

Research Article

The Effect of Ketogenic Metabolic Therapy on Recurrent High-Grade Gliomas: Case Series

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Abstract

High-grade gliomas represent the most prevalent primary malignant brain tumors in the adult population. Despite extensive efforts dedicated to advance in therapeutic modalities, treatment options remain very limited in this field, leading to a worse prognosis for affected patients. Moreover, a considerable number of cases exhibit refractory disease following the initial management. Ketogenic Metabolic Therapy (KMT) has emerged as a promising adjunctive approach for recurrent high-grade gliomas, offering them a synergistic effect enhancement of the effectiveness of conventional therapies against this type of cancer. The underlying hypothesis relies on the use of high-fat, low-carbohydrate diet, with adequate protein content can potentially induce metabolic reprogramming in cancer cells. Currently, the use of KMT is on the rise and has shown positive effects on the control of selected neurological symptoms and improvements in patient's quality of life. This is a descriptive observational multicenter study (case series) that includes patients with recurrent high-grade gliomas who underwent Ketogenic Metabolic Therapy (KMT) and were supplemented with a liquid ketogenic formula (in a 3:1 ratio) as a complementary treatment to the ongoing medical regimen for recurrence. The results show a positive impact on seizure control, as well as significant improvements in cognition, memory and functionality, as reported by patients and/or their families (caregivers). Regarding the disease status, assessed by the RANO criteria, the 12-month follow-up evaluation indicated stable disease in 55% and a partial response in 20% of cases. Although the results of this work are promising, more conclusive clinical data are still needed to support the use of KMT in the treatment of high-grade gliomas.

Keywords: Glioma; Cancer; Ketogenic Diet; Nutrition Therapy; Neurologic Manifestations

Key Points

- Evidence has shown that the use of Ketogenic Metabolic Therapy (KMT) significantly reduces the amount of glucose available to tumor cells, which in turn leads to increased apoptosis and a slowing of cell growth and proliferation
- The current treatments for the management of recurrent high-grade gliomas are insufficient, making it necessary to develop novel therapeutic approaches
- The use of KMT can be considered as a complementary treatment for patients with recurrent high-grade gliomas, as it may be associated with better clinical outcomes in these patients

Importance of the Study

Current treatments for the management of recurrent high-grade gliomas are insufficient, making it necessary to develop novel therapeutic approaches, where the use of KMT may be associated with better clinical outcomes in these patients.

Introduction

The Ketogenic Metabolic Therapy (KMT) consists of a complementary treatment based on a high-fat, low-carbohydrate diet with adequate protein content, which has been widely used in programs addressing metabolic disorders or abnormalities in recent years. Some research has explored the effects of the Ketogenic Diet (KD) in treating numerous diseases, including cancer, due to its role in promoting ketolysis, ketogenesis and modifying many other metabolic pathways with potential beneficial effects on health [1]. Regarding this, some studies have identified that hyperglycemia and hyperinsulinemia are strong stimuli for tumor growth in various types of cancer [2]. In fact, it is known that cancer cells primarily produce energy in the cytosol through a process of anaerobic glycolysis meaning through high rates of glycolysis followed by a process of lactic fermentation, instead of generating energy through the aerobic oxidation pathway of pyruvate in the mitochondria, as is typical in most normal cells [3]. This process is known as the Warburg effect [4]. For this reason, slowing down the Warburg effect and reducing access to glucose using KMT may have positive effects on cancer control, as it generates a metabolic adjustment and consequently slows down the growth of tumor cells [5].

Among the highlighted pathophysiological mechanisms of cancer are inflammation, oxidative stress, resistance to cell death, cell proliferation, neurohormonal stress, angiogenesis, genomic instability and metabolic adjustments [6]. In this regard, it is well known that in tumor cells, the process of oxidative phosphorylation in mitochondria is affected, as these cells use aerobic fermentation for energy production. Therefore, the use of KMT (replacing carbohydrates with ketones as the primary energy source) limits their growth and proliferation, as energy production in these cells requires the use of efficient mitochondria [7]. Regarding this, some studies have shown that KMT significantly reduces the amount of glucose available to produce glucose 6-phosphate, pyruvate and the production of NADPH (components related to increased oxidative stress in tumor cells), which in turn leads to an increase in apoptosis and a slowdown in cell growth and proliferation [8].

Similarly, another factor involved in the etiology and progression of various types of cancer is systemic inflammation. Some publications have highlighted that ketone metabolites, specifically β -hydroxybutyrate, can directly suppress NLRP3 and its related cytokine cascades [9]. Studies have demonstrated that the use of KMT promotes cancer control because the increased availability of β -hydroxybutyrate (due to its enhanced production) inhibits NLRP3, resulting in anti-inflammatory functions that could eliminate tumor cells through pro-apoptotic mechanisms [10].

