HHS Public Access

Author manuscript

*Curr Treat Options Oncol*. Author manuscript; available in PMC 2016 May 04.

Published in final edited form as:

*Curr Treat Options Oncol*. 2015 August ; 16(8): 36. doi:10.1007/s11864-015-0356-2.

# The Role of Glucose Modulation and Dietary Supplementation in Patients With Central Nervous System Tumors

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**Keywords**

Glucose; Ketone; Ketogenic diet; Modified Atkins diet; Dietary supplement; Vitamin; Mineral; Herb

## Introduction

Gliomas are the most common type of primary brain tumor and account for approximately 28 % of all primary central nervous system (CNS) tumors [1]. Surgery forms the backbone of both the diagnostic and initial therapeutic intervention. Radiation therapy has been demonstrated to prolong survival, but recurrence is routine and progression often is very rapid. Chemotherapy administered concurrently with radiation and for about 6 months following completion of radiation lengthens median survival in high-grade astrocytomas and oligodendrogliomas. However, the median survival in patients with glioblastoma (GBM) receiving optimal therapy remains only 12–15 months for patients with newly diagnosed GBM and 2–5 years for anaplastic gliomas [2, 3]. Over the past decade, there have been few advances in the treatment of these cancers. Bevacizumab, which targets the vascular endothelial growth factor receptor (VEGF), was initially thought to hold promise in this disease, though subsequent phase III investigation has failed to demonstrate survival advantage [4, 5]. To date, targeted therapies have been similarly disappointing. Recently, there has been a resurgence of interest in harnessing immunologic approaches to cancer therapy, although efficacy has yet to be demonstrated in gliomas. As a result, other therapeutic strategies continue to be sought.

The role of glucose modulation and dietary supplementation in cancer therapy has become increasingly popular in the modern era. Studies suggest that patient interest in and utilization

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**Compliance with Ethics Guidelines**

**Human and Animal Rights and Informed Consent**

This article does not contain any studies with human or animal subjects performed by any of the authors.

**Conflict of Interest**

Roy E. Strowd III and Stuart A. Grossman declare that they have no conflict of interest.

of these therapies is common. Existing data suggests that up to 73 % of Americans report using a dietary supplement (i.e., vitamin, mineral, herb, or other supplement). Of these, 77%report use of a specialized or single-ingredient vitamin or mineral (i.e., not a multivitamin), and 42 % report using herbs or botanicals [6]. Up to 20–33 % of persons report substituting a dietary supplement for a prescription drug, but only about 60 % speak to their physician about supplement use.

This is also true in patients with brain cancer. A study of 186 high-grade glioma patients enrolled in the Glioma Outcomes Project explored complementary and alternative medicines including biologically based modalities (e.g., vitamins, herbs) as well as alternative medical systems (e.g., acupuncture), mind-body modalities (e.g., meditation), manipulative and body-based therapies (e.g., yoga, massage), and energy-based modalities (e.g., therapeutic touch). In this study, biologically based therapies were most commonly used with 23%of patients taking vitamins, 22%herbs, 12% shark cartilage, and 7 % a macrobiotic diet [7]. In another study of 167 brain tumor patients in Canada, 49% were aware of complementary approaches, and of the 24 % who had incorporated these, 65 % used herbs, 20%vitamins, and 15%diet-based therapies [8]. In this study, patient desire to “take charge” over this difficult disease and influence from family members and caregivers were cited as important drivers of supplement use [8]. In a more recent cross-sectional study of 100 primary brain tumor patients, 34 % reported incorporating some complementary therapy with an average cost of $69 per month (and >$100 in 20 % of patients). Seventy-four percent of these reported that their physicians were unaware of this therapy [9].

