Could Metabolic Therapy Become a Viable Alternative to the Standard of Care for Managing Glioblastoma?

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Abstract

Little progress has been made in the long-term management of glioblastoma multiforme (GBM) for more than 40 years. The current standard of care (SOC) for GBM involves radiotherapy with concomitant adjuvant temozolomide chemotherapy. Perioperative corticosteroids are also administered to the majority of GBM patients. The current standard treatment strategy for GBM increases availability of glucose (from steroids) and glutamine (from radio-necrosis) in the tumor microenvironment. Emerging evidence indicates that GBM, like most cancers, is a metabolic disease displaying a robust Warburg effect. It is well documented that glucose and glutamine are major metabolic fuels that drive tumor progression. Recent evidence suggests that neoplastic cells with macrophage/microglia properties can contribute to the most invasive cell subpopulation within GBM. Glucose and glutamine are major fuels for myeloid cells as well as for the more rapidly proliferating cancer cells. Metabolic therapy exploits the biological differences between tumor cells and normal cells for the non-toxic targeting of the tumor cells. Studies in preclinical models show that calorie restricted ketogenic diets (KD-R), anti-glycolytic drugs, and hyperbaric oxygen therapy can reduce availability of glucose and glutamine in the tumor microenvironment while enhancing oxidative stress in tumor cells. The predominant ketone body (β-hydroxybutyrate) reduces oxidative stress in normal brain cells. The potential success of metabolic therapy was also seen in human glioma case studies suggesting that this therapeutic strategy could become a viable alternative to the SOC.

Keywords

Glioblastoma, standard of care, metabolic therapy, anti-glycolytic drugs, ketogenic diets, hyperbaric oxygen therapy, Warburg effect

Disclosure: The authors have no conflicts of interest to declare.

Acknowledgments: This research was supported in part by National Institutes of Health (NIH) grants (HD-39722, NS-55195, and CA-102135), a grant from the American Institute of Cancer, the Boston College Expense Fund (to Thomas N Seyfried, PhD), Scivation, and the Office of Naval Research (to Dominic P D'Agostino, PhD).

Received: February 9, 2014 **Accepted**: March 5, 2014 **Citation**: *Oncology & Hematology Review,* 2014;10(1):13–20 *DOI: 10.17925/OHR.2014.10.1.13*

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Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is the most malignant of the primary brain cancers with only about 12 % of patients surviving beyond 36 months (long-term survivors).[1–4] Most GBMs are heterogeneous in cellular composition consisting of tumor stem cells, malignantly transformed mesenchymal cells, and host stromal cells; hence, the name 'glioblastoma multiforme.'[5–11] Primary GBM appears to arise *de novo*, while secondary GBM is thought to arise from low-grade gliomas.[7,12,13] The incidence and timing of malignant progression from low-grade glioma to GBM is variable and unpredictable.[14] In addition to the neoplastic cell populations, tumor-associated macrophages/monocytes (TAM) also comprise a significant cell population in GBM sometimes equaling the number of tumor cells.[15–20] TAM can indirectly contribute to tumor progression through release of pro-inflammatory and pro-angiogenic factors.[16,18,20,21] Neoplastic cells with myeloid/macrophage characteristics (CD68 expression) can also contribute to the sarcomatoid characteristics of GBM.[5,11,12,22] We suggested that many cells appearing as TAM within GBM could be neoplastic with properties of macrophages/microglia.[22] Using the secondary structures of Scherer, the neoplastic cells in GBM invade through the neural parenchyma well beyond the main tumor mass, making complete surgical resections exceedingly rare.[2,23–26] Although systemic metastasis is rare for GBM, GBM cells can be metastatic if given access to extraneural sites.[27–31] Despite extensive analysis from the cancer genome projects, no mutation is known that is unique to the GBM and no genetic alterations are seen in major signaling pathways in about 15 % of GBM.[32,33] Moreover, few of the personalized molecular markers available are considered important for GBM analysis or therapy.[34] Recent evidence also suggests that the genomic abnormalities seen in cancer cells arise as downstream secondary effects of disturbed energy metabolism and are unlikely to provide useful information for therapeutic treatment strategies for the majority of GBM patients.[13,35,36]