Some studies have also shown that the combination of chemotherapy and KMT (less than 70 g/day of presented carbohydrates) can have positive effects on aspects of quality of life and it has no severe side effects in advanced cancer patients [11]. Also, in patients with high-grade glioma the KMT has proven to be safe and effective [12].

Material and Methods

This is a descriptive observational multicenter study (case series) that includes patients treated in Instituto Nacional de Cancerología, Clínica Universitaria Colombia, Hospital Universitario San Ignacio and Hospital San Vicente Fundación - Colombia, with recurrent high-grade gliomas who underwent KMT and were supplemented with a liquid ketogenic formula (in a 3:1 ratio) as a complementary treatment to the ongoing medical regimen for recurrence. Despite the new WHO classification, patients with glioblastoma morphology and IDH1 or 2 mutations are also included (n=18).

The distribution by frequencies and percentages was determined for categorical or nominal variables and for continuous or numerical variables, measures of central tendency such as mean, median and ranges were calculated. The results are presented through tables encompassing sociodemographic, clinical, pathological and nutritional aspects, along with detailed descriptions of medical treatments and the corresponding outcomes associated with the use of KMT.

Ethics Statement

To carry out the present work, the scientific, technical and administrative norms for health research dictated by the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, CIOMS and Resolution 8430 of 1993 which in its article 11. a. cites: "Research without risk": considering that this is a descriptive observational study. Additionally, the four bioethical principles (non-maleficence, justice, beneficence and autonomy) were taken as a basis, in addition to respect for human dignity.

All participants were asked to read and complete the informed consent form to voluntarily participate in this research study.

Data Availability

Considering that it is research on human subjects, all deidentified data obtained were transferred to a computerized public access data base (Excel, version 2019), where it was verified that the recorded data matched the type of variable, its corresponding unit and the conceptual definition. This database is available in an organized manner, to guarantee the verification and review by publishers, editors, authors and reviewers.

Results

A total of 29 patients (16 women and 13 men) were included in the follow-up, encompassing diagnoses of glioblastoma multiforme (n=15), grade 3 astrocytoma (n=6), grade 3 oligodendroglioma (n=5) and grade 3 pilocytic astrocytoma (n=3), with a mean age of 45 years (ranging from 17 to 64 years). IDH1/2 mutation was present in 62.1% of the patients (n=18), MGMT mutation in 10.3% (n=3) and 65.5% (n=19) experienced neurological symptoms at disease onset, including seizures or basal abnormal movements (Table 1,2).

Sociodemographic features	n= 29
Variable	n, (%)
Gender	
Female	16, (55,2)
Male	13, (44,8)
Health insurance	
Contributory	21, (72,4)
Subsidized	8, 27,6)
Economic incomes	
Very low	3, (10,3)
Low	18, (62,1)
Medium	8, (27,6)
Familiar support	
Good familiar support	22, (75,9)
Regular familiar support	7, (24,1)
Age (years)	
Mean	45
Median [Min – Max]	46 [17 – 64]

Table 1: Sociodemographic features.

Pathological features	n= 29
Variable	n, (%)
Histological type	
Glioblastoma Multiforme	15, (51,7)
Grade 3 Astrocytoma	6, (20,7)
Grade 3 Oligodendroglioma	5, (17,2)
Grade 3 Pilocytic Astrocytoma	3, (10,3)
Mutational status	
MGMT (Promoter methylation)	
Yes	3, (10,3)
No	19, (65,5)
Unknown	7, (24,1)
IDH 1/2 mutated	
Yes	18, (62,1)
No	3, (10,3)
Unknown	8, (27,6)
BRAF mutated	
Yes	0
No	10, (34,5)
Unknown	19, (65,5)
NTRK	
Yes	0
No	9, (31)
Unknown	20, (69)
Initial ECOG	
ECOG 0	4, (13,8)
ECOG 1	18, (62,1)
ECOG 2	4, (13,8)
ECOG 3	3, (10,3)
Disease debut neurological symptoms	
Seizures	16, (55,2)
Basal abnormal movements	3, (10,3)
None	10, (34,5)

Table 2: Pathological features.

Successful compliance with KMT was achieved in 69% of the participants, all of whom followed a classic ketogenic diet and consumed a ketogenic nutritional formula (Ketovie 3:1, unflavored). The most prevalent gastrointestinal symptom associated with KMT was grade 1 acute diarrhea (17.2% - n=5), followed by grade 1 vomiting (10.3% - n=3) and grade 1 constipation (6.9% - n=2). It is noteworthy that no impact on body weight was observed (Table 3,4).