Despite increasing interest and popularity, formal scientific studies of the majority of these interventions are lacking. The Natural Standard Research Collaboration was established in 2000 to provide access to peer-reviewed, evidence-based data and encourage scientific rigor around these alternative and complementary approaches [10]. Despite an increase in credible websites and online resources for searching complementary and alternative medicines [11], limited prospective data powered to accurately determine the safety and efficacy of these agents exists for many medical conditions including cancer [12, 13]. Furthermore, over the past decade, several published studies have suggested that without clear evidence supporting these approaches, diet- and supplement-based interventions should be approached with caution. The 10-year Physicians’ Health Study II was a randomized, double-blind, placebo-controlled factorial trial of vitamin E and vitamin C designed to study the impact of these agents on major cardiovascular events in men. This study failed to demonstrate a reduction in cardiovascular events and actually demonstrated a 74 % increased risk of hemorrhagic stroke with the supplement-based intervention (HR 1.74, 95 % confidence interval (CI) 1.04–2.91, $p = 0.04$) [14]. In a randomized, placebo-controlled study of over 35,000 men at risk for prostate cancer, vitamin E with or without high-dose selenium was associated with a 17%higher risk of prostate cancer in patients randomized to vitamin E [15]. In lung cancer, after conflicting results were published on the relationship between beta-carotene and lung cancer in the 1990s, a meta-analysis of four large randomized studies evaluating 109,394 patients treated with high-dose beta-carotene revealed that this was associated with a significantly increased risk of lung cancer in smokers [7]. Such studies underscore the importance of similarly rigorous evaluation of diet and supplement-based therapies which, like other pharmacologic therapies, require appropriately designed and powered prospective

safety and efficacy data to determine optimal doses, define combinations, avoid patient harm, and prevent serious public health problems.

Given the dismal prognosis of the majority of primary brain tumors, the strong patient and provider motivation to explore “natural” therapeutic strategies, and the common and costly use of diet and supplement-based treatments which are not without risk, clinicians must maintain awareness of these therapies and research must approach these with the same scientific rigor as nondietary pharmacologic agents. Here, we review recent critical data on (1) glucose modulation through macronutrient adjustment (i.e., dietary approaches), (2) nondietary glucose modulation, and (3) dietary supplements in patients with primary brain tumors.

## Treatment

### Dietary glycemic modulation

The modulation of glucose homeostasis through adjustment of macronutrient intake (i.e., carbohydrates, protein, and lipids) has existed as a therapeutic approach in medicine for over a century. A variety of “anti-cancer diets” have been variably explored including those low in meat, high in anti-oxidants, low in carcinogens, and high in fiber intake. Diets which specifically reduce carbohydrate intake and result in a state of systemic ketone body production have been termed ketogenic diets (KDs). To date, KDs have been the most widely studied and rigorously explored, primarily in the management of medically refractory epilepsy, though studies are beginning to investigate their role in neurodegenerative conditions, migraine management, and oncology.

**The Warburg effect—**The impact of metabolism on tumorigenesis has been recognized for over 50 years [16, 17]. Early research demonstrated preferential metabolism of glucose through aerobic glycolysis as opposed to oxidative phosphorylation (i.e., Warburg effect). This property has been exploited in tumor diagnostics with the incorporation of fluorodeoxyglucose positron emission tomography (FDG-PET) in systemic solid tumors, though imaging characteristics of normal brain parenchyma have limited the application to brain tumors. Therapeutic strategies for targeting this metabolic phenotype have been less studied. Recently, interest in exploring the metabolic pathways underlying gliomagenesis has increased.

**Biochemical basis for glycemic modulation—**Unlike normal glia which utilize glucose as the primary energy store but can activate alternative energy metabolism when needed, gliomas have both a high intrinsic glycolytic rate and are dependent upon glucose for energy metabolism [18]. Glioma cell lines metabolize glucose at rates three times greater than those of normal glial cell lines [19]; withdrawal of glucose has been found to induce apoptosis in rat glioma xenograft models [20], and utilization of ketone bodies, a primary alternative energy source in glucose-restricted environments, appears to be reduced in glioma cells [21–23].

In recent years, the biochemical pathways underlying this apparent metabolic preference toward glucose metabolism have become increasingly defined. Circulating glucose and

insulin are known to act on cell surface receptor tyrosine kinases altering cell signaling through the Akt/phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathways [24–26]. Activation of this pathway, which is present in gliomas, promotes glucose influx by increasing cell surface expression of glucose transporters and alters cellular biochemical signaling to promote glycolysis, shunt excess carbons toward biosynthesis, and regulate cellular redox potential [25–27].

