and during specific timeframes, especially during radio-chemotherapy. To ensure adherence to the KD, strong commitment and cooperation from both the patient and their family are crucial for maintaining dietary-induced ketosis (63,73). Tracking and maintaining adherence to a KD is essential for evaluating its effectiveness. In adults, methods for measuring adherence beyond self-reporting include frequent testing of serum β-hydroxybutyrate or urine acetoacetate levels during the initial weeks on the diet, along with keeping detailed records of dietary intake (71,74) (Table 2) (Figure 3).

Table 2. Summary of Side Effects of Ketogenic Diet.

Study	Side Effects
Rieger 2014 (78)	eight loss, diarrhea, constipation, hunger
Champ 2014 (15)	Constipation, asthenia, weight loss, nephrolithiasis, hypoglycemia
Martin-McGill 2018 (91)	Constipation
Van der Louw 2019 (88)	Hypoglycemia, hyperketosis, vomiting, refusal to eat, asthenia, constipation
Van der Louw 2019 (87)]	Constipation, nausea/vomiting, hypercholesterolemia, hypoglycemia, diarrhea, low carnitine concentration
Martin-McGill 2020 (72)	Hypokalemia, hypocalcemia, pernatremia, hyperkalemia, constipation
Panhans 2020 (86)	Asthenia, weight loss, nausea, vomiting, headache, decreased appetite
Perez 2021 (66)	ypoglycemia, constipation, hyperketosis, vomiting, asthenia, hyperuricemia

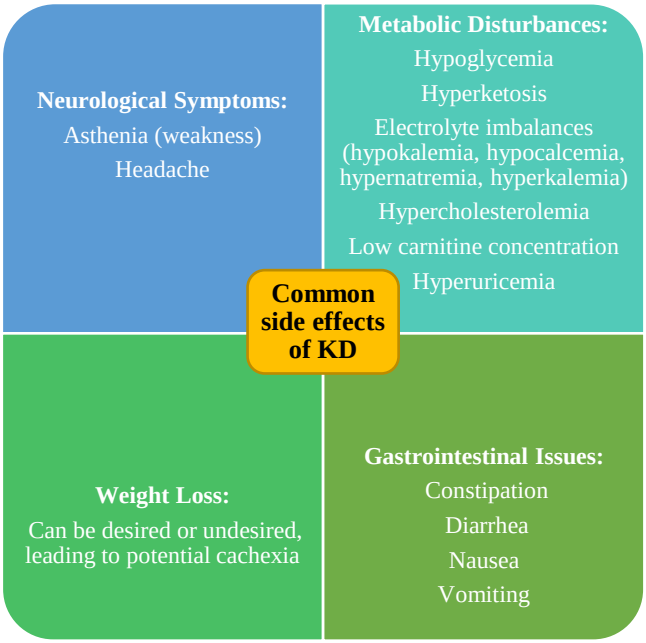


Figure 3. Summary of Side Effects of Ketogenic Diet.

Discrepancies Between Preclinical and Clinical Findings

Pre-Clinical Studies (Table 3)

Table 3. Summary of some preclinical effects on glioblastoma and other brain tumors.

Study	Summary of pre-clinical study Findings

(75,76)	Dietary interventions like fasting and ketogenic diet can modulate metabolic pathways and suppress tumor growth.
(77,78)	3:1 KD in glioblastoma models showed inconsistent results.
(54,79)	4:1 or 6:1 KD improved survival in glioblastoma models, alone or with RT.
(78)	KD combined with bevacizumab showed synergistic effects in glioblastoma models.
(51)	KD, alone or with RT and temozolomide, prolonged survival and slowed tumor growth in glioblastoma models.
(80)	Higher fat-to-carb ratio in KD did not benefit medulloblastoma models.
(41,81)	KD and caloric restriction reduced tumor growth and improved survival in glioblastoma models. KD combined with DON had synergistic effects.
(82)	KD induced metabolic stress in tumor cells but spared healthy tissue.
(83)	Gliomas can adapt to ketogenic state, challenging the metabolic rigidity hypothesis.
(76,84)	Meta-analyses showed survival benefit of KD in various animal tumor models.
(85)	Impact of IDH mutations on KD response is unclear. Further research needed to identify predictive genetic markers.

Animal models have demonstrated that dietary interventions, such as fasting and the ketogenic diet, can modulate metabolic pathways and suppress tumor growth in the brain (75,76).

While some preclinical studies have explored the potential of a 3:1 KD in glioblastoma mouse models, the results have been inconsistent, with some studies failing to show significant therapeutic benefits (77,78). A higher fat-to-carbohydrate ratio of 4:1 or 6:1 in the ketogenic diet (KD) has demonstrated enhanced survival benefits in glioblastoma model (54,79) and in combination with RT (14)**.** The combination of the ketogenic diet (KD) and bevacizumab has shown a synergistic effect, leading to increased survival, reduced tumor volume, and decreased ATP concentration in glioblastoma models (78)**.** Further supporting the therapeutic potential of the ketogenic diet (KD), preclinical studies have shown that KD can enhance survival and reduce tumor growth in glioblastoma models, both as a standalone therapy and in combination with conventional treatments like radiotherapy (RT) and temozolomide (51)**.**

While a higher fat-to-carbohydrate ratio in the KD has shown promise in glioblastoma, similar dietary modifications did not yield significant benefits in medulloblastoma mouse models (80)**.** Preclinical studies have shown that the ketogenic diet (KD) and caloric restriction can have significant anti-tumor effects in glioblastoma. Moreover, combining KD with the chemotherapeutic agent DON can potentiate these effects, resulting in improved survival, reduced tumor growth, and decreased inflammation and edema (41,81).