Feeding features	n= 29
Variable	n, (%)
Feeding mode	
Oral feeding	27, (93,1)
Enteral feeding tube	2, (6,9)
Ketogenic Metabolic Therapy	
Yes	29, (100)
No	0
Ketogenic ratio	
Classic 1,4:1	3, (10,3)
Classic 1,5:1	16, (55,2)
Classic 1,8:1	1, (3,4)
Classic 2:1	7, (24,1)
Classic 2,5:1	1, (3,4)
Classic 3:1	1, (3,4)
Use of ketogenic nutritional fomula	
Yes	29, (100)
No	0
Fomula per day amount	
Ketovie 3:1 unflavored - 1 tetraprism of 250ml/day	9, (31)
Ketovie 3:1 unflavored - 1,5 tetraprism of 250ml/day	13, (44,8)
Ketovie 3:1 unflavored - 2 tetraprism of 250ml/day	5, (17,2)
Ketovie 3:1 unflavored - 3 tetraprism of 250ml/day	2, (6,9)
KMT compliance	
Yes	20, (69)
No	9, (31)

Table 3: Feeding features.

General KMT-Related Outcomes		n= 29
Variable		n, (%)
Gastrointestinal symptoms		
Grade 1 Acute diarrhea		
Yes		5, (17,2)
No		24, (82,8)
Grade 1 Emesis		
Yes		3, (10,3)
No		26, (89,7)
Grade 1 Constipation		
Yes		2, (6,9)
No		27, (93,1)
Body weight		
Initial weight (Kg)		
Mean		66,2
Median [Min – Max]		65 [42 – 91]
Follow-up (Kg)		
Mean		65,9
Median [Min – Max]		65 [42 – 91]
Body weight changes		
Gain		0
Loss		5, (17,2)
Maintenance		24, (82,8)
Mean % weight loss		2,8%

Table 4: General KMT-Related outcomes.

In the primary line of treatment, all patients underwent surgical intervention (Gross tumor resection: 65.5%, subtotal resection: 20.7% and biopsy: 13.8%). Additionally, 82.8% (n=24) followed the Stupp protocol (CATNON trial for the case of astrocytomas or CODEL trial for the case of high-grade oligodendrogliomas). Regarding medical treatment for recurrence, 62.1% of the patients underwent a new surgical operation, while 65.5% received re-irradiation in conjunction with a specific chemotherapy regimen (Table 5).

Medical treatment	n= 29
Variable	n, (%)
Initial medical treatment	
Surgical treatment	
Gross tumor resection	19, (65,5)
Subtotal resection	6, (20,7)
Biopsy	4, (13,8)
Radiotherapy	
Concomitant (Chemotherapy - Temozolomide)	24, (82,8)
Conventional fractionation - Sequential	2, (6,9)
Hypofractionation	2, (6,9)
Treatment refusal	1, (3,4)
Chemotherapy scheme	
Yes (Adjuvant Temozolomide - 6 cycles)	24, (82,8)
Yes (Adjuvant Temozolomide - 12 cycles)	4, (13,8)
No	1, (3,4)
Recurrence medical treatment	
Surgical reoperation	
Yes	18, (62,1)
No	11, (37,9)
Re-irradiation	
Yes	19, (65,5)
No	10, (34,5)
Pharmacotherapy	
Previous lines of treatment	
1st line	11, (37,9)
2nd line	12, (41,4)
3rd line	4, (13,8)
4th line	2, (6,9)
Chemotherapy scheme	
Temozolomide: 150-200 mg/m² (Days 1 to 5: Cycles of 28 days) until toxicity or progression	
Yes	24, (82,8)
No	5, (17,2)
Temozolomide metronomic: 50 mg/m² each day until toxicity or progression	
Yes	3, (10,3)
No	26, (89,7)
Bevacizumab: 15 mg/kg every 21 days + Irinotecan: 340 mg/m² (Day 1)	
Yes	5, (17,2)
No	24, (82,8)
Bevacizumab (monoagent): 15 mg/kg every 21 days	
Yes	2, (6,9)
No	27, (93,1)
Regorafenib: 160 mg (days 1 to 21 and 7 days off - Cycles of 28 days)	
Yes	2, (6,9)
No	27, (93,1)

Table 5: Medical treatment.