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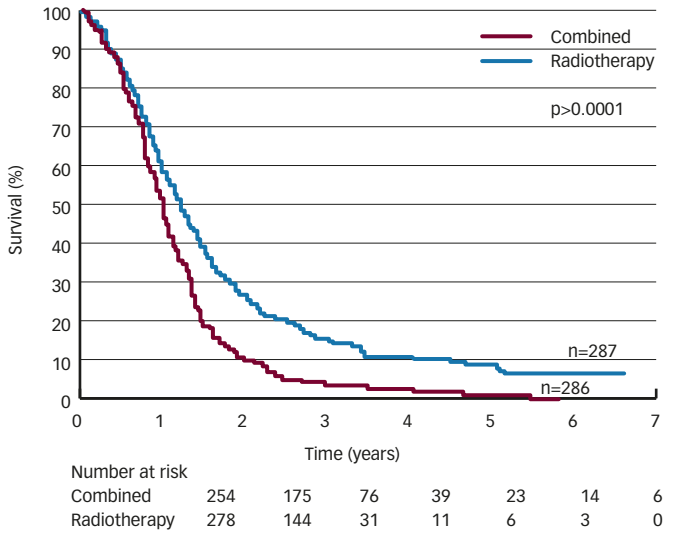
Figure 1: Kaplan-Meier Estimates of Overall Survival of Patients with Glioblastoma Multiforme by Treatment Group



The two patient groups included radiotherapy alone (n=287) and radiotherapy with temolozomide (n=286). Overall patient survival has remained largely unchanged from the study published in 2005.[45] Reprinted with permission from Stupp et al.[3]

The Current Standard of Care for Glioblastoma

The current standard of care (SOC) for GBM and many malignant brain cancers includes maximum surgical resection, radiation therapy, and chemotherapy.[2,3,37,38] The toxic alkylating agent temozolomide (TMZ) is the most common chemotherapy used for treating GBM. Most GBM patients also receive perioperative corticosteroids (dexamethasone), which are often extended throughout the course of the disease.[39,40] There have been no major advances in GBM management for over 50 years, though use of TMZ has produced marginal improvement in patient survival over radiation therapy alone.[3,41] Marginal benefits from the use of TMZ are also observed in those GBM patients who express promoter methylation of their DNA-repair enzyme O6-methylguanine DNA methyltransferase (*MGMT*) gene.[42,43]

Despite conventional treatments, prognosis remains poor for most patients with high-grade brain tumors (see *Figure 1*).[2–4,37,41,44,45] The optimal therapeutic strategy for recurrent high-grade gliomas is unknown, and an effective SOC does not exist. Re-irradiation together with the anti-angiogenic drug, bevacizumab (Avastin®), is also often offered to some GBM patients with recurrent disease despite the removal of bevacizumab for breast cancer due to toxicity and lack of efficacy by the US Food and Drug Administration (FDA).[46–48] Bevacizumab treatment increases progression-free survival in GBM patients, but does not increase overall patient survival.[49] It seems that bevacizumab treatment delays the time-to-progression by technically changing the magnetic resonance imaging (MRI) findings. Bevacizumab substantially decreases contrast enhancement on T1-weighted MRI in recurrent GBM compared with high-dose dexamethasone suggesting that the major benefit of bevacizumab is in its anti-edema action. Consequently, bevacizumab appears to act like steroids in reducing edema, but not in killing the most invasive tumor cells.

Do the Current Standard Treatments for Glioblastoma Multiforme Enhance Recurrence and Progression through Effects on Energy Metabolism?

Emerging evidence indicates that cancer is primarily a disease of energy metabolism.[35,50] In light of this information it is our view that the current SOC for GBM and other malignant brain cancers could contribute to tumor recurrence and progression through effects on tumor cell metabolism. Our suggestion comes from new information describing how the SOC can enhance the availability of glucose and glutamine within the tumor microenvironment.[18,47,51] Glucose and glutamine are major drivers of tumor cell energy metabolism.[48,52–54] It is well documented that neurotoxicity from mechanical trauma (surgery), radiation therapy, and chemotherapy, will increase tissue inflammation and glutamate levels.[24,55–58] Damage to brain tissue can induce hyperglycolysis and an increased demand for glucose.[59] Necrotic brain injury can arise from radiotherapy.[60,61] Tumor radiation will also up-regulate the PI3K/Akt signaling pathway, which drives glioma glycolysis and chemotherapeutic drug resistance.[62–66] Fatigue is not uncommon in GBM patients that receive the SOC.[67,68] Radiation of tissues is known to induce systemic inflammation, which is suggested to underlie the fatigue associated with cancer therapy.[69] It is not yet clear if the fatigue seen in some GBM patients might arise in part from brain irradiation or from other toxic effects of SOC. Tissue inflammation also enhances local hypoxia while providing a plethora of growth factors that facilitate angiogenesis and tumor cell rescue.[18] Local astrocytes rapidly clear extracellular glutamate, metabolizing it to glutamine for release to neurons.[70] In the presence of dead or dying neurons, however, surviving tumor cells and the TAM will use astrocyte-derived glutamine for their energy and growth. TAM also release pro-angiogenic growth factors, which further stimulate tumor progression.[18,20,48] Most neoplastic GBM cells are infected with human cytomegalovirus (HCMV), which could further accelerate tumor cell growth through increased metabolism of glucose and glutamine.[71,72] In contrast to normal glia that metabolize glutamate to glutamine, Takano and co-workers showed that neoplastic glioma cells secrete glutamate.[55] Glioma glutamate secretion is thought to contribute in part to neuronal excitotoxicity and tumor expansion.[55] Lawrence and co-workers suggested that survival was better for glioma patients who experienced less neurologic toxicity than for patients who experienced more neurologic toxicity.[73] It appears that therapies that enhance neurotoxicity could facilitate GBM progression. This raises the question of whether the current SOC creates a metabolic environment that could promote GBM progression.