To date, several standard dietary interventions that modulate glucose homeostasis have been developed and employ varying degrees of carbohydrate, lipid, and protein consumption including the conventional KD and its variants (Table 1). To date, only three early phase clinical trials evaluating the safety, feasibility, and tolerability of these interventions have been performed though numerous studies are currently underway.

## Conventional KDs

The conventional KD is characterized by a 4:1 ratio of [fat]/[carbohydrate + protein] intake in grams. Approximately 90 % of calories are derived from fat with limitations on calorie and fluid intake. An initial inpatient admission for supervised fast is often employed. Urine ketones are used to measure and monitor systemic ketone body production, and adjustments in the ratio of fat to carbohydrate and protein are used to maintain ketosis. This diet has been well studied in prospective randomized clinical trials in children with medically refractory epilepsy where efficacy, as measured by percent of patients with 50% seizure reduction, has been estimated around 70–80 % and tolerability at varying predefined study endpoints around 80 % [28–30]. Currently, two prospective studies are evaluating the safety and tolerability of the conventional KD in patients with brain tumors. One study employs a 4:1 ratio conventional KD with calorie restriction (1600 kcal) for 6 months in six patients with recurrent GBM (NCT01865162). A second study is investigating tolerance and self-reported compliance to a conventional KD (4:1 ratio) in patients with newly diagnosed GBM (NCT02046187). Results of these studies will further define the tolerability and feasibility of the conventional KD. Given that the translation of the conventional KD from children to adults with medically refractory epilepsy has been limited by the restrictive nature of this intervention, these data will be important to determine whether this approach should be further pursued.

## Alternatives to the conventional KD

Several alternatives to the conventional KD are available. These include the following:

• **Low-ratio KDs—**Diet interventions that employ lower ratios of carbohydrate restriction (i.e., 3:1, 2:1 or 1:1 ratio of [fat]/[carbohydrate + protein] intake in grams) have been studied as an alternative to the conventional KD. These interventions can be less restrictive with varying requirements for calorie and nutrient consumption and an initial inpatient fast. In patients with medically refractory epilepsy, tolerability has been similar to the conventional KD with slightly lower efficacy (i.e., percent with 50 % seizure reduction around 50–60 %) though head-to-head comparison has not been performed. In oncology, formal low-ratio KDs have not been systematically studied [30].

• **Modified Atkins diet—**The modified Atkins diet (MAD) is a carbohydrate-restricted diet which induces ketone body production without total calorie restriction, fluid restriction, inpatient admission, or the need for weighing foods. The MAD has proven tolerable and has similar efficacy to the conventional KD in patients with medically refractory epilepsy. It has become an attractive alternative in adults where studies have demonstrated safety, long-term tolerability ranging 60–80 %, and acceptable anti-convulsant efficacy [31].

Two studies employing less rigorous total carbohydrate restriction have been conducted in patients with systemic solid tumors [32, 33]. Both prospective phase II studies employed total carbohydrate reduction that varied in the degree of restriction. In one study employing total carbohydrate restriction to <5 % total estimated energy expenditure, 50 % of ten advanced solid tumor patients remained on the diet at 4 weeks [33]. In a second study, only 31 % of 15 patients with advanced solid tumors were able to remain on a 70 g/day carbohydrate-restricted diet at 3 months [32]. While these trials were not formally powered to determine efficacy, one partial response and ten stable diseases were observed.

To date, one study has been published on the feasibility of a similar diet intervention in patients with recurrent brain tumors [34••]. In this study, 20 patients were placed on a 60 g/day carbohydrate-restricted diet without calorie restriction. At a median of 36 days, 85%of patients remained on diet with three patients discontinuing due to its negative impact on quality of life. Median progression-free survival was 5 weeks (range 3–13 weeks), though the study was not powered or designed to confirm efficacy.

No published studies have investigated a dietary intervention with the degree of carbohydrate restriction formally defined in the MAD. However, one study is currently investigating such an approach employing a MAD-based diet combined with intermittent fasting in 25 patients with high-grade gliomas (NCT02286167). This study is designed to determine the feasibility and biologic activity as assessed by pre- and post-diet magnetic resonance spectroscopy (MRS).