Main Observations Related to KMT

The KMT had a positive impact on seizure control (95%) and demonstrated improvements in cognition (80%), memory (60%) and functionality (55%), as reported by patients and/or their families (caregivers). Regarding the disease status, assessed by the RANO criteria, the 12-month follow-up evaluation indicated stable disease in 55% of cases, partial response in 20% and disease progression in 25% (Table 6).

Patients with adherence KMT-Outcomes		n= 20
Variable		n, (%)
Disease status (RANO criteria)		
Complete response		0
Partial response		4, (20)
Stable disease		11, (55)
Progression disease		5, (25)
ECOG		
Initial		
ECOG 0		4, (20)
ECOG 1		13, (65)
ECOG 2		2, (10)
ECOG 3		1, (5)
Follow-up		
ECOG 0		5, (25)
ECOG 1		14, (70)
ECOG 2		0
ECOG 3		1, (5)
Neurological symptoms		
Seizure control		
Yes		19, (95)
No		0
N/A		1, (5)
Cognition improvement (perceived by the patient and/or family)		
Yes		16, (80)
No		2, (10)
Unknown		2, (10)
Memory improvement (perceived by the patient and/or family)		
Yes		12, (60)
No		5, (25)
Unknown		3, (15)
Functionality improvement (perceived by the patient and/or family)		
Yes		11, (55)
No		5, (25)
Unknown		4, (20)

Table 6: Patients with adherence KMT-outcomes.

Discussion

High-grade gliomas are the most common primary brain malignancies and account for more than half of all malignant primary brain tumors [13]. It is characterized by a high grade of malignancy and an extremely unfavorable prognosis [14]. Therapeutic advances have been minimal over the past 2 decades. The standard of care in patients with high-grade gliomas eventually involves maximal safe surgical resection, followed by radiotherapy and chemotherapy and it is well known that successful surgery (complete resection or supramarginal resection) is the main factor related to overall survival in these patients [15]. The use of chemotherapy and radiation therapy is well known to be used as adjuvant treatment and in the case of glioblastoma, the use of concomitant chemoradiotherapy (Stupp trial) has a positive impact on overall survival as it also happens with the CATNON and CODEL trials for astrocytomas and oligodendrogliomas, respectively [16-18]. Regarding the initial medical management of the patients included in this study, it can be observed that 65.5% underwent Gross tumor resection (n=19); as well as 82.8% received concomitant radiotherapy (Chemotherapy - Temozolomide), while 6.9% received conventional fractionation - Sequential and 6.9% received hypofractionation.

Generally, when a high-grade glioma experiences a relapse or if the target lesion increases in size, new lesions appear or it is associated with the onset of new neurological symptoms, it usually indicates dedifferentiation and progression of tumor cells and perhaps resistance to treatment. When these events occur, they indicate a worse prognosis due to several variables (ineffective treatment, faster patient deterioration, accumulation of toxicity due to radiation therapy or chemotherapy and other clinical features) [14]. The treatment for recurrent high-grade gliomas is not well defined and decision-making is usually based on prior strategies, as well as several clinical and radiological factors [13]. When facing a relapse or progression of the disease, treatment options are really limited, involving re-resection, re-irradiation or chemotherapy, with disheartening results [19,20]. Regarding chemotherapy and other treatment options in Colombia or in low-income countries, there are not available tumor treatment fields, important option that could be used from the beginning or even in case of relapse [21]. Currently, treatment options for relapse vary, including the use of bevacizumab with camptothecins or nitrosureas and the rechallenge with temozolomide [22-26]. In the recurrence treatment, the patients included in this study underwent surgical reoperation: 62.1%, re-irradiation: 65.5% and different chemotherapy options: Temozolomide: 150-200 mg/m² (Days 1 to 5: Cycles of 28 days) until toxicity or progression; Temozolomide metronomic: 50 mg/m² each day until toxicity or progression; Bevacizumab: 15 mg/kg every 21 days + Irinotecan: 340 mg/m² (Day 1); Bevacizumab as a monotherapy: 15 mg/kg every 21 days and Regorafenib: 160 mg (days 1 to 21 and 7 days off - Cycles of 28 days). But, due to refractoriness, these patients with progression were managed with KMT as a complementary treatment.