In addition to the potential tumor-enhancing effects of radiation and HCMV on GBM energy metabolism, most GBM patients are also given glucocorticoids (dexamethasone).[40] Although dexamethasone is given to reduce radiation-associated brain swelling and tumor edema, dexamethasone elevates blood glucose levels.[64,74–78] Glucose fuels the Warburg effect as well as serving as a precursor for glutamate synthesis and nucleotide synthesis through the pentose phosphate pathway.[35,50,70,79,80] It is not likely that therapies, which elevate blood glucose, will improve patient survival. Indeed, prognosis was considered worse for glioma patients with higher blood glucose levels than in patients with lower glucose levels.[81,82] These observations in GBM patients support our original work in a preclinical glioma model.[78]

Many GBM patients are also treated with anti-angiogenic drugs, such as bevacizumab. These drugs target leaky blood vessels thus enhancing

hypoxia and radiation-induced necrosis in the tumor microenvironment. Increased hypoxia will further enhance tumor cell glycolysis and select for those tumor cells with greatest invasive properties.[48,83–85] This will be especially advantageous to those tumor cells that arise from macrophage or microglial fusion and are already capable of surviving in hypoxic environments.[22,86] Further studies are needed to determine if anti-angiogenic drugs exacerbate radiation-induced necrosis, which could create a more favorable environment for tumor recurrence.[87] When viewed together these findings illustrate how the current GBM-treatment strategies could create a microenvironment that facilitates the energy needs of tumor cells and recurrence of the tumor. The process is illustrated in *Figure 2*.

Although the existing SOC for malignant brain cancer will increase patient survival over the short term (months) compared with the 'no therapy' option,[88] it is clear from extensive *in vitro* and *in vivo* (animal) experiments how this therapeutic strategy could enhance the Warburg effect in surviving tumor cells. Moreover, the malignant phenotype of brain tumor cells that survive radiotherapy is often greater than that of the cells from the original tumor.[64] Treatments that increase the Warburg effect in tumor cells will facilitate tumor cell growth and invasion.[50] It is not likely that survival will be improved in patients receiving therapies that would increase the Warburg effect. The data from Stupp et al. show that none (0/278) of the patients receiving radiation alone survived, whereas only about 2 % (6/254) of patients receiving radiation and TMZ became long-term survivors (see *Figure 1*). These findings address the general inadequacy of current therapies in providing long-term management of GBM. The slight improvement of patient survival with TMZ is remarkable in light of recent findings showing that TMZ enhances the number of driver mutations in the tumor tissue.[13] How might TMZ improve overall patient survival if the drug is suggested to increase the number of driver mutations in the tumor? Driver mutations are thought to provoke tumor progression by conferring a growth advantage to the most neoplastic cells.[32,33,89–91] These findings illustrate the disconnect between driver mutations and tumor progression and further question the gene theory of cancer.[35] While GBM is certainly a deadly disease, is it possible that current treatment strategies might make the disease even worse?