• **Medium-chain triglyceride oil (MCT) diets—**In the classic KDs, fat consumption is primarily achieved by long-chain triglycerides. MCTs, however, provide more ketones per kilocalorie and enter the circulation more readily. MCT diets, which substitute medium-chain for long-chain fatty acids, have also been studied primarily in patients with epilepsy. Tolerability and anti-convulsant efficacy were similar for children on an MCT and KD in a prospective randomized controlled trial, though ketosis was higher in those on the conventional KD [35]. To date, no studies have evaluated MCTs in patients with primary brain tumors.

• **Low glycemic index (GI) diets—**The GI is a system for ranking the effect of carbohydrates on blood glucose concentrations. Carbohydrates are compared across individual foods gram-for-gram and ranked in terms of the degree of postprandial glycemia (i.e., higher index associated with higher postprandial glycemia). Studies have suggested an association between high GI diet and cancer risk including colorectal, endometrial, and breast cancer among others [36, 37]. Studies evaluating the association between GI and

glioma have not been performed, and prospective clinical trials of low-GI diets have not been comprehensively studied in patients with brain tumors.

**Future directions—**While the anti-convulsant properties of these diet interventions have been strongly linked to degree of ketosis, recent preclinical data suggests that the degree of calorie restriction as opposed to simply induction of ketosis may be an important anti-neoplastic component and measures of systemic ketosis may not be reliable biomarkers of anti-tumor response. Furthermore, the frequent use of corticosteroids in patients with primary brain tumors raises question as to whether systemic ketosis can be similar achieved in this patient population. Studies employing greater degrees of carbohydrate restriction with calorie restriction are ongoing and will help inform both the feasibility as well as potential optimal dosing strategy of these interventions (NCT01535911, NCT01092247, NCT01754350, NCT02286167).

## Nondietary glycemic modulation

Modulation of systemic glycemia through macronutrient dietary adjustment is not the only means of targeting glucose homeostasis. Interest in nondietary approaches is also increasing, and efforts are underway to identify agents (1) which target glucose dysregulation directly and reduce systemic hyperglycemia or (2) which target the underlying biochemical pathways which contribute to this metabolic phenotype and alter cancer-specific metabolism.

**Targeting glucose dysregulation and hyperglycemia—**A substantial amount of data suggests that systemic hyperglycemia is associated with worse outcomes in many medical conditions. Studies suggest that hyperglycemia is associated with a 3-fold increased risk of death with intensive care hospitalization, a 3.9-fold risk with myocardial infarction, and a 75 % increased risk of death with ischemic stroke [38–40]. Similarly, patients hospitalized with acute myelogenous leukemia have a 34%adjusted increased risk of death with each 10% increase in hyperglycemia [41]. Independent associations have been suggested in patients with acute lymphoblastic leukemia, prostate, and breast cancer but not in metastatic colon cancer [42–45]. While prospective randomized studies evaluating tight glycemic control in hospitalized ICU patients failed to demonstrate survival advantage, the mechanisms underlying its impact in cancer may be much different.

Similar negative associations between hyperglycemia and survival have been suggested in patients with brain tumors. In one study, 50%of high-grade brain tumors patients had random time-weighted mean glucose values greater than 110 mg/dL with 25 % having values greater than 137 mg/dL. Poorer survival from tumor progression was independently associated with increasing blood glucose with an adjusted hazard ratio of 1.03 (95 % CI 1.00–1.06) with each 10 mg/dL increase in time-weighted mean glucose ($p = 0.035$) [46]. In a second study, isolated postoperative hyperglycemia (e.g., single outpatient blood glucose >180 mg/dL) and persistent postoperative hyperglycemia (three or more outpatient blood glucose >180 mg/dL) were evaluated in 367 patients with malignant gliomas who had undergone craniotomy [47]. In this retrospective study, 19 % of patients had isolated and 8 % persistent hyperglycemia. Persistent outpatient BS >180mg/dL was associated with a 79%increased risk of death (95%CI 5–205 %, $p = 0.03$) which was independent of age,

Karnofsky performance status (KPS), prolonged dexamethasone administration, or other treatment variables.

