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Ketogenic diet and its treatment for brain and other nervous system cancers

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Abstract. A growing body of empirical evidence indicates the paramount importance of nutrition in cancer treatment, especially glioma. Among the various strategies proposed to enhance traditional anticancer therapy, ketogenic diets (KD) have emerged as a noteworthy approach. In this review, seven papers highly relevant to the effects of ketogenic diet on glioma are selected and the factors involved are summarized. A Google Scholar search with the subject terms "ketogenic diet" and "brain cancer" or "ketone bodies" and "glioma" results in the selection of seven papers highly relevant to the topic. Animals injected with tumor cells or patients diagnosed with glioma, which had received a ketogenic diet for at least ten days, are included in the analysis. The metabolism-related measurements are also taken. The seven papers show that the ketogenic diet can lower glucose levels, increase β-OHB levels, and reduce tumor size or weight. Additionally, it can also impact brain tumor vascularity and gene expression and potentially influence survival time, making it a promising approach for managing brain cancer in humans. In conclusion, there is evidence showing that the Ketogenic diet has the potential to treat brain cancer. Due to the duration and sample volume of the previous studies, future research still needs to continue.

Keywords: Ketogenic Diet, Brain Cancer, Glioma, Ketone Bodies

1. Introduction

The ketogenic diet is a low-carbohydrate, high-fat, and adequate-protein diet, and it has been popular among people for its ability to treat type 2 diabetes and obesity, as well as for weight control.. In recent decades, more functions of KD have been determined, such as the treatment of cancer. Despite a relatively low incidence rate compared to other cancers, such as lung and breast cancer, brain cancer has a high mortality rate. According to the National Cancer Institute, the 5-year mortality rate of brain and other nervous system cancer was about 66% from 2013 to 2019 [1]. Apart from that, the traditional treatments for brain cancer are radiotherapy or chemotherapy, which are invasive and have limited efficacy. Therefore, the ketogenic diet can treat or prevent glioma, which is one of the main brain cancer types with a high malignancy risk like other types of brain cancer. However, the ketogenic diet for the treatment of glioma is a novel therapy that has not yet been systematically applied on a large scale in clinical settings. As a result, this paper discusses the treatments of KD for brain glioma and its limitations by reviewing seven previous papers.

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2. Methods

This paper conducted a literature research using subject headings such as “ketogenic diet” and “brain cancer” or “ketone bodies” and “glioma” to identify relevant studies. The inclusion criteria for studies included animals injected with tumor cells or patients diagnosed with glioma, which were fed with a ketogenic diet for at least ten days. The reviews and non-glioma brain cancer research were excluded.

The single-group experimental studies of mice and two case studies are included in this review. In some of the mouse studies, the tumor was implanted into in the cerebral cortex of mice. Then, the relative metabolic index was measured, like the glucose level, weight changes of the mouse body, the tumor weight, insulin growth factor 1 (IGF-1), cholesterol, and lipid levels. According to Figure 1, 54 papers were screened, and seven papers will be discussed in this review through selection. Meanwhile, the table of study characteristics is listed below in table 1.