Mitochondrial Abnormalities in Malignant Brain Tumors

Although mitochondrial abnormalities are found in all cancers including brain cancer,[35,36,92–94] mitochondrial abnormality is not generally recognized as a major cancer hallmark.[95] Mitochondrial abnormalities will reduce energy production through oxidative phosphorylation (OxPhos).[51,66,92–94,96–103] The ultrastructure of mitochondria in malignant brain tumors differs markedly from the ultrastructure of normal tissue mitochondria.[93,98,104] In contrast to normal mitochondria, which contain numerous cristae, mitochondria from GBM tissue samples showed swelling with partial or total cristolysis (see *Figure 3*). Cristae contain the proteins of the respiratory complexes, and play an essential structural role in facilitating energy production through OxPhos.[94,105–107] The structural defects in human glioma mitochondria are also consistent with lipid biochemical defects in murine gliomas. We showed that cardiolipin, the signature phospholipid of the inner mitochondrial membrane, was abnormal in five independently derived mouse brain tumors.[108,109] Cardiolipin controls the efficiency of OxPhos, and any alterations in the content or fatty acid composition of cardiolipin will reduce cellular respiration.[110–112] In addition to these findings, Poupon and colleagues also indicated that the high glycolytic activity seen in malignant gliomas could arise from mitochondrial structural abnormalities.[113] Hence, substantial morphologic and biochemical evidence exists showing that respiratory capacity is defective in gliomas.

The Warburg Effect in Glioblastoma Multiforme

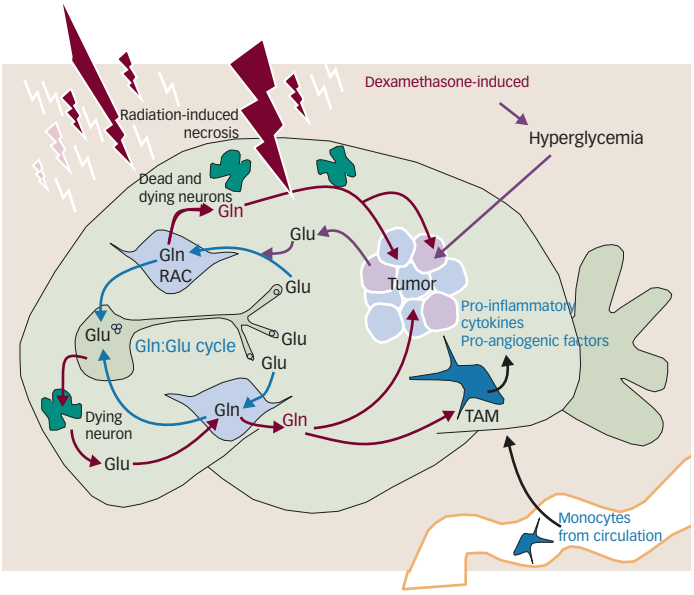
Based on an extensive analysis of human and animal tumors, Otto Warburg first proposed that all cancers arise from irreversible damage to cellular respiration.[80,114] As a result, cancer cells increase their capacity to ferment lactate even in the presence of oxygen in order to compensate for their insufficient respiration.[80,114] Although confusion has surrounded Warburg's hypothesis on the origin of tumor cells,[115,116] his hypothesis has never been falsified and remains a credible explanation for the origin of cancer.[66,117–121] The key points of Warburg's theory are: 1) insufficient respiration initiates tumorigenesis and ultimately cancer, 2) energy through glycolysis gradually compensates for insufficient energy through respiration, 3) cancer cells continue to ferment lactate in the presence of oxygen, and 4) respiratory insufficiency eventually becomes irreversible.[80,114,122–124] Warburg referred to the phenomenon of enhanced glycolysis in cancer cells as 'aerobic fermentation' to highlight the abnormal production of lactate in the presence of oxygen.[80,114,122–124] The 'Warburg effect' refers to the aerobic fermentation of cancer cells.[118,119] Substantial evidence exists showing that malignant gliomas produce lactate.[50,125,126] Lactate is the end product of pyruvate fermentation. This would be expected for any tumor cell with quantitative or qualitative abnormalities in mitochondria.

As the result of insufficient respiration, cancer cells must rely on non-oxidative mechanisms to maintain energy balance and viability. Consequently, aerobic fermentation plays a role in producing energy through substrate level phosphorylation in the cytoplasm (glycolysis).[51,66,123,127] Besides aerobic fermentation in the cytoplasm, tricarboxylic acid (TCA) cycle substrate level phosphorylation might also produce ATP through non-oxidative metabolism in the mitochondria.[35,50,128] It can be difficult to determine, however, the degree to which mitochondrial ATP production arises from coupled respiration or from TCA cycle substrate level phosphorylation.[129–132] A protracted reliance on non-oxidative energy metabolism, involving glucose and amino acid fermentation with substrate level phosphorylation, can cause genomic instability and other recognized hallmarks of cancer.[51,66,128] Emerging evidence indicates that the function of DNA repair enzymes and the integrity of the nuclear genome are dependent to a large extent on normal respiration and mitochondrial function.[133–140] In other words, genomic instability ultimately arises from a protracted insufficiency of OxPhos and is considered a downstream epiphenomenon of damaged or insufficient respiration.[35] In many instances, tumor-associated mutations do not produce tumors when the tumor nucleus is placed in normal cytoplasm containing normal mitochondria.[35,141] These observations also question the gene theory of cancer and the attempt to define the genetic nature of a disease that is not genetic.[35]