Regarding the use of KMT, international guidelines recommend it, without a strong recommendation, indicating that using it possibly helps improve neurological symptoms, as trials and meta-analyses show positive results in quality of life and neurological deficit. One of the main limitations represented in those trials is patient adherence, as it involves following a high ketogenic ratio (higher amount of fat in the diet), resulting in a low overall compliance rate [12,27,28]. In relation to this, the results obtained from this study show that patients managed with KMT demonstrated a 69% adherence (n=20), with promising outcomes on the control of neurological symptoms such as seizure control in 95% and brain functions (perceived by the patient and/or family) such as cognition improvement (80%), memory improvement (60%) and functionality improvement (55%). The KMT should be part of a well-designed program, where the nutritionist has adequate and assertive communication with the oncologist, establishing the needs of each patient according to their chemotherapy or radiation therapy regimen, considering intensive ketogenic ratios during treatment days (3:1) and on the rest days of each cycle, it could be useful to use lower ketogenic ratios like 1.5:1. This can significantly favor adherence to the diet, maintaining quality of life features and improving neurological function in almost all patients, considering mainly that the presence of neurological deficits and seizures can significantly impact quality of life. During nutritional treatment, which not only involves drinking the supplementary liquid formula but also educating the patient and their family about the different preparations and dietary modifications that should be made to achieve a high-fat, low-carbohydrate diet, could have a positive impact on these patients and their adherence to the prescribed diet [29]. This study demonstrated that when an appropriate calculation of the nutritional requirements for each patient is carried out, it does not generate a negative impact on their body weight during the treatment. Furthermore, this dietary adjustment showed minimal impact on gastrointestinal symptoms such as grade 1 acute diarrhea (17.2%), grade 1 emesis (10.3%) and grade 1 constipation (6.9%).

Several clinically relevant molecular markers that assist in diagnosis and prognosis have recently been identified for high-grade gliomas. Knowing the current changes in the classification of high-grade gliomas, it is important to note that all those observed impacts were positive, regardless of the IDH mutation [30,31]. However, it is still unclear whether the MGMT status could have an impact on the results obtained with the use of KMT.

On the other hand, there is evidence suggesting that ligand-gated ion channels may serve as a valuable biomarker and diagnostic tool in the pathogenesis of gliomas, as they have the potential to be altered, modifying the homeostatic activity of neurons, microglia and astrocytes, further exacerbating the symptoms and progression of this clinical entity. Consequently, glutamate-activated receptors have been the subject of clinical trials for their potential therapeutic benefit in diagnosis and treatment (32). This is considering that KMT has an impact on glutamate levels, which may indirectly reduce hyperexcitability and related inflammation, thereby favoring the biological functioning of neuronal cells.

Regarding oncological outcomes, there are some trials that suggest that fasting mimicking diets as the ketogenic diet could have a positive impact, even on progression-free survival and overall survival [33-35]. However, due to the number of patients and overall adherence to treatment, determining the effect on these oncological outcomes with the use of KMT is challenging for this study. Nevertheless, in the present case series, it was observed that, despite the ominous prognosis of a recurrent high-grade glioma to standard treatment, 55% of the patients at the time of follow-up were in stable disease according to the RANO criteria.

Finally, considering that that systemic inflammation within malignant glioma is a topic of constant importance KMT has a primary role on the amount of reactive oxygen species and the generation of free radicals, which may enhance the effect of antineoplastic therapy [36].

Conclusion

The current efficacy of established treatments for recurrent high-grade gliomas is insufficient, necessitating the prompt development of novel therapeutic approaches. The use of KMT potentially creates an unfavorable metabolic environment for cancer cells and, therefore, can be considered a complementary treatment for patients with recurrent high-grade gliomas undergoing conventional oncological medical management. Adherence could be ensured in treated patients, where there is excellent communication between the oncologist and the nutritionist, being flexible with the ketogenic ratio during treatment and employing educational strategies to facilitate understanding of the preparations and foods included and excluded in the diet. A crucial aspect is achieving ketosis in these patients, measured through urine or blood tests. More data are still needed to support the use of KMT in high-grade gliomas and phase 2 or 3 clinical trials are required to verify the impact on oncological outcomes such as progression-free survival or overall survival, as well as the benefits on quality of life and neurological symptoms.

Conflict of Interests

Sponsorship of WaMa Pharma SAS.

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Authors Contributions

Martin Ignacio Zapata Laguado: Medical assessment and follow-up, definition and adjustment of oncologic treatment, patient selection for KMT management according to the clinical characteristics of the disease.

Jorge Aponte Monsalve: Medical assessment and follow-up, definition and adjustment of oncologic treatment, patient selection for KMT management according to the clinical characteristics of the disease.

Camilo Vallejo Yepes: Medical assessment and follow-up, definition and adjustment of oncologic treatment, patient selection for KMT management according to the clinical characteristics of the disease.

Laura Aya Ramos: Nutritional assessment and follow-up, definition of the ketogenic rate according to each case, calculation and adjustment of the nutritional plan.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work
- Drafting the work or reviewing it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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