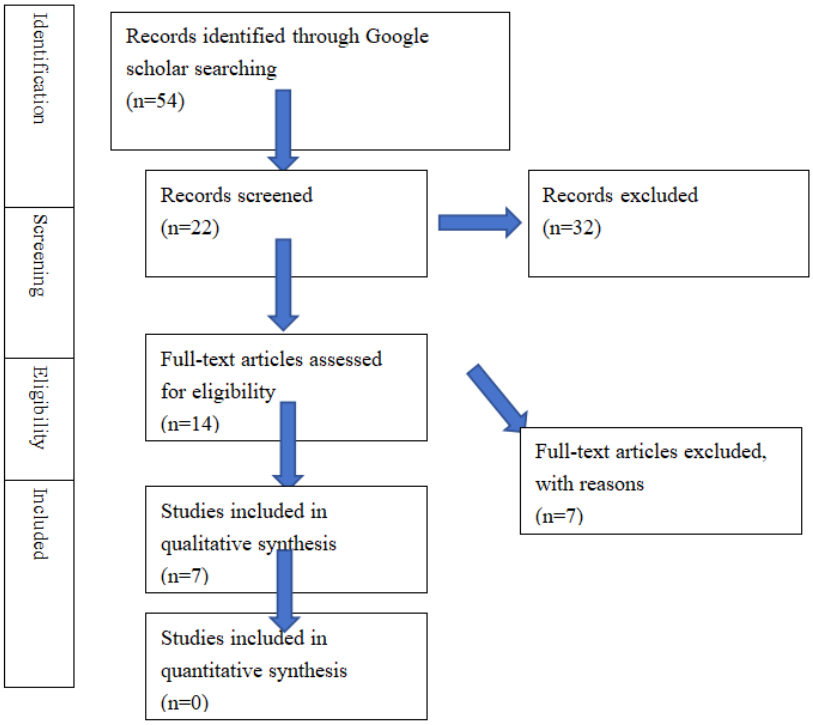

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Chart

Table 1. Study Characteristics

Reference/Year	Design	Samples	Age range	Intervention	Duration	Outcomes
Seyfried et al. (2003) [2]	Single-arm pilot trial	33 (6 KD-R;14 KD-UR)	10 - 12 weeks old male mice	SD-UR, SD-R, KD-UR, KD-R	13days	Energy intake, body weight, tumor dry weight, plasma glucose, beta-HB, IGF-1
Zhou et al. (2007) [3]	Single-arm pilot trial	36-42 (12–14 mice per group)	10 - 12 weeks old male mice; human	SD-UR, KC-UR, KC-R	11 days	Body weight, Glucose level, Beta-OHB, Tumor wet weight, SCOT and beta-OHBDH expression

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Table 1. (continued)

Woolf et al. (2015) [4]	Single-arm pilot trial	11 (6 KC)	10 week old female mice	SD, KC	21 days	Beta-HB, hypoxic response, tumor microvasculature, edema, gene expression, junction protein and aquaporins; body weight
Abdelwahab et al. (2016) [5]	Single-arm pilot trial	11 KC	10 weeks mice	SD, KC	150-200 days	cohort size, percentage of survival, Blood ketone, glucose levels, Animal weights
Stafford et al. (2010) [6]	Single-arm pilot trial	20	female C57BL/6 mice	KD, SD	Two weeks to 36 days	β-hydroxybutyrate levels, blood glucose level, ROS; body weight; percentage of survial
Schwartz et al. (2015) [7]	Case study	7	Patients with advanced brain tumors (age: 56; 5.5)	KD	12 weeks; 5 years	Blood glucose, ketones, and daily weights.
Perez et al. (2010) [8]	Case study	5	Pales, n = 3; median age 4.4 years; range, 2.5-15 years	KD	9 months to 30 months	Glucose level, Ketone bodies, body weight, serum lipid levels, the disorders of taking KD diet

3. Results

3.1. Glucose Level, β-OHB Level, and Their Effects on Tumor

All the studies assessed the glucose level, or the β-OHB level. They all found that glucose levels decreased and/or the β-OHB level increased significantly with the KD implied. Only one patient from a case study showed the KD related high ketosis of 7.2 mmol/L in the blood (hyperkeratosis defined as >6 mmol/L) and one borderline glucose level of 2.4 mmol/L (hypoglycemia defined as <2.5 mmol/L) on the 26 and 3 days after adapting the KD diet, but the two indexes returned to normal range in the other days. Two studies showed that consuming the KD ad libitum does not induce substantial modifications in plasma glucose levels. However, the restricted group's glucose level was significantly lower than the unrestricted one. Three studies reported that the β-OHB level increased in the KD or energy-restricted groups but showed no relationship with the glucose level. Additionally, the restricted

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dietary conditions in mice result in significantly higher circulating β-OHB levels than unrestricted conditions.

3.2. Body Weight

All seven studies reported body weight changes with time, with five illustrating a faster weight decrease with time for the KD group than the standard diet. One case study showed no change in the five patients' body weight, and one mice study showed no significant difference between SD and KD diet. One study found that the unrestricted dietary pattern has no difference between KD and the standard diet, and the restricted were more physically active than the unrestricted.

3.3. Tumor Size or Weight

Six studies reported tumor size or weight decreasing in the KD group, which is highly related to survival length, according to Stafford et al. [6]. One study found that the restricted group decreased more significantly than the unrestricted group. Tumor dry weight was 86% lower in the SD-R group compared to the SD-UR group and 80% lower in the KD-R group than the KD-UR group.

3.4. Oxygen Species in Tumor Cells

One study showed increased ROS in the SD group in vivo analysis, while ex vivo analysis revealed a significant reduction in ROS levels in the KD group. Some tumor cells displayed higher ROS levels, indicating potential resistance.