Role of Glucose and Glutamine in Brain Tumor Progression

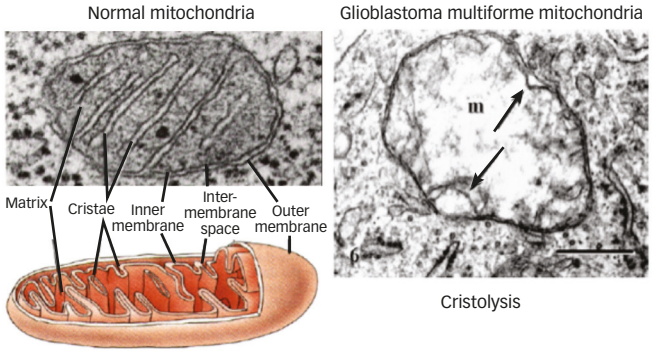
Glucose is the predominant fuel of the brain, but also fuels tumor cell glycolysis as well as serving as a precursor for glutamate synthesis.[50,70,79,80] Using linear regression analysis, we showed that the growth rate of an

Figure 2: How the Standard of Care Can Accelerate Brain Tumor Growth and Recurrence



Glioblastoma multiforme (GBM) and other high-grade brain tumors consist of multiple neoplastic cell types as well as tumor-associated macrophages/monocytes (TAM), which release pro-inflammatory and pro-angiogenic factors. All these cells will use glucose and glutamine (Gln) as major metabolic fuels for their growth and survival. Recent evidence suggests that nearly all GBMs are infected with human cytomegalovirus, which enhances glucose and Gln metabolism in the tumor cells. Increased glutamate (Glu) concentrations will arise after radiation/drug-induced necrosis. Reactive astrocytes (RAC) take up and metabolize glutamate to Gln, whereas hyperglycemia will arise after corticosteroid (dexamethasone) therapy. Together, these standard treatments will provide a microenvironment that facilitates tumor cell growth, survival, and the likelihood of tumor recurrence.[18] With permission from Lancet Oncology.

Figure 3: Typical Ultrastructure of a Normal Mitochondrion and a Mitochondrion from Glioblastoma Multiforme Tissue



Normal mitochondria contain elaborate cristae, which are extensions of the inner membrane and contain the protein complexes of the electron transport chain necessary for producing adenosine triphosphate (ATP) through oxidative phosphorylation (OxPhos). The mitochondrion from the glioblastoma multiforme (GBM) (m) is enlarged and shows a near total breakdown of cristae (cristolysis) and an electron-lucent matrix. The absence of cristae in GBM mitochondria indicates that OxPhos would be deficient. The arrow indicates an inner membrane fold. Bar: 0.33 µm. Method of staining: uranyl acetate/lead citrate. The GBM mitochondria was reprinted with permission from Journal of Electron Microscopy.[93] *The normal mitochondria and diagram were from http://academic.brooklyn.cuny.edu/biology/bio4fv/page/mito.htm*

experimental mouse astrocytoma was directly dependent on blood glucose levels.[79] The higher the blood glucose levels, the faster the tumors grew. As glucose levels fall, tumor size and growth rate falls. Hyperglycemia not only contributes to rapid tumor cell growth, but also enhances white matter damage in patients receiving radiation therapy.[142] Hyperglycemia is also linked to poor prognosis in humans with malignant brain cancer.[81,82]

Moreover, we found that the expression of insulin-like growth factor 1 (IGF-1) was also dependent on circulating glucose levels.[79,143] IGF-1 binds to IGF-1 receptor (IGF-1R), a cell surface receptor linked to rapid tumor growth through the PI3K/Akt signaling pathway.[143] The association of plasma IGF-1 levels with tumor growth rate is due in part to elevated levels of blood glucose. These findings in animal models and in brain cancer patients indicate that tumor growth rate and prognosis is dependent to a significant extent on circulating glucose levels. Glucose is the prime fuel for glycolysis, which drives growth of most brain cancer.[50,113,144] As long as circulating glucose levels remain elevated, brain tumor growth will be difficult to manage.