A recent preclinical study highlighted the metabolic advantages of the ketogenic diet (KD) over a standard diet (SD) in high-grade glioma models. KD induced metabolic stress in tumor cells by limiting the availability of essential amino acids and impairing their ability to utilize ketone bodies for energy production. In contrast, healthy brain tissue was able to adapt to the ketogenic state and maintain normal energy metabolism (82).

Despite promising preclinical results, the efficacy of the ketogenic diet (KD) in treating brain tumors remains inconsistent. A 2016 study challenged the hypothesis of metabolic rigidity in brain tumors, demonstrating that gliomas can adapt to a ketogenic state by upregulating MCT1 and utilizing ketone bodies. This finding highlights the complex interplay between tumor metabolism and dietary interventions, underscoring the need for further research to elucidate the underlying mechanisms and optimize KD therapy (83)**.** Meta-analyses of preclinical studies have shown a survival benefit associated with the ketogenic diet (KD) in various animal tumor models, including brain tumors (76,84)**.** Although the impact of specific genetic mutations on the efficacy of the ketogenic diet (KD) remains largely unexplored, studies on IDH mutations in gliomas have not revealed significant differences in KD response. Further research is needed to identify potential genetic markers that may predict patient response to KD therapy (85)**.**

Clinical Studies (Table 4)

Table 4. Summary of some clinical effects on glioblastoma and other brain tumors.

Study	Patients	Intervention	Key Findings
(78)	20 with recurrent glioblastoma	KD + standard therapy	Longer PFS with stable ketosis, improved PFS with KD+bevacizumab
(15)	53 with high-grade glioma	KD + standard therapy	Improved glucose control, potential for enhanced treatment response
(86)	12 with various glioma types	3:1 KD + standard therapy	Improved quality of life, reduced seizures, potential tumor response
(63)	Various grades of glioma	MAD + standard therapy	Improved seizure control, better quality of life
(87)	12 with glioblastoma	MAD or MCT diet + standard therapy	Positive impact of MAD on glucose homeostasis
(88)	3 with DIPG	KD + standard therapy	Safe and well-tolerated, but limited sample size for survival assessment
Ongoing Trials	Various glioma types	KD + standard therapy	Currently investigating the impact of KD on gliomas

DIPG: diffuse intrinsic pontine glioma.

Recent clinical trials have explored the use of the ketogenic diet (KD) in treating CNS tumors, particularly glioblastoma. The ERGO study, for instance, evaluated 20 patients with recurrent glioblastoma who received KD therapy. While all patients experienced disease progression, those who maintained stable ketosis demonstrated a longer progression-free survival (PFS) compared to those with unstable ketosis. Moreover, combining KD with bevacizumab resulted in a longer PFS compared to bevacizumab monotherapy (78).

A retrospective study in 2014 explored the safety and tolerability of combining the ketogenic diet (KD) with standard therapies in 53 patients with high-grade gliomas. Six patients concurrently followed a KD, demonstrating its feasibility and potential benefits. By reducing serum glucose levels, even in patients receiving high-dose steroids, KD may enhance the efficacy of standard treatments and improve patient outcomes (15).

A 2020 study demonstrated the positive impact of the ketogenic diet (KD) on the quality of life of patients with various glioma types. Twelve patients treated with standard therapy and a 3:1 KD reported improvements in energy levels, mood, neurocognitive function, and overall well-being, along with reduced seizure frequency. Furthermore, imaging studies suggested a potential tumor response to the combined therapy of KD and standard treatment (86)**.** A study exploring the use of the Modified Atkins Diet (MAD) in combination with standard therapy for various grades of glioma demonstrated its potential to improve seizure control and patient quality of life (63)**.**

The 2020 KEATING study and a 2019 study investigated the effects of different dietary interventions on glioblastoma patients. While the KEATING study demonstrated the positive impact of a Modified Atkins Diet (MAD) on glucose homeostasis, the 2019 study, which used a 4:1 ketogenic diet (KD), failed to show significant improvements in quality of life, neurological function, or survival (87)**.**

A pilot study investigated the feasibility and safety of combining a ketogenic diet with standard therapy in three children with diffuse intrinsic pontine glioma (DIPG). Although the diet was well-tolerated, the small sample size limited the ability to assess its impact on survival (88). These findings were further corroborated by a more recent review of diffuse intrinsic pontine glioma in children (66)**.**

A recent meta-analysis assessed the potential benefits of combining the ketogenic diet (KD) with standard therapies for gliomas. While some studies suggested improved overall survival, the small sample sizes, inclusion of various glioma types, and absence of a control group limit the strength of these findings and warrant further investigation (67)**.** Ongoing clinical trials are actively investigating the impact of KD on gliomas (89)**.**

Conclusion

The majority of preclinical and clinical data analyzed in this review suggest that the KD can positively impact the treatment of central nervous system (CNS) tumors. By targeting tumor metabolism, inflammation, gene expression, and the tumor microenvironment, KD

offers a promising adjuvant therapy. KD offers several advantages, including low toxicity, affordability, and ease of implementation. However, potential side effects and poor compliance can lead to significant dropout rates. Additionally, the metabolic plasticity of cancer cells, which allows them to adapt to different metabolic conditions, remains a concern. In the near future, KD may be proposed as a combination therapy with conventional chemotherapy (CT) and radiotherapy (RT). This combination therapy could offer synergistic toxicity toward cancer cells and potential protection of healthy cells from the toxic effects of standard therapies by increasing cellular oxidative stress. To strengthen the evidence for KD's efficacy in treating CNS tumors, larger-scale clinical trials are essential. Oncology departments should collaborate with nutrition experts to integrate KD into conventional treatment regimens. Additionally, both in vivo and in vitro studies are necessary to definitively elucidate the cellular responses to the ketogenic environment and uncover the underlying mechanisms of its therapeutic effects.

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Author contribution

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