Routine best practices throughout medicine include prompt recognition and management of glucose dysregulation, insulin resistance, and diabetes mellitus. These data suggest that similar practices should be considered in patients with primary brain tumors. Given the various parameters that are used to monitor glycemic status (i.e., fasting blood glucose, glycosylated hemoglobin, and oral glucose tolerance testing) as well as the numerous agents and classes of therapies which currently exist to lower blood glucose, a structured approach to addressing these important questions is necessary. Subsequent investigation will prospectively define the prevalence of hyperglycemia using validated screening measures, determine optimal strategies for lowering blood glucose, investigate the potential negative impact of increasing circulating insulin, and independently link glycemic intervention to survival.

**Targeting other pathways in the glioma metabolic phenotype—**In addition to these approaches to targeting glucose dysregulation in general, ongoing developments of drugs which directly target the pathways underlying glioma tumor metabolism are being explored. Preclinical studies in glioma cell lines have demonstrated that monocarboxylate transporter (MCT) inhibitors which block the lactate efflux necessary to maintain cellular integrity are present in gliomas and may inhibit invasiveness and induce necrosis [48, 49]. In gliomas expressing the mutant isocitrate dehydrogenase enzyme 1 (IDH1), glutaminase inhibitors which prevent conversion of glutamine to glutamate may slow tumor growth [50]. Similarly, IDH1 inhibitors are also being explored as a direct mechanism to target this IDH1 mutant phenotype [51]. At present, none of these agents are available. In contrast, metformin is an orally available normoglycemic agent which has also been shown to potentially enhance the cytotoxic effects of standard glioma therapy in preclinical models. A phase I factorial trial which includes metformin and temozolomide (TMZ), memantine, and mefloquine in the post-radiation setting is underway for those with newly diagnosed GBM (NCT01430351). A phase I safety study is also evaluating the combination of metformin and repeat radiation therapy in recurrent glioma (NCT02149459). While interest exists in these potentially novel therapeutic targets, until further study is performed, these agents are not ready to be incorporated into standard clinical care.

## Dietary supplements and natural substances

In addition to the dietary and nondietary approaches to targeting glucose homeostasis, a number of dietary supplements and naturally occurring substances which target other metabolic pathways have also been explored. This large and diverse group of biologically active agents includes vitamins, minerals, herbs, and other natural substances. Patient use is high, financial burden is nontrivial, and, in certain circumstances, important safety concerns exist. A recent study of over 1100 glioma patients suggested that incorporation of dietary supplements and other naturally occurring substances varies widely by patient, tumor type, and histologic grade. Associations with survival were inconsistent with both poorer survival and more favorable survival being reported with various supplements [52].

Despite frequent patient use and continued expansion of available dietary supplements, only a small number of these agents have undergone rigorous scientific evaluation. Preclinical study in glioma cell lines and rodent models of glioma have been the most commonly employed method of investigation. Only a few agents have been studied in phase I or II clinical trials (Table 2) [53]. Where these studies have been conducted, safety concerns and early signals of the lack of efficacy have been reported (e.g., copper and penicillamine, fenretinide).

A selected review of commonly used or previously studied agents is provided below:

- **Copper and penicillamine**
  - A series of preclinical studies in the late 1990s and early 2000s demonstrated anti-angiogenic properties of copper reduction [54, 55]. Copper depletion was shown to preferentially impact peritumoral angiogenesis by reducing peri-tumoral edema in animal models of primary brain tumors [56]. Penicillamine, an oral agent which chelates copper and is used in the management of Wilson's disease (i.e., intra-cerebral copper overload), was studied as a potential anti-angiogenic agent. A well-designed, prospective, single-arm feasibility, safety, and efficacy study was conducted in 40 GBM patients treated with a low-copper diet and escalating doses of penicillamine [57]. While the therapy successfully reduced serum copper levels, no prolongation in survival was observed and further study has not been pursued.