In addition to glucose, glutamine is also suggested to play an important role in tumor energy metabolism.[145–148] In contrast to extracranial tissues where glutamine is the most available amino acid, glutamine is tightly regulated in the brain through its involvement in the glutamate–glutamine cycle of neurotransmission.[70,149] Glutamate is a major excitatory neurotransmitter that must be cleared rapidly following synaptic release in order to prevent excitotoxic damage to neurons.[55,149] Glial cells possess transporters for the clearance of extracellular glutamate, which is then metabolized to glutamine for delivery back to neurons. Neurons metabolize the glutamine to glutamate, which is then repackaged into synaptic vesicles for future release.[149] The glutamate–glutamine cycle maintains low extracellular levels of both glutamate and glutamine in normal neural parenchyma. Disruption of the glutamate–glutamine cycle can cause neurotoxicity and provide neoplastic GBM cells access to glutamine as we recently described.[51]

Cytomegalovirus—An Oncomodulator of Brain Tumor Energy Metabolism

Many cancers including GBM are infected with HCMV, which acts as an oncomodulator of tumor progression.[71,150,151] Products of the virus can damage mitochondria in the infected tumor cells thus contributing to a further dependence of these cells on glucose and glutamine for energy metabolism.[72,152–154] The virus often infects cells of monocyte/macrophage origin, which are considered the origin of many invasive and metastatic cancers, including GBM.[22,86,155–157] Indeed, we proposed that neoplastic microglia/macrophages were the most invasive cells within GBM.[22] GBM malignancy is correlated with the titer of HCMV infection. The higher the titer, the greater the malignancy.[71] We suggest that HCMV infection in these neoplastic cells could contribute to the progression of GBM through an oncomodulatory effect on tumor cell energy metabolism.

Exploiting Mitochondrial Dysfunction for the Metabolic Management of Glioblastoma Multiforme—Role of Ketones and Ketogenic Diets

The high glycolytic rate and Warburg effect seen in GBM indicates that GBM, like most cancers, is primarily a disease of energy metabolism.[36,47,50,54,113] Rational strategies for GBM management should therefore be found in therapies that can specifically target glycolytic tumor cell energy metabolism. As glucose is the major fuel for tumor energy metabolism through lactate fermentation, the restriction of glucose emerges as a

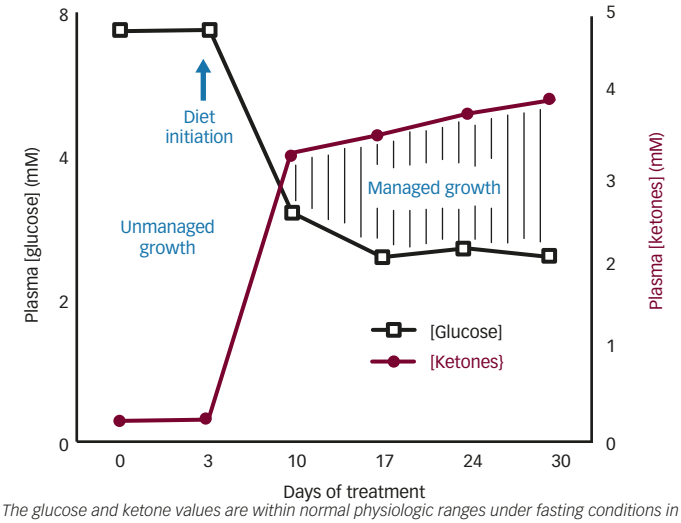
rational therapeutic target for GBM management. However, most normal cells of the brain also need glycolytic pathway products, such as pyruvate, for energy production through OxPhos. It therefore becomes important to protect normal brain cells from drugs or therapies that disrupt glycolytic pathways or cause systemic reduction of glucose.

It is well known that ketones can replace glucose as an energy metabolite and can protect the brain from severe hypoglycemia.[158–160] Ketone bodies (β-hydroxybutyrate [β-OHB] and acetoacetate) are generated almost exclusively in liver hepatocytes largely from fatty acids of triglyceride origin during periods of fasting.[158,161,162] George Cahill considered ketones 'good medicine' for several neurologic and neurodegenerative diseases in patients with normal physiology.[158,160,163–165] Ketone body metabolism reduces oxidative stress while enhancing metabolic efficiency of normal cells.[161,166–168] In addition to providing an alternative fuel to glucose, β-OHB also acts as a histone deacetylase inhibitor, which could reduce glucose and glutamine metabolism.[161] Tumor cells are unable to use ketone bodies for energy due to abnormalities in mitochondria structure or function.[47,169–171] Moreover, our findings and those of others suggest that elevated ketones can be toxic to some tumor cells.[35,172] A shift in energy metabolism associated with a low carbohydrate, high-fat ketogenic diet (KD) administered in restricted amounts (KD-R) will protect normal brain cells from glycolytic inhibition and the brain from hypoglycemia.