3.5. Brain Tumor Vascularity

Three studies reported the effects of KD on brain tumor vascularity. One study used Factor VIII immunostaining to examine blood vessel densities in brain tumors. The results showed fewer blood vessels in the restricted KD group, and no significant differences were found in the unrestricted KD and SD groups. Another study found that the KD significantly decreased VEGFR2 protein expression.

3.6. Gene Expression

One study found that mice with the KD diet had 1129 genes differentially expressed in tumors compared to normal brains, while SD animals had 1015 differentially expressed genes (614 genes were commonly differentially expressed in both groups). According to ANOVA analysis, the KD significantly impacted gene expression, causing a shift towards a pattern closer to that observed in normal brains. Woolf et al. [4] also determined that the KD can alter the expression of carbonic anhydrase IX and proteins involved with the hypoxic response: Tumors from mice fed a KC exhibited notable decreases in both CA IX and Hypoxia-inducible factor-1α (HIF-1α) levels compared to those fed a SD. Additionally, a significant reduction in VEGFR2 expression was observed in the KC group.

3.7. Survival Time

Four studies reported the KD effects on the survival of samples. The results illustrated that the restricted KD could extend survival time in mice with metastatic cancer, while the difference was insignificant for the unrestricted KD compared to SD. One of the four papers also found that one mouse sample treated with KD appeared to be cured of its tumor, and no evidence showed the tumor regrowth for an additional 200 days.

4. Discussion

The ketogenic diet shows the potential to decrease the glucose level, increase β-OHB level, and lower the tumor size or weight. Additionally, it can control body weight and affect survival time, which has the potential to be a practical approach for managing brain cancer in humans. Stafford et al. [6] found the KD diet can reduce the ROS level, which has dual effects on tumorigenesis and tumor heterogeneity. They can act as signaling molecules that promote tumor growth. Still, high levels of ROS can also be

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detrimental to cancer cells, causing genotoxicity and potentially inducing apoptosis, according to de Sá Junior [9].

Additionally, the reduction of CA IX HIF-1α levels and VEGFR2 was found in KC group. HIF-1α and CA IX are hypoxia markers, and the expression of CA IX is also controlled by HIF-1α. The overexpression of CA IX in malignant glioma is strongly associated with poor patient survival by Proescholdt et al. [10].VEGFR2 is the main regulator of tumor angiogenesis, inhibiting it can produce radiologic response, normalize tumor vasculature, reduce edema, and improve patient quality of life by Jain [11]. Therefore, the restricted KD more efficiently affects brain tumor vascularity and adjusts the expression of several proteins involved in malignant progression. Accordingly, the ketogenic diet can be used as adjuvant therapy combined with radiation or chemotherapy by Seyfried et al. [2], reducing the invasive harm of the traditional treatment.

However, individual patient dietary preferences limit the feasibility of implementing uniform ketogenic diet regimens in clinical trials. Perez et al. [8] found some side effects of adapting KD in their case study. Vomiting, food refusal, fatigue, headache, and inability to swallow occurred in the five patient samples. Furthermore, the small sample sizes and lack of proper randomization and control groups in most human studies make it difficult to draw conclusive and generalizable findings regarding the effects of the ketogenic diet on cancer growth and survival in humans. Plenty of studies still need to be done to confirm the feasibility of clinical practice.

5. Conclusion

In conclusion, the ketogenic diet can potentially treat glioma by decreasing the metabolism process, gene expression, and oxygen species in tumor cells, reducing the tumor size, and increasing the survival time summarized from these seven studies. However, some side effects also appear in some clinical samples, and some syndromes have been mentioned above. The experimental duration is also limited, usually from a few days to a few months. Additionally, whether the ketogenic diet has been reversed, whether it has had a positive effect on the treatment of cancer, or whether it has had a detrimental effect in other areas is unknown, or there is very little research data available.

Anyway, the therapy of KD on glioma is still a new field of treating glioma. As a standalone treatment or as an adjuvant therapy alongside radiation or chemotherapy, it can potentially improve clinical outcomes and enhance the quality of life for brain tumor patients, reducing the invasive harm the traditional methods cause. Accordingly, it can be combined with traditional therapy to enhance the overall efficacy of brain cancer treatment. The exact mechanism also needs to be determined in future studies, which can help identify novel therapeutic targets and develop more targeted approaches. Therefore, further long-term effects, safety studies, and clinical practice are needed to test its safety and feasibility.

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