- **Vitamin A and retinoids**
  - Vitamin A and retinoids (e.g., synthetic and nonsynthetic chemical compounds that are related to vitamin A) have been studied in a variety of cancers. In glioma cell lines, they have been shown to strongly inhibit proliferation, migration, and angiogenesis [58]. Single-agent fenretinide, a synthetic retinoid, was evaluated in a two-stage phase II study of recurrent high-grade glioma but not found to be active, and this study was subsequently closed [59]. Another single-arm phase II study of 13-*cis*-retinoic acid administered in combination with TMZ was found to prolong progression-free survival at 6months (PFS-6) in patients with recurrent malignant glioma [60]; however, a subsequent randomized phase II adjuvant factorial study of dose-dense TMZ in combination with isotretinoin, celecoxib, or thalidomide recently demonstrated worse progression-free (10.5 vs 6.5, $p = 0.043$) and overall (21.2 vs 11.7, $p = 0.037$) survival compared to dose-dense TMZ alone [61••]. Thus, no prospective clinical data support its incorporation into existing therapeutic algorithms, and further study is required to determine if optimal combinations of this therapy exist. Currently, a study combining isotretinoin with vorinostat is recruiting patients with embryonal CNS tumors (NCT00867178).

- **Vitamin D**
  - In addition to its role in calcium homeostasis, the vitamin D receptor also has an impact on cell growth and differentiation. In a recent study of human glioma

tissue microarrays, the vitamin D receptor was found to be more highly expressed in tumor compared to nonmalignant brain tissues and expression of this receptor was associated with improved outcomes [62]. In this same study, pharmacologic modulation of these receptors in glioma cell lines altered cellular migration. A phase II study in the 1990s demonstrated the safety of adding alfacalcidol, a vitamin D analogue, to standard therapy at that time and concluded that this agent may have synergistic effects with standard chemoradiation. This study, however, was not designed to establish such a relationship, and we are not aware of subsequent publication of this combination [63]. A nonrandomized single-arm safety study adding vitamin D3 to adjuvant chemotherapy in patients with histologically confirmed GBM has been planned (NCT01181193).

- **Vitamin C**
  - Vitamin C has been shown to have anti-proliferative and apoptotic effects on in vitro models of glioma possibly through modulation of insulin-like growth factor-1 [64]. A prospective clinical evaluation has not been published, though multiple trials combining vitamin C with TMZ in recurrent glioma (NCT02168270) and with combination chemoradiation in newly diagnosed glioma (NCT01752491) are ongoing. Of note, recent studies of ascorbate (vitamin C) administered in combination with alpha-tocopherol (vitamin E) suggest that this combination may have anti-inflammatory effects on dendritic cell function and important inflammatory pathways [65]. Given the growing interest in immunologic therapies and increasing understanding of the immune system in cancer care, caution should be exercised when considering the incorporation of such therapies without sufficient data.

- **Curcumin and turmeric**
  - Curcumin, a polyphenolic compound contained in turmeric, has gained increasing popularity in multiple cancer types including primary brain tumors. Preclinical studies suggest that curcumin may block brain tumor formation and eliminate brain tumor cells, a process that may be mediated through inhibition of the JAK1/STAT3 pathway [66, 67]. Studies have also suggested activity in preclinical models of medulloblastoma including evidence that curcumin may inhibit signaling through the Sonic Hedgehog pathway [68]. It has been shown to be well tolerated in a phase II study of 25 pancreatic cancer patients [69]. To date, however, limited clinical data exists on its safety and efficacy in brain tumor patients. A surgical study evaluating the bioavailability of curcumin in brain tumor patients has been completed, but results are not yet published (NCT01712542).

- **Frankincense and boswellic acid oil**
  - Boswellic acid is a major component of the oleogum resin of the *Boswellia serrata*, a species of plant also known as frankincense or olibanum. Historically used in the traditional medicine practices in India and Africa, this substance has

become increasingly popular for its potential anti-inflammatory and anti-neoplastic properties. Studies have demonstrated proapoptotic properties in a rat glioma model [70], induction of epigenetic alterations in colorectal cancers [71], and suppression of growth and metastasis in pancreatic cancer models [72]. We are not aware of existing published clinical data on its safety and efficacy in patients with brain tumors.