Nebeling and co-workers first showed that the KD was an effective non-toxic management for advanced stage astrocytoma in children.[173] More recent studies in adult GBM patients support these early studies in children.[174,175] It is important to mention that the therapeutic benefit for the KD is best when the diet is consumed in moderately restricted amounts rather than in unrestricted amounts. Restricted diets are those that deliver fewer total calories in order to lower circulating glucose and insulin levels. We showed in preclinical models of epilepsy and astrocytoma that blood glucose levels are lower while ketone levels are higher when the diet is consumed in restricted amounts than in unrestricted amounts.[79,176,177]

Humans, however, usually restrict intake of the KD due to the high fat content of the diet.[178] Ketone bodies and fatty acids target appetite centers to reduce weight naturally.[179] Moreover, prolonged unrestricted consumption of the KD can cause dyslipidemia, insulin resistance, and elevated glucose levels.[180,181] It is also important to recognize that circulating ketone levels will rarely exceed 7–9 mmol in most patients without diabetes since excess ketones will be excreted in the urine.[168] Ketoacidosis (above 15 mmol) is therefore not likely to occur in most GBM patients who would implement the KD-R. A moderate restriction of food intake in patients with GBM might reduce adverse effects even in the presence of steroids.[174] It should also be recognized that the weight loss associated with dietary restriction is considered 'healthy' weight loss,[182] whereas the weight loss associated with radiation and chemotherapy (fatigue, nausea, etc.) arises from the disease itself or from the toxic therapies used to treat the disease. Weight loss under these conditions is considered pathologic weight loss. This type of weight loss is in contrast to the mild weight loss associated with metabolic therapy, which will improve the overall health of the patient. The Longo group showed that water-only therapeutic fasting could improve the tolerance of patients to toxic cancer therapies.[183] Hence, the KD-R can enhance general physiologic health while placing metabolic stress on tumor cells.

Figure 4: Relationship of Circulating Levels of Glucose and Ketones (β-hydroxybutyrate) to Tumor Management



The glucose and ketone values are within normal physiologic ranges under fasting conditions in humans and will produce anti-angiogenic, anti-inflammatory, and pro-apoptotic effects. We refer to this state as the zone of metabolic management. Metabolic stress will be greater in tumor cells than in normal cells when the whole body enters the metabolic zone. The values for blood glucose in mg/dl can be estimated by multiplying the mM values by 18. The glucose and ketone levels predicted for tumor management in human cancer patients are 3.1–3.8 mM (55–65 mg dl) and 2.5–7.0 mM, respectively. These ketone levels are well below the levels associated with ketoacidosis (blood ketone values >15 mmol). Elevated ketones will sustain metabolic pressure on tumor cells, buffer daily fluctuations in blood glucose levels, and protect the brain from hypoglycemia. Modified from a previous version.[188]

The metabolic shift from glucose metabolism to ketone body metabolism creates an anti-angiogenic, anti-inflammatory, and pro-apoptotic environment within the tumor microenvironment.[59,79,169,184–186] There are no known drugs as effective in reducing angiogenesis and inflammation as calorie restriction.[59,185] The general concept of a survival advantage of tumor cells over normal cells occurs when fermentable fuels are abundant, but not when they become limiting.[35,187] *Figure 4* illustrates the changes in whole body levels of blood glucose and ketone bodies (β-OHB) that are predicted to metabolically stress tumor cells while enhancing the metabolic efficiency of normal cells.[188] This therapeutic strategy was illustrated previously in cancer patients and in preclinical models.[167,173,175,177,189–191]

In addition to lowering glucose availability to the tumor microenvironment, the KD-R could potentially lower brain glutamine levels thus restricting availability of this energy metabolite for tumor growth.[192,193] The KD-R could be even more therapeutic if combined with non-toxic drugs that also target glycolysis, e.g., 2-deoxyglucose or 3-bromopyruvate.[194,195] The KD-R could also further enhance GBM patient survival when combined with valganciclovir, which targets HCMV.[196] HCMV infection of tumor cells contributes to elevated metabolism of glucose and glutamine.[73,197] Recent evidence indicates that valganciclovir could significantly enhance survival of GBM patients.[196] Further studies are needed to determine which combinations of drugs and treatments can act synergistically with the KD-R to target GBM energy metabolism.

