Ketogenic diet in glioma

- Metabolic flux analysis of glioblastoma neural stem cells reveals distinctive metabolic phenotypes in ketogenic conditions
- Pitfalls in 2HG detection with TE-optimized MRS at 3T
- Safety, Feasibility, and Effectiveness of Ketogenic Diet in Pediatric Patients With Brain Tumors: A Systematic Review
- Ketogenic diet induces an inflammatory reactive astrocytes phenotype reducing glioma growth
- Critical Review of Ketogenic Diet Throughout the Cancer Continuum for Neuroglioma: Insights from a Medical Nutrition Therapy (MNT) Perspective
- Ketogenic diet with oxyresveratrol and zinc inhibits glioblastoma and restores memory function and motor coordination
- Clinical research framework proposal for ketogenic metabolic therapy in glioblastoma
- Systematic Review and Clinical Insights: The Role of the Ketogenic Diet in Managing Glioblastoma in Cancer Neuroscience

Rationale for Using the Ketogenic Diet in Glioma

The ketogenic diet is hypothesized to benefit glioma patients through several mechanisms:

Energy Restriction: Cancer cells, including glioma cells, are highly dependent on glucose for energy and rapid proliferation. By reducing carbohydrate intake, the ketogenic diet lowers blood glucose levels, potentially starving tumor cells.

Ketone Utilization: Normal brain cells can adapt to utilize ketone bodies for energy, whereas glioma cells may lack the metabolic flexibility to effectively use ketones, giving healthy cells a survival advantage.

Reduced Insulin and IGF-1 Levels: Lower insulin and insulin-like growth factor 1 (IGF-1) levels may inhibit tumor growth and proliferation.

Anti-inflammatory Effects: The ketogenic diet may exert anti-inflammatory effects, which could be beneficial in the tumor microenvironment.

Safety profile

Clinical and experimental research on brain tumors has shown that the ketogenic diet has a satisfactory safety profile. This safety profile has been established in a variety of applications, including the management of obesity and the treatment of drug-resistant epileptic cases. However, in human studies, the impact of ketogenic therapy on the growth of tumors and the life expectancy of patients has not provided results that are well characterized.

The purpose of Valerio et al. was to improve the comprehension of these features by succinctly presenting the developments and conclusions that have been gained from the most recent study that pertains to this non-pharmacological technique. According to the findings of the study, patients with brain tumors who stick to a ketogenic diet are more likely to experience improved survival rates. However, it is required to conduct additional research on humans in order to more accurately define

the anti-tumor efficiency of this diet as well as the underlying processes that support the therapeutic effects of this dieting regimen [1].

Glucose and glutamine are suggested to facilitate tumor progression. Recent evidence suggests that many glioblastoma GBMs are infected with cytomegalovirus, which could further enhance glucose and glutamine metabolism in the tumor cells. Emerging evidence also suggests that neoplastic macrophages/microglia, arising through possible fusion hybridization, can comprise an invasive cell subpopulation within GBM. Glucose and glutamine are major fuels for myeloid cells, as well as for the more rapidly proliferating cancer stem cells. Therapies that increase inflammation and energy metabolites in the GBM microenvironment can enhance tumor progression. In contrast to current GBM therapies, metabolic therapy is designed to target the metabolic malady common to all tumor cells (aerobic fermentation), while enhancing the health and vitality of normal brain cells and the entire body. The calorie restricted ketogenic diet (KD-R) is an anti-angiogenic, anti-inflammatory and pro-apoptotic metabolic therapy that also reduces fermentable fuels in the tumor microenvironment. Metabolic therapy, as an alternative to the standard of care, has the potential to improve outcome for patients with GBM and other malignant brain cancers [2].

There are two ongoing clinical trials set to be completed by 2016 studying the efficacy of a Ketogenic Diet (KD) in Glioblastoma (GBM) patients: a Phase 1 randomized controlled trial/Phase 2 randomized controlled trial and a Phase II trial. In the Phase I/II trial, GBM patients will be administered a traditional 4:1 ratio of fat to carbohydrate KD while being treated chemoradiotherapy for six weeks. Monthly chemotherapy will be given afterwards. Patients will have an initial MRI scan, weekly blood tests to monitor ketone levels and a final MRI test [3].

In the Phase II trial, recurrent GBM will be treated with a similar KD as the previous trial, along with chemoradiation. Following the treatment, bevacizumab may be administered [4].

Both studies aim to determine the tolerability and safety of a KD, along with its efficacy as a tumor-shrinking agent. Preclinical and clinical studies have both been able to suggest the effectiveness and tolerability of the KD and the KD-UR; however, the precise success of tumor shrinkage exhibited in the preclinical trials has not been explicitly carried over into the clinic. It is difficult to draw conclusions based on these studies given their lack of large cohorts—the largest being a group of six patients being treated with a KD [5].

Moreover, the exact scientific mechanisms of how the KD works are still unclear. Studies dissecting the aspects of a KD and finding the exact attribute of a KD that provides benefits are warranted. Furthermore, larger cohort studies to show a more conclusive and statistically significant improvement of KD therapy on GBM patient prognosis are needed [6].

A program was developed (Glucose Ketone Index Calculator, GKIC) that tracks the ratio of blood glucose to ketones as a single value. We have termed this ratio the Glucose Ketone Index (GKI).

The GKIC was used to compute the GKI for data published on blood glucose and ketone levels in humans and mice with brain tumors. The results showed a clear relationship between the GKI and therapeutic efficacy using ketogenic diets and calorie restriction.

The GKIC is a simple tool that can help monitor the efficacy of metabolic therapy in preclinical animal models and in clinical trials for malignant brain cancer and possibly other cancers that express

aerobic fermentation [7].

The effectiveness is based on the “Warburg Effect” of cancer metabolism and the microenvironment of glioblastoma (GBM) tumors.

A consumed fat molecule (triacylglycerol) is catabolized into free fatty acids and eventually Acetyl-CoA. If increased fatty acid oxidation elevates the levels of Acetyl-CoA to surpass the capacity of the citric acid cycle, excessive levels of ketone bodies accumulate (Beta hydroxybutyrate (BHB) and acetoacetate (ACA)). Normal neurons and glial cells are able to metabolize BHB and ACA; however, neoplastic cells appear less able to utilize these sources for energy derivation. Cancer (CP1) cells also have markedly elevated levels of reactive oxygen species (ROS) that have been associated with angiogenesis and cell proliferation through mediation of vascular endothelial growth factor (VEGF) and hypoxia inducible factor 1 (HIF-1). Ketone bodies have been linked to ROS reduction in vivo. Due to tumor cells’ metabolic dependence on glucose and glutamate, elevated levels of ketone bodies in the intracranial region diminish glycolytic levels and inhibit angiogenesis.

A calorically-restricted diet administered to mice infused with a malignant mouse astrocytoma (CT-2A) or a human glioma (U87-MG) was effective in decreasing vascularity, increasing programmed cell death, and was associated with diminished levels of insulin-like growth factors [8].

Recent clinical findings have demonstrated that induced hypoglycemia and ketogenic diet are tolerable and can potentially be an adjuvant to standard treatments, such as surgery and chemoradiation. Other findings have advocated for KD as a malignant cell growth inhibitor, and indicate that further studies analyzing larger cohorts of GBM patients treated with a KD are needed to determine the breadth of impact a KD can have on GBM treatment [9]

The KD directly or indirectly alters the expression of several proteins involved in malignant progression and may be a useful tool for the treatment of gliomas [10].

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