- **Selenium**
  - Selenium is a chemical compound with important anti-oxidant functions including activity in the glutathione peroxidase and thioredoxin reductase enzymes. Studies have suggested that selenium may augment the effects of TMZ and contribute to cell death [73]. In metastatic brain tumors, mice bearing brain metastases who were fed selenium-enriched diets were found to have slower rates of progression and longer survival than those without dietary enrichment [74]. A prospective observational study of 95 patients with brain metastasis from nonsmall cell lung cancer treated with radiation therapy revealed significant declines in serum selenium levels during the course of radiation, though the clinical significance of this is not clear. A study of 32 glioma patients receiving infusions of 1000 μg of sodium selenite in combination with other active therapies published in 1997 concluded that selenium infusion was tolerated and improved serum selenium and other hematologic parameters [75]. Survival data was not reported, and recent consensus has suggested that further study is required of the role of selenium in cancer therapeutics specifically to determine the benefits of selenium supplementation, identify the specific cancers where benefit is observed, clarify optimal dosage strategies, and ensure sufficient balance between risk and benefit [76••].

## Conclusions

In conclusion, therapies that target the metabolic phenotype of cancer and palliate symptoms or improve quality of life are important in oncologic care and scientific investigation. Over the past decades, clinical trial designs to optimize pharmacologic drug development have been established. These provide mechanisms to document feasibility, safety, and efficacy in early phase studies of new therapeutic approaches. A similarly rigorous approach is required in the investigation, and incorporation of novel strategies aimed at glucose modulation and dietary supplementation for patients with CNS tumors.

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## Opinion statement

Central nervous system gliomas are the most common primary brain tumor, and these are most often high-grade gliomas. Standard therapy includes a combination of surgery, radiation, and chemotherapy which provides a modest increase in survival, but virtually, no patients are cured, the overall prognosis remains poor, and new therapies are desperately needed. Tumor metabolism is a well-recognized but understudied therapeutic approach to treating cancers. Dietary and nondietary modulation of glucose homeostasis and the incorporation of dietary supplements and other natural substances are potentially important interventions to affect cancer cell growth, palliate symptoms, reduce treatment-associated side effects, and improve the quality and quantity of life in patients with cancer. These approaches are highly desired by patients. However, they can be financially burdensome, associated with toxicities, and have, on occasion, reduced the efficacy of proven therapies and negatively impacted patient outcomes. The lack of rigorous scientific data evaluating almost all diet and supplement-based therapies currently limits their incorporation into standard oncologic practice. Rigorous studies are needed to document and improve these potentially useful approaches in patients with brain and other malignancies.

**Table 1**

Diet composition of dietary interventions for glycemic modulation

| Type of diet | Percent fat (%) | Percent carbohydrate (%) | Percent protein (%) | Other features |
|---|---|---|---|---|
| Normal diet | 20–35 | 50–70 | 15–20 | |
| US Government guidelines | 10–20 | 45–65 | 10–35 | |
| Conventional ketogenic diet | 88–90 | 2–4 | 6–8 | Requires inpatient admission, weighing of foods, and calorie, and nutrient calculation |
| Low-ratio ketogenic diet | 69–82 | 3–10 | 10–15 | Requires inpatient admission, weighing of foods, and calorie, and nutrient calculations |
| Modified Atkins diet | 60–65 | 5–10 | 10–20 | No inpatient admission, no weighing of foods, and no calorie restriction but requires carbohydrate counting and meal planning |
| Low glycemic index diet | 60–70 | 20–30 | 10–20 | No inpatient admission or weighing of foods but requires carbohydrate counting and meal planning |

Compositions of the various dietary interventions which modulate glycemic status. Data adapted from Cervenka et al. [71] and Klein et al. [77]

## Table 2

Selected dietary supplement clinical trials in patients with primary brain tumors

| Dietary supplement/substance | Preclinical | Phase I | Phase II | Phase III |
|---|---|---|---|---|
| Copper and penicillamine | X [54–56] | | X [57] | |
| Vitamin A/retinoids | X [58] | | X [59, 60, 61••] | |
| Vitamin D/vitamin D analogs | X[62] | | X [63] | |
| Vitamin C/ascorbic derivatives | X[64] | | | |
| Curcumin and turmeric | X [66–68] | | | |
| Boswellic acid/frankincense | X [70] | | | |
| Selenium | X [73, 74] | X [75] | | |

Summary of preclinical and clinical (phase I, II, and III) trials conducted for selected dietary supplements