Hyperbaric Oxygen Therapy Used in Conjunction with the Ketogenic Diet

Hyperbaric oxygen therapy (HBO_2T) involves administration of 100 % oxygen at elevated pressure (greater than sea level, or 1 ATA). HBO_2T

increases plasma oxygen saturation and facilitates oxygen delivery to the tissue independent of hemoglobin O_2 saturation.[198,199] HBO_2T has been used with radiotherapy to enhance brain tumor cell killing or to reduce brain tissue damage from the radiotherapy itself.[11] HBO_2T has not yet been used with the KD-R for brain cancer management. Poff et al. also recently showed a synergistic interaction between the KD and HBO_2T for managing systemic metastatic cancer in mice (HBO_2T).[199] The KD reduces glucose for glycolytic energy, while also reducing NADPH levels for anti-oxidant potential through the pentose–phosphate pathway. HBO_2T will increase reactive oxygen species (ROS) in the tumor cells while the ketones will protect normal cells against ROS damage and from the potential for central nervous system oxygen toxicity.[161,169] Glucose deprivation will enhance oxidative stress in tumor cells, while increased oxygen can reduce tumor cell proliferation.[200,201] In contrast to radiation therapy, which also kills tumor cells through ROS production,[202] the KD + HBO_2T will likely kill tumor cells without causing toxic collateral damage to normal cells.[203] It will be interesting to determine if HBO_2T + KD-R can be as effective as radiation therapy for managing malignant brain cancer.

According to the evidence presented here, the KD-R could provide a viable non-toxic option to the current SOC for managing malignant brain cancer. The potential efficacy of the KD-R could be enhanced further when combined with drugs and HBO_2T, which create additional metabolic stress on tumor cells. The KD-R can target tumor cells globally without harming normal neurons and glia. The blood–brain barrier is less of a concern with the KD-R therapy than with conventional therapies. Although the KD-R therapy could be a more rational approach to malignant brain cancer management than is the current standard of cancer, the KD-R is not without some shortcomings. Compliance can be a major obstacle in attempting to implement the KD-R.[47] Some people can have difficulty in maintaining blood glucose and ketones in the ranges needed to target angiogenesis and to control tumor growth and inflammation. Presently, considerable patient discipline and motivation is required for implementing the KD-R as a therapy. Many neurosurgeons and neurooncologists are also unfamiliar with the link between nutrition, tumor metabolism, tumor growth, and how the glycolytic phenotype of brain tumor cells can be exploited with metabolic therapy, either as an alternative approach or as an adjuvant to standard care. Consequently, some patients might be discouraged from using non-toxic strategies like the KD-R even when evidence suggests that dietary ketosis is safe and associated with improved outcome and quality of life. Nevertheless, we remain hopeful that the metabolic approach to brain cancer management using the KD-R together with synergistic drugs, HBO_2T, and possibly a non-toxic antiviral therapy, will improve quality of life and longer-term survival for GBM patients. Neurooncologists should test this hypothesis.

Radiotherapy Used in Conjunction with the Ketogenic Diet

Despite the provocative effects of radiation on GBM growth and tumor cell survival, most GBM patients receive radiation as part of the SOC. Scheck and co-workers reported that radiation therapy against glioma growth in mice could be enhanced when combined with the KD.[204] Klement and Champ recently described how calorie restriction and the KD could reduce the adverse effects of radiation therapy to enhance overall therapeutic efficacy for cancer management.[175,205,206] It will be important to determine if radiation therapy can eventually be replaced with more effective and less toxic therapies. Until such time, it might be best to administer radiation therapy together with the KD-R or with another form of metabolic therapy that can lower blood glucose and elevate ketones.

Conclusions

As long as brain cancer is viewed as something other than a metabolic disease, it is unlikely that major progress will be realized in improving survival.[49] The current SOC for GBM offers little hope of improved quality of life or long-term patient survival.[89] If GBM becomes viewed as a metabolic disease, however, we might anticipate major advances in treatment and substantial improvement in quality of life and overall survival. Metabolic therapy will target the abnormalities in tumor cell energy metabolism without damaging normal brain tissue or producing adverse systemic effects. We think it is possible that non-toxic therapies could eventually replace toxic therapies for GBM management. Unfortunately, there is a critical lack of clinical trials in using metabolic therapy for GBM management as an alternative to the current treatments. In this vision of personalized metabolic medicine, clinical personnel specialized in metabolism, endocrinology, and nutrition will become part of neurooncology teams to enroll patients who refuse aggressive chemotherapy treatments in phase I\II clinical trials using the KD-R + HBO_2T. The application of metabolic therapy for brain cancer management is gaining momentum, but progress has been slow.[207] We remain hopeful that the metabolic approach to brain cancer management using the KD-R together with synergistic drugs and HBO_2T will offer the best chance for improved patient outcome. Metabolic therapy could become the new SOC if the impressive results in preclinical studies and in human case reports can be replicated in larger patient populations